الجمهورية الجزائرية الديمقراطية الشعبية وزارة التعليم العالي والبحث العلمي

PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA
MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH

University years 2023/2024

Higher School of Biological Sciences of Oran

Department of Second cycle

Pedagogical Handout
Subject

Genetic of eukaryote

Level: 2 year

Option: Molecular Biology

Specialty: Biotechnology

Sector: Biological Sciences

Domain: Science of Nature and Life

Realized by :

Dr. Wefa BOUGHRARA

Subject taught during the university years

2018/2019
2019/2020
2020/2021
2021/2022
2022/2023

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Preamble

The program "I-Architecture du noyau eucaryote" assumes paramount significance for students in their fourth year of the Molecular Biology Engineering diploma at higher school of biological sciences of Oran. Through a comprehensive exploration of the nuclear constituents, including the nuclear envelope (A-L'enveloppe nucléaire) and nuclear bodies (B-Les corps nucléaires), students are immersed in a comprehensive understanding of their roles in spatial compartmentalization, nucleo-cytoplasmic transport, and gene regulation. The subsequent investigation into chromatin (II-La chromatine) delves into the hierarchical organization of genomic DNA, ranging from nucleosomes to higher-order structures, elucidating the interplay between chromatin architecture, histone modifications, and epigenetic regulation. This program extensively covers the structural dimensions of chromatin (A-Organisation structurale de la chromatine), encompassing nucleosome positioning and higher-order chromosomal territories, as well as the transformative impact of various histone modifications (B-Modifications de la chromatine) on gene accessibility and expression. The exploration extends into the functional facets of chromatin organization (C-Organisation fonctionnelle et condensation de la chromatine), explicating the correlation between chromatin compaction, transcriptional activity, and genome stability. Moreover, the program delves into the dynamic orchestration of chromatin across multiple scales (D-Niveaux supérieurs de l'organisation chromatinienne), revealing how genomic domains interact to facilitate regulatory processes.

Furthermore, the program critically dissects the process of transcription (III-La transcription), offering profound insights into the underlying molecular mechanisms that drive gene expression. Encompassing general transcriptional principles (A-Généralités), the program elucidates the interplay between transcription factors, co-activators, and the RNA polymerase machinery, underscoring the essentiality of these interactions in transcription initiation and elongation. A rigorous analysis of DNA accessibility (B-L'accessibilité de l'ADN) expounds upon nucleosome remodeling and chromatin-modifying complexes, elucidating their role in facilitating or impeding transcriptional initiation. The subsequent modules delve into the activation of transcription for RNA polymerase II-dependent genes (C-Activation de la transcription de gènes ARN-PII-dépendants), encompassing promoter recognition, pre-initiation complex assembly, and the multifaceted role of enhancer elements. The program further unveils the intricacies of transcriptional activity at enhancer regions (D-La transcription aux enhancers), shedding light on their distant communication with promoters and their role in orchestrating cell-specific gene expression. Lastly, the exploration of transcriptional repression

(E-La répression transcriptionnelle) elucidates the array of repressive mechanisms, including chromatin condensation, histone deacetylation, and the involvement of non-coding RNAs, thereby comprehensively depicting the multifaceted transcriptional landscape.

In essence, for students pursuing their fourth year in Molecular Biology Engineering at ESSBO, the program "I-Architecture du noyau eucaryote" offers a profound scientific voyage into the nucleus, chromatin, and transcriptional dynamics. This knowledge equips them with a robust foundation required to comprehend and manipulate the intricate machinery that governs eukaryotic cellular processes and gene regulation, a skill set vital for their future roles as molecular biologists and researchers.

Summarize

Abbreviation List

A: acide aminé
ADN : acide desoxyribonucléique
ADP : adenosine diphosphate
AF : activation function
AID : activation induced deaminase
AR : androgen receptor
ARN: acide ribonucléique
ARNi: ARN interference
ARNm: ARN messager
ARNs nc: ARNs non codant
ARN-PII : ARN polymerase II
ARNr: ARN ribosomique
ARNt: ARN de transfert
ATM : ataxia telangiectasia mutated
ATP : adenosine triphosphate
BAFs : Brg1 associated factors
BER : base excision repair
Brg1 : Brm-related gene 1 protein
hBrm: Brahma
CBP : creb binding protein
CHD : chromodomain helicase DNA binding protein
ChEC : chromatin endogenous cleavage
CREB: cAMP response element
CstF: cleavage stimulation factor
CTs: chromosome territories
CTD: C terminal domain
CTE: C terminal extension
DBD: DNA binding domain
DNMT: DNA methyl transferase
ER: estrogen receptor
ERE: estrogen responsive element
ERR:ER-related receptor
ES: embryonic stem cell
E1 : œstrone
E2 : 17β-œstradiol
E3 : œstriol
FAIRE : Formaldehyde Assisted Isolation of Regulatory Elements
FISH : fluorescent in situ hybridization
GFP : green fluorescent protein
GO: gene ontology
GR: glucocorticoid receptor
GTFs: general transcription factors
HAT: histone acetyl transferase
HCP: High CpG promoter
HDAC: histone deacetylase
HMT: histone methyl transferase
HSP: heat shock protein
HP1: heterochromatin protein 1
ICD: intra chromosomal domain

ICN: intra chromosomal network
ICR: imprinting control region
KO: knock out
KRAB: Krueppel associated box
LAP2β: lamina-associated polypeptide 2 β
LBD: ligand binding domain
lincARN: long intergenic non coding RNA
LINEs: long interspersed nuclear elements
MAPK: mitogen activated protein kinase
MBD: methyl binding domain
MeDIP: methylated DNA immunoprecipitation
miRNA: micro RN
MR: mineralocorticoid receptor
NORs: nucleolar organizer regions
PR: progesterone receptor
NPC : nuclear pore complex
Nups : nucléoporines
OPT : Oct1/PTF/Transcription
Pb: paire de base
PBX1: pre B cell leukemia homeobox-1
PcG: polycomb group
PML: promyelocytic leukemia
PPAR: peroxisome proliferator activated receptor
PRE: PcG responsive element
qPCR: PCR en temps reel
RAL : raloxifène
RAR : retinoic acid receptor
RXR : 9-cis retinoid acid retinoid X receptor
SAGA : Spt-Ada-Gcn5-Acetyltransferase
SANT domain: Swi3, Ada2, N-CoR, TFIIB domain
SINEs: short interspersed nuclear elements
siRNA: small interference RNA
SLIDE: SANT like ISWI domain
snRNP: small nuclear ribonucleoproteins
SWI/SNF: switch/sucrose non fermentable
SWR1: swi/snf related protein
TAFs: TBP associated factors
TALE: three amino acid loop extension
TAM: tamoxifène
TBP: TATA binding protein
TDG: thymine DNA glycosylase
TES: transcriptional end site
TET: ten eleven translocation
TF: facteur de transcription
THC: tetrahydrochrysène
TR: thyroid hormone receptor
TSS: transcription start site
TRD: transcriptional repression domain
VDR: vitamin D receptor
Xi: X inactive

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Requirement

A profound investigation into the intricate realms of eukaryotic nucleus architecture, chromatin dynamics, and gene expression regulation requires an advanced comprehension of the underlying molecular mechanisms orchestrating these fundamental cellular processes.

Within the sphere of eukaryotic nucleus architecture, a comprehensive grasp of the biophysical properties of cellular membranes is essential, encompassing the intricate lipid composition and protein-lipid interactions that define membrane integrity. An exhaustive exploration of nuclear pore complexes becomes imperative, demanding an in-depth understanding of the diverse nucleoporins that constitute these multiprotein assemblies, their dynamic gating mechanisms, and their role in mediating selective nucleocytoplasmic transport. Furthermore, a meticulous dissection of the nuclear lamina's complex protein network, comprising lamin isoforms, nuclear membrane proteins, and chromatin-interacting factors, unravels its intricate involvement in not only maintaining nuclear shape and mechanical stability but also modulating gene expression through chromatin organization and mechanosensing pathways.

Transitioning to nuclear bodies, an intricate knowledge of their molecular architecture and constituent biomolecules is indispensable. Nucleoli, as highly dynamic subnuclear compartments rich in ribosomal RNA genes, ribosomal proteins, and diverse assembly factors, necessitate a comprehensive understanding of the intricate molecular choreography orchestrating ribosome biogenesis. Concurrently, delving into Cajal bodies, enriched in coilin, SMN, and other proteins, requires a deep dive into the multifaceted RNA processing events they mediate, including small nuclear ribonucleoprotein assembly and spliceosomal functions.

Navigating the complexities of chromatin dynamics demands an advanced exploration of histone biology, including histone variants, histone modification enzymes, and the regulatory roles of histone tails. A comprehensive analysis of chromatin remodeling complexes, ATP-dependent chromatin modifiers, and non-coding RNAs unveils the intricate interplay between epigenetic marks like DNA methylation, histone acetylation, and chromatin accessibility, orchestrating gene expression programs.

In the realm of gene expression, an exhaustive inquiry into the dynamics of euchromatin and heterochromatin transitions necessitates an advanced understanding of epigenetic regulators, such as Polycomb and Trithorax group proteins, and their roles in gene silencing and activation. Furthermore, a profound exploration of three-dimensional chromatin architecture, facilitated by techniques like chromosome conformation capture (Hi-C), uncovers the dynamic interactions

between distal enhancers, promoters, and insulator elements, offering insights into the spatial orchestration of transcriptional networks.

In conclusion, the comprehensive investigation of eukaryotic nucleus architecture, chromatin dynamics, and gene expression regulation requires a sophisticated mastery of lipid bilayer biophysics, nucleoporin interactions, lamin networks, histone biology, chromatin remodeling mechanisms, and three-dimensional chromatin organization. This advanced journey ventures into the intricate molecular symphony governing cellular identity, function, and adaptation.

Chapter I: Nuclear Architecture

I. Introduction

The nuclear architecture differs significantly between eukaryotic and prokaryotic cells. In eukaryotic cells, the nucleus is enclosed within a double-membrane structure called the nuclear envelope, which separates the genetic material from the cytoplasm. The nucleus houses linear DNA molecules organized into multiple chromosomes, and within the nucleus, a distinct region called the nucleolus is responsible for ribosome synthesis. Eukaryotic cells also possess a complex network of proteins and fibers collectively known as the nuclear matrix, which helps organize and support the overall structure of the nucleus. In contrast, prokaryotic cells lack a defined nucleus and nuclear envelope. Instead, their genetic material consists of a singular, circular DNA molecule that floats freely in the cytoplasm, forming a region called the nucleoid. The nucleoid lacks the membrane-bound compartmentalization seen in eukaryotes. Moreover, prokaryotic cells do not have a nucleolus or a nuclear matrix. The genetic material in prokaryotes is often in close proximity to the ribosomes, as protein synthesis occurs directly in the cytoplasm. This fundamental distinction in nuclear architecture reflects the broader division between eukaryotic and prokaryotic cellular organization.

The nucleus, in eukaryotic cells, contains the majority of the cell's genetic material and serves two primary roles. Firstly, it regulates the chemical processes taking place within the cytoplasm, and secondly, it stores the essential information needed for cell division. With dimensions ranging from 10 to 20 micrometers, it holds the distinction of being the largest organelle. Enclosed by a membrane envelope, the nucleus is segregated from the cytoplasm (Figure 01). This envelope comprises three components: the inner and outer nuclear membranes, which periodically merge to create nuclear pores, protein complexes that constitute the nuclear pores, and the nuclear lamina. This structure effectively segregates chemical reactions occurring within the cytoplasm and those within the nucleus. Initially, the nucleus garnered significant attention due to the pivotal role of nuclear pores in facilitating transport between the nucleus and cytoplasm. This led to the identification of nuclear pore complex constituents and a detailed understanding of the mechanisms governing cytoplasmic-nuclear transport.

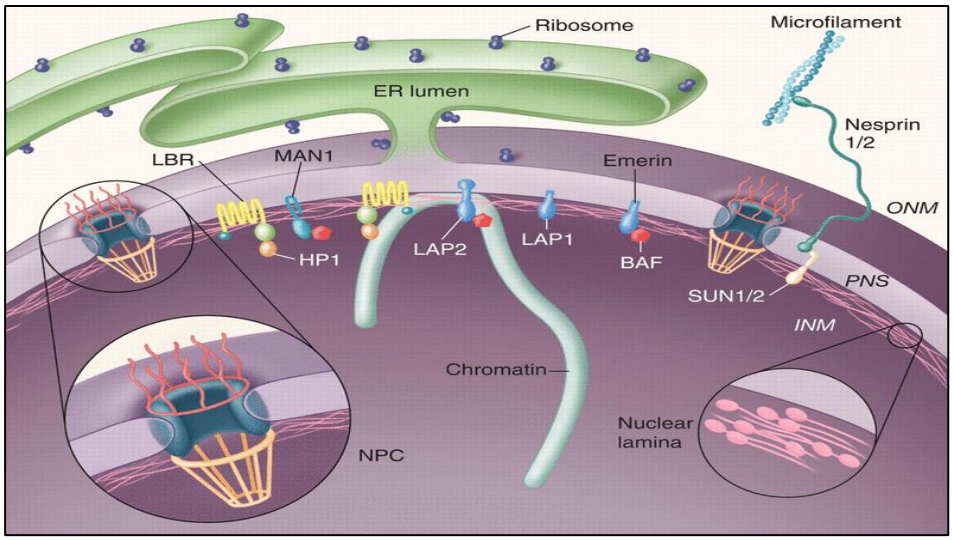

Figure 01: Nuclear envelop organization (Stewart CL et al., 2004).

More recent findings have unveiled those mutations in various proteins located in the nuclear envelope underlie severe hereditary diseases (Somech et al., 2005). Scrutinizing the impact of these mutations has led to a better understanding of the nuclear envelope's role in nuclear structure. It has also led to the proposition of novel functions for envelope proteins in organizing chromatin and regulating gene expression (Bengtsson and Wilson, 2004; Gruenbaum et al., 2005; Worman, 2006). Due to the significant variation in the affected tissues caused by these pathological mutations, as well as the tissue-specific nature of certain nuclear envelope proteins during differentiation, it has been hypothesized that the nuclear lamina serves as a platform for recruiting factors crucial in cell differentiation, particularly in muscle and adipose tissues (Gotzmann and Foisner, 2006).

Moreover, the identification of specific diseases characterized by exceedingly premature aging, linked to a mutation in the gene of a major component of the lamina, has triggered contemplation about the roles of the nuclear envelope and DNA damage repair mechanisms in the aging process (Lans and Hoeijmakers, 2006). In this context, the observation that the molecular mechanisms behind Hutchinson-Gilford progeria, a severe aging-related disorder, are even present at a lower level in normally aged cells, as noted by Scaffidi and Misteli (Scaffidi and Misteli, 2006), suggests the involvement of lamin A in the natural aging process.

In light of these considerations, our laboratory embarked on the endeavor of characterizing the atomic-scale, three-dimensional structure of nuclear envelope proteins. The focus was placed on three proteins - lamin A/C, emerin, and MAN1 - all implicated in hereditary

diseases. The goal was to establish a link between their three-dimensional structure and the impaired functional mechanisms associated with these diseases. To illuminate the significance of our structural investigations, this endeavor began by providing an overview of current knowledge about the nuclear envelope and its constituent proteins. Subsequently, the work delved into the study of MAN1, accompanied by two related articles. Finally, an account was provided of the advances in the research involving lamin A/C with SREBP1, along with the inclusion of an article concerning the clinical and molecular analysis of the R439C mutant of lamin A/C.

The nuclear envelope encompasses nuclear membranes, nuclear pore complexes, and the nuclear lamina (Figure 02). The nuclear membranes are categorized into three interconnected domains with distinct morphologies: outer, inner, and pore membranes. The pore membranes act as connectors between the outer and inner membranes at various points. They harbor distinctive integral proteins, such as gp210 and POM121 in mammals, as well as POM152 in yeast, all of which constitute nuclear pore complexes. These complexes consist of approximately fifty diverse types of proteins known as nucleoporins (Cronshaw et al., 2002; Rout et al., 2000). The composition and roles of nuclear pore complexes, alongside their structural aspects, have been extensively reviewed in recent literature (Bednenko et al., 2003; Cronshaw and Matunis, 2003; Fahrenkrog and Aebi, 2003; Rabut et al., 2004; Suntharalingam and Wente, 2003).

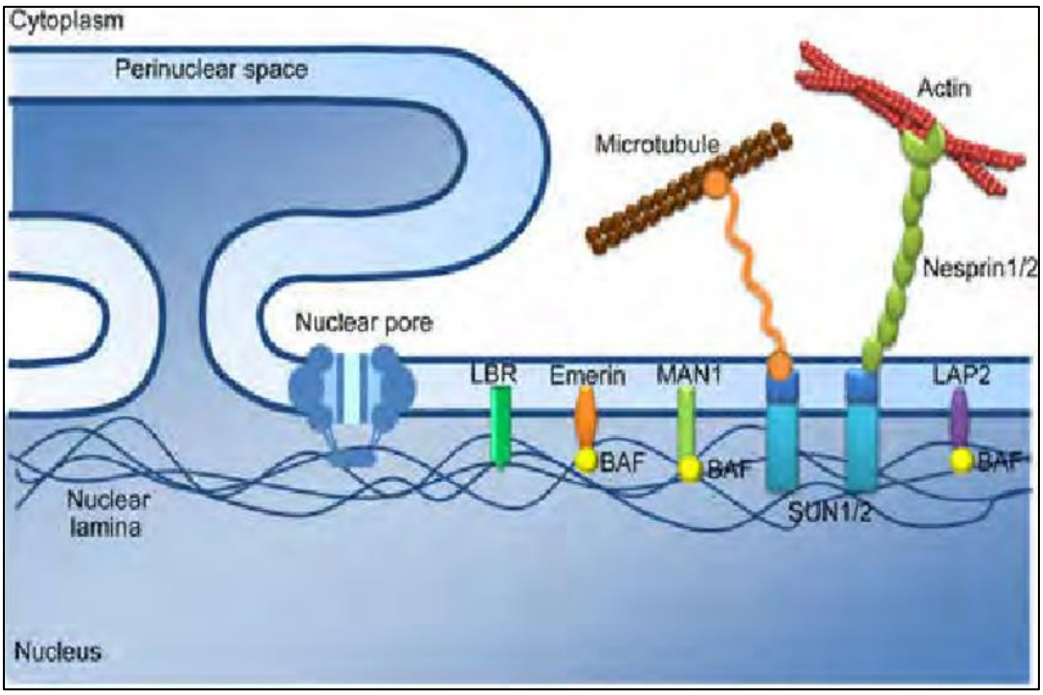

Figure 02: Nuclear envelope and their composition (Chi et al., 2009).

Within this chapter, I will commence by elucidating the constituents of the outer nuclear membrane and their interplay with protein networks that play a role in cytoplasmic organization. Following that, I will illustrate the mechanisms through which nuclear pore complexes govern the transport between the nucleus and the cytoplasm. Subsequently, I will outline the proteins inherent to the inner nuclear membrane and the nuclear lamina, crucial for mediating interactions between the nuclear envelope and chromatin. Concluding this chapter, I will delve into contemporary revelations concerning the contributions of these proteins to the regulation of gene expression.

II. The Crucial Role of the Outer Nuclear Membrane in Establishing Nuclear Positioning

The outer nuclear membrane boasts an array of ribosomes dotting its cytoplasmic surface. For a considerable period, it was widely assumed to possess an identical protein composition to that of the rough endoplasmic reticulum membrane, given their seamless continuity. Nonetheless, recent evidence has overturned this notion, indicating that the outer nuclear membrane harbors a distinct set of proteins that contribute to nuclear positioning and are absent in the endoplasmic reticulum (Starr and Han, 2003).

Among these pivotal proteins lie the outcomes of two genes, namely nesprin 1 and nesprin 2, also recognized as syne-1 and syne-2, or by other names such as Nuance, Myne1, ENAPTIN, or ANC-1. These genes encode polypeptides characterized by spectrin-like sequence repetitions (Young and Kothary, 2005; Zhang et al., 2001). Initially discerned within larger proteins, notably cytoplasmic ones like dystrophin and α-actinin, these repetitions encompass distinct elements: a central domain housing self-associating repetitions, an N-terminal segment that binds actin and consists of two calponin-homology domains, and a C-terminal domain imbued with specific functional attributes. The C-terminal domains contribute to various functions, including membrane attachment, interaction with intermediate filaments, and engagement with microtubules. In the case of nesprins, alternative initiation of transcription and splicing processes give rise to multiple isoforms characterized by molecular weights spanning from around 50 kDa (Nesprin-α2) to 800 kDa (Nuance). Some nesprin isoforms lack the C-terminal domain, while others incorporate a KASH domain (Klarsicht, Anc-1, Syne-1 Homology, or "Klarsicht-like domain," Figure 3) as their C-terminal region. This domain consists of a transmembrane segment followed by a proline-rich 35-residue portion.

The mobility of nesprins within the endoplasmic reticulum membrane exhibits lateral diffusion. However, while the smaller isoforms manage to access the inner nuclear membrane, the larger

counterparts find themselves excluded from this region. This exclusion is likely attributed to the restricted dimensions of the channels within the nuclear pore complexes (Soullam and Worman, 1995).

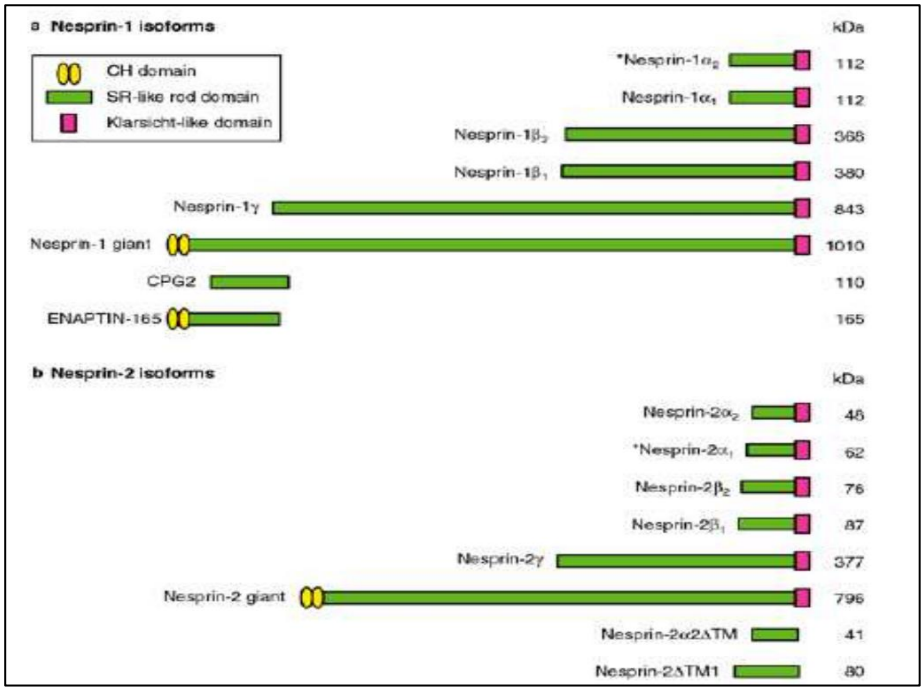

Figure 03: isoform principal architecture of nesprin-1 and nesprin-2 genes (Warren et al; 2005)

The larger isoforms of nesprin interact through their N-terminal domain with the actin cytoskeleton (Zhang et al., 2002). Furthermore, they attach through their C-terminal KASH domain to the perinuclear SUN domains of inner nuclear membrane proteins such as UNC84 (Lee et al., 2002b; Malone et al., 1999) and Matefin in Caenorhabditis elegans, and SUN1 and SUN2 (Hodzic et al., 2004) in mammals. An example of this is the C. elegans protein ANC-1, which contains a spectrin-like sequence repeat and a perinuclear domain that interacts directly or indirectly with the perinuclear SUN domain of UNC84 (Starr and Han, 2002). The smaller isoforms associate with emerin and lamins A/C within the nucleus (Zhang et al., 2005). Lastly, certain isoforms anchor to organelle membranes other than the nucleus, such as the endoplasmic reticulum or mitochondria, through their transmembrane segment (Starr and Han, 2002).

III. Proteins of the Inner Nuclear Membrane

Analysis of the proteome has indicated the presence of at least 80 proteins localized at the inner nuclear membrane in interphase mammalian cells (Schirmer et al., 2003). However, as of now, only around a dozen of these proteins have undergone comprehensive characterization. Numerous integral proteins of the inner nuclear membrane feature their N-terminal domains on the nucleoplasmic side, coupled with one or more transmembrane

segments. These proteins are synthesized at the rough endoplasmic reticulum membrane and subsequently diffuse laterally to reach the inner nuclear membrane, where they establish interactions with the lamina and/or chromatin (Ellenberg et al., 1997; Ostlund et al., 1999; Soullam and Worman, 1993; Soullam and Worman, 1995; Wu et al., 2002). Nevertheless, the lateral channels of nuclear pore complexes appear to impose size limitations that hinder access to the inner nuclear membrane for proteins featuring nucleoplasmic domains exceeding 60 kDa (Soullam and Worman, 1995; Wu et al., 2002).

Throughout mitosis, proteins associated with the inner nuclear membrane disengage from the lamina and chromatin, scattering within the residual endoplasmic reticulum. After chromatin decondensation, these proteins diffuse within the membranous structure to reform the nuclear envelopes of daughter cells (Ellenberg et al., 1997; Yang et al., 1997). Similar to lamins, proteins of the inner nuclear membrane undergo phosphorylation at specific sites during the disassembly of the nuclear envelope in mitosis (Courvalin et al., 1992; Ellis et al., 1998; Foisner and Gerace, 1993). Furthermore, several inner nuclear membrane proteins partake in the "early" decondensation of chromatin as part of the nuclear reassembly process preceding lamin assembly. This is achieved through their interactions with components of chromatin (Buendia and Courvalin, 1997; Chaudhary and Courvalin, 1993; Haraguchi et al., 2000).

III.1. Lamin B Receptor (LBR)

Lamin B receptor (LBR) emerged as the pioneer gene responsible for encoding an inner nuclear membrane protein, a discovery attributed to Worman et al. in 1988. This gene comprises 13 exons and is positioned on chromosome 1q42.1, as outlined in studies by Schuler et al. in 1994 and Wydner et al. in 1996. Mutations within LBR are accountable for the manifestation of two distinct conditions: an autosomal dominant disorder impacting the granulocytic lineage known as Pelger-Huët syndrome, and a skeletal dysplasia termed Greenberg/HEM syndrome, which unfortunately leads to fetal demise while in utero (Hoffmann et al., 2002 ; Waterham et al., 2003).

LBR, spanning 615 amino acids, showcases an N-terminal region of 200 amino acids oriented toward the nucleoplasm, followed by eight transmembrane segments, as elucidated by Worman et al. in 1990 and Ye and Worman in 1994. This nucleoplasmic region comprises a projected Tudor domain, analogous to domains found in various proteins that bind methylated peptides. Subsequently, there exists a segment low in hydrophobic amino acids, succeeded by a second domain projected to possess a globular structure, as hypothesized by Ye and Worman in 1996. When coupled with glutathione-S-transferase (GST) and attached to beads displaying

glutathione, LBR exhibits interactions with type B lamins, an observation originating from the work of Worman et al. in 1988 and Ye and Worman in 1994. Notably, its sequence rich in serine, glycine, and arginine, alongside its diminished content of hydrophobic amino acids, plays a pivotal role in its in vitro engagement with double-stranded DNA

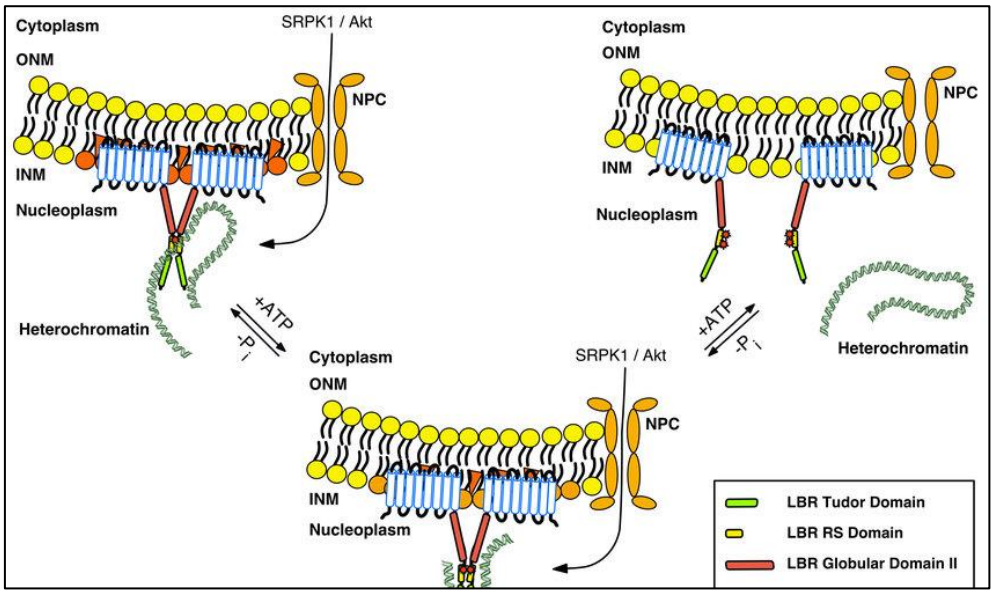

Figure 04: LBR interactions (Nikolakaki E et al., 2017)

The transmembrane region of LBR shares a notable degree of sequence identity with sterol reductases found in the endoplasmic reticulum of plants, yeast, and animals (Holmer et al., 1998; Schuler et al., 1994). Additionally, human LBR exhibits C14-sterol reductase activity upon expression in yeast (Silve et al., 1998). This suggests the multifunctionality of LBR as a protein involved both in nuclear organization and sterol metabolism. Coinciding with this, mutations within LBR that lead to genetic disorders result in deformations of granulocyte nuclei and disruptions in cholesterol metabolism (Hoffmann et al., 2002; Waterham et al., 2003).

III.2. Lamina-Associated Proteins (LAPs)

Lamina-associated proteins LAP1A, 1B, and 1C arise from alternative splicing of a shared gene located on human chromosome 1p36. They exhibit a nucleoplasmic N-terminal region followed by a transmembrane domain (Martin et al., 1995). While LAP1A and LAP1B interact with lamin A, C, and B1, LAP1C does not engage with lamins (Foisner and Gerace , 1993). Nonetheless, LAP1C demonstrates in vivo association with a high-molecular-weight protein complex encompassing a protein kinase and type-B lamins, a revelation presented by Simos et al. (1996). Distinct from the complexes containing LAP2 or LBR, those comprising

LAP1 appear to inhabit unique domains within the inner nuclear membrane (Maison et al.,1997).

A total of six isoforms of LAP2, alternatively referred to as thymopoietins, have been distinguished in mammals. These isoforms originate from alternative splicing of a single gene located on chromosome 12q22. Notably, recent research has unveiled that a mutation affecting the C-terminal domain of LAP2α leads to cardiomyopathy (Taylor et al., 2005).

The various LAP2 isoforms share a consistent N-terminal region consisting of 187 amino acids (figure 05). LAP2β, LAP2γ, LAP2δ, and LAP2ε secure their place within the inner nuclear membrane through a transmembrane segment, with their N-terminal region localized within the nucleoplasmic region. On the contrary, LAP2α and LAP2ζ are entirely confined to the nucleoplasm. Among these, LAP2β stands out with an elongated nucleoplasmic segment spanning 408 residues. Meanwhile, LAP2γ, LAP2δ, LAP2ε, and LAP2ζ possess partial segments of this region. Further distinguishing itself, LAP2α showcases a distinct C-terminal domain spanning 506 residues (Furukawa et al.,1995; Harris et al., 1995; Vlcek et al.,2001; Vlcek et al., 1999).

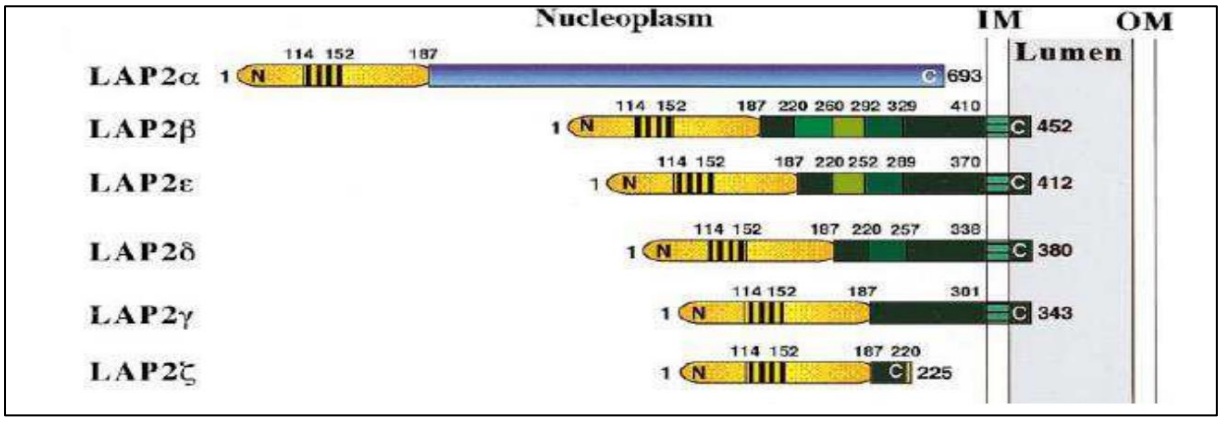

Figure 05: LAP2 proteins Family organization (Dechat et al., 2000)

In the N-terminal region of all LAP2 isoforms, there is a globular domain of about 50 residues, common to various inner nuclear membrane proteins: the LEM domain (LAP2-Emerin-MAN1) (Lin et al., 2000). Furthermore, in all LAP2 isoforms, a LEM-like domain has been identified upstream of the LEM domain (Lin et al., 2000). The three-dimensional structure of these two domains of LAP2β has been resolved in the laboratory (Laguri et al., 2001) and by the group of M. Clore (Cai et al., 2001)(figure 06). These domains consist of two long parallel α-helices. They interact either with the protein BAF (barrier-to-integration factor), which binds to DNA for the LEM domain, or directly with DNA for the LEM-like domain, according to the study

by M. Clore's NMR group (Cai et al., 2001). Additionally, the region 1-85 containing the LEM-like domain binds to chromosomes in vivo (Furukawa et al., 1998).

The nucleoplasmic segment 298-408 of LAP2β interacts with the central domain of lamin B1 in double-hybrid experiments (Furukawa et al., 1998) and is responsible for LAP2β's retention at the nuclear envelope (Foisner and Gerace, 1993). The LAP2β/lamin B-type interaction is inhibited by mitotic phosphorylation (Foisner and Gerace, 1993). Finally, the region 137-242 containing a portion of the LEM domain binds to the nuclear protein HA95, and when this binding is inhibited, DNA replication is no longer initiated in vitro, entry into S phase is blocked in vivo, and the Cdc6 protein (cell-division-cycle protein-6) is proteolyzed (Martins et al., 2003).

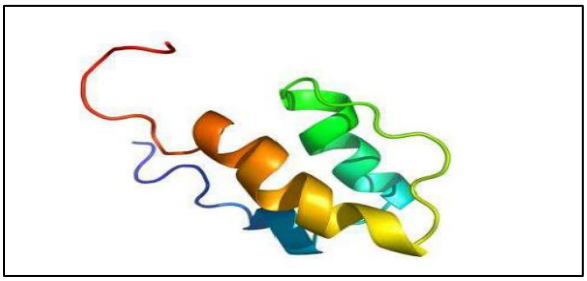

Figure 06: LEM and LAP2 tridimentional domain (Laguri et al., 2001)

III.3. Emerin

In 1994, a significant finding emerged from D. Toniolo's research team, unveiling the identification of a gene on the X chromosome that encodes a 254-amino acid protein named emerin. This protein was found to be mutated in X-linked Emery-Dreifuss Muscular Dystrophy (EDMD), a disorder characterized by contractures in multiple areas including elbows, Achilles tendons, and posterior neck muscles. This condition also entails a gradual muscular decline coupled with cardiomyopathy that leads to cardiac arrest (Bione et al., 1994). Subsequent investigations by K. Arahata's and G.E. Morris' teams solidified emerin's identity as an inner nuclear envelope protein, often missing in patients afflicted with X-linked EDMD (Manilal et al., 1996; Nagano et al., 1996). As a consequence, the mutation or absence of emerin was identified as the causative factor behind a form of EDMD that mirrors symptoms induced by certain mutations in lamin A-type lamins (Nagano et al., 1996).

Emerin is characterized by a nucleoplasmic N-terminal region consisting of 220 residues, succeeded by a transmembrane segment and a brief luminal tail. The significance of the nucleoplasmic region lies in its capability to retain emerin at the inner nuclear membrane, as shown by Ostlund et al. in 1999. At the N-terminus, an essential LEM domain is situated,

facilitating interaction with a nucleoplasmic DNA-binding protein named BAF, as demonstrated by K. Wilson's group through blot overlay and co-immunoprecipitation experiments (Lin et al., 2000; Wolff et al., 2001; Lee et al., 2001).

The nucleoplasmic domain of emerin forms interactions with lamin A and C (figure 07). The co-immunoprecipitation technique applied to nuclear lysates by the teams of J.A. Ellis and C.J. Hutchison validated this interaction (Fairley et al., 1999; Vaughan et al., 2001), a conclusion confirmed using Biacore by G.E. Morris' team (Clements et al., 2000). Further refinement of the interaction regions of these two proteins was accomplished by subsequent research. K. Wilson's team, employing emerin mutants in blot overlay experiments, pinpointed the central region of emerin, encompassing residues 70 to 178, as crucial for interaction with lamin A (Lee et al., 2001). Meanwhile, S. Ishiura's team delved into the emerin-lamin interaction through double-hybrid screens, revealing that the region 384-566 of lamin A was both necessary and sufficient for interacting with emerin 1-225 (Sakaki et al., 2001).

Emerin's associations extend to actin filaments within the nucleus, as demonstrated by cosedimentation experiments (Holaska et al., 2004). Recent insights from E.M. McNally's group disclosed emerin's binding to nesprin-1α and lamin A through blot overlay (Mislow et al., 2002). Moreover, I. Karakesisoglou's team unveiled direct interactions through GST pulldown experiments, occurring among nesprin-2, emerin, and the C-terminal region of lamin (Libotte et al., 2005). This interaction was subsequently affirmed by C.M. Shanahan's team employing co-immunoprecipitation experiments, substantiating the involvement of nesprin-2, emerin, and lamin A/C (Zhang et al., 2005). Consequently, it is plausible that nesprin-2 serves to stabilize a complex that involves lamin and emerin.

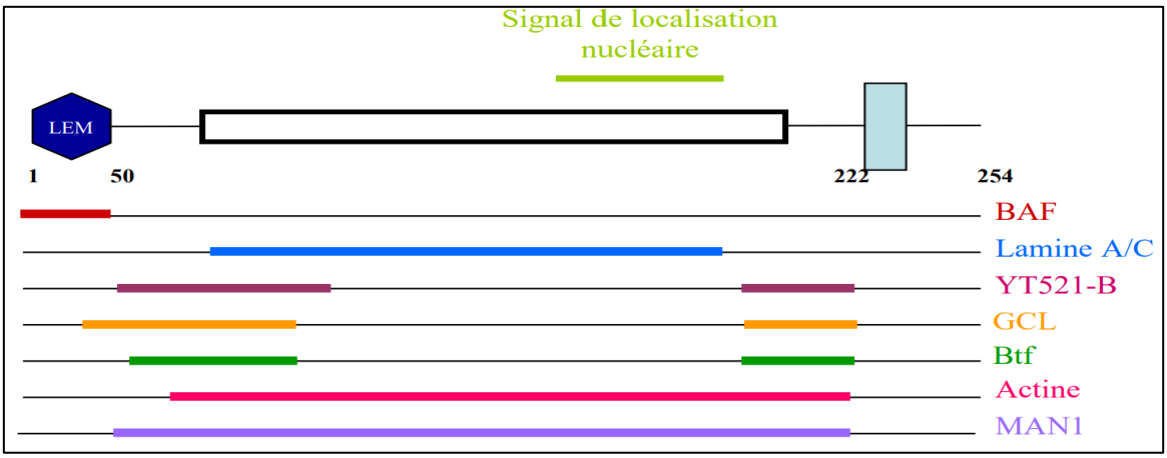

Figure 07: Emirin and their interaction.

Nonetheless, despite the notable attention garnered by emerin in recent times, the underlying physiological importance of these protein-protein interactions and the precise molecular repercussions stemming from emerin deficiency remain obscure.

Evaluation of fibroblasts from either patients or cells transfected with emerin mutant-encoding genes has shed light on the feeble interactions between emerin and lamin A-type lamins (Clements et al., 2000; Fairley et al., 1999), leading to an escalation in the solubility of all lamins (Markiewicz et al., 2002). In fact, biochemical assays segregating soluble and insoluble fractions highlight the presence of all lamins from healthy control fibroblasts in the insoluble fraction. In contrast, fibroblasts from individuals afflicted with X-linked EDMD display a portion of lamins within the soluble fraction. This analogous mechanism may also be at play in autosomal variations of EDMD stemming from mutations in lamin A-type lamins. However, the structural arrangement of chromosomes, as scrutinized in cells derived from X-linked EDMD patients, remains unaltered (Boyle et al., 2001).

III.4. MAN1

The human MAN1 protein was first identified as the target of autoantibodies in a patient with collagenosis (Paulin-Levasseur et al., 1996). Comprising 911 residues, it is encoded by a gene situated on chromosome 12q14 (Lin et al., 2000). More recently, it has been demonstrated that osteopoikilosis, Buschke-Ollendorff syndrome, and melorheostosis are variants stemming from mutations in the MAN1 gene (Hellemans et al., 2004). Osteopoikilosis is an autosomal dominant skeletal dysplasia marked by the presence of hyperostotic areas at different locations. It can manifest as an isolated condition or alongside other bone and skin anomalies (Chigira et al., 1991). Buschke-Ollendorff syndrome combines osteopoikilosis with tissue lesions (Giro et al., 1992). Melorheostosis is characterized by limb hyperostosis (bone enlargement affecting structure and shape), coupled with muscle atrophy and alterations in the dermis and epidermis. Fibroblasts derived from patients with these disorders show irregular upregulation of TGF-β target genes.

MAN1 comprises an extensive N-terminal region of approximately 450 residues, succeeded by two transmembrane segments and a C-terminal segment spanning about 230 residues. Both the N- and C-terminal regions are found in the nucleoplasm. The N-terminal region of MAN1 plays a crucial role in retaining the protein at the inner nuclear membrane (Wu et al., 2002). Although MAN1 can move freely within the endoplasmic reticulum membrane, its lateral diffusion is restricted in the inner nuclear membrane, hinting at an interaction with a component of the nuclear lamina. Bioinformatics analysis of the MAN1 sequence discloses the presence of an

LEM domain at the N-terminus, shared with other inner nuclear membrane proteins like LAP2 and emerin (Lin et al., 2000). In the C-terminal region of MAN1, a UHM (U2AF Homology Motif) domain is predicted, which exhibits a folding pattern similar to the widely recognized RNA-binding domain RRM, although it is generally involved in protein-protein interactions (Kielkopf et al., 2004) (figure 08).

Y. Gruenbaum's team demonstrated common functionalities between MAN1 and emerin in C. elegans. Like emerin, MAN1 interacts with the C. elegans lamin B-type lamin and with BAF in vitro. Furthermore, in yeast cells lacking emerin expression, partial reduction of MAN1 leads to lethality (Liu et al., 2003).

Blot overlay experiments have unveiled that the entire nucleoplasmic N-terminal region of human MAN1 binds to the "tail" regions of prelamin A (residues 394 to 664) and lamin B1 (residues 395 to 586), as well as emerin. K.L. Wilson's team also revealed that both the N- and C-terminal regions of MAN1 interact with the BAF protein through bead-based microtiter assays (Mansharamani and Wilson, 2005).

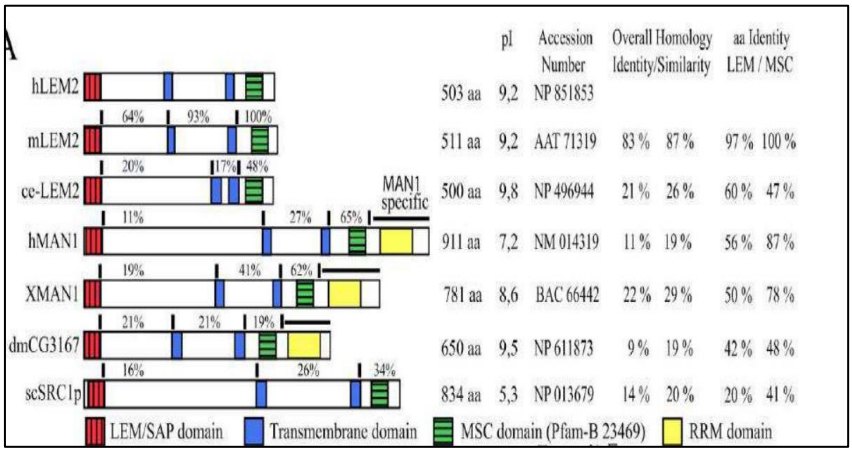

Figure 08: LEM2 and MAN1 familly (Brachner et al., 2005).

Finally, J. Gotzmann's team recently discovered a human protein, LEM2, consisting of 503 amino acids, which has a similar domain organization to MAN1: an LEM motif at the N-terminus, two transmembrane segments, and a highly conserved C-terminal region (figure 08). MAN1 differs from this LEM2 protein by the presence of the UHM domain in its C-terminal region (Brachner et al., 2005).

VI. The Nuclear Lamina

For the first time in 1966, using electron microscopy, D.W. Fawcett described the nuclear lamina of vertebrate cells as a fibrous structure underlying the inner nuclear membrane

(figure 09) (Fawcett, 1966). About a decade later, G. Blobel's team demonstrated that the vertebrate lamina is associated with nuclear pore complexes and is mainly composed of three polypeptides called lamin A, lamin B, and lamin C (Aaronson and Blobel, 1975; Dwyer and Blobel, 1976; Gerace et al., 1978). Around the same time, Franke and colleagues provided biochemical and morphological evidence that a fiber network connects nuclear pore complexes in amphibian oocytes (Scheer et al., 1976). In 1980, L. Gerace and G. Blobel first showed that depolymerization of the nuclear lamina during the mitosis of the cell cycle correlates with the hyperphosphorylation of its major protein components (Gerace and Blobel, 1980). A decade later, specific phosphorylation sites associated with lamina disassembly were identified (Heald and McKeon, 1990; Peter et al., 1990; Ward and Kirschner, 1990). In 1986, two groups provided biochemical and morphological evidence of the intermediate filament structure of the nuclear lamina (Aebi et al., 1986; Goldman et al., 1986). In the same year, the cloning of cDNAs for lamina components in the laboratories of G. Blobel (Fisher et al., 1986) and M.W. Kirschner (McKeon et al., 1986) demonstrated that nuclear lamins were members of the intermediate filament protein family. Therefore, the lamina is a network of lamin polymers that interposes between chromatin and the inner nuclear membrane of the nuclear envelope.

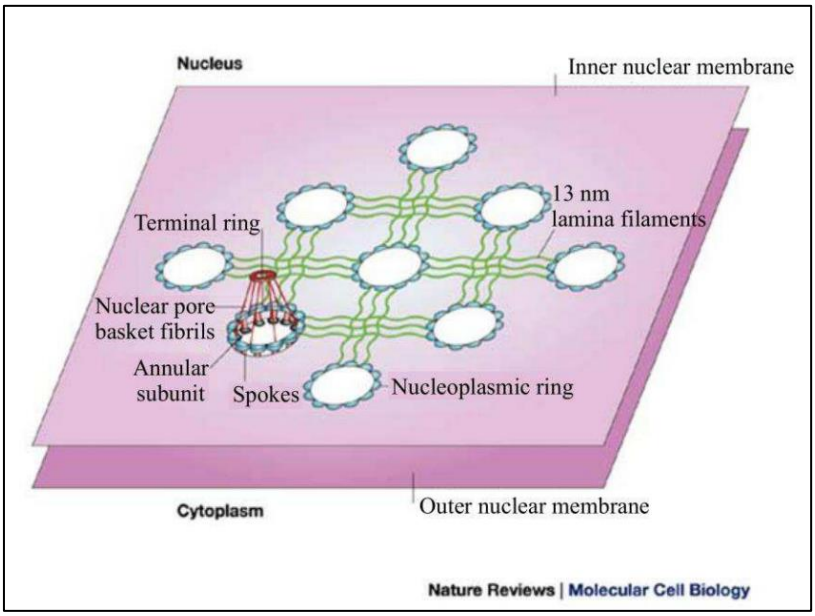

Figure 09: Lamina and nuclear membrane filaments organization

In the germinal vesicles of Xenopus laevis oocytes, the lamina forms a two-dimensional network of intertwined filaments that are connected to nuclear pore complexes (NPCs) (Aebi et al., 1986; Zhang et al., 1996), while in somatic cells, it appears to be a three-dimensional structure (Belmont et al., 1993). The lamina provides support and solidity to the inner nuclear

membrane (Hutchison et al., 2001) and differs from the architectural arrangement of cytoskeletal networks, which are typically three-dimensional and highly branched (Quinlan et al., 1995).

VI.1. Lamin Genes

Intermediate filament proteins are present in nearly all metazoan cells and contribute to the cytoskeleton, while they have not been identified in any examined plants or fungi (Fuchs and Weber, 1994; Herrmann and Aebi, 2000). Within mammals, there are about 60 members in the intermediate filament superfamily, categorized into 5 groups; 4 of these groups (I-IV) are cytoplasmic (Karabinos et al., 2002). Type V of the intermediate filament family is constituted by lamins, believed to be precursors of the intermediate filament superfamily (Doring and Stick, 1990). In mammals, the type V family encompasses three genes (LMNA, LMNB1, and LMNB2) that encode seven proteins (figure 10).

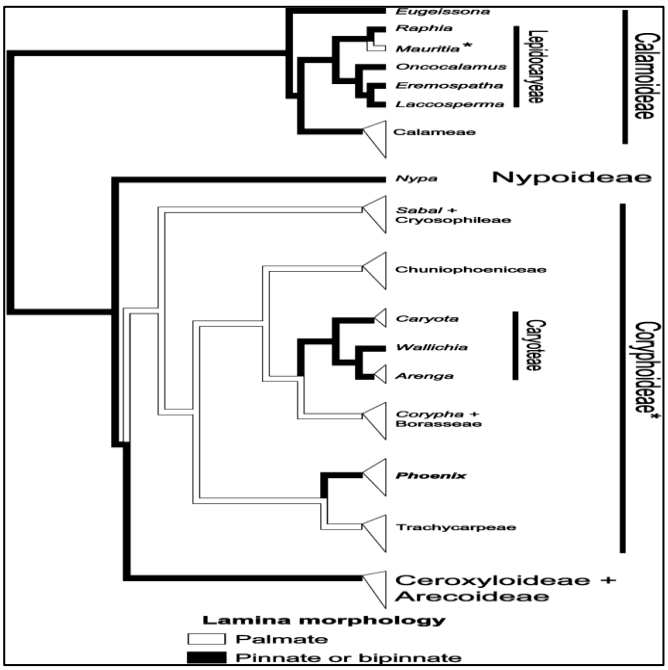

Figure 10: Evolution of lamina anatomy in the palm family(arecaceae) (Horn JW et al., 2009)

These proteins are categorized into type-B and type A lamins based on their biochemical characteristics and behavior during mitosis. The presence of at least one type-B lamin is crucial for cell viability in metazoans. These lamins are present in all cells during development, exhibit an acidic isoelectric point, and undergo post-translational modifications like isoprenylation. This modification permits type-B lamins to bind to the inner nuclear membrane (along with inner nuclear membrane proteins) during interphase, allowing them to stay connected with

membranes, particularly the endoplasmic reticulum membranes, when the nuclear envelope disintegrates during mitosis (Gruenbaum et al., 2000; Lehner et al., 1987; Stewart and Burke, 1987; Stick and Hausen, 1985; Wills et al., 2001).

Type A lamins are further divided into two primary subclasses: lamins A and lamins C. These two variants share an identical initial sequence of 566 residues and vary only in their C-terminal regions. Lamin C has 7 distinct residues, whereas lamin A has 99 unique residues at its C-terminus. Type A lamins (prelamin A: 664 residues, mature lamin A: 646 residues, lamin C: 572 residues) are predominantly found in differentiated tissues, have a neutral isoelectric point, and become completely soluble in the cytoplasm during mitosis. Furthermore, type A lamins are likely integrated into the nuclear lamina at a later stage than type B lamins. Certain type A lamins, such as A and AΔ10, are initially subjected to isoprenylation, but the C-terminal segment carrying the modification is subsequently cleaved by a specific metalloprotease, ZMPSTE24, to yield the mature protein. Lamins C and C2 neither undergo isoprenylation nor cleavage.

Mammals, amphibians, and fish all express multiple types of lamins (Hofemeister et al., 2002; Stick, 1988). In contrast, invertebrates generally have a smaller variety of lamins. For example, Drosophila melanogaster produces two lamins known as Lamin Dm0 (a type-B lamin) and Lamin C (a type-A lamin) (Lenz-Bohme et al., 1997), whereas Caenorhabditis elegans generates a sole lamin, a type-B lamin, LMN-1 (also identified as Ce-lamin) (Lee et al., 2000).

VI. 2. Role of Lamins

Lamins are involved in nuclear architecture and play a supporting role in many fundamental nuclear processes (Figure 11).

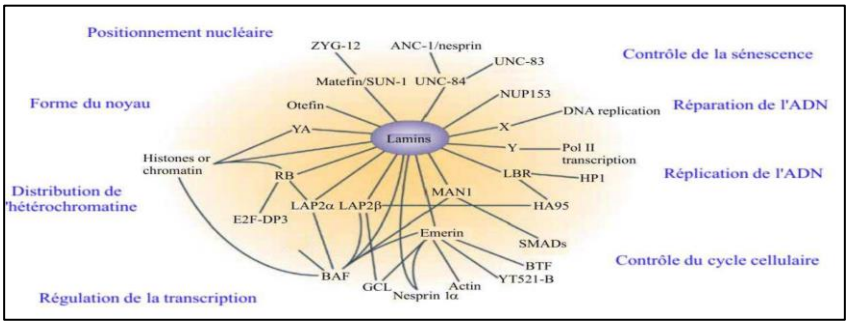

Figure 11: Lamina interaction and biological function (Gruenbaum et al., 2005).

Lamins govern nuclear size and shape and play a role in positioning nuclear pore complexes (NPCs) and arranging chromatin. They're also present at DNA replication and RNA processing

sites, associating with replication and RNA polymerase proteins, suggesting involvement in gene duplication and expression (Cai et al., 2001; Gruenbaum et al., 2000). If this theory holds true, it raises significant inquiries regarding the impact of nuclear scaffold proteins, exclusive to metazoan lineages, on nuclear metabolism. Lamins are additionally implicated in apoptosis (Cohen et al., 2001), being early caspase targets. Lamin degradation precedes DNA cleavage and chromatin condensation, a vital step in nuclear envelope breakdown. Moreover, lamins interact with actin and titin, mainly cytoplasmic filamentous proteins potentially having nuclear forms (Sasseville and Langelier, 1998; Zastrow et al., 2006). Nuclear titin aids chromosome condensation and segregation, while nuclear actin might facilitate dynamic repositioning of chromatin domains or alteration of chromatin structure. Although the interactions between lamins and actin or titin remain poorly understood, they could relate to nuclear organization during interphase.

VI. 3. Lamins Determine Nuclear Size and Shape

VI. 3.1. Nuclear Shape

Several investigations have significantly contributed to our understanding of the integral role played by the nuclear lamina in determining the structural characteristics of the nucleus (Noronha et al., 2001; Furukawa and Hotta, 1993; Lee et al., 2000; Schirmer et al., 2001; Sullivan et al., 1999; Vigouroux et al., 2001). The nuclear lamina, a meshwork of intermediate filaments and associated proteins lining the inner nuclear membrane, has been implicated in various nuclear activities, including chromatin organization, gene regulation, and mechanical support (Furukawa and Hotta, 1993). In a noteworthy study involving mouse spermatocytes, it was revealed that nuclei adopt a distinctive hooked morphology as a consequence of the specific expression of lamin B3, a component of the nuclear lamina (Furukawa and Hotta, 1993). This observation was further supported by experiments where the ectopic expression of lamin B3 in somatic cells resulted in the formation of nuclei bearing similar hook-like configurations. This finding emphasized the direct influence of lamin B3 on nuclear shape.

Recent research endeavors have delved into the functional implications of specific mutations in lamina components. One such study introduced a lamin B1 mutant, referred to as B1ΔRod, which harbored a deletion of 54 amino acids within its central domain (Schirmer et al., 2001). Despite this deletion, the B1ΔRod mutant exhibited the capacity to form filaments in vitro and subsequently integrate into the nuclear lamina following transfection into cultured cells. However, a notable consequence of B1ΔRod expression was the substantial deformation of the

nuclear envelope. This observation underscores the critical role of the central domain in maintaining nuclear structural integrity.

Furthermore, studies employing RNA interference (RNAi)-mediated inhibition of the lmn-1 gene in the nematode Caenorhabditis elegans have provided additional insights into the relationship between lamina proteins and nuclear morphology (Vigouroux et al., 2001). The inhibition of lmn-1 gene expression led to discernible alterations in nuclear shape, highlighting the evolutionary conservation of lamina's influence on nuclear architecture and morphology across species. a comprehensive body of research encompassing various experimental approaches, including investigations on lamin mutants and genetic manipulations, has substantiated the pivotal role of the nuclear lamina in shaping the nucleus.

VI. 3.2. Nuclear Size

Numerous studies have provided significant insights into the role of nuclear lamins in governing nuclear dimensions, often employing Xenopus egg cell nuclear extract assembly as a model system (Hutchison, 1994). Through these investigations, it has become evident that lamins exert a profound influence over nuclear size and morphology. When nuclear extracts lacking lamins are used in assembly experiments, they still manage to form the nuclear envelope, but the resultant nuclei are notably smaller in size (Meier et al., 1991; Newport et al., 1990). This underscores the pivotal role that lamins play in determining the dimensions of the nucleus. Intriguingly, experiments involving lamin mutants with dominant negative characteristics have further reinforced this notion. These mutant forms of lamins have the capacity to interfere with the assembly of the nuclear lamina in Xenopus egg cell nuclear extracts, resulting in the formation of nuclei that are considerably smaller than those formed under normal conditions (Ellis et al., 1997; Spann et al., 1997). This manipulation of lamin function underscores their significance not only in nuclear size control but also in the regulation of nuclear envelope assembly.

Expanding on this concept, specific mutants of the inner nuclear membrane protein LAP2β have been explored for their impact on lamin dynamics and nuclear growth. LAP2β is known to interact with lamin B both within cellular contexts and in vitro. Studies introducing these LAP2β mutants into Xenopus egg cell extracts have revealed their inhibitory effect on lamina assembly, consequently leading to a notable suppression of nuclear growth (Gant et al., 1999). This observation provides further evidence of the intricate network of interactions and processes that collectively govern nuclear size determination.

Collectively, these investigations utilizing Xenopus egg cell nuclear extract assembly as an experimental model have significantly contributed to our comprehension of lamins' role in regulating nuclear size. The findings underscore the multifaceted contributions of lamins and associated proteins in orchestrating nuclear envelope assembly and maintaining nuclear dimensions, shedding light on the intricate mechanisms governing nuclear architecture.

VI. 3.3. Resistance to Deformation

The dynamic process of lamin assembly within living cells has been recently investigated using a GFP-lamin chimera, yielding valuable insights into nuclear envelope behavior (Broers et al., 1997; Moir et al., 2000). This innovative approach has illuminated the continuous deformation experienced by the nuclear envelope's surface. Interestingly, despite this deformation, there exists a notable resilience; regions undergoing deformation swiftly revert to their original shape. This observation suggests the existence of a robust mechanism resisting deformation, and growing evidence supports the hypothesis that the nuclear lamina plays a pivotal role in conferring this resistance.

Support for the idea that the nuclear lamina underpins this resistance comes from research involving nuclei of the nematode Caenorhabditis elegans where the expression of lmn-1 is suppressed. In these instances, a weakened resistance to deformation is apparent, and any distortion in the nuclear envelope persists throughout subsequent cell cycles (Liu et al., 2000). This enduring deformation underscores the importance of proper lamin expression for maintaining nuclear integrity and shape. The profound impact of lamina composition and the presence of lamin mutants on nuclear dimensions, morphology, and envelope strength further substantiates the proposition that the lamina functions as a crucial tension element for the nucleus. The ability of specific lamin mutants to disrupt nuclear lamina assembly and subsequently lead to alterations in nuclear size and shape underscores the critical role that lamins play in governing nuclear architecture. This in turn affects the overall mechanical stability of the nucleus.

The utilization of the GFP-lamin chimera and studies involving lmn-1 suppression in C. elegans nuclei have provided dynamic insights into the interplay between the nuclear lamina, nuclear deformation, and mechanical resilience. These findings offer a deeper understanding of how the lamina contributes to maintaining the integrity of the nuclear envelope, its resistance to deformation, and its role as a fundamental determinant of nuclear tension.

VI. 4. Association of Lamins with DNA and Chromatin

Many of studies strongly suggest the intricate involvement of both type A and type B lamins in interactions with chromatin, underscoring their multifaceted roles in nuclear organization and function (Glass et al., 1993; Luderus et al., 1992; Luderus et al., 1994; Taniura et al., 1995). Notably, these investigations have illuminated specific instances where lamin-chromatin interactions have profound implications for nuclear architecture and cellular processes. In mouse embryo fibroblasts with suppressed Lmna gene expression, a remarkable disarray of heterochromatin at the nuclear periphery is observed, indicative of the significance of lamin-chromatin interactions in maintaining chromatin organization (Sullivan et al., 1999). This finding highlights the pivotal role of lamin proteins in orchestrating proper chromatin positioning and nuclear structure.

Further insights into lamin-chromatin interactions have been garnered through the examination of intranuclear lamin foci subsequent to the transfection of GFP-lamin fusion constructs. These foci have been observed to localize at sites associated with DNA replication (Kennedy et al., 2000; Spann et al., 1997), indicating a connection between lamins and the replication process. Additionally, these foci have been linked to transcriptional complexes, elucidating the potential involvement of lamins in gene regulation (Jagatheesan et al., 1999).

Studies led by R.D. Goldman's group have revealed the association of lamin B with DNA replication foci during the S phase, shedding light on the temporal dynamics of lamin-chromatin interactions (Moir et al., 1994). This observation further underscores the multifunctional nature of lamins in coordinating nuclear events.

Moreover, investigations focusing on type A lamins have highlighted their presence in DNA replication foci encircling the nucleolus at the initiation of the G1 phase. These foci host essential replication proteins like p150, PCNA, and members of the pRb family (Kennedy et al., 2000). This suggests a coordinated role of type A lamins in regulating DNA replication and cell cycle progression. The amalgamation of studies exploring lamin-chromatin interactions has illuminated the intricate connections between lamins and nuclear processes. These interactions have far-reaching implications for chromatin organization, DNA replication, and gene expression, underscoring the multifaceted functions of lamins in maintaining proper nuclear structure and facilitating crucial cellular activities.

VI. 5. Lamins Dynamics

Throughout the cell cycle, the behavior of the nuclear lamina undergoes intricate changes, particularly during interphase. The dynamics of organized lamins within the lamina

have been meticulously explored using advanced fluorescence techniques such as fluorescence recovery after photobleaching (FRAP) and fluorescence loss in photobleaching (FLIP) (Broers et al., 1999). These studies have unveiled essential insights into the mobility and behavior of lamins within the nuclear lamina. Investigations employing FRAP techniques to analyze type A GFP-lamins within the lamina have revealed a significant level of immobility. Following photobleaching, the fluorescence signal's recovery is notably delayed, with recuperation not occurring until approximately 90 minutes later (Broers et al., 1999). This observation suggests that organized lamins within the lamina exhibit limited mobility, likely due to their structural role in maintaining nuclear integrity.

When considering type C GFP-lamins, FLIP experiments have demonstrated substantial fluorescence signal reduction within the lamina of several irradiated cells (Broers and Ramaekers, 2004). This phenomenon is in alignment with prior biochemical studies that have indicated the relatively higher solubility of lamin C compared to lamin A during interphase (Gerace and Blobel, 1982). These findings shed light on the distinct dynamics exhibited by different lamin isoforms within the nuclear lamina and their potential roles in maintaining nuclear architecture.

Additional photobleaching investigations targeting lamin B1 have underscored its immobility within the lamina, persisting even up to 45 hours post-photobleaching (Daigle et al., 2001). This observation is consistent with previous biochemical studies suggesting that type B lamins exhibit significant insolubility during interphase (Gerace and Blobel, 1982).

The contrasting mobility patterns of different lamin isoforms within the nuclear lamina prompt further exploration into their functional significance. The more dynamic behavior of lamin C compared to lamin A and lamin B1 underscores the intricate regulation of lamin interactions within the nuclear lamina during interphase. These dynamics likely play crucial roles in nuclear architecture maintenance, mechanical support, and potentially contribute to various cellular processes. Clarifying the precise functional implications of lamin isoform-specific mobility variations is an exciting avenue for future research in the field of cell biology.

VI. 6. Dynamics During Mitosis

The most striking alterations in nuclear lamina architecture transpire during cell division (Figure 12). As cells progress from prophase to prometaphase, the nuclear membrane and lamina disintegrate in vertebrate cells. This disintegration is governed by the phosphorylation of lamins through the p32cdc2 kinase (Peter et al., 1990; Ward and Kirschner, 1990). Following

hyperphosphorylation, lamin polymers dismantle, and lamin proteins disperse throughout the cytoplasm. Initially, it was held that type A and B lamins displayed distinct phosphorylation responses. Type A lamins were presumed to become soluble and fully scatter into the cytoplasm, while type B lamin particles were thought to stay tied to nuclear membrane structures (Nigg, 1992). Nonetheless, this perspective has recently been questioned by 4D imaging experiments coupled with fluorescence, revealing that type B lamins are soluble at mitosis onset and lack affiliation with any potential mitotic membranes (Beaudouin et al., 2002; Daigle et al., 2001).

Previously, it was believed that phosphorylation, among other factors, was the initial step in nuclear envelope breakdown. However, recent evidence illustrates that at prophase's conclusion, microtubules bind to the nuclear membrane via dynein and pull membrane fragments away from the nucleus. This partial nuclear envelope disruption allows kinases to access the nucleus and phosphorylate lamin molecules, rendering them soluble (Beaudouin et al., 2002).

By anaphase/mid-telophase's culmination, lamin B1 amasses at chromosome peripheries. Gradually encircling the chromosomes, it delineates a perimeter around condensed chromatin until G1 phase (Moir et al., 2000). Lamin A/C's periphery accumulation occurs later, observed solely at telophase's end when chromatin decondenses. Type A lamins persist within the nucleoplasm, steadily incorporating into a stable structure at the nuclear envelope during G1 phase. Consequently, type A and B lamins manifest differing assembly pathways upon mitotic exit, coinciding with nuclear lamina reformation.

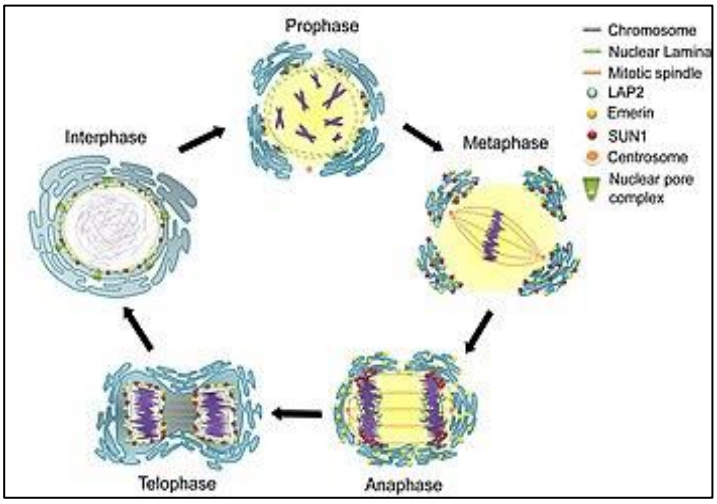

Figure 12: Lamina during mitose (Chi Ya-Hui et al., 2009).

V. Nuclear Pores and Nucleo-Cytoplasmic Transport

V.1. Pore Structures

Eukaryotic cell nuclei are adorned with periodic, extensive multiprotein assemblies termed nuclear pores, or NPCs (Nuclear Pore Complexes). These complexes encompass approximately fifty distinct proteins known as nucleoporins (Nup) (Cronshaw et al., 2002; Rout et al., 2000). Nup form is an integral part of the nuclear pore complex (NPC), a complex macromolecular assembly responsible for mediating molecular exchange between the nucleus and cytoplasm. These proteins are meticulously organized within the NPC, contributing to its intricate architecture and functionality. Nups can be broadly categorized into scaffold Nups, which provide the structural framework of the NPC, and transport Nups, which govern the selective passage of molecules. Scaffold Nups contribute to the overall stability and integrity of the NPC by forming the structural backbone, while transport Nups play a pivotal role in regulating cargo recognition, translocation, and interactions with transport receptors. The diversity of Nups allows for the precise control of nucleocytoplasmic transport, ensuring that only specific molecules are permitted to traverse the nuclear envelope. Dysfunction in Nup-mediated processes has been associated with a variety of diseases, underscoring their significance in cellular health. By dissecting the roles of these fifty distinct nucleoporins and their contributions to the NPC's architecture and function, researchers can deepen their understanding of cellular compartmentalization, gene regulation, and the intricate molecular choreography that sustains cellular life.

The count of nuclear pores varies in accordance with the operational state of the cell, spanning between 4000 and 6000 within a mammalian cell.

Under the lens of electron microscopy, a nuclear pore manifests on the surface of the membrane as a ring spanning approximately a hundred nanometers in diameter. In actuality, it comprises a pair of rings – one situated in the cytoplasmic region and the other within the nucleoplasmic realm – both adorned with an architecture featuring an eight-fold symmetry (Figure 13). These two rings are interconnected by spokes originating from each of the eight subunits, collectively fashioning a cylindrical enclosure (Suntharalingam and Wente, 2003).

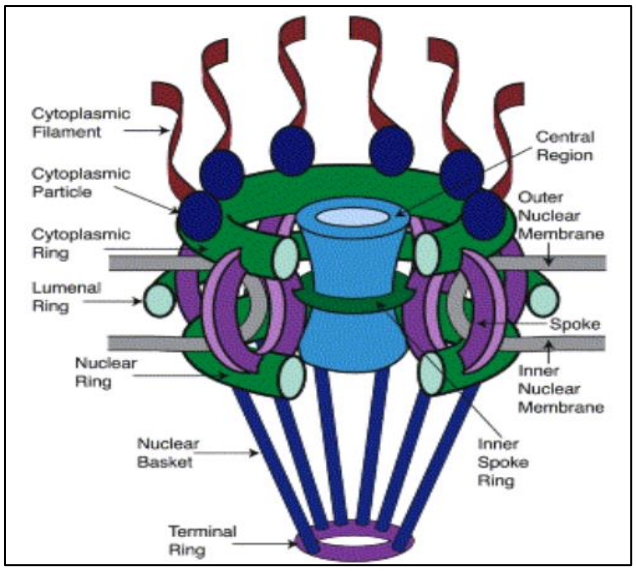

Figure 13: Nuclear pores complexe (Suntharalingam and Wente, 2003).

The cytoplasmic ring's subunits project eight fibrils outward into the cytoplasm, while the nuclear ring's subunits produce eight elongated filaments that attach to a distal ring of smaller dimensions, culminating in the formation of a "nuclear basket" or cage. Nestled within the nuclear envelope, this entire architecture is enveloped by an inner ring, fortified by interactions with diverse types of membrane proteins and nuclear intermediate filaments. Nucleoporins are strategically positioned within these ring subunits, along the fibrils and filaments, contributing to the identification and guidance of molecules traversing the nuclear pore complexes.

V.2. Transport between the Nucleus and Cytoplasm

Nuclear pores allow the passage of small molecules, such as ions and nucleotides, with a molecular weight below 5 kDa, through passive diffusion. Molecules ranging from 5 to 50 kDa undergo facilitated diffusion, where their rate of movement is proportionate to their size. For larger molecules exceeding 50 kDa, like ribosomal subunits, RNA, or components of the replisome, active and selective transport mechanisms are employed. In a proliferating mammalian cell, for example, approximately one million molecules per minute traverse the nuclear pores.

The conveyance of proteins and RNAs, often as ribonucleoproteins, relies on carrier molecules featuring Nuclear Localization Signals (NLS) – sequences consisting of 4 to 8 basic amino acids. These NLS sequences can be organized into two blocks separated by about ten amino acids. Their activation and deactivation can be controlled through phosphorylation and dephosphorylation. Similarly, export relies on Nuclear Export Signals (NES) sequences. Once complexes form between carriers and cargo molecules, these complexes interact with

nucleoporins (Figure 14). The direction of transport (nucleus to cytoplasm or vice versa) hinges on the asymmetrical distribution of diverse nucleoporin types on the nuclear and cytoplasmic faces of the pore.

Karyopherins (Kap) form a family of carriers that recognize specific NLS or NES sequences. Importins facilitate the movement from the cytoplasm to the nucleus, while exportins perform the reverse function. Over twenty such carriers have been identified in human cells. These molecules bind the "cargo" molecule via their C-terminal domain, and they bind the Ran-GTP/GDP protein via their N-terminal domain, crucial for addressing the cargo to the nucleus or cytoplasm. Ran, a member of the small GTPase protein family, can hydrolyze GTP into GDP. The direction of transfer hinges on the concentration gradient of Ran-GTP/Ran-GDP and the varying affinity of exportins and importins for these two states. Maintaining this equilibrium between the nucleus and cytoplasm necessitates the recycling of Ran.

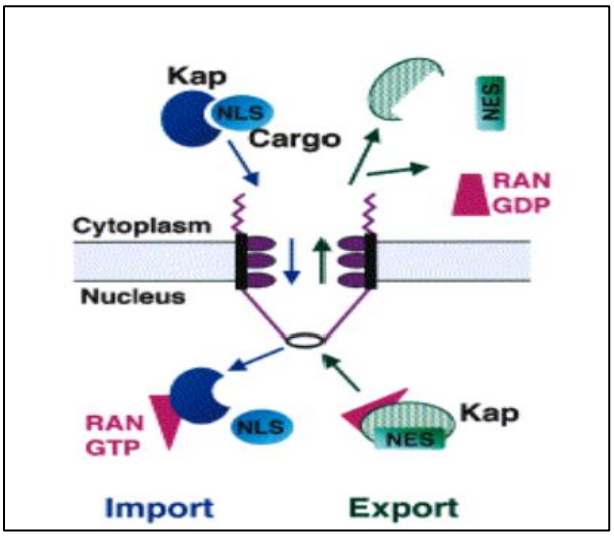

Figure 14: Transport model with Karyopherins (Suntharalingam and Wente, 2003).

Importins engage their cargo within the cytoplasm through a mechanism contingent on Ran-GDP. After translocation into the nucleus, they release the cargo by converting Ran-GDP to Ran-GTP via the activity of a phosphorylation enzyme (RCC1).

Conversely, exportins bind their cargo within the nucleus under the influence of Ran-GTP. Upon passing through nuclear pores, they relinquish the cargo by activating the GTPase function of Ran, converting Ran-GTP to Ran-GDP. In the cytoplasm, this GTPase activity is induced by an activator known as GAP (GTPase Activating Protein), positioned on the cytoplasmic face of the pore.

Finally, other families of transporters have been identified. In particular, the export of mRNAs is carried out by non-karyopherin transporters (Reed and Hurt, 2002).

V.3. Interactions of Nuclear Pores with the Lamina

In vertebrate cells, studies have been conducted on the stability of the network formed by nuclear pores (Suntharalingam and Wente, 2003). Once assembled, NPCs appear as immobile in interphase, within the plane of the nuclear envelope (Daigle et al., 2001). A hypothesis has been put forward that lamins associated with the inner nuclear membrane serve as anchors for NPCs in intranuclear architecture. This hypothesis is supported by studies in S. cerevisiae, where there is no nuclear lamina. These studies indicate that lateral mobility of NPCs is more significant in yeast (Belgareh and Doye, 1997; Bucci and Wente, 1997). Similarly, in Drosophila lacking wild-type lamina, NPCs cluster into foci on the nuclear envelope (Lenz-Bohme et al., 1997). It has also been shown that nucleoporins Nup153 and Nup53 interact with lamins and might thereby participate in anchoring the pores to the lamina (Hawryluk-Gara et al., 2005; Smythe et al., 2000).

VI. Nucleare bodies

On the eukaryotic nucleus, there are various types of domains that could be defined as regions with distinct morphologies from their surroundings (figure 15).

Firstly, the nucleolus is a sub-compartment of the nucleus that is quite easy to observe using basic stains like Giemsa, but the true characterization of its organization was enabled by electron microscopy. It consists of a nucleolar organizer region (NORs) corresponding to chromosomal regions that are particularly enriched in genes coding for ribosomal RNAs (rRNAs). In addition, there is the presence of RNA polymerase I, class I transcription factors, and topoisomerases (Strouboulis and Wolffe, 1996). The nucleolus is surrounded by a dense component consisting of nascent transcripts and splicing machinery, and a granular component including mature rRNAs and ribosomal subunits in various stages of assembly at different stages (Qumsiyeh, 1999). The perinucleolar compartment is a structure associated but distinct from the nucleolus, containing rRNAs transcribed by RNA polymerase III (Matera et al., 1995). OPT domains (Oct1/PTF/Transcription), ranging from 1 to 1.5 µM in diameter, are also located near the nucleolus (Grande et al., 1997) and appear in the G1 phase of the cell cycle, disappearing in the S phase. This region is named as such because Oct 1, PTF (a complex involved in activating the transcription of certain genes), as well as RNA-PII and PIII-dependent transcription, are detected there (Pombo et al., 1998).

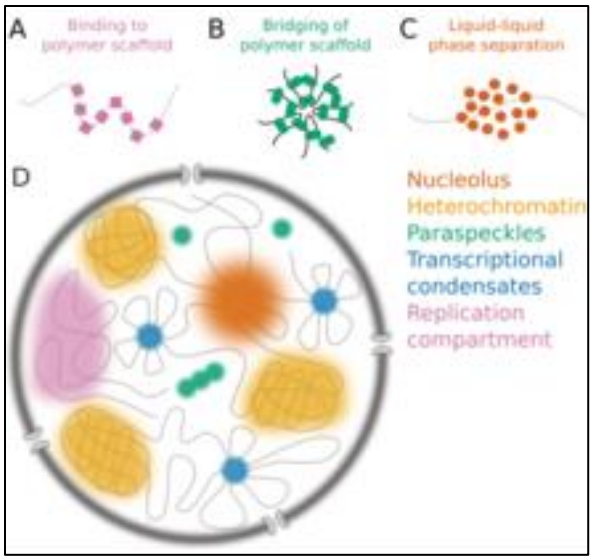

Figure 15: Nuclear body (Peng A et al., 2019)

Four other types of structures, with relatively independent locations from the nucleolus, have also been described. "Cajal bodies" or "coiled bodies," first mentioned in 1903 by Cajal, are structures that include small ribonucleoproteins, DNA, and a protein called coilin. These structures, not delimited by a membrane, are involved in RNA-related metabolic processes, such as the synthesis of small nuclear ribonucleoproteins (snRNPs), RNA maturation and recycling, and telomere maintenance (Zhao et al., 2011). "Nuclear speckles" are clusters of granules measuring 20 to 25 nm in diameter, which are involved in the modification and assembly of splicing factors, as well as certain transcription factors (Jimenez-Garcia and Spector, 1993; Huang and Spector, 1996). There is no transcription within these "speckles," but it seems that RNA P-II is stored there before being recruited to transcription sites. Finally, "PML bodies" do not have known functions.

Specific details have been established, although it is possible that this structure may have a role in transcriptional regulation, protein storage for intranuclear concentration regulation, or even as an active site for proteolysis (Zhong et al., 2000). In certain cell types, the presence of CBP (CREB binding protein), p300, and RNA P-II has been determined in these PML (promyelocytic leukemia) bodies (La Morte et al., 1998; Von Mikecz et al., 2000; Boivert et al., 2001).

From a general standpoint, it appears that the presence of these structures in specific locations within the nucleus is not random but a direct consequence of the transcriptional status of certain genes at that level. Indeed, studies conducted by Olson et al., 2000 have demonstrated

that the introduction of a plasmid containing genes encoding rRNAs leads to the formation of mini nucleoli near the plasmid.

Chapter II: Chromatin

I. Introduction

The study of chromatin organization (figure 16) and its dynamic structural modifications holds paramount significance in deciphering the intricate mechanisms underpinning gene regulation and orchestrating cellular functions. Chromatin, an intricate amalgamation of DNA, histones, and an array of associated proteins, serves as a dynamic platform where genetic information is not only stored but is also subjected to intricate modulation, enabling precise control over gene activation, repression, and cellular responses (Alberts B et al., 2002).

Delving into chromatin's spatial organization provides critical insights into the higher-order architecture that underlies gene regulation. This architecture dictates the spatial arrangement of genes, regulatory elements, and chromosomal domains, influencing their accessibility and interactions with transcriptional machinery. Consequently, a comprehensive understanding of chromatin organization is indispensable for unraveling the molecular intricacies governing cellular differentiation, development, and adaptive responses to stimuli. Additionally, an in-depth exploration of the post-translational modifications (PTMs) that chromatin components undergo, including DNA methylation and histone acetylation, unveils the captivating landscape of epigenetic regulation. These PTMs imprint heritable marks that exert regulatory control over gene expression patterns without modifying the primary DNA sequence. This epigenetic regulation serves as a versatile regulatory layer, influencing cellular identity, plasticity, and responses to environmental cues (Berger S et al., 2009).

Intriguingly, the misregulation of chromatin modifications is implicated in a spectrum of pathological conditions. These encompass malignancies, such as cancer, where aberrant chromatin states can drive oncogenic processes, as well as neurological disorders where epigenetic dysregulation contributes to disease manifestation (Baylin SB et al., 2011; Sweatt JD et al., 2013). These insights underline the pivotal role of chromatin organization and modifications in the etiology of diverse human ailments. In essence, probing both the architectural organization of chromatin and the intricacies of its modifications offers a foundational framework for deciphering the molecular tapestry that underlies the complexity of biological systems. This knowledge holds the promise of advancing fundamental insights into cellular behavior and facilitating innovative therapeutic interventions. As researchers navigate the intricate landscape of chromatin, opportunities emerge to engineer targeted interventions that rectify aberrant epigenetic states, paving the way for novel treatment strategies with transformative potential for human health.

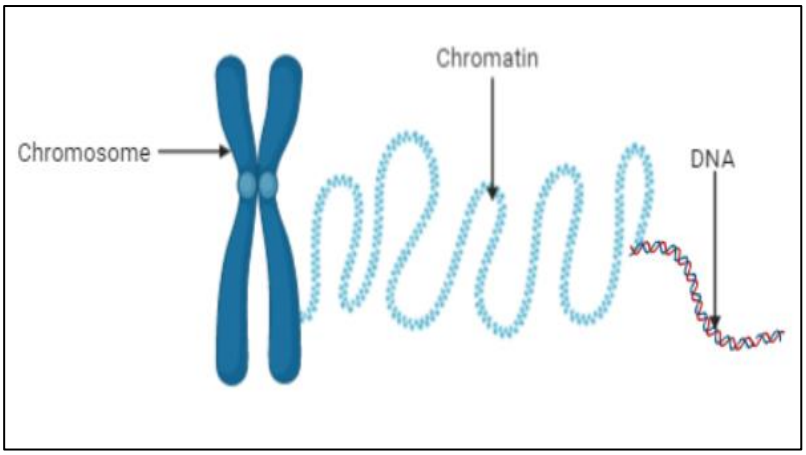

Figure 16: Chromatin localization (https://www.vedantu.com/question-answer/chromatin-is-made-up-of-a-dna-and-proteins-b-dna-class-11-biology-cbse-5fa36a35fa26f310998a9319. Update18/08/2023).

II. Structural Arrangement of Chromatin

II.1. The Bead on a String Paradigm

Inside the cell nucleus, DNA is not exposed but rather organized within a structure referred to as chromatin: segments of the 2nm double helix, consisting of 146 base pairs (bp), are entwined around a core of histones (H2A, H2B, H3, and H4, each in pairs). This configuration, recognized as the nucleosome, constitutes the fundamental repetitive unit of chromatin (11nm fiber) (Wolffe, 1998) (figure 17), with the relative spacing between nucleosomes influencing the extent of chromatin compaction, thereby modulating the accessibility of genetic data for transcription factors (Felsenfeld, 1992). The incorporation of histone H1 into this arrangement results in more extensive compaction of chromatin (30nm fiber) (Misteli et al., 2000), culminating in the maximal level of compaction seen in mitotic chromosomes (14000nm) (Wolffe, 1998).

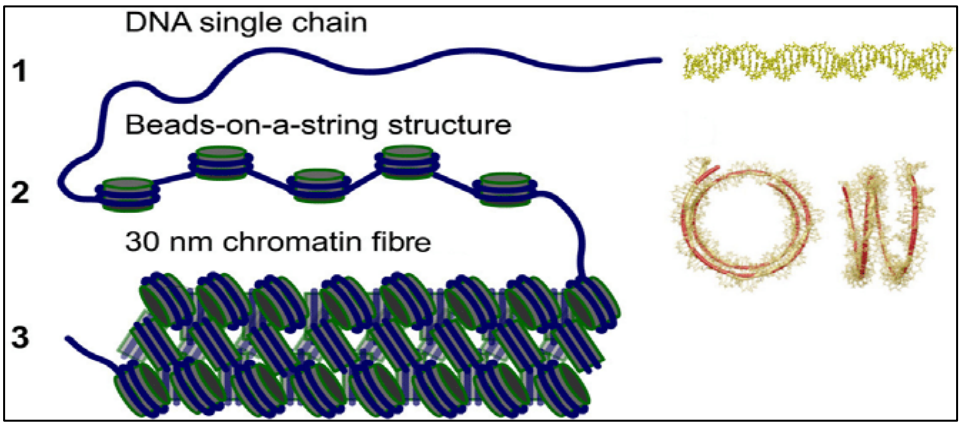

Figure 17: Bead on a String Paradigm (From Anatoly Zinchenko)

II.2.Histones

Histones, small and conserved basic proteins, are structurally divisible into three domains (Luger et Hansen, 2005). The central histone domain remains remarkably consistent across evolutionary lineages, exemplified by histone H4, which diverges by merely 2 amino acids between calf thymus and pea plants (DeLange et al., 1969). This domain adopts a structural organization featuring three alpha helices separated by two loops (Arents et Moudrianakis, 1995) (figure 18). Correspondingly, the other two histone domains correspond to their amino-terminal and carboxy-terminal ends, denoted N-terminal and C-terminal, respectively. In contrast to the structured central domain, these histone "tails" lack structure and exhibit compositional variations; they represent primary sites for post-translational modifications, bearing intricate significance in gene regulation (Tagami et al., 2004). Inside the nucleus, histones H3 and H4 assemble as heterodimers, paralleling the assembly of histones H2A and H2B, ultimately leading to octamer formation (Wolffe, 1998).

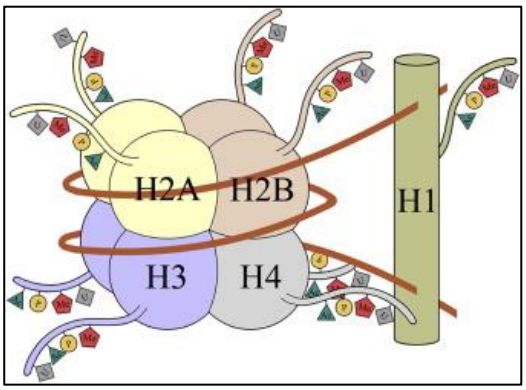

Figure 18: Histones organization (Li J et al., 2014)

II.3. Linker histone H1 Variants Histone

H1, including its variant H5 (figure 19), pervades the chromatin landscape of eukaryotic genomes. It plays a crucial role in folding chromatin into an intricate, compact conformation: the 30nm fiber (Huynh et al., 2005). This arrangement restricts accessibility to chromatin-modifying enzymes and curbs transcription activity (Horn et al., 2002). Eleven H1 subtypes are recognized, encompassing 7 somatic variants, 3 sperm-specific forms, and 1 specific to oocytes (Clausell et al., 2009). Structurally resembling the aforementioned histones, linker histones encompass three domains: a conserved globular domain, an N-terminal span of 20 to 35 amino acids, and a C-terminal portion comprising approximately 100 amino acids, stabilizing chromatin folding (Caterino et Hayes, 2011). Despite H1's pervasive presence across the genome and within diverse chromatin types, certain regions lack this histone, primarily enriched in gene-dense regions, particularly at gene transcription start sites (TSS). Nevertheless, around

10% of H1-deficient sites are located in intergenic regions, potentially functioning as regulatory elements (Braunschweig et al., 2009).

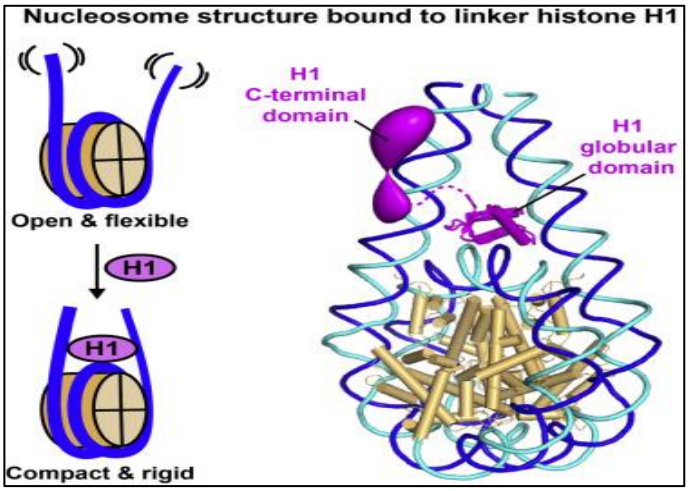

Figure 19: Linker histone H1 (Bednar J et al., 2017)

II.4. Histone variants and Their Functions

Histone variants, evident in diverse eukaryotic species, display varying degrees of divergence from conventional histones in terms of sequence and incorporation into nucleosomes (Malik et Henikoff, 2003). These disparities confer distinct functionalities upon these variants, delineating roles in processes such as centromeric organization, DNA repair, X chromosome inactivation (Xi), and transcription (Malik et Henikoff, 2003)(figure 20).

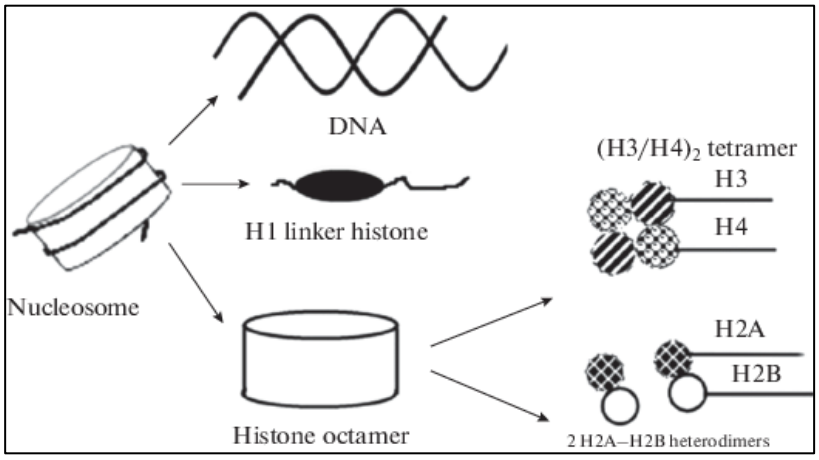

Figure 20: Histone's variants (Chikhirzhina E. V. et al., 2020).

a-H2A Variant

Contributions H2A.Z, a histone H2A variant, is essential in mice, as its inactivation leads to lethality (Faast et al., 2001). Nucleosomes harboring H2A.Z exhibit specific biochemical and physical attributes, rendering them resilient to specific post-translational modifications. H2A.Z serves multifarious roles, including participation in gene transcription

regulation and serving as a boundary that restricts the diffusion of histone variants and transcription factors across chromatin (Faast et al., 2001).

Heterochromatin-related processes are influenced by H2A.Z during embryonic development (Guillemette and Gaudreau, 2006; Eirin-Lopez and Ausio, 2007; Kusch and Workman, 2007). In euchromatin, H2A.Z might be found exclusively in the promoter region of the subpopulation of RNA-PII-transcribed genes lacking a TATA box. This variant could be "deposited" in this location by the SWR1 complex (Swi/Snf related protein) in yeast or its human homolog (swr1) (Zhang et al., 2005) (Figure 21). An alternative recruitment of H2A.Z is plausible as studies within Madhani's laboratory (Raisner et al., 2005) indicated H2A.Z presence on promoters of active or inactive genes containing a specific DNA motif consisting of two redundant 10-bp segments containing the Reb1 protein binding site followed by a 7-bp sequence: dT:dA. H2A.Z target genes display a nucleosome-free region situated about 200 bp upstream of the transcription start site (TSS), flanked by two H2A.Z nucleosomes (Raisner et al., 2005; Yuan et al., 2005).

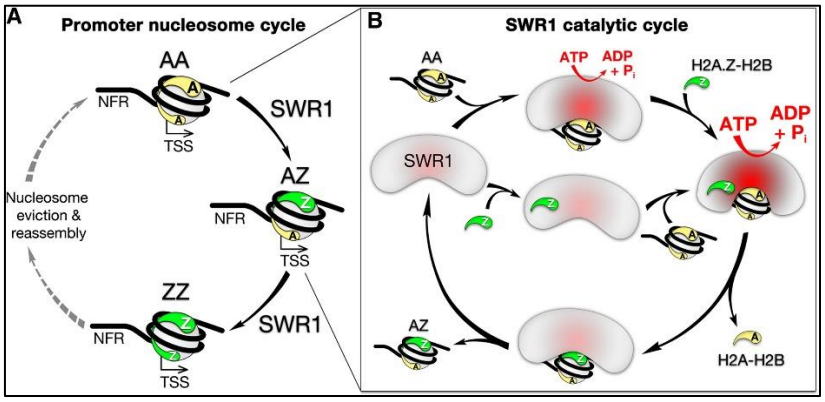

Figure 21: SWR1 Requires Dual Activation with Histone H2A.Z (Luk E et al., 2010)

Additionally, H2A.Z is preferentially associated with the promoters of repressed genes during substantial transcriptome changes in yeast post "heat shock," with loss from active gene promoters associated with an increase in this variant at inhibited promoters (Zhang, 2005). This H2A.Z loss might be linked to lower nucleosome stability compared to those containing H2A. In heterochromatin, H2A.Z seems to play two roles. Firstly, its presence near telomeres maintains boundaries between telomeric heterochromatin and adjacent genes, linked to histone H4 acetylation. In yeast, lack of H2A.Z or H4 acetylation deficiency leads to Sir proteins, involved in heterochromatization, diffusing from telomeres to adjacent genes (Zhang et al., 2004). This role has been affirmed in Chickens (Bruce et al., 2005). Secondly, H2A.Z has a pivotal role in early embryonic development, highly enriched in constitutive heterochromatin,

where it interacts with HP1α and INCENP, crucial for chromosome segregation (Rangasamy et al., 2003). In ES cells, H2A.Z enrichment is noted on numerous genes associated with development, indicated by the Gene Ontology annotations of H2A.Z target genes primarily corresponding to transcription factors with pivotal roles in developmental processes like FOX and GATA factors (Creyghton et al., 2008).

The MacroH2A variant comes in three forms: MacroH2A1.1, MacroH2A1.2, and MacroH2A.2. The N-terminal part of MacroH2A.1 is 64% identical to that of H2A, but its C-terminal part is notably distinct. Being of considerable size, the C-terminal region serves as a non-histone region (Pehrson and Fried, 1992) containing a domain called "Macro," which has the capacity to bind to ADP-ribose (Adenosine diphosphate-ribose) and other associated small molecules (Kustatscher et al., 2005); however, its function remains unknown for now. MacroH2A is particularly enriched on the X chromosome in mammalian cells (Ladurner, 2003) as well as on certain repressed genes awaiting activation (Buschbeck et al., 2009). However, a recent study led by Lee Kraus' laboratory (Gamble et al., 2010) showed that MacroH2A is located upstream of the TSS of certain genes involved in development regulation and signaling cascades. Moreover, in certain cases, MacroH2A might have the ability to positively regulate transcription, which expands its historical role as a variant generally associated with negative regulation.

H2AX is a variant of histone H2A discovered in the 1980s, having a structure similar to H2A except for a motif on its C-terminal end (Redon et al., 2002). H2AX is involved in the repair of double-strand DNA breaks, as phosphorylation of its serine 139 facilitates the recruitment of numerous proteins engaged in responding to such DNA damage (Paull et al., 2000).

b-H3 Variants

H3.3 is a variant of histone H3 (Hake and Allis, 2006), prominently enriched on genes with high CpG content at promoters (HCP), whether transcriptionally active or not, across their regulatory sequences, bodies, and termination signals. This enrichment is seen in both embryonic stem cells (ES cells) and differentiated cells. However, it's noteworthy that H3.3 is lost from pluripotent genes like Nanog or Oct 4 during cellular differentiation. H3.3 is incorporated into chromatin through two distinct pathways. The first, involving the chaperone protein HIRA, is active on HCP genes, while the second, involving Atrx, is relevant to H3.3 loading at telomeres (Glodberg et al., 2010) (figure 22). An anti-correlation has also been established between the presence of the H3.3 histone variant (predominantly located in transcriptionally active regions) and that of H1 in chromatin, likely for genes and to Regulatory

elements remain accessible to various factors involved in transcriptional regulation (Braunschweig et al., 2009).

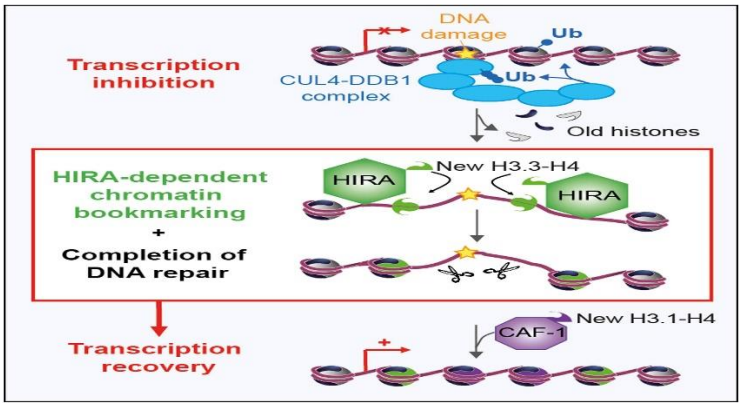

Figure 22: H3.3 histone and transcription (Adam S et al., 2013).

The protein CENP-A is an H3 variant in vertebrates. It is exclusively found at centromeres, where it facilitates the formation of a specific nucleosome with a structure yet to be determined (Henikoff and Ahmad, 2000). Two studies have demonstrated the replacement of histone H3 by CENP-A at centromeres, including ChIP-chip studies (chromatin immunoprecipitation followed by microarray analysis) showing in vivo H3 depletion within domains where CENP-A is present (Lo et al., 2001). Similarly, microscopy studies in Drosophila highlight an absence of H3-GFP (Green Fluorescent Protein) at CID binding domains (CENP-A ortholog) (Ahmad and Henikoff, 2001). Paradoxically, other studies indicate the presence of alternating nucleosomes containing CENP-A and others with H3 within the centromere (Blower et al., 2002). CENP-A is vital for kinetochore organization and function, as depletion by RNA interference (RNAi) in C. elegans (Buchwitz et al., 1999) or D. melanogaster (Blower and Karpen, 2001), or its knockout in mice (Howman et al., 2000), leads to significant problems in chromosome segregation and even lethal phenotypes in certain cases.

III. Chromatin Modifications

III.1. Histone Modifications

Histones undergo numerous post-translational modifications such as acetylation and methylation of their lysine or arginine residues, phosphorylation on serines and threonines, as well as ubiquitination, sumoylation, ADP-ribosylation, and more (Peterson and Laniel, 2004) (Figure 23). Moreover, a higher level of complexity in these modifications is achieved due to the possibility of accommodating one, two, or three methyl groups for each lysine residue, and one or two methyl groups for each arginine residue.

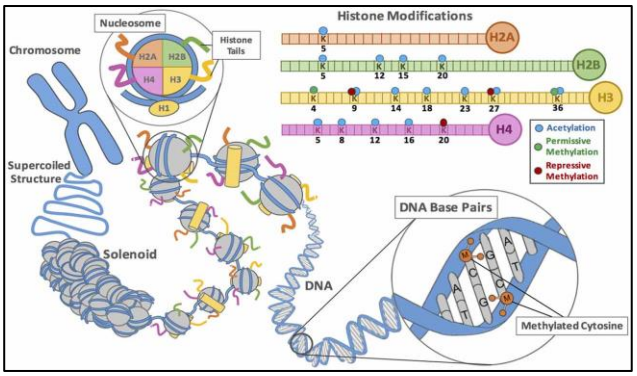

Figure 23: Histone modification (Post Translational Histone Modification : Post-translational Histone Modifications in Circulating ... : Proteins are synthesized by ribosomes translating mrna into polypeptide chains, which may then undergo ptm to form the mature protein product. (dudukberdua04.blogspot.com. Uploade: 20/08/2023)

These modifications are catalyzed by proteins, with the first discovered being a histone acetyltransferase (HAT) in yeast in 1996 (Peterson and Laniel, 2004). Subsequently, several transcriptional coactivators like CBP/p300 were identified as having HAT activity (Couture and Trievel, 2006). Additionally, the identification of enzymes responsible for histone deacetylation, histone methyltransferases (HMTs), and histone demethylases (HDMs) further expanded the understanding of histone modification regulation. These modifications play essential roles in regulating chromatin structure and gene expression by influencing the recruitment of regulatory proteins and chromatin remodeling complexes (Peterson and Laniel, 2004). The 'histone code' theory posits that specific combinations of histone modifications can dictate distinct functional outcomes in gene regulation (Strahl and Allis, 2000). Furthermore, these modifications can establish a dynamic landscape that responds to environmental stimuli, developmental cues, and disease conditions, thereby contributing to cellular diversity and adaptability (Jenuwein and Allis, 2001).

In various ways, several co-repressors of transcriptional activity have been highlighted, such as Rpd3, which exhibits HDAC activity. Enzymes capable of modifying histones are currently classified into families, including HATs (histone acetyltransferases), HDACs (histone deacetylases), HMTs (histone methyltransferases), and kinases.

At the genomic level, the addition of post-translational marks to histones occurs at specific sites, with this targeting primarily due to the combined effect of histone-modifying enzymes and regulators of certain biological functions like transcriptional regulation. The SAGA complex serves as an example, possessing a subunit with HAT activity that can interact with

proteins involved in the activation of specific genes. These interactions direct SAGA to a given region. However, for certain processes like DNA repair, the targeting of post-translational histone modifications might be more direct. DNA damage, for instance, triggers the direct recruitment of the ATM kinase (ataxia telangiectasia mutated) to the site of double-strand breaks, leading to the phosphorylation of histone H2A or its variant H2AX (Peterson and Laniel, 2004).

Post-translational histone modifications can directly impact the local organization of chromatin by altering histone-DNA interactions. For instance, the histone H3 tail, consisting of 13 amino acids with positive charges, acetylation of 1/4 of these residues could reduce positive charges by 10 to 30%, thereby disrupting interactions with negatively charged molecules like DNA or other proteins (Peterson and Laniel, 2004). These modifications can also indirectly affect transcriptional outcomes by modulating the recruitment of specific proteins capable of recognizing them (Martin and Zhang, 2005; Couture and Trievel, 2006). Various examples include bromodomain-containing proteins that specifically bind to acetylated lysines. Acetylation of lysine 9 on histone H4 (H4K9ac), for instance, facilitates the recruitment of the ATP-dependent chromatin remodeling complex SWI/SNF (switch/sucrose nonfermentable) via the bromodomain of its Brg1 subunit. Regarding methylated residues, these are recognized by proteins harboring specific domains such as chromodomains, Tudor domains that can bind to both methylated lysines and arginines, and WD40 repeat domains forming a β helix, found in proteins implicated in various biological processes like transcriptional regulation, RNA splicing, and more.

Histones that are methylated can also recruit other proteins, such as HP1 (heterochromatin protein 1) or Polycomb group proteins, involved in chromatin compaction, based on their localization and the number of methyl groups present on their residues (Margueron et al., 2005). Due to their direct or indirect roles in modulating chromatin structure and organization, post-translational histone modifications are implicated in all DNA-related processes, including gene transcription, X inactivation, heterochromatin formation, cell division, DNA replication, and repair (Peterson and Laniel, 2004; Ho and Crabtree, 2010). New modifications are continually being discovered, and it's possible that each accessible residue could be targeted by a defined or as-yet-undetermined modification. The collective set of "histone marks" may give rise to a histone code (Strahl and Allis, 2000), where specific modifications at certain sites could be linked to distinct biological functions. For example, acetylation of histone H3 lysine 9 (H3K9ac) or trimethylation of histone H3 lysine 4

(H3K4me3) are associated with transcriptional activation, while trimethylation of histone H3 lysine 9 and hypoacetylation of histones H3 and H4 are more linked to transcriptional repression (Li et al., 2010).

III.2.DNA Modifications

a.Cytosine Methylation

The most well-characterized change is undoubtedly its methylation at the carbon 5 position of cytosines (5m-C, often referred to as the fifth DNA base). This occurs within a CG dinucleotide context: 5m-CpG. Regarded as an epigenetic alteration, it can be heritable, passed down through cell generations. CpG sites are not evenly distributed throughout the human genome, being underrepresented (figure 24). They are notably concentrated in short CpG-rich sequences known as CpG islands, which constitute about 60% of gene promoters in both mice and humans. Additionally, these islands are abundant in the initial gene exon and in regions close to the 3' end of genes (Jones and Takai, 2001).

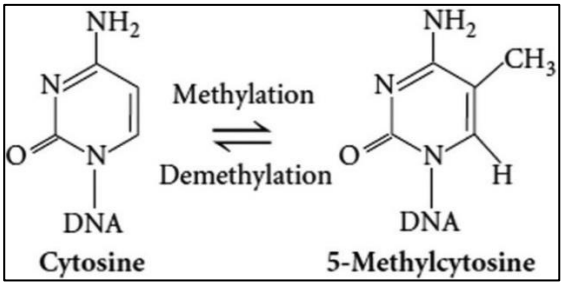

Figure 24: DNA methylation (Saini A et al., 2013)

Not all eukaryotes possess methylation; indeed, it's absent in the C.elegans genome (Bird et al., 2002). In Drosophila, methylation is quite limited, primarily targeting the CpT dinucleotide instead of CpG, as seen in vertebrates (Gowher et al., 2000; Lyko et al., 2000). In the mammalian genome, 5m-C represents only 1% of the bases, but concerning CpG sites, there's a notable increase in the level of methylated bases, with 70 to 80% of CpG sites being methylated. Large-scale DNA methylation studies encompassing the entire genome have been made easier with the development of the bisulfite-seq technique (Clark et al., 1994). This technique involves converting unmethylated cytosines to uracil, followed by high-throughput sequencing. It has highlighted the presence, albeit rarely, of methylation events on other dinucleotide types, CHG and CHH, where H represents A, C, or T, within undifferentiated cells. However, this non-CpG methylation is lost during cellular differentiation (Lister et al., 2009). Bisulfite technique implementation is challenging, and pinpointing methylation targets through sequencing is technically intricate. To simplify these studies, D. Schubeler's laboratory

introduced another technique, MeDIP (methylated cytosine immunoprecipitation), which utilizes an antibody against 5m-C to selectively immunoprecipitate methylated sequences. MeDIP can be analyzed using microarrays or sequencing methods (Weber et al., 2005).

Maintaining Methylation

During embryonic development, a phase of global demethylation of the genome has been noted, succeeded by a phase of de novo methylation, aiming to determine the methylation pattern of somatic cells. Methyl groups are added by enzymes referred to as DNMTs ("DNA methyltransferases"), of which there are three with this capability in mammals: DNMT1, DNMT3a, and DNMT3b. Maintaining methylation during replication is intricate. It is primarily facilitated by the semi-conservative nature of DNA replication, where DNMT1 methylates the new strand based on the parental strand (Pradhan et al., 1999) (figure 25). Nonetheless, another mechanism seems to underlie methylation maintenance during replication, as preservation of methylation in a DNMT1-deficient context has been observed (Jaenisch, 1997). DNMT3a and 3b, on the other hand, are mainly implicated in de novo methylation events (Okano et al., 1998a). They are highly expressed in embryonic cells, precisely when the genome re-methylation phase occurs.

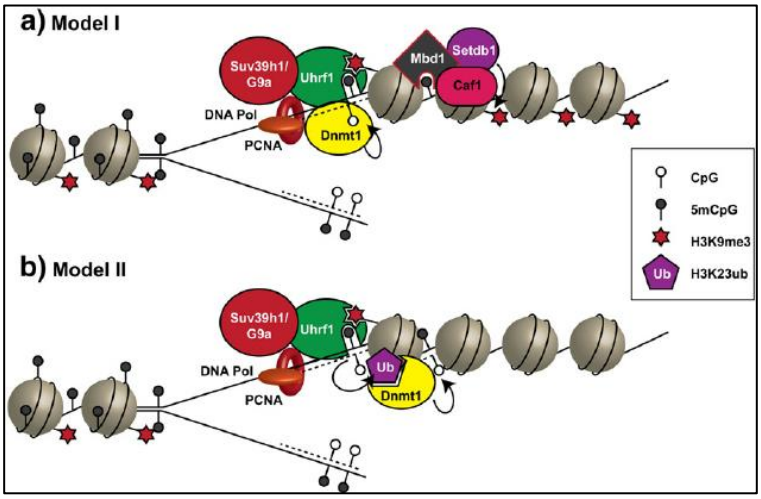

Figure 25: Methylation maintaining process (uploaded by Nathan R Rose).

Two models have been proposed regarding DNA methylation. The first model suggests that methylation could potentially impact all CpG sites, but this model appears inadequate. This is because the targeting of DNMT3b to specific sequences, such as repetitive DNA sequences and CpG islands on the Xi chromosome (Miniou et al., 1994), supports the second model where methylation is directed towards specific CpG sites.

Roles of Methylation

The involvement of cytosine methylation has been demonstrated in various functions within the adult organism, including transcriptional regulation, genome integrity maintenance, genome structure and organization, as well as replication. Methylation present on repetitive sequences like satellites, SINEs (short interspersed nuclear elements), and LINEs (long interspersed nuclear elements) contributes to their repression (Zemach and Zilberman, 2010). For instance, the Alu sequence family constitutes significant portions of the genome and artificial demethylation of these sequences is adequate to enhance their regulatory functions (Wodcock et al., 1997). DNA methylation can facilitate transcriptional repression through two distinct mechanisms. The first involves direct interference of the methyl group in the binding of a transcription factor to its target sequence. An example of this is observed at the H19/IGF2 locus subject to parental imprinting, where methylation prevents the binding of the CTCF protein to the paternal allele, thereby enabling Igf2 gene expression (Bell and Felsenfeld, 2000). Conversely, the second mode of action entails proteins with specific affinity for 5m-C, such as the Methyl Binding Domain (MBD) family of proteins. Among these, five proteins contain a 5m-C binding domain. Four of them (MBD1, MBD2, MBD3, and MeCP2) are implicated in transcriptional repression via methylation (Bird and Wolffe, 1999). In the case of MeCP2, it includes a Transcriptional Repression Domain (TRD) in addition to the MBD, capable of interacting with the SIN3A protein, which in turn interacts with HDACs. The role of HDACs in histone deacetylation establishes a repressive chromatin environment (Knoepfler and Eisenman, 1999). Such a connection between DNA and histone modifications has also been demonstrated, as MBD2 is part of a multiprotein complex containing HDAC1 and HDAC2 (Ng et al., 1999).

b- Hydroxymethylation of Cytosines

A second modification of DNA was recently rediscovered by two distinct laboratories simultaneously: 5-hydroxymethylcytosine (5-hmC) (Kriaucionais and Heintz, 2009; Tahiliani et al., 2009). This alteration, recognized as the sixth DNA base, emerges from the hydroxylation of 5-mC through proteins belonging to the TET (ten-eleven translocated) family (Tahiliani et al., 2009). 5-hmC is relatively uncommon (constituting 4% of cytosines within a CpG context) and is present only on chromosome arms, excluding pericentromeric chromatin and its repeated regions (Szulwah et al., 2011) (figure 26).

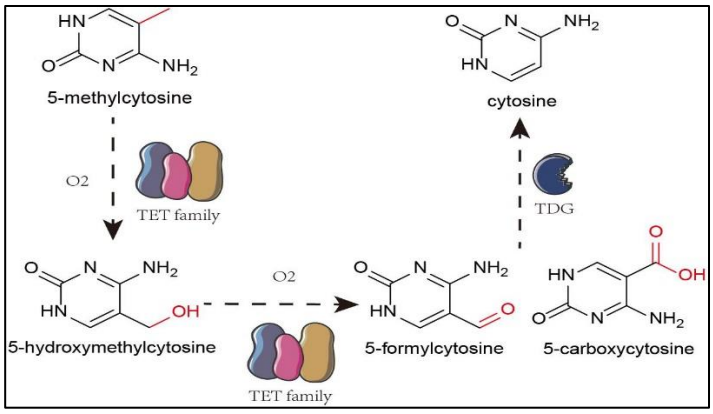

Figure 26: Hydroxymethylation of Cytosines (Zhu H et al., 2020).

The localization of 5-hmC is highly specific, exhibiting enrichment in gene bodies, particularly within exons and around the transcription start site (TSS). The distribution of 5-hmC at proximal gene promoters is influenced by their expression levels. Specifically, moderately expressed genes display a bimodal distribution around the TSS and enrichment within gene bodies, contrasting with lowly expressed genes that exhibit enrichment of 5-hmC at their TSSs but not within their gene bodies. This distribution correlates with certain histone marks, such as H3K4me1 and K4me2, showing similar enrichment patterns to 5-hmC in moderately expressed genes. Concerning enhancers, the presence of specific histone post-translational modifications, like H3K27ac and H4K5ac, are prerequisites for the presence of 5-hmC (Szulwach et al., 2011).

It is plausible that DNA hydroxymethylation impacts chromatin structure and local transcriptional activity by facilitating the recruitment of proteins with specific recognition of 5-hmC or by excluding proteins that recognize 5-mC, such as MeCP2, which is incapable of binding to a hydroxymethylated sequence (Tahiliani et al., 2009). However, 5-hmC does not exclusively correlate with transcriptional activity (Wu et al., 2011).

c-Dynamics of DNA Modifications

Methylation is not a static feature of the genome; rather, it is notably dynamic and thus requires demethylation mechanisms. Several instances of active demethylation exist, such as in the paternal genome post-fertilization (Mayer et al., 2000), or during the formation of primordial germ cells. Germline Lineage in Embryos is the first mechanism proposed for demethylation involves the deamination of 5-mC by proteins from the AID (Activation-Induced Deaminase) and APOBEC (Apolipoprotein B mRNA Editing Enzyme) families, converting it into thymine (Conticello, 2008). This substitution would be corrected through successive involvement of specific T:G mismatch glycosylases like TDG (Thymine DNA Glycosylase) or

MBD4 in mammals (Millar et al., 2002; Hardeland et al., 2003). Subsequently, the created abasic site is recognized by the Base Excision Repair (BER) system, facilitating the incorporation of an unmethylated cytosine (Fritz and Papavasiliou, 2010). However, more recent studies appear to indicate an incapability of AID/APOBEC proteins to demethylate 5-mC (Guo et al., 2011). This work emphasizes the necessity of an initial hydroxylation step converting 5-mC to 5-hmC. The DNA's sixth base would then be recognized by AID/APOBEC deaminases (primarily APOBEC1 and APOBEC2) (Morgan et al., 2004; Rai et al., 2008), leading to the formation of 5-hydroxyuracil, which is processed by proteins in the Base Excision Repair (BER) system (Gua et al., 2011). Another potential mechanism involves a cascade of oxidation by TET proteins. In this scenario, 5-mC is successively hydroxylated to 5-hmC, 5-formylcytosine (5-fC), and then 5-carboxylcytosine (5-caC). The latter two are recognized by the BER repair system (Ito et al., 2011).

III.3. Functional Organization and Chromatin Condensation

It has been widely accepted for a number of years that euchromatin, a partially decondensed form of chromatin, houses particularly active genes, in contrast to heterochromatin, which is considered transcriptionally inactive chromatin. However, it has become apparent that this notion is an oversimplification of reality (figure 27).

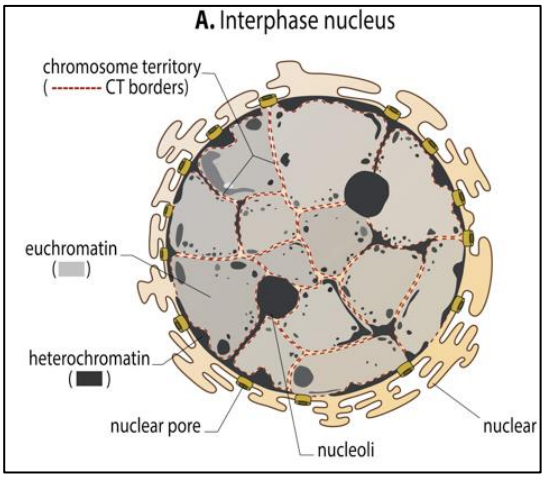

Figure 27: Chromatin condensation on the cell (What is chromatin, heterochromatin and euchromatin? | MBInfo (mechanobio.info) uploade : 20/08/2023)

III.3.1.Heterochromatin

In the early 1960s, Mirsky and colleagues discovered highly condensed chromatin at the nuclear periphery, known as heterochromatin. This compaction can be associated with a predominantly repressive structure regarding regulatory events. However, this type of

chromatin can be further categorized into constitutive heterochromatin, which is transcriptionally silent consistently in a differentiated cell, and facultative heterochromatin, containing temporarily repressed genes. Heterochromatin represents the major part of the mammalian genome (approximately 96%) and mainly consists of non-coding or repetitive sequences.

a-The Mechanisms

The establishment of a heterochromatin structure is associated with the involvement of the histone linker H1 and/or modifications in the chromatin state involving specific proteins, HP1, and/or proteins from the polycomb group. Among other mechanisms driving heterochromatinization, a recent discovery has linked it to what is known as non-specific transcription. The presence of double-stranded RNAs, a characteristic of this phenomenon, is recognized by the DICER complex which transforms them into siRNAs (small interfering RNAs). This allows the targeting of the implicated region by the protein complex RITS, resulting in histone deacetylation, methylation of certain lysines, recruitment of HPA, and eventually leading to DNA methylation. Knocking out factors involved in siRNA processing leads to defects in H3K9 trimethylation and HP1 binding. In yeast, heterochromatinization doesn't involve this mechanism but initiates at specific genome sites, spreading along the chromatin and inhibiting the entire region (Renauld et al., 1993). This process involves proteins known as Sirs (figure 28), particularly Sir2, Sir3, and Sir4, which interact physically with chromatin, rendering it inaccessible to the binding of other factors like RNA-PII. Generally, this type of heterochromatin diffusion is halted by well-defined chromatin boundaries, notably evident in yeast.

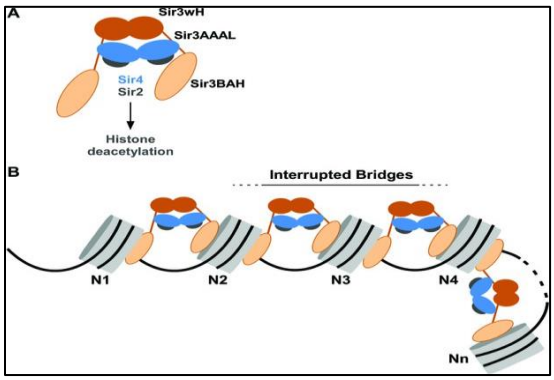

Figure 28: Heterochromatin assembly (Behrouzi R et al., 2016)

This mechanism also holds true for other species, both mammalian and non-mammalian. (Bi, 2012).

b-Facultative Heterochromatin

This form of heterochromatin encompasses regions of DNA encoding the genome in which the transcriptional repression of genes relies on specific developmental decisions. Depending on the cell type, various portions of the genome can become condensed and subsequently inactivated. Similarly, for a given cell type, a specific chromatin segment can be more or less condensed based on the level of differentiation. A prominent example of facultative heterochromatinization is the inactivation of the X chromosome in female mammals.

Case of the X-inactivation

In mammals, males possess one X and one Y sex chromosome, while females carry two X chromosomes. To prevent functional imbalance due to gene overexpression, mammals have developed a compensation mechanism involving the inactivation of one X chromosome in female cells. This process occurs early during embryogenesis when cells initiate differentiation, giving rise to the three primary embryonic lineages: ectoderm, endoderm, and mesoderm. It leads to the random transcriptional silencing of one X chromosome in each cell. The Xi exhibits characteristic properties of constitutive heterochromatin under microscopy: it remains visible in interphase cells as a Barr body and replicates late during the S phase. However, it's important to emphasize that the Xi is part of facultative heterochromatin, not constitutive, and notably lacks repeated satellite sequences typical of constitutive heterochromatin (figure 29).

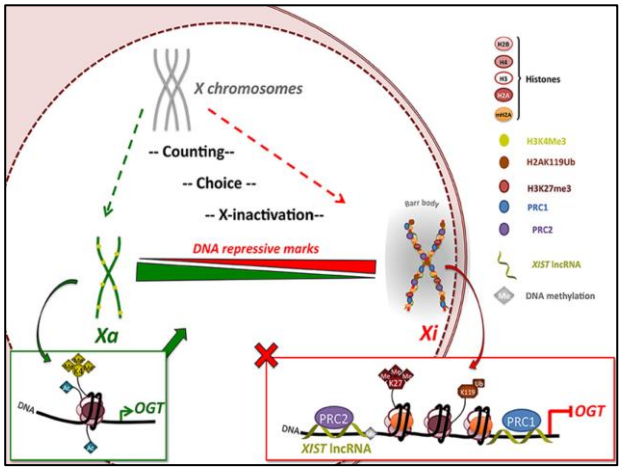

Figure 29: Lyon hypothesis (hétérochromatine and x-inactivation - Bing images upload 20/08/2023)

The X inactivation process initially involves a "sensing" step, during which each cell determines the number of X chromosomes relative to the number of autosomes. This step adheres to a strict rule known as the n-1 rule, discovered by Ohno in 1967, which dictates that

regardless of the number of X chromosomes in the cell, all but one will be inactivated. The steps of X inactivation are controlled by a locus located on the X chromosome, known as the X inactivation center or Xic. This locus contains, among other elements, the Xist gene crucial for the inactivation process (Brown et al., 1991). Indeed, its large non-coding RNA has the ability to coat the X chromosome that produces it, inducing its silencing (Heard and Disteche, 2006). The expression of Xist is regulated by a second RNA located in the same region but transcribed in the antisense direction: Tsix (Lee et al., 1999). A hypothesis put forth by Rastan in 1983 suggests that the chosen active X chromosome is the one where Xist allele expression is blocked, though the nature of the blocking factor remains unknown. The inactivated X chromosome is also subject to epigenetic modifications such as:

- Post-translational modifications of histone tails like trimethylation of H3K9 and H3K27 (H3K9me3 and H3K27me3) regionally found on the Xi (Chadwick and Willard, 2005), and H4K20 (H4K20me3), a mark predominantly associated with constitutive heterochromatin, as well as deacetylation of histones H2A, H2B, H3, and H4 (O'Neill et al., 2003).
- The inclusion of histone variants such as Macro H2A (Costanzi et al., 2001).
- The binding of characteristic heterochromatin proteins such as HP1. The interplay of histone modifications, the presence of variants, incorporation of non-histone proteins, along with Xist, is believed to contribute to the establishment of a transcriptionally silent state for the targeted X, its late replication, and its condensed appearance within the nucleus.

However, it's important to note that certain genes (about 15%) present on the inactive X have the ability to escape this transcriptional silence. These genes can be classified into two categories. The first consists of genes also present on the Y chromosome, eliminating the need for dosage compensation. The second includes genes located on the short arm of the X chromosome, acquired relatively recently during evolution. Illustrating the predominantly facultative nature of Xi heterochromatinization, reactivation of the Xi occurs in the germ line, the precursor to gametes. This coincides with a general epigenetic reprogramming, including erasure of parental imprints and genome-wide DNA demethylation.

c-Constitutive Heterochromatin

This type of chromatin corresponds to seemingly inactive portions of chromosomes found in all cells and containing repetitive sequences. The majority of these regions are located near centromeres (peri-centromeric regions) and telomeres, and they are replicated late during the S phase.

Centromere Case

Centromeres are specialized regions of eukaryotic chromosomes that ensure equitable segregation of sister chromatids between daughter cells during cell division. Centromeres consist of repetitive sequences, known as satellite sequences, with variable copy numbers across specie. Introducing a plasmid carrying these satellite sequences into a cell is sufficient to create neo-centromeres (Harrington et al., 1997). Another feature of centromeres is the presence of the histone variant CENP-A within nucleosomes, alternating with histone H3 (Blower et al., 2000). Post-translational modifications of histones in this constitutive heterochromatin primarily involve a high level of H3K9me3 and low histone acetylation. Additionally, the protein HP1 is also present. Paradoxically, dimethylated histones on lysine 4 can also be found within this region, indicative of an active chromatin structure (Casperson, 1998)

(H3K4me2), a mark more closely associated with transcriptional activity. On the other hand, within interphase nuclei, centromeres from multiple chromosomes have the ability to coalesce, forming chromocenters visible in all cell types (Alcobia and Dilao, 2000).

Telomere Case

At the ends of eukaryotic chromosomes lie specialized structures known as telomeres. Comprising one to several dozen repeats of a sequence motif "TTAGGG" spanning several kilobases, telomeres serve as protective elements against potential fusions between chromosome ends. They also shield chromosomes from DNA repair machinery, which might otherwise perceive the chromosome ends as double-strand breaks, as well as from exonucleases that could degrade them. In undifferentiated cells, telomere length, which decreases with each replication, is maintained by telomerase activity. During each cell division, the telomere structure is shortened due to the mechanism of DNA polymerase action, requiring a 5’ end to replicate the DNA strand. The 3’-OH end is replicated using small RNA fragments called Okazaki fragments. To fulfill their role, these fragments must hybridize to the 3’-OH end, a process occurring at a certain distance from the end, resulting in gradual shortening with each cell division. Beyond a certain limit, this shortening ultimately leads to replicative senescence, which is cellular death due to replication limitations (Blasco, 2005). Telomeric regions share chromatin properties similar to those of centromeric regions. Furthermore, studies investigating epigenetic modifications of telomeres in humans and Drosophila have indicated that these regions recruit HP1 and exhibit methylated H3K9, which is believed to be necessary for telomere elongation (Perrini et al., 2004).

III.3.2.Euchromatin

Euchromatin is a decondensed form of chromatin in an 11nm fiber, enriched with genes. It is differentially organized in time and space based on transcriptional state. The histones H3 within this chromatin are significantly acetylated and hypomethylated. Euchromatin in humans encompasses various types of sequences, including:

- Genes whose quantity varies depending on the context (cell type, environmental cues, etc.).
- Repeated non-coding DNA ·
- Non-repeated non-coding DNA ·
- Duplicated coding DNA ·
- Unannotated sequences

III.3.3. Chromatin Domains

With the emergence of large-scale analysis techniques, it has become evident that the dichotomous view of chromatin as heterochromatin and euchromatin requires a more nuanced classification into functional chromatin domains, whose number varies depending on the studied organism.

Case of C. elegans

The chromosomes of this organism differ from those studied in mammals. They are holocentric chromosomes, which can be divided into domains: a central domain and two arms containing numerous sequence repetitions and a notable depletion of genes. During the ENCODE project, initiated in 2003 to study the human genome, the C. elegans model was incorporated (2007). The investigation of 19 histone marks, 2 histone variants (H2A.Z and H3.3), and several chromatin-associated proteins in this model organism led to the identification of three main chromatin groups. These groups are not necessarily uniform in the nature of their included sequences, but they exhibit specific enrichments in histone marks and proteins (Gerstein et al., 2010).

Group 1: This group encompasses marks such as H3K4 and H3K36 methylation, H3 acetylation, and a depletion of H3K9me1/me2 and me3. This group seems enriched in the central region of autosomes. ·

Group 2: It includes H3 mono-, di-, or trimethylated on K9 and is present on the arms of autosomes. Despite the presence of marks typically associated with condensed chromatin, DAPI staining does not reveal heterochromatin on these regions, which are, however, strongly associated with the nuclear lamina through the protein LEM-2. ·

Group 3: This group is associated with the X chromosome, which significantly differs from autosomes. It displays various histone marks, uniformly distributed, such as H4K20me1, H3K9me1, and H3K27me1, often linked to highly expressed genes on the X chromosome. In hermaphrodite organisms (XX), both X chromosomes undergo dosage compensation through the recruitment of proteins DPY-26, 27, and 28, along with SDC-3. Furthermore, their interaction with LEM-2 is comparatively weak.

case of H. sapiens

The characteristics of chromatin structuring the Human genome have been extensively investigated in two major studies. The first study conducted by Ernst and Kellis (Ernst and Kellis, 2010) on T4 lymphocytes focused on the analysis of 38 histone post-translational modifications (methylation or acetylation) and the enrichment of H2A.Z, RNA-PII, and CTCF. The second study analyzed 9 histone post-translational marks in 9 different cell types (Ernst et al., 2011). These two works have identified six main classes of chromatin:

-Promoters, enriched in CpG islands and conserved motifs for the binding of various transcription factors, divided into 3 subgroups:

- Active promoters, exhibiting significant enrichment in RNA-PII and H2A.Z, high levels of H3K4 methylation, as well as acetylation of H3K27 and H3K9, along with an enrichment of DNase I-sensitive sites.
- Enhanceable promoters, characterized by methylated H3K4 and non-acetylated H3K27.
- Inactive promoters, displaying low levels of H3K4 methylation but high enrichment in H3K27me3.

-Enhancers, categorized into two types:

- Active enhancers, marked by methylated H3K4, numerous acetylations (H2BK120, H3K27, and H2BK5), significant DNase I sensitivity, and strong enrichment in H2A.Z.

Inactive regions: These regions are not active, lacking acetylation and showing lower sensitivity to DNAse I compared to active enhancers.

-Insulators: Mainly characterized by a significant enrichment of CTCF.

-Transcribed regions: Defined by a combination of 7 marks (H3K79me1/me2/me3, H3K27me1, H2BK5me1, H4K20me1, and H3K36me3). Transcribed chromatin can be divided into 3 subgroups:

- Spliced exons: Marked by a specific combination of H3K36me3, H2BK5me1, H4K20me1, H3K79me3, and the absence of H3K4me2, H3K9me1, and H3K79me2/me3.
- Transcriptional end sites (TES): Enriched in H3K36me3, H4K20me1, and RNA-PII, but lacking H3K4me1/me2/me3.
- Specific category representing zinc finger genes: Strongly enriched in H3K9me3, H4K20me3, H3K36me3, and depleted in other aforementioned post-translational modifications.

-Non-transcribed regions: Involving polycomb-type proteins and often associated with H3K27me3.

-Heterochromatin and its repetitive regions: Differing from non-transcribed regions due to their enrichment in H3K9me3.

III.4. Higher Levels of Chromatin Organization

III.4.1. Concept of Chromosomal Territories

The concept of chromosomal territories (CTs) was initially proposed in 1885 by Rabl and Boveri (figure 30). However, its confirmation through fluorescent in situ hybridization (FISH) occurred a century later. Within the interphase nucleus, there is indeed a specific organization of chromosomes, enabling a spatial segregation of genetic material for each chromosome. This segregation doesn't occur randomly but rather within defined regions (Misteli, 2005). These territories are not solid structures. Chromosomes with a higher gene count tend to be positioned towards the inner part of the nucleus, in contrast to the chromosomes that have fewer genes.

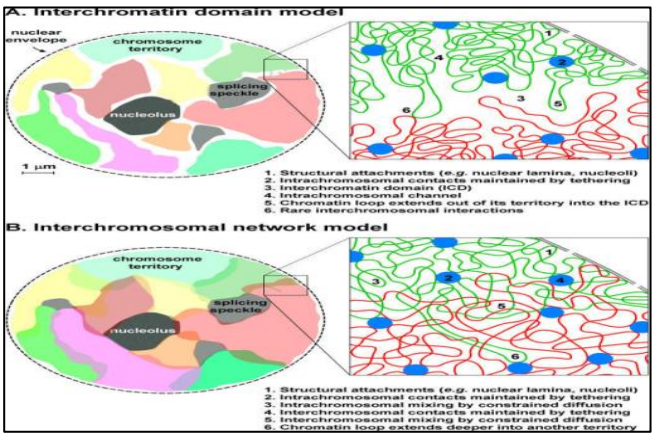

Figure 30: ICD and Interchromosomal Network (ICN) Models of Chroma (Branco MR et al ., 2016)

The arrangement of chromosomal territories (CTs) is closely tied to gene content, as evidenced by their localization within the nuclear space. Chromosomes rich in genes are primarily situated in the nuclear interior, while those with fewer genes are predominantly located at the nuclear periphery (Croft et al., 1999; Cremer et al., 2001). However, this trend is nuanced by two factors. Firstly, a "patchwork" organization of chromosomes exists, with varying gene densities, leading to a peripheral localization of certain gene-rich chromosomes (Mahy, 2002). Secondly, organization varies among cell types; for instance, lymphocytes exhibit an organization based on gene density rather than individual gene activity, while fibroblasts organize based on chromosome size (Misteli, 2005). Two models can explain CT organization:

a-Interchromatin Domain Model (ICD)

The model proposed by Zirbel et al. in 1993 introduces a concept that focuses on the arrangement of gene transcripts and components of RNA splicing machinery within chromatin territories (CTs). This model posits that these elements are concentrated along the CTs. However, a significant implication of this model is that CTs are highly compact, which implies that transcription and splicing activities would be limited to the surface of CTs. This arrangement would result in transcribed genes being positioned at the periphery while non-coding sequences reside within the CTs. Despite this proposition, empirical research has presented certain challenges to this compact CT model.

Empirical investigations have pointed out that the distribution of gene-rich and gene-poor domains along chromosomes is more balanced than what the compact CT model would suggest (Visser et al., 1998; Mahy et al., 2002b). These studies have highlighted that genes and non-coding regions are not strictly confined to distinct locations within the nucleus.

In response to these findings, an adapted model known as the interchromosomal domain (ICD) model has been introduced. This modified framework incorporates additional structural elements, such as channels, within CTs. These channels facilitate the access of regulatory factors and other necessary components to the enclosed chromatin. Within this model, transcription and RNA splicing take place not just at the CT surface, but rather within the interchromosomal space created by the channels. This adjustment allows for a more flexible and versatile arrangement that accommodates the observed distribution of gene-rich and gene-poor domains along chromosomes (Cremer and Cremer, 2001). While the original CT model by Zirbel et al. provided a foundation for understanding the spatial organization of gene transcripts and splicing machinery, the limitations posed by the highly compact nature of CTs

were addressed by the adapted ICD model. This newer model, incorporating interchromosomal spaces and channels, offers a more plausible explanation for the balanced distribution of genomic elements and regulatory activities observed within the nucleus.

b- Interchromosomal Network Model (ICN)

In contrast to previous models, the paradigm proposed by Ana Pombo's laboratory (Branco and Pombo, 2006), as outlined in the work of Branco and Pombo in 2006, challenges the notion of strict physical separation among chromatin territories (CTs). This novel perspective suggests a departure from the idea of discrete CTs and introduces the concept of intermingling and translocation between neighboring CTs. This model is underpinned by the intriguing possibility of CTs becoming intertwined and undergoing interchromosomal translocation. Instead of rigid physical boundaries, the interactions of CTs with neighboring CTs, the nuclear membrane, and various nuclear compartments are proposed to play a crucial role in determining their potential for intertwining.

This dynamic viewpoint suggests a higher degree of spatial complexity within the nucleus than previously thought. The notion that CTs can intertwine and move between different nuclear regions underscores the flexible nature of nuclear organization. It also implies a level of plasticity in chromatin interactions that can contribute to diverse regulatory mechanisms and gene expression patterns.

The model proposed by Pombo's laboratory challenges the conventional idea of CTs as isolated entities and offers a more nuanced understanding of their behavior and interactions within the three-dimensional nuclear space. This perspective underscores the need to consider not only physical proximity but also the intricate network of molecular interactions that shape nuclear organization. By elucidating the potential for intertwining and interchromosomal translocation, this model contributes to a more comprehensive comprehension of nuclear architecture and its impact on cellular processes.

III.4.1. Proteins Involved in Chromatin Loop Organization

a. Cohesin Protein

The cohesin protein, initially described in 1997 by Michaelis et al., is composed of four protein subunits that have been conserved throughout evolution. The cohesin complex, comprised of SCC1 and SCC3, as well as SMC1 and SMC3, plays a pivotal role in maintaining

the structural integrity of chromosomes. Homologs of these subunits have been identified across diverse organisms, from bacteria to humans (Hirano, 2005). SMC proteins are highly conserved both in their sequences and structures and exhibit ATPase activity. They have the ability to dimerize through their hinge domain and are subsequently connected by SCC1, which also binds to SCC3, thus forming the cohesin complex. The cohesin complex can also interact with a wide range of partner proteins (figure 31).

Defects in the SMC1 and SMC3 subunits or in the protein responsible for loading cohesin onto DNA (Nipbl) underlie Cornelia de Lange syndrome (Liu and Krantz, 2009). This syndrome is characterized by developmental issues including intellectual disabilities, growth delays, and autism.

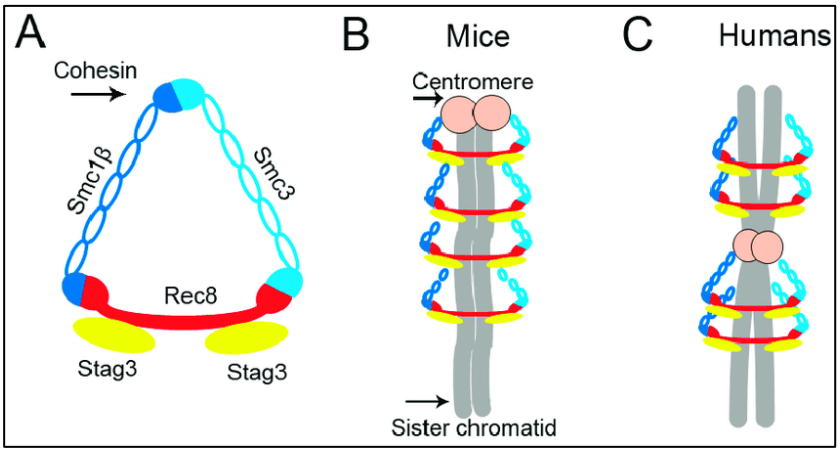

Figure 31: Cohesin structure in mice and humans (CC BY licence).

While the primary role of cohesin is to prevent premature separation of sister chromatids during cell division, ensuring proper cell proliferation (Wendt and Peters, 2009), its association with chromatin in vertebrates at the end of mitosis, well before the need for sister chromatid cohesion in the cell cycle, suggests a potential function of this complex in DNA-related processes beyond replication (Wendt et al., 2008). Chromatin immunoprecipitation followed by microarray analysis (ChIP-chip) experiments in post-mitotic cells demonstrated cohesin's binding to chromatin, independent of its cohesion role, particularly at intergenic regions (49%, as opposed to 35% in introns and 13% within 5kb of genes) (Wendt et al., 2008).

Regarding gene regulation, the role of cohesin appears to vary across different organisms. In the yeast S. pombe, it facilitates the termination of transcription between convergent genes, involving DICER (known for its role in miRNA machinery) and Swi6. In this process, cohesin is recruited both before and during the S phase, and its presence during G2 phase hinders RNA-

PII activity in intergenic regions (Gullerova and Proudfoot, 2008). In Drosophila, studies on the gipsy insulator highlighted the role of the Scc2 ortholog, Nipped B, in the interaction between gene promoters and enhancers of cut and ultrabithorax genes (Rollins et al., 1999).

Due to its role in maintaining close proximity between sister chromatids, the cohesin complex is also involved in repairing double-strand breaks, with the sister chromatid serving as a template for mending the broken chromatid. Additionally, during this process, it is plausible that cohesin contributes to the DNA reparation.

b. CTCF

CTCF, a DNA-binding protein, is highly conserved among higher eukaryotes, particularly in its central domain encompassing 11 zinc fingers (Phillips and Corces, 2009). These zinc fingers can differentially combine based on the target sequence, optimizing chromatin binding (Filippova et al., 1996). The central domain exhibits remarkable conservation, with nearly 100% sequence homology between Mouse, Chicken, and Human (Phillips and Corces, 2009), with variations primarily in the N- and C-terminal ends.

CTCF was identified independently in two instances. Initially recognized as a protein binding to sequences in the promoter region of the MYC oncogene (Lobanenkov et al., 1990), it was later also discovered as a protein binding to a silencer element in the promoter of the H amyloid gene in Chicken, along with sequences regulating the Chicken β-globin gene (Ohlson et al., 2001). CTCF also binds to the X chromosome (Chao et al., 2002), imprinted parental genes (Bell and Felsenfeld, 2000), and at the boundaries between active and inactive chromatin (Cho et al., 2005) (figure 32).

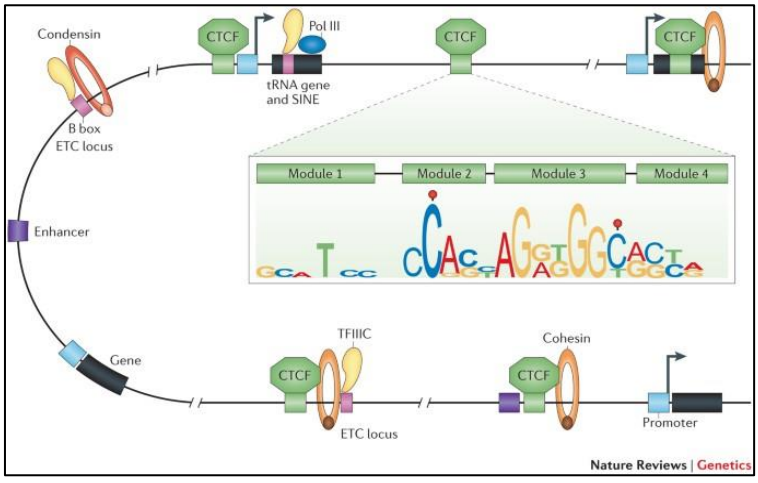

Figure 32: CTCF architectural protein (Ong CT et al., 2014).

ChIP-chip experiments in human fibroblasts (IMR90 cells) have outlined CTCF's genomic distribution (Kim et al., 2007). Notably, CTCF primarily binds to intergenic regions (46%), along with introns (22%), exons (12%), and within a 2 kb window around promoters (20%). However, recent studies using ChIP-seq techniques in different cell types revealed a slightly different distribution (Barsky et al., 2007), with 45% intergenic, 29% in introns, 3% in exons, 7% in the 5'-UTR, 2% in the 3'-UTR, and 13% around the transcription start site (TSS). Despite these discrepancies, 70% of CTCF binding sites seem to be conserved across various cell types (Kim et al., 2007). These observations have led to the hypothesis that CTCF binding sites are primarily invariant across cell types, with minor differences indicating either significant functional relevance or potential biases in sensitivity arising from the use of different techniques.

c. Cohesin Complex and CTCF

CTCF and the cohesin complex (figure 33) exhibit varying degrees of colocalization depending on cell types (Rubio et al., 2008; Wendt et al., 2008), hinting at a functional interrelationship between these two factors. A hypothesis proposed as early as 2008 (Rubio et al., 2008; Wendt et al., 2008) suggests that CTCF might be necessary for the binding of a major portion of the cohesin pool at specific DNA sites. However, soluble forms of these two factors do not appear to be stably linked in nuclear extracts from HeLa cells (Wendt et al., 2008), which would seemingly exclude the existence of a direct relationship between CTCF and the cohesin complex.

CTCF's influence on cohesin could potentially be indirect, affecting the binding configuration and distribution of the cohesin complex across the genome. It has been proposed that CTCF's presence might impact chromatin architecture and looping patterns, which could subsequently influence the accessibility of the cohesin complex to different chromosomal regions (Hadjur et al., 2009). In this scenario, CTCF's role would be pivotal in establishing a structural framework for the cohesin complex to operate effectively.

Conversely, the cohesin complex's role in chromosome segregation and sister chromatid cohesion during cell division appears to be distinct from CTCF's role in chromatin looping and gene regulation. The cohesin complex's primary function revolves around mediating sister chromatid cohesion and preventing premature separation, ensuring genomic stability (Wendt et al., 2009). In contrast, CTCF's involvement in chromatin looping and organization affects long-

range interactions between distant genomic elements and contributes to transcriptional regulation (Phillips and Corces, 2009).

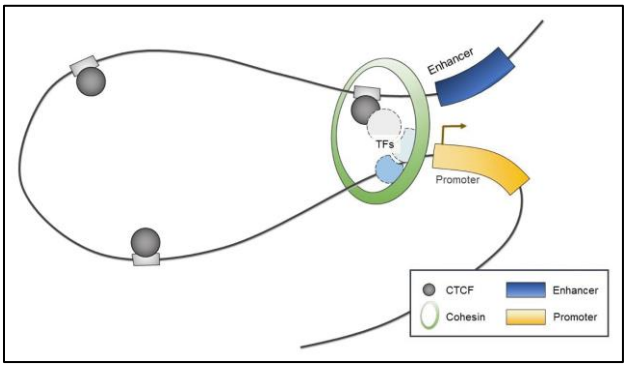

Figure 33: CTCF and the cohesin complex (Song SH et al., 2017)

Therefore, while there might be instances of colocalization and potential indirect influences, the cohesin complex and CTCF predominantly serve separate functions within the broader context of chromatin organization and gene regulation. In the context of a specific locus, the interaction between CTCF and the cohesin complex leads to chromatin structuring and results in the accumulation of cohesin at that site (Wendt et Peters, 2009). Conversely, a portion of the cohesin pool has the capability to bind to chromatin independently of CTCF. This occurs through interaction with other proteins since cohesin lacks a direct DNA-binding domain. For instance, such CTCF-independent cohesin sites have been identified near binding sites for specific transcription factors like ERα in MCF-7 cells or HNF4α in HepG2 cells (Schmidt et al., 2010).

Chapiter III: Transcription

I. Introduction

In prokaryotic cells, such as bacteria, transcription takes place in the cytoplasm since there is no distinct nucleus. The DNA in prokaryotes is organized into a single, circular chromosome located within the nucleoid region. During transcription, a single RNA polymerase enzyme is responsible for synthesizing RNA directly from the DNA template. The resulting mRNA molecule is usually polycistronic, meaning it can code for multiple proteins in a single transcript. Prokaryotic transcription lacks the elaborate processing steps seen in eukaryotes, as prokaryotic mRNA is typically ready for translation soon after its synthesis. This contrast in transcription processes highlights the divergent strategies employed by these two cell types for gene expression. The process of DNA transcription exhibits notable differences between eukaryotic and prokaryotic cells. In eukaryotes, which include plants, animals, and fungi, transcription occurs within the nucleus, where the DNA is enclosed by the nuclear envelope. Transcription involves the synthesis of a pre-messenger RNA (pre-mRNA) molecule from a DNA template. This pre-mRNA undergoes various modifications, including the removal of introns and the addition of a 5' cap and a poly-A tail, before it is transported to the cytoplasm for translation into proteins. Eukaryotic transcription is complex and involves the cooperation of multiple transcription factors and RNA polymerase enzymes.

Transcription is a highly regulated phenomenon in eukaryote cell, finely tuned to enable a cell to respond appropriately to external and internal stimuli, such as changes in local hormone concentrations. The transcription process encompasses distinct stages: initiation, elongation, and termination. These stages were traditionally considered independent, each involving different protein factors. In eukaryotic cells, three different RNA polymerases (Burley and Roeder, 1996) – RNA Pol I, RNA Pol II, and RNA Pol III (figure 34); are responsible for transcription. This distinction gives rise to three gene classes based on the polymerase involved:

- Class I: These genes contribute to the production of ribosomal RNAs (rRNAs) 18S, 28S, and 5.8S. They are organized in tandem repeats.
- Class II: They lead to the formation of proteins through the transcription of messenger RNA molecules (mRNAs). The transcription of these genes will be the central focus of this section.
- Class III: These genes produce 5S RNA, transfer RNAs (tRNAs) involved in mRNA translation, as well as various small non-coding RNAs (ncRNAs), including diverse types of small RNAs. They are primarily transcribed during the interphase.

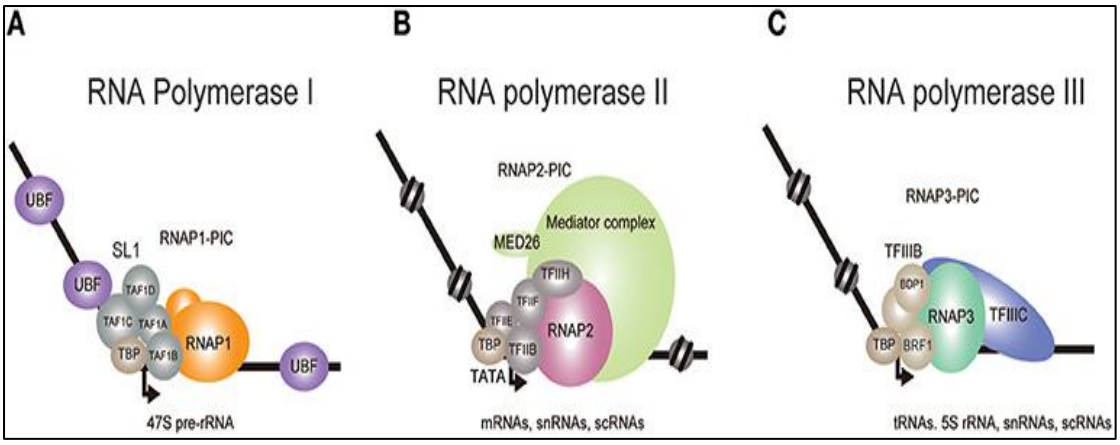

Figure 34: Transcriptional initiation complexes of the three eukaryotic RNA polymerases (Yokoyama A, 2019)

The mechanisms underlying transcription vary in complexity and differ between prokaryotes and eukaryotes. In this work, we will exclusively address eukaryotes and primarily concentrate on the transcription of class II genes, which is mediated by RNA Pol II.

I.2. RNA synthesis

During the process of transcription, RNA polymerase identifies and engages a specific genomic locus situated upstream of a gene's coding sequence, referred to as the promoter site (Alberts et al., 2015). This pivotal step will be expounded upon in greater detail during the initiation phase, constituting the foremost juncture of transcriptional activity (figure 35).

Subsequent to transcription, the RNA transcript undergoes a series of maturation events (also known as post-transcriptional modifications) before translation, encompassing two additional pivotal stages in protein biosynthesis (Gilbert, 2016). Remarkably, in prokaryotic organisms, the progression to translation obviates the requirement for maturation.

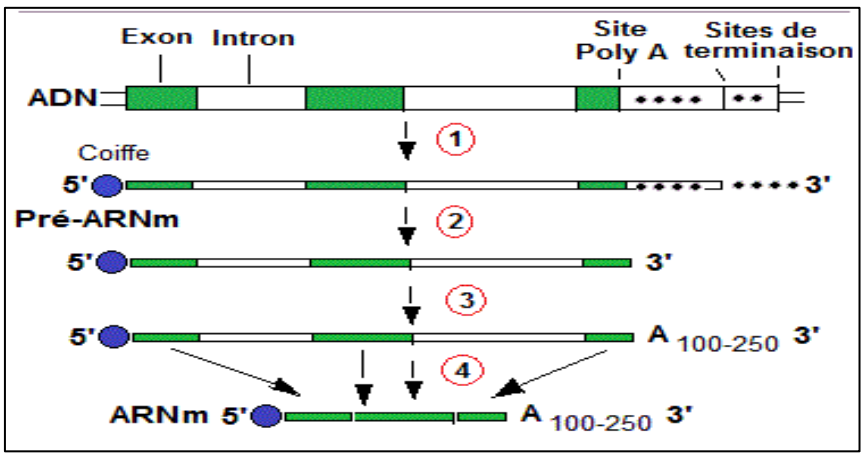

Figure 35: RNA maturation

I.2.1. Capping

In the context of RNA maturation, the nascent RNA molecule, synthesized de novo utilizing the DNA template (pre-messenger RNA or pre-mRNA), is subject to 3' polyadenylation and 5' capping, involving the addition of a methylated nucleotide (7-methylguanosine) via a 5'-5' phosphodiester linkage (Proudfoot et al., 2007). This 5' cap structure serves multifarious functions, including exonuclease protection, splicing facilitation, and promotion of ribosomal association with mature mRNA (Shatkin, 1976; Maniatis et al., 1982). Importantly, this capping event is expedited prior to the culmination of transcription.

Concurrently, during the RNA maturation process, the primary mRNA transcript resides within the cellular nucleus and is subsequently subject to splicing, wherein intronic sequences are excised and exonic sequences are conjoined by the spliceosome complex (Wahl et al., 2011). Upon completion of this maturation, the RNA species transmutes into mature mRNA, a truncated form that is proficiently conveyed to the cytoplasm, where translation is orchestrated. This translation entails the conversion of RNA-encoded information into protein sequences utilizing amino acids, orchestrated by ribosomal machinery and transfer RNAs (tRNAs) (Jackson et al., 2003; Lodish et al., 2016).

the transcriptional, maturation, and translational processes of gene expression orchestrate a highly intricate molecular symphony that culminates in the synthesis of functional proteins, each phase tightly regulated and laden with intricate molecular mechanisms (Alberts et al., 2015; Lodish et al., 2016).

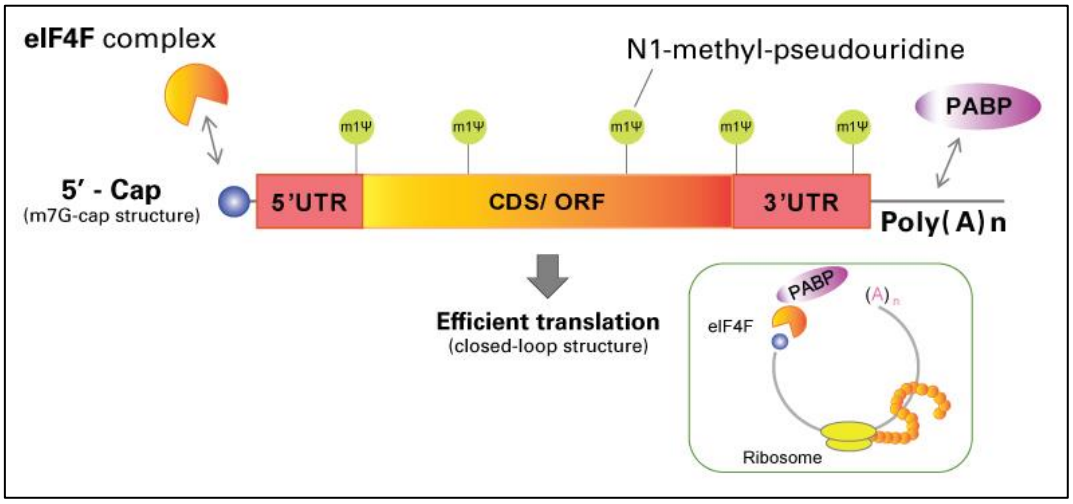

Figure 36: 5-prime capping of mRNA (TAKARA)

I.2.2. Polyadenylation

Polyadenylation is a post-transcriptional modification that plays a pivotal role in the maturation and regulation of eukaryotic mRNA molecules. It involves the addition of a string of adenine nucleotides to the 3' end of the pre-mRNA, forming what is known as the polyadenine tail or polyA tail. This process is guided by the activity of a specialized enzyme called poly(A) polymerase (figure 37).

a-Process of Polyadenylation

***Cleavage*:** After the pre-mRNA is synthesized during transcription, a sequence of nucleotides called the polyadenylation signal sequence (AAUAAA) is recognized downstream of the coding region. This sequence acts as a signal for the cleavage and polyadenylation machinery to assemble.

Cleavage Factors: A complex of proteins, known as cleavage factors, assembles at the polyadenylation signal. This complex directs the cleavage of the nascent RNA chain, precisely after the polyadenylation signal sequence. This cleavage separates the newly transcribed pre-mRNA from the elongating RNA polymerase.

Polyadenylation Polymerase: Poly(A) polymerase then adds a series of adenine nucleotides (usually around 200) to the 3' end of the cleaved pre-mRNA. This addition occurs through a process involving adenosine triphosphate (ATP) as the source of adenine residues.

Poly(A) Tail Formation: The repeated addition of adenine nucleotides forms the polyadenine tail, which extends beyond the cleavage site. This tail does not code for any specific protein sequence but rather serves important regulatory functions.

b-Functions of the Poly(A) Tail

Stability: The presence of a polyA tail significantly enhances the stability of the mRNA molecule. This extended tail helps protect the mRNA from enzymatic degradation by exonucleases in the cytoplasm, thereby prolonging the mRNA's lifespan and availability for translation.

***Export*:** The polyA tail also aids in the export of the mRNA from the nucleus to the cytoplasm. Mature mRNA molecules with a polyA tail are recognized and transported through nuclear pores more efficiently than those lacking this tail.

Translation Efficiency: The polyA tail is intimately involved in translation initiation. It interacts with translation initiation factors and ribosomal subunits to enhance the efficiency of translation initiation, thereby influencing the rate at which proteins are synthesized from the mRNA.

Regulation of Gene Expression: The length of the polyA tail can vary, and this variation can impact gene expression. Certain regulatory processes can modulate the length of the polyA tail, influencing the stability and translation efficiency of the mRNA.

Polyadenylation is a fundamental process that contributes to the maturation, stability, transport, and translation of eukaryotic mRNA. It showcases the complexity of gene expression regulation, ensuring that the genetic information encoded in DNA is efficiently and accurately translated into functional proteins in response to cellular needs and environmental cues (Beaudoing et al., 2000; Proudfoot, 1995).

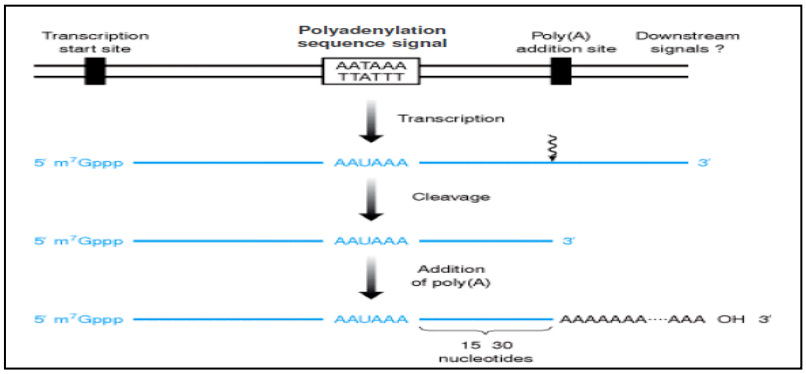

Figure 37: Polyadenylation of RNA

I.2.3. Spiling

Splicing is a sophisticated post-transcriptional process that underpins the maturation of primary RNA transcripts in eukaryotic genes. It entails the intricate orchestration of removing internal segments, known as introns, while concomitantly ligating the contiguous segments, referred to as exons (figure 38).

a-Mechanism of Splicing

Recognition of Intron-Exon Boundaries: Splicing begins with the recognition of specific nucleotide sequences that demarcate the boundaries between introns and exons. These recognition sequences are highly conserved and include the 5' splice donor site (marked by a GU dinucleotide at the 5' end of the intron) and the 3' splice acceptor site (characterized by an AG dinucleotide at the acceptor end of the intron).

Spliceosome Assembly: The spliceosome, a complex of small nuclear ribonucleoproteins (snRNPs) and associated proteins, assembles onto the intron-exon junctions. The spliceosome components recognize and interact with the splice donor and acceptor sites, positioning themselves for the splicing reaction.

Cleavage and Ligation: Within the assembled spliceosome, two sequential reactions take place. First, a precise cut is made at the 5' splice donor site, resulting in the formation of a "lariat" intermediate, where the 5' end of the intron is covalently linked to an adenosine residue within the intron itself. Subsequently, the 3' end of the exon is ligated to the 5' end of the downstream exon, effectively excising the intron and joining the adjacent exons.

Spliceosome Dissociation: After the intron is removed and the exons are joined, the spliceosome disassembles, and the mature mRNA molecule is left ready for further processing and translation.

b-Functions of Splicing

Protein Diversity: Alternative splicing, a phenomenon where different combinations of exons are included or excluded, leads to the generation of multiple mRNA isoforms from a single gene. This process greatly expands the repertoire of proteins that can be produced from a limited number of genes.

Regulation of Gene Expression: Splicing is a key regulatory point in gene expression. By controlling which exons are included or excluded, cells can fine-tune protein function, abundance, and localization.

Disease Implications: Dysregulation of splicing can result in genetic disorders and diseases. Mutations in splice sites or splicing regulatory elements can lead to aberrant splicing and the production of malfunctioning proteins.

Evolutionary Innovation: Alternative splicing contributes to the evolution of new functions in genes. Evolutionary changes in splicing patterns can lead to the emergence of novel protein functions.

Splicing represents a sophisticated molecular mechanism by which eukaryotic cells achieve exquisite control over gene expression, protein diversity, and ultimately, cellular functions (Wahl et al., 2011; Black, 2013).

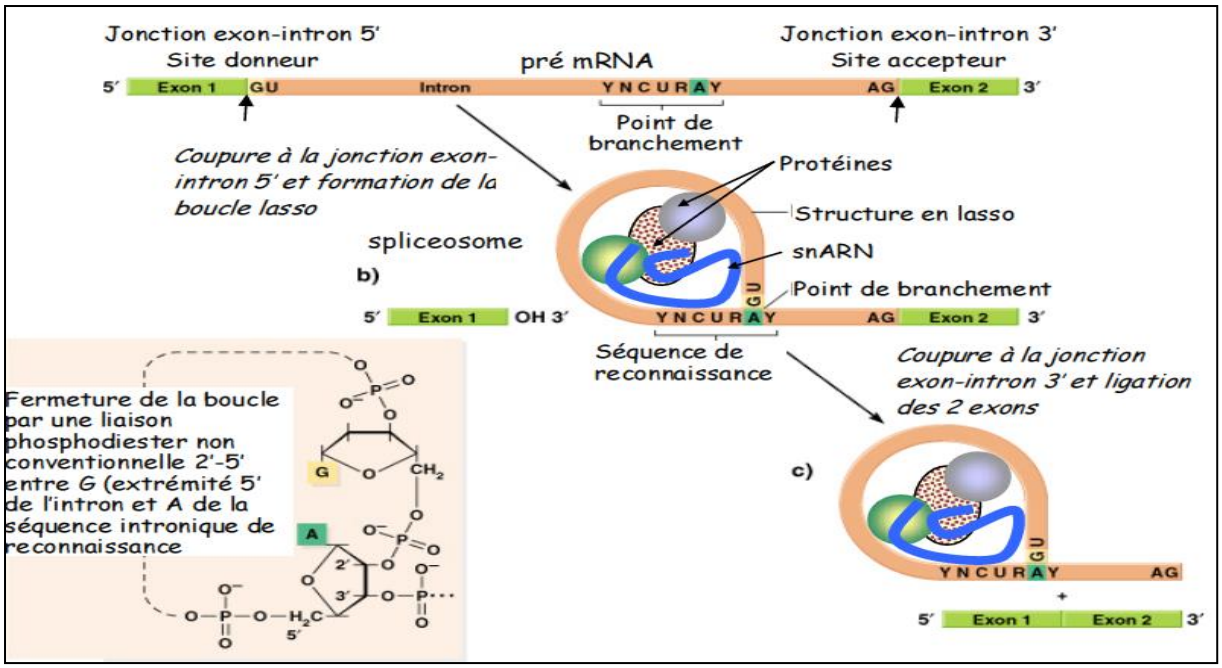

Figure 38: Spiling process.

II. DNA Accessibility

Within the nucleus, the chromatin's inherent structure poses challenges for factors involved in transcriptional regulation to access their target DNA sequences. Chromatin remodeling can be facilitated by two types of multiprotein complexes. The complexes in the first group utilize ATP hydrolysis energy to alter the position or destabilize nucleosomes (Kingston et al., 1996). This initial group can be categorized into five families: SWI/SNF, ISWI, Mi-2/NuRD, INO80, and SWR1. The second group of complexes involved in chromatin structure remodeling includes enzymes capable of directly modifying histones, such as HATs, HMTs, HDACs... (figure 39; 40).

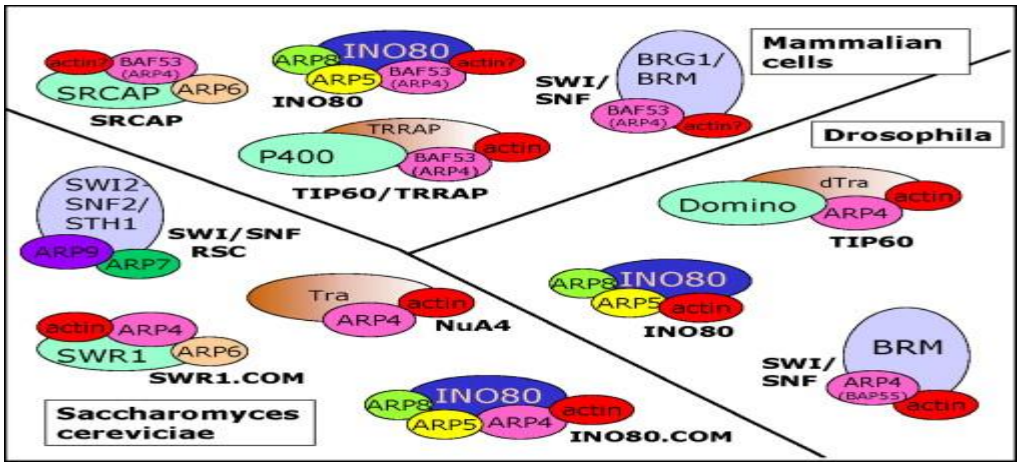

Figure 39: Chromatin remodeling and actin organization (Stournaras C, 2008)

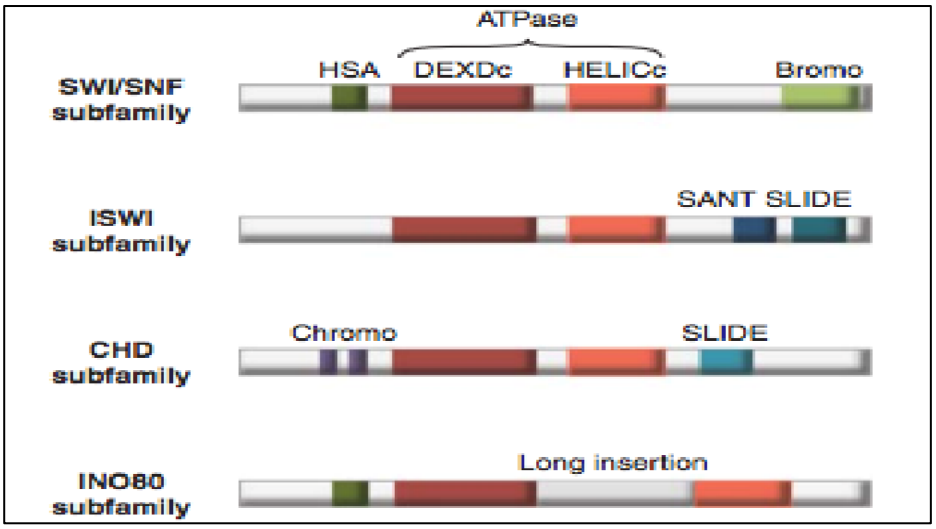

Figure 40 : Organization of different domains of ATP-dependent chromatin remodeling complexes (uploaded by Julien Matysiak)

II.1.ATP-Dependent Remodeling Complexes

II.1.1. The SWI/SNF Family

SWI/SNF was the first family identified in the yeast S. cerevisiae. This complex comprises 11 subunits (table 01), including Snf2, Snf5, and Swi1 (Cairns et al., 1994; Coté et al., 1994; Peterson et al., 1994). It is required for the expression of certain genes like HO, SUC2, or INO1 (Biggar and Crabtree, 1999) by virtue of its ability to remodel chromatin structure during transcription activation. This is mediated through its subunit Swi2, the sole protein presenting ATPase activity in this complex (Laurent et al., 1993; Coté et al., 1994). Additional studies have demonstrated that the role of Swi/Snf extends beyond transcription initiation, encompassing other stages of the process (Biggar and Crabtree, 1999).

Table 1: SWI/SNF subunit details from organisms, human, mouse, fruit fly, round worm, and yeast (Mani U et al., 2017).

S. No.	Subunit name	Type of subunit	BAF (human)	PBAF (human)	BAF (mouse)	PBAF (mouse)	BAP (fruit fly)	PBAP (fruit fly	BAF (round worm)	PBAF (round worm)	SWI/SNF (yeast)	RSC (yeast)
1	ATPase	Core	BRG1/BRM	BRG1	BRG1/BRM	BRG1	Brm	Brm	SWSN-4	SWSN-4	SNF2	STH1
2	BAF47/INI1/Snr1/SNF5/SFH1	Core	BAF47	BAF47	BAF47	BAF47	Snr1	Snr1	SNFC-5	SNFC-5	SNF5	SFH1
3	ARID domain containing subunit	Signature	BAF250A/B	BAF200	BAF250A/B	BAF200	Osa	Bap170	LET-526	SWSN-7	SWI1	RSC9
4	BAF155/Moira/SWI3/RSC8	Core	BAF155	BAF155	BAF155	BAF155	Moira	Moira	SWSN-1	SWSN-1	SWI3	RSC8
5	BAF170/Moira/SWI3/RSC8	Core	BAF170	BAF170	BAF170	BAF170	Moira	Moira	SWSN-1	SWSN-1	SWI3	RSC8
6	BAF60/Bap60/SWP73/RSC6	Accessory	BAF60A/B/C	BAF60A/B/C	BAF60A/B/C	BAF60A/B/C	Bap60	Bap60	SWSN-2.1/SWSN-2.2	SWSN-2.1/SWSN-2.2	SWP73	RSC6
7	Actin	Accessory	β-actin	β-actin	β-actin	β-actin	Act5C	Act5C			ARP7	ARP7
8	Actin-related protein	Accessory	BAF53A/B	BAF53A/B	BAF53A/B	BAF53A/B	Bap55	Bap55	SWSN-6	SWSN-6	ARP9	ARP9
9	Polybromo-1/Polybromo/RSC1/2/4	PBAF specific		Polybromo-1		Polybromo-1		Polybromo		PBRM-1		RSC1/2/4
10	Bromodomain containing protein	Signature	BRD9	BRD7	BRD9	BRD7	CG7154	CG7154	SWSN-9	SWSN-9		
11	BAF45/D4/SAYP	Signature	BAF45B/C/D	BAF45A	BAF45B/C/D	BAF45A	D4	SAYP	DPFF-1	PHF-10		
12	BAF57/Bap111	Accessory	BAF57	BAF57	BAF57	BAF57	Bap111	Bap111	SWSN-3	SWSN-3		
13	BCL7	BAF specific	BCL7A/B/C		BCL7A/B/C		BCL7-like		BCL-7			

In humans, SWI/SNF complexes exhibit relatively heterogeneous compositions, with some subunits differing based on the cellular context (cell type, differentiation state, and developmental stage). The ATPase activity of these complexes is carried by two proteins in humans: Brg1 (Brm-related gene 1 protein) and hBrm (human Brm) (Khavari et al., 1993). These two proteins, displaying strong homology with Swi2/Snf2, are found in complexes called hSWI/SNFA and hSWI/SNFB (Kwon et al., 1994). They enhance the functionality of chromatin regions activating transcription (Muchardt and Yanic, 1993) by altering the nucleosomal organization of these sequences (Imbalzano et al., 1994; Kwon et al., 1994). This chromatin modification, for instance, improves the recruitment of TFIIA and TBP (TATA binding protein) to the TATA box in the promoters of specific genes, a critical step in transcription activation (Wilson et al., 1996). The differential inclusion of proteins like BAFs (Brg1 Associated Factors) with varying DNA-binding domains into SWI/SNF-type complexes the same request: ensures their targeting to different chromatin domains (Wu et al., 2009). However, this recruitment does not occur in a sequence-specific manner but rather through the recognition of specific structures (Quinn et al., 1994). Certain subunits of SWI/SNF possess

domains allowing for the specific recognition of post-translational histone modifications, such as acetylation of lysines through bromodomains (Singh et al., 2007).

Other's role of SWI/SNF were demonstrated as on cycline E and A (figure 41). The interplay between the retinoblastoma protein (Rb), histone deacetylases (HDACs), the SWI/SNF complex, Cyclin D-Cdk4, and Cyclin E-Cdk2 forms a complex regulatory nexus crucial for orchestrating the cell cycle. Rb acts as a pivotal checkpoint by inhibiting cell cycle progression through its binding to E2F transcription factors, restraining their ability to activate genes required for cell cycle advancement. HDACs contribute to this restraint by promoting chromatin compaction and gene repression. However, the SWI/SNF complex counteracts HDAC-mediated repression by remodeling chromatin and enabling transcriptional activation. In this context, Cyclin D-Cdk4 complex plays a decisive role in G1 phase, phosphorylating Rb and releasing E2F for transcriptional activation, thus initiating cell cycle progression. As cells transition to S phase, Cyclin E-Cdk2 becomes prominent, further inactivating Rb and promoting E2F-mediated gene expression essential for DNA replication. This intricate interplay between Rb, HDACs, SWI/SNF, Cyclin D-Cdk4, and Cyclin E-Cdk2 underscores their collective influence on precise cell cycle control, ensuring accurate cellular replication and division.

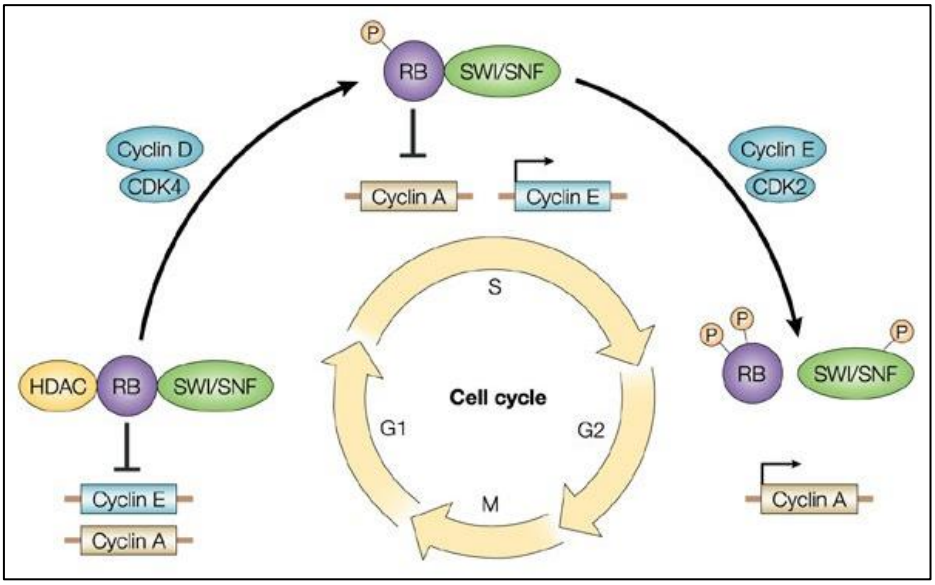

Figure 41: Role of SWI/SNF and cyclin (Roberts Charles W. M. et al 2004)

II.1.2. The ISWI Family

Similar to the SWI/SNF-type complexes, it is the ATPase activity-bearing subunit, ISWI (figure 42), that defines this family of complexes that disrupt chromatin structure in the presence of ATP (Elfring et al., 1994). Thus, in Drosophila, three complexes of this type have been identified: NURF (Tsukiyama and Wu, 1995), CHRAC (Varga-Weisz et al., 1997), and

ACF (Ito et al., 1997). In addition to its ATPase portion, ISWI also possesses a histone-binding domain (primarily to histone H4): the SANT domain (Swi3, Ada2, N-CoR, TFIIB), which also acts as an interaction platform for certain proteins (Boyer et al., 2004), and a SLIDE domain (SANT Like ISWI Domain) enabling interactions with nucleosomal DNA (Grune et al., 2003). Homologs of ISWI have been identified in all higher eukaryotes, suggesting an important role for this protein. In humans, two ATPase subunits, differing in their C-terminal and N-terminal ends, have been identified: SNF2-L and SNF2-H (Okabe et al., 1992; Aihara et al., 1998). These two proteins are not expressed in the same tissues, suggesting tissue-specific functions (Lange et al., 2011), and are not included in the same ISWI-type complexes. In addition to these catalytic cores, ISWI complexes comprise several alternative subunits that not only enable the differential recognition of specific chromatin domains but also fulfill multiple functions, such as transcription activation (Strohner et al., 2001), regulation of transcription elongation and termination (Morillon et al., 2003), as well as replication regulation (de la Serna and Imbalzano, 2002).

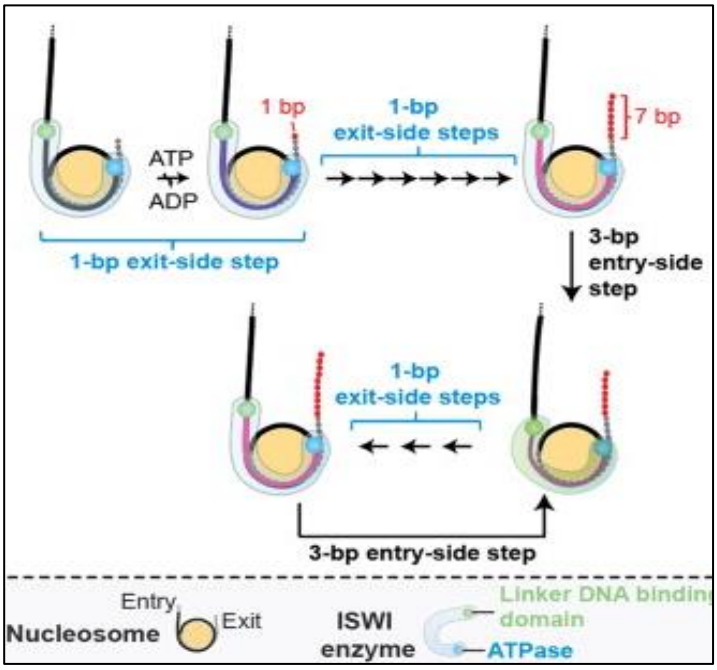

Figure 42: ISWI Remodelers Slide Nucleosomes (Deindl S et al., 2013)

II.1.3. The Mi2-NuRD

Just as the two preceding chromatin remodeling families exhibit a striking diversity in composition, the Mi2-NuRD family stands as a testament to this heterogeneous nature. The defining feature of this remodeling complex lies in the Mi-2/CHD (Chromodomain helicase

DNA binding protein) unit, which possesses intrinsic ATPase activity (Figure 43). In the realm of humans, this family bifurcates into two distinct isoforms: Mi-2α/CHD3 and Mi-2β/CHD4, as identified by Woodage et al. in 1997.

The distinctive architecture of Mi-2 subunits extends its grasp through chromodomains, molecular entities with an innate affinity for methylated lysine residues (Lange et al., 2011). Beyond this, the Mi-2 subunits boast the presence of a KRAB domain, known as krueppel-associated box, renowned for its role in transcriptional repression. This role hinges on the engagement of the KAP-1 subunit (Schultz et al., 2001). The intricate constitution of the Mi-2/NuRD complex also encompasses MBD-type subunits, which exhibit a remarkable penchant for binding to methylated DNA. In a synchronized symphony, this complex marries the concerted actions of HDAC1 and HDAC2, orchestrating the delicate yet pivotal act of histone deacetylation (Humphrey et al., 2001). The ensemble is further enriched by the presence of proteins hailing from the MTA family – MTA1, MTA2, or MTA3 – each lending their unique signatures to distinct transcriptional responses (Bowen et al., 2004).

Within this labyrinthine arrangement, the specific amalgamation of these diverse subunits within Mi2-NuRD complexes, echoing the patterns observed in prior complexes, engenders an intricate tapestry of functional specialization. This orchestration underscores the complex interplay between these subunits, which culminate in the nuanced modulation of chromatin architecture, gene expression dynamics, and ultimately, cellular responses.

The Mi2-NuRD family exemplifies the intricate choreography inherent in chromatin remodeling complexes. This intricate ballet of molecular players showcases their profound influence on the regulation of gene expression, highlighting the interwoven mechanisms that shape the epigenetic landscape and cellular behavior. Understanding this symphony of molecular interactions holds promise not only for unraveling the intricacies of cellular biology but also for paving the way toward innovative therapeutic strategies.

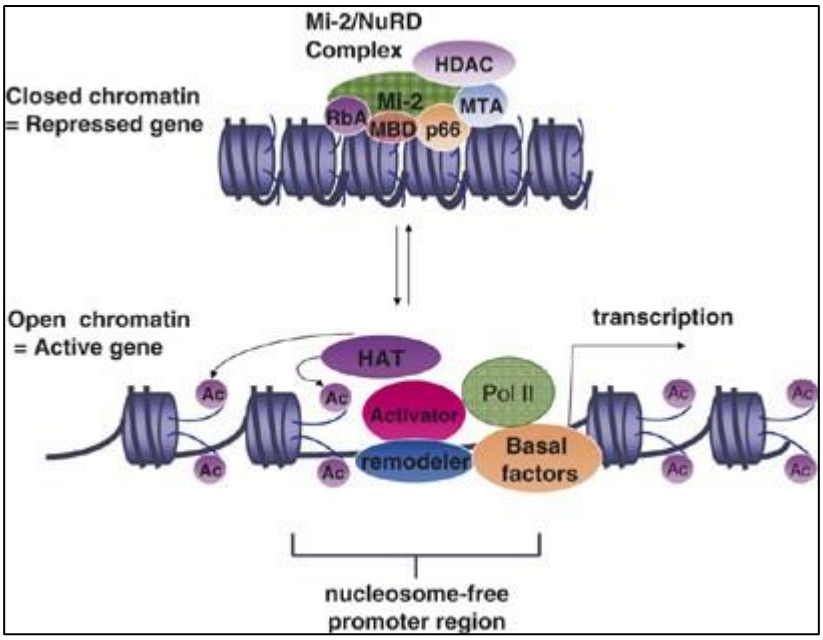

Figure 43: The human Mi-2/NuRD complex (Denslow S A et al., 2007)

II.1.4. INO80

The revelation of the Ino80 protein emerged through the lens of sequence homology, notably bearing resemblance to the ATPase ISWI of the NURF complex (Ebbert et al., 1998) (Figure 44). This protein entity is firmly nestled within the expansive SNF2/SWI2 protein family and lays claim to an exquisitely conserved ATPase domain (Tsukiyama et al., 1999), a feature shared by its counterparts in both Drosophila (dIno80) and humans (hIno80). Within the context of the yeast Saccharomyces cerevisiae, Ino80 serves as an integral component of a chromatin remodeling ensemble termed INO80.

The INO80 complex, in a symphony of protein interactions, assembles with a G-actin subunit, Arp4, Arp5, Arp8 proteins, as well as Rvb1 and Rvb2 (Figure 44). This intricate collaboration paints a vivid picture of the intricacies within chromatin remodeling assemblies. Notably, the INO80 complex's role is believed to extend predominantly to DNA repair processes. This remit involves a meticulous remodeling of chromatin at genes that become activated in response to DNA damage (Shen et al., 2000).

The discovery of Ino80 and its integration into the INO80 complex underscores the evolutionary conservation of chromatin remodeling strategies across species. The homage to the highly conserved ATPase domain reflects its indispensable role in orchestrating the dynamic conformational changes required for chromatin remodeling. The assemblage of diverse protein

constituents, including G-actin and various ARP proteins, echoes the multi-dimensional choreography within these complexes, shaping the intricate chromatin landscape.

The Ino80 protein and its participation in the INO80 complex offer a glimpse into the molecular mechanics that underpin chromatin remodeling. This molecular interplay not only molds the chromatin architecture but also plays an indispensable role in modulating gene expression and, notably, DNA repair processes. Understanding these intricate mechanisms enriches our comprehension of cellular processes and lays the groundwork for potential therapeutic interventions.

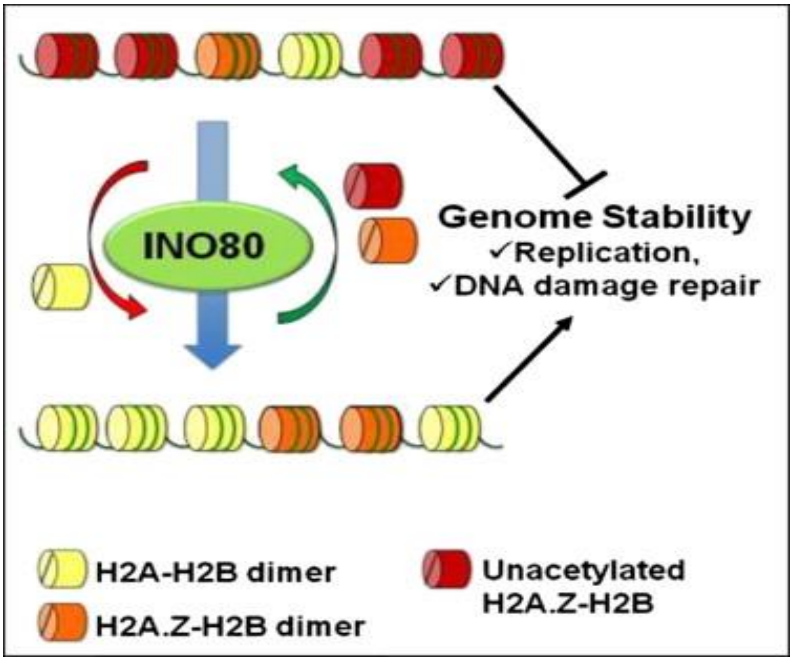

Figure 44: Regulation of H2A.Z by the INO80 Chromatin-Remodeling (Papamichos-Chronakis M et al., 2011)

II.1.4. SWR1

Much akin to the architectural role played by the Ino80 complex (Figure 45), Swr1 stands as a prominent member of the SNF2/SWI2 protein family. This protein entity orchestrates a sophisticated assembly with approximately a dozen other proteins, including constituents such as G-actin, Arp4, Rvb1, and Rvb2, which intriguingly are shared components amongst various chromatin remodeling complexes. In congruence with this cooperative assembly, the Swr1 complex also integrates histone molecules, most notably histone H2A.Z, which assumes a pivotal role in establishing both physical and functional liaisons with Swr1.

The primary thrust of the SWR1 complex's function revolves around an intricate task: the energy-dependent replacement of canonical H2A histones with their variant counterpart, H2A.Z. This intricate molecular exchange is orchestrated in an ATP-dependent manner, with Swr1 serving as a central orchestrator of this process (Mizuguchi et al., 2004). This orchestrated replacement has been attributed to contributing significantly to chromatin structure and, by extension, gene expression regulation and the epigenetic landscape.

The orchestrated collaboration of Swr1 with its compatriot proteins underscores the complexity of chromatin remodeling. The convergence of diverse protein subunits within the SWR1 complex, including the shared components with other remodeling entities, reflects the intricate interplay within the cellular machinery that modulates chromatin architecture. Notably, the integration of histone H2A.Z into this intricate network highlights the nuanced strategies employed by cells to fine-tune their chromatin states for various regulatory outcomes.

In essence, the Swr1 complex's orchestrated interactions and its role in the ATP-dependent replacement of histones portray a remarkable example of molecular choreography. This intricate dance within chromatin remodeling not only reshapes the chromatin landscape but also intricately modulates gene expression patterns and, consequently, cellular responses. Understanding these dynamic processes enriches our comprehension of the molecular symphony that governs biological complexity and potentially opens avenues for innovative therapeutic interventions.

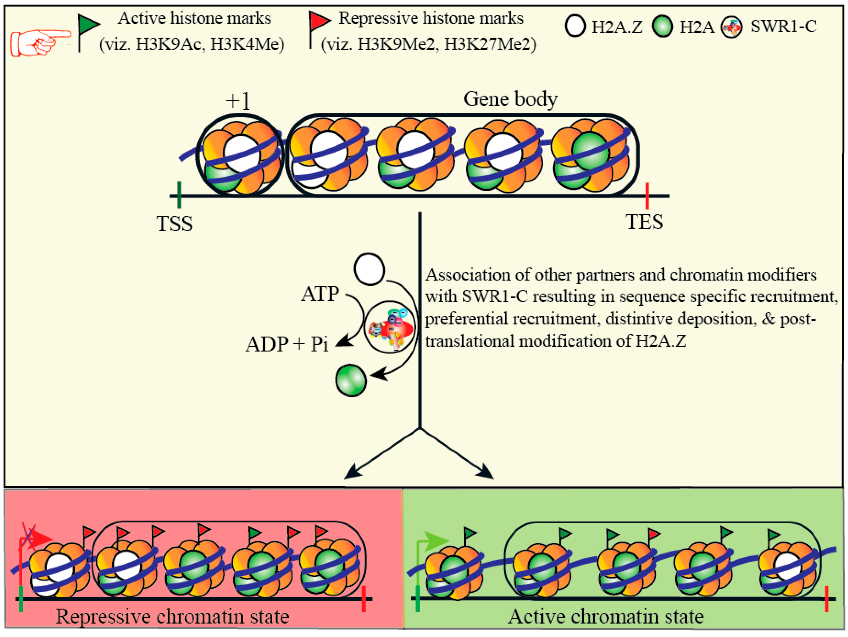

Figure 45: SWR1 Chromatin Remodeling Complex (Aslam M et al., 2019)

II.2. Histone Modification Enzymes and Histone Variants

Post-translational modifications present on the N-terminal tails of histones (figure 46), such as acetylation or methylation of specific residues, are involved in chromatin accessibility to transcription machinery proteins. The inclusion of certain histone variants, like H2A.Z, also creates chromatin regions containing unstable nucleosomes, enabling recruitment of transcription-associated factors.

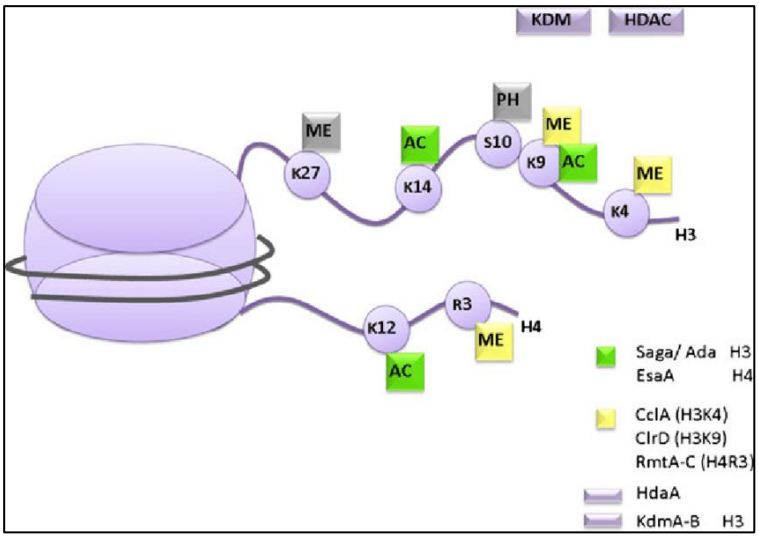

Figure 46: post-translational modifications of N-terminal tails in histones H3 and H4 (uploaded by Agnieszka Gacek- Matthews).

III. Transcription Activation of RNA Pol II-Dependent Genes

III.1. Promoters and Regulatory Sequences

Initially, accurately defining the regulatory sequences for transcription of class II genes is crucial based on current knowledge. These genes, which encompass exonic sequences corresponding to coding regions and non-coding introns that are spliced out, are initially controlled by a basal promoter, often restricted to sequences closest to the transcription start site (TSS). The simplest of these promoters might contain a TATA box sequence, rich in A/T and with a consensus of TATAA (Sandelin et al., 2007), located around -25 to -30 bp upstream of the TSS. Additionally, an initiator element, rich in pyrimidines and found at the TSS, known as Inr, with a consensus sequence YYANWYY (Y: C or T; N: A/T/C or G; W: A or T), where A corresponds to +1 of the TSS, can also be present. From this basal promoter, a proximal promoter can be distinguished, encompassing DNA sequences positioned further/distal from

the TSS (between -50 and -200 bp). Examples of such sequences include the CAAT box (around -70) and the GC box (between -80 and -160 bp) (figure 47).

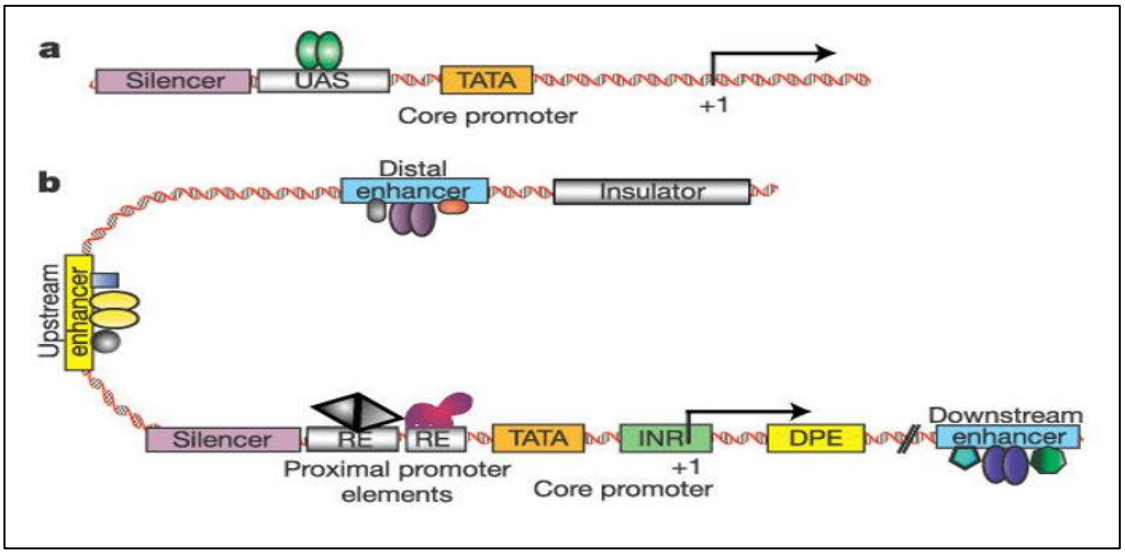

Figure 47: Comparison of a simple eukaryotic promoter and an extensively diversified metazoan regulatory module (scitable by nature education)

This promoter can also include specific binding sequences for transcription regulatory factors. While the distinction between these two types of promoters can be made based on their relative distance from the TSS, this distinction is particularly relevant to the initiation of transcription itself. Basal transcription would mainly occur through mechanisms initiated at the basal promoter, where the binding of TBP and TAFs (TBP associated factors) enables the recruitment of general transcription factors (GTFs) – seven in mammals (Conaway and Conaway, 1993) – and RNA Pol II, culminating in the formation of a pre-initiation complex (PIC). The presence of regulatory elements at the proximal promoter, on the other hand, would modulate this basal transcription. Further transcriptional regulatory sequences can be defined as enhancers and silencers, responsible for recruiting proteins that either activate or inhibit gene transcription located at a distance from these regions. These elements can be found in intergenic regions or within introns/exons of the genes they regulate, or even on other chromosomes. It's worth noting that defining these elements based on distance criteria in terms of base pairs can sometimes blur the semantic distinction between a proximal promoter and enhancers/silencers when the latter are located within a 5 kb window around the TSS. Other regulatory regions, called insulators, would isolate specific sequences from surrounding transcriptional activity.

III.2. Assembly of the Pre-initiation Complex (PIC) for Transcription

Initiation Despite recent in vivo advancements, a full understanding of protein-protein and protein-DNA interactions involved in transcription initiation and its mechanisms has not been achieved. While several cases and models of PIC assembly have been described (as detailed in the following paragraphs), regardless of the model, transcription initiation itself requires the presence of nucleotides, separation of the DNA strands at the TSS, and direct or indirect phosphorylation of the RNA Pol II C-terminal domain (CTD) on serine 5 (Drapkin and Reinberg, 1994) (figure 48).

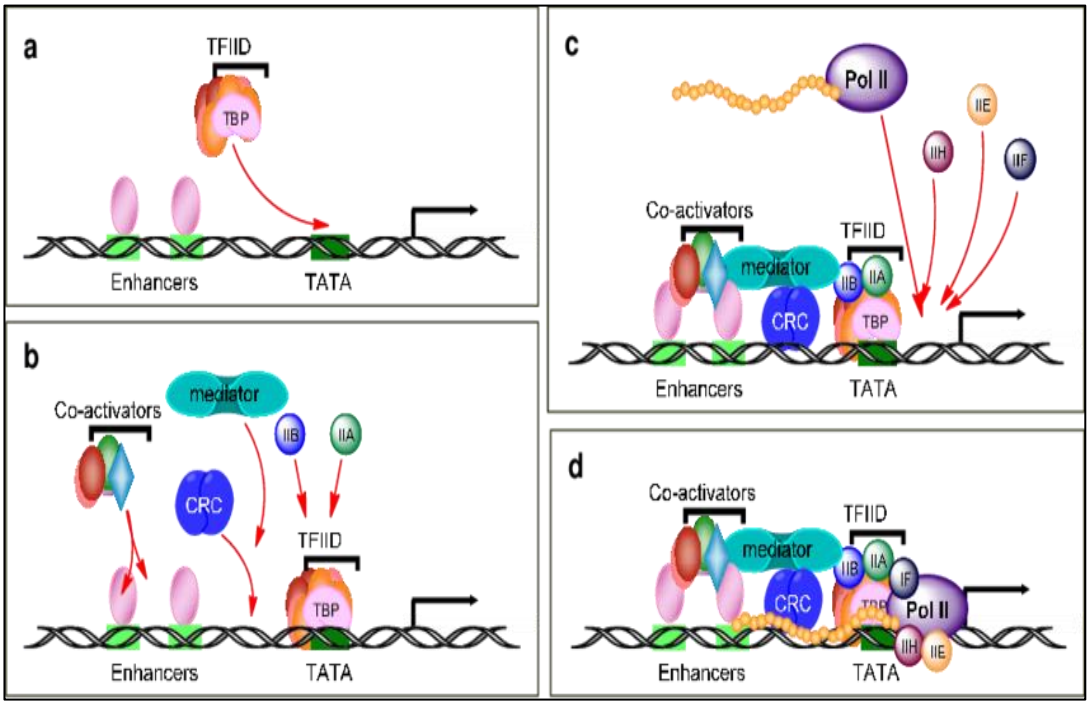

Figure 48: diagram of the formation of the pre-initiation complex. (a) Recruitment of transcription factor IID (TFIID). (b) Mobilization of mediator, chromatin remodeling complex (CRC), and other co-activators. (c) Recruitment of Pol II and the transcription factors IIE, IIF, and IIH. (d) The completed pre-initiation complexes. (Uploaded by Christine M Stellrecht)

III.2.1. Case of TATA+

Promoters (figure 49) have two models (figure 50) for recruiting the various factors comprising the PIC are prominent: a sequential ("multistep") model and a holoenzyme-type model.

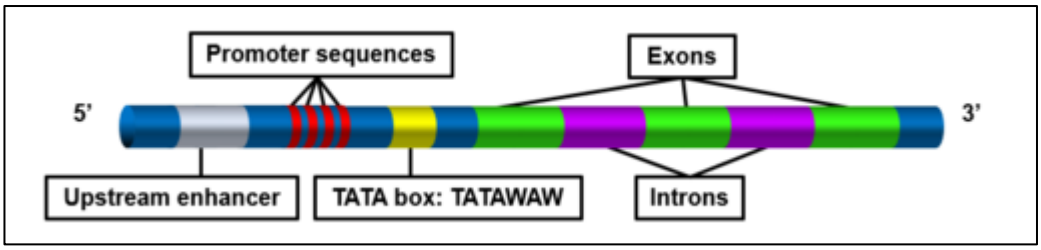

Figure 49: TATA Box localization

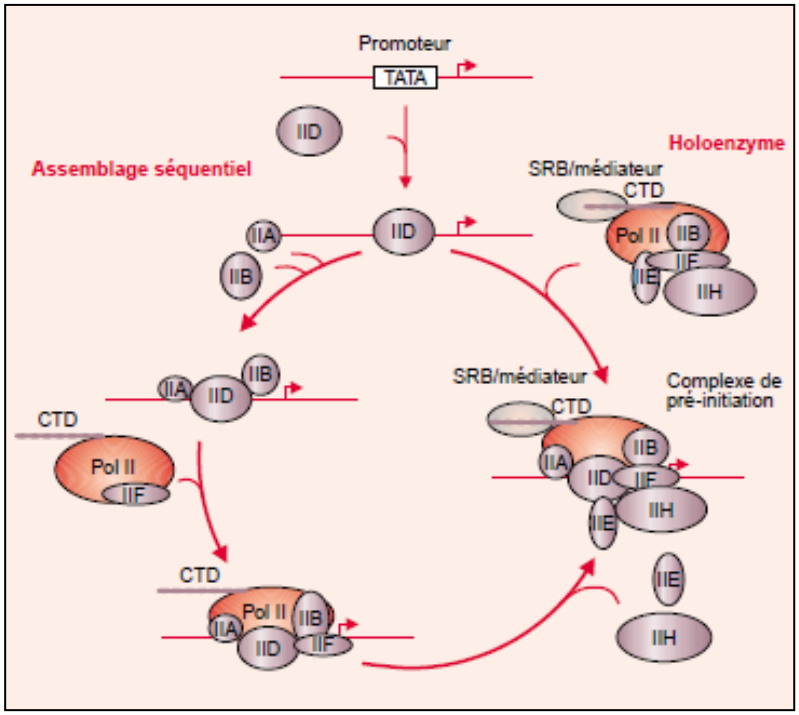

Figure 50: description of two models

Sequential model: RNA Pol II alone is insufficient to initiate transcription and necessitates the formation of the PIC on the promoter (Burley and Roeder, 1996). In this model, the sequential assembly of GTFs would drive this process (Maldonado and Reinberg, 1995). The first step of initiation involves the recruitment of TBP to the TATA box (Nikolov and Burley, 1991). TBP is a universal initiator factor as it is involved in the transcription of most RNA Pol II-dependent genes. The TBP-TATA interaction is stabilized by additional GTFs, including TFIIB, which aids in positioning the RNA Pol II enzyme accurately on the promoter.

However, the exact order and mechanism of GTF assembly and RNA Pol II recruitment remain areas of active research and may vary depending on specific gene contexts and cellular conditions.

The first step of initiation involves the recruitment of TBP to the TATA box, a universal initiator factor involved in transcription initiation regardless of the RNA Pol II (Hernandez, 1993) (Nikolov and Burley, 1991). The mobilization of TAFs by TBP forms the multi-protein complex TFIID (Cler et al., 2009), capable of engaging both physical and functional interactions with GTFs. Among these, the first to be recruited in the assembly of the PIC is TFIIB, which ensures the proper targeting of RNA Pol II to the promoter. In yeast systems, TFIIB depletion results in a misplacement of RNA Pol II on the TSS (Burley and Roeder, 1996). The TFIIB-TFIID complex on the promoter is subsequently recognized by a complex comprising RNA Pol II and TFIIF, joined by TFIIE, TFIIH, and TFIIJ. Additionally, TFIIA joins this complex, with a triple role: (1) stabilizing the DNA-TFIID binding, (2) enhancing transcription activation through activators like Sp1, VP16, NTF1, and Zta (Ozer et al., 1994; Yokomori et al., 1994), and (3) preventing the action of transcriptional inhibitors targeting TFIIB, such as NC1 and NC2 (Auble et al., 1994). Transcription initiation occurs when the CDK7 subunit of TFIIH phosphorylates the RNA Pol II CTD on serines 2 and 5.

Holoenzyme model: Initially identified in yeast, this model highlights the presence of a pre-existing complex in cells, formed by RNA Pol II, TFIIB, TFIIH, and TFIIF, as well as unidentified polypeptides (Koleske and Young, 1994). This complex would be directly recruited to the promoter after TBP/TFIID binding to the TATA box.

III.2.2. Case of TATA-

Promoters with a TATA box are a minority in mammalian genomes—only 10 to 20% of them have a functional TATA box (Gershenzon and Ioshikhes, 2005). In these cases, the presence of an Inr is sufficient to direct transcription (Weis and Reinberg, 1997; Smales et al., 1998). Residues -1 and +1 within these Inr sequences show significant conservation among orthologous gene sequences, featuring a pyrimidine/purine (py/pu) consensus, mainly consisting of dinucleotides CG, TG, and CA (Carninci et al., 2006). This py/pu consensus is directly recognized by TFIID, facilitating the recruitment of other GTFs and RNA Pol II to the TSS. Furthermore, for these TATA-less promoters, studies have shown that TFIID can recognize the promoter through its TAFs. Some TAFs are mobilized on chromatin due to the presence of other specific promoter sequences (DPE...).

Moreover, certain TAFs possess specific recognition domains for histone post-translational modifications such as H3K4me3 and H3K9ac, typically associated with active promoters. For instance, this is the case with the bromodomain of TAF1 and the homeodomain

of TAF3, as well as the WD40 repeat domain of TAF5. These TAFs are likely to enable indirect recruitment and/or stabilization of the TFIID complex on these TATA-less promoters.

III.2.3. Initiation via the SAGA

Complex Other studies have highlighted the role of the SAGA complex (figure 51), which has the capacity to replace TFIID at certain promoters to facilitate PIC formation. It is, for example, involved in the activation of 10% of genes in yeast, primarily related to responses to environmental stresses (Baker and Grant, 2007; Rodriguez-Navarro, 2009; Koutelou et al., 2010). The SAGA complex comprises 21 proteins conserved from yeast to humans (Koutelou et al., 2010) and is organized into four subcomplexes, each with a well-defined function: the DUB module, capable of removing ubiquitin from lysine 123 of histone H2B (Daniel et al., 2004) via Ubp8, allowing the recruitment of Ctk1, which phosphorylates the RNA Pol II CTD (Wyce et al., 2007); the HAT module, responsible for acetylating H3K9, H3K14, H3K18, and H3K24 (Daniel et al., 2005) through Gcn5; and finally, the SPT and TAF modules, involved in PIC recruitment (Samara and Wolberger, 2011).

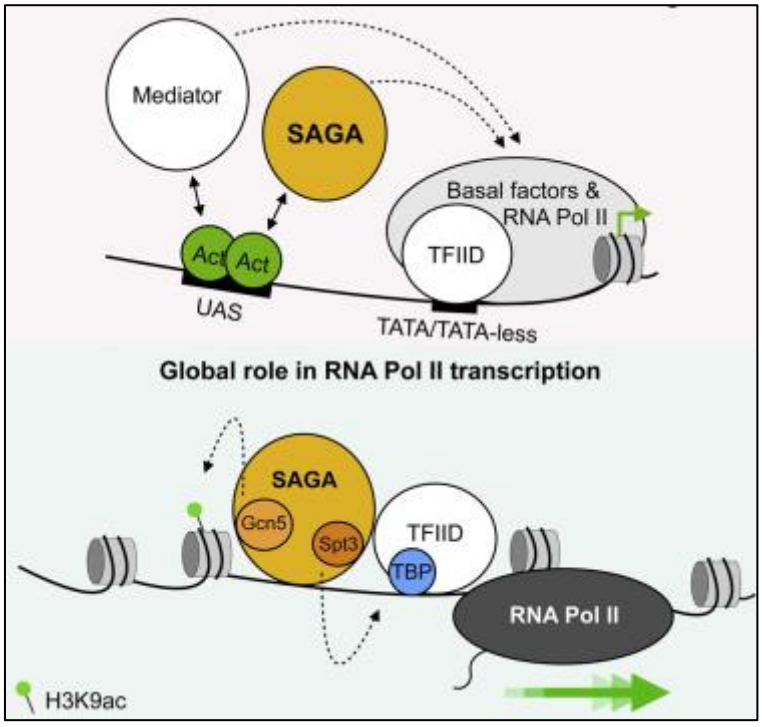

Figure 51: SAGA Cofactor for RNA Polymerase II Transcription (Baptista PT et al., 2017)

SAGA can interact with chromatin through a protein called Sgf73, which is part of the DUB module (Bonnet et al., 2010). This interaction, however, depends on prior methylation of H3K4, recognized by the chromodomain of a SAGA protein (Lee et al., 2011). This interaction could

also play a crucial role in regulating the HAT function of Gcn5. SAGA is also believed to be involved in transcription elongation (Govind et al., 2007) as well as the export of newly synthesized mRNAs through the protein Sus1, also associated with nuclear pores (Pascual-Garcia et al., 2008) (figure 51).

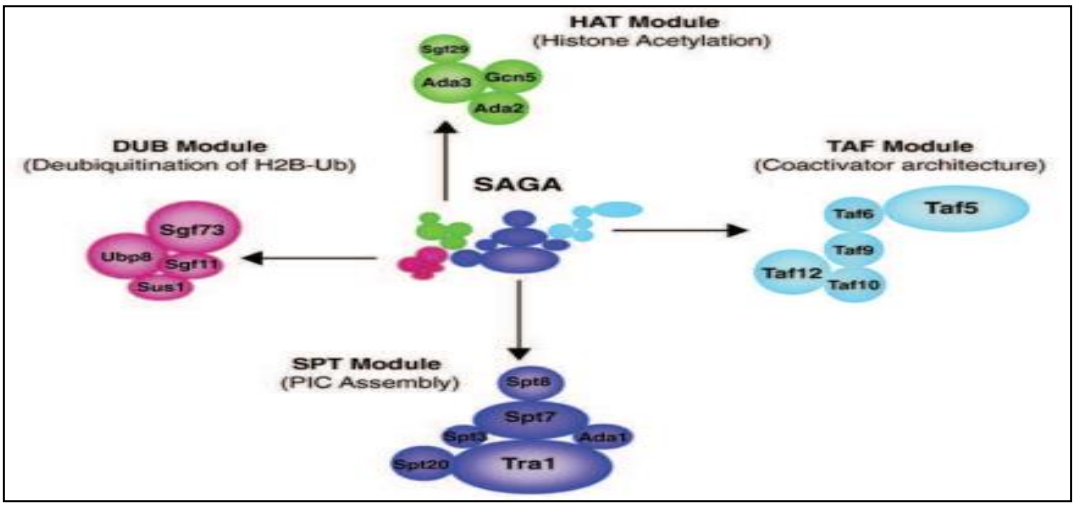

Figure 51: four module of SAGA complex

III.3. Modulation of Initiation by Proximal Promoters

III.3.1. Differential Assemblies

The differential assembly of the PIC based on the promoter is an important regulatory parameter that could impact the structural dynamics of the complex. The complex can adopt an open or closed conformation of its central cavity, with their respective roles in the function of the PIC not yet fully understood (Cler et al., 2009) (figure 52). This differential assembly can be partly linked to the regulatory elements carried by proximal promoters, with certain TAFs being preferentially involved in mediating the regulatory activity of specific transcription factors. For example, the action of factor NT1 requires TBP, TAFII250, and TAFII150, whereas Sp1 requires these three proteins plus TAFII110 (Chen et al., 1994). Furthermore, in the case of TATA-less promoters, Sp1 can also interact with TAF4 to recruit TFIID (Gill et al., 1994).

III.3.1. The Mediator Complex

During transcriptional regulation events mediated by the recruitment of transcription factors (TFs) to the proximal promoter or distant enhancer elements, the information provided by these proteins must be transmitted to the GTFs present on the basal promoter to modify its function. This is one of the roles of the multiprotein complex Mediator, initially characterized as an alternative holoenzyme complex in yeast, including RNA Pol II and proteins SRB, Gal II, Sug 1, and TFIIF (Kim et al., 1994). Subsequent work has better characterized this complex,

composed of 21 subunits, divided into three sub-modules (Davis et al., 2002): the head and the body, involved in interactions with RNA Pol II, and the tail, which serves as a platform for interactions with TFs. The establishment of this bridge can be facilitated by local modulation of DNA conformation due to the binding of TBP at the basal promoter. TBP binds in the minor groove of the chromatin, causing significant distortion to coordinate and stabilize the PIC formation, as well as spatially bringing the PIC closer to the TFs bound at enhancers (Burley and Roeder, 1996).

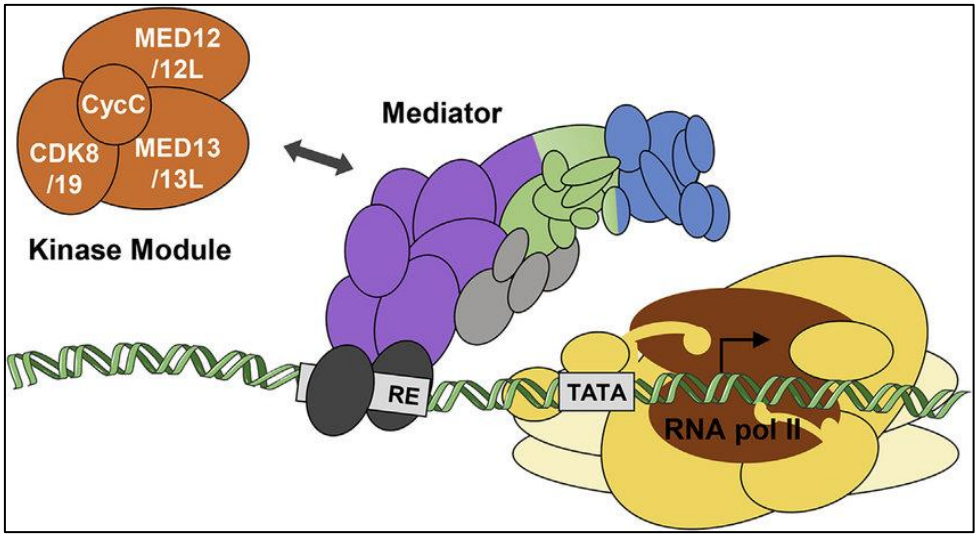

Figure 52:

llustration of the Mediator Complex and the RNA Pol II Machinery at the Promoter (uploaded by Eduardo Calpena)

It should be noted that while Mediator was initially considered only as a transcriptional co-activator due to its interactions with RNA Pol II and its ability to promote PIC formation and maintenance during different transcription rounds (Reeves and Hahn, 2008), other studies have indicated that it can also be involved in gene inhibition. In the yeast model, Mediator can be co-recruited with Cdk8 (Liu et al., 2001; Samuelsen et al., 2003), the loss of which results in the derepression of a set of genes. However, the presence of Cdk8 and the inhibition of gene transcription do not seem to be directly related, and the exact mechanisms underlying Mediator's dual roles are still being investigated.

III.4.Transcription Elongation and Termination

III.4.1.mRNA Synthesis

The process of transcription elongation is a highly dynamic phenomenon subject to numerous regulations. It begins with a "clearance" step during which the complex containing RNA Pol II leaves the promoter (figure 53). This phenomenon is well-defined for TATA-containing genes, which have been the most studied. The fusion (or unwinding) of the two strands required for the initiation of mRNA synthesis does not occur at the TSS but upstream, around nt -9. This leads to the formation of a "bubble" between this fixed position and the nucleotide at position 2.

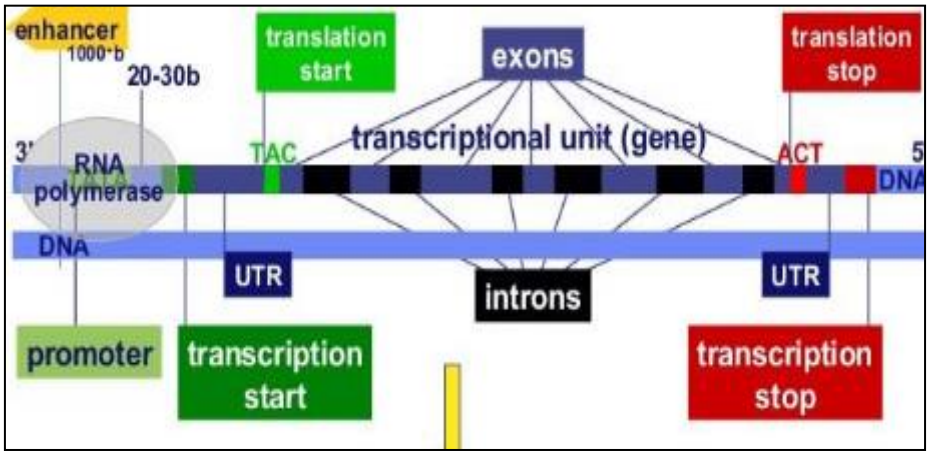

Figure 53: Gene organization (upoalde by Akila Wijerathna Yapa)

The formation and advancement of this bubble in the 3' direction are central to the "clearance" process. The synthesis of the first nucleotides of the mRNA during this elongation phase remains critical until the mRNA reaches a certain size. The initial DNA/RNA hybrid formed is too small to be stable and can be released from the transcription complex, leading to an abortive cycle. It's worth noting that RNA Pol II has a weak tendency to enter such abortive cycles due to the presence of TFIIH and its XPB helicase subunit at this stage, which limits DNA reannealing (Dvir et al., 1996; Dvir et al., 1997; Moreland et al., 1999; Lin et al., 2005). Transcription is considered productive when an 8-mer RNA has been synthesized. At this point, a collapse of the bubble occurs in the 5' direction, returning it to its initial size, which involves a fusion of the two strands over approximately 10 nt. This collapse marks the end of the clearance phenomenon (Luse, 2012) and the requirement for the presence of TFIIH for RNA Pol II functions (Pal et al., 2005).

Following "clearance," transcription elongation can be regulated while the polymerase is actively synthesizing the RNA, especially when it reaches 30 to 50 nts downstream from the

TSS. At this point, depending on the studied model genes, it has been observed that RNA Pol II can backtrack or stop (Pal et al., 2001; Újvári et al., 2002). Certain protein complexes can influence RNA Pol II pausing. DSIF and NELF, for instance, have inhibitory roles in elongation (Conaway and Conaway, 2012). The exact role of DSIF is intricate to define, as in some contexts, particularly in the presence of P-TEFb, it seems to decrease the number of RNA Pol II pauses (Conaway and Conaway, 2012; Hartzog and Fu, 2012). On the other hand, factors like TFIIS and elongin are involved in RNA Pol II processivity (Fish and Kane, 2002; Shandilya and Roberts, 2012). After such pausing, if the transcription machinery resumes, it has acquired all the characteristics of a mature elongation complex (Luse, 2012).

Numerous other transcription factors are involved in elongation regulation, often specific to cell type and gene. While detailing this diverse array of phenomena is not essential for understanding the subject of this thesis, it's important to highlight the involvement of histone chaperones in these regulations, which facilitate nucleosome eviction during elongation. Additionally, the CTD of RNA Pol II plays a crucial role acting as a recruitment platform for various protein factors associated with the regulation of initiation, elongation, termination, and mRNA maturation. It allows the modulation of the enzyme responsible for adding the 5' cap to the mRNA, a process that occurs in parallel with elongation (Hahn, 2004).

III.4.2. Termination

In eukaryotes, the majority of protein-coding genes possess a conserved poly(A) signal (figure 54): 5'-AATAAA-3', followed by a G/T-rich sequence. Transcription of the poly(A) signal leads to a decrease in RNA Pol II processivity, causing it to pause, which results in cleavage of the newly synthesized mRNA. In humans, mRNA cleavage at the polyadenylation site is dependent on an intact CTD (Lee and Young, 2000), required for the binding of the CPSF (cleavage polyadenylation specificity factor) and CstF (cleavage stimulation factor) factors. Once transcription is completed, dephosphorylation of serines 2 and 5 of the RNA Pol II CTD leads to its "release" from the gene.

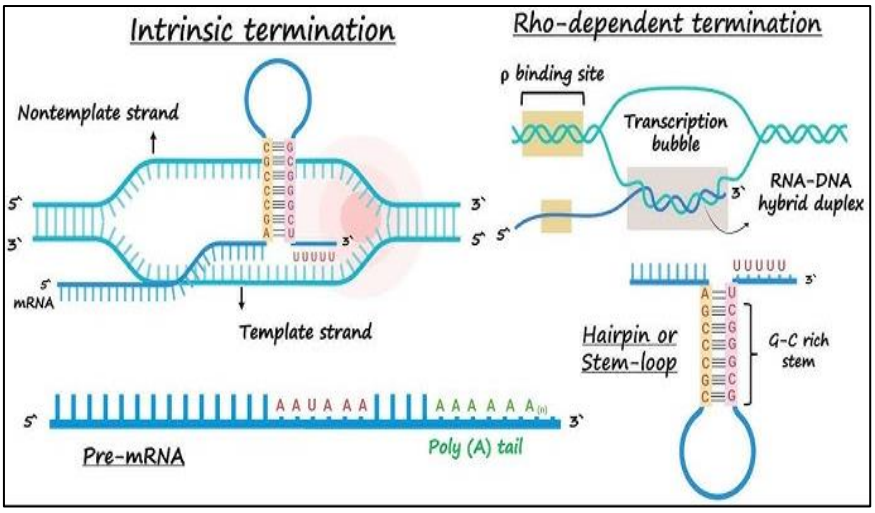

Figure 54: Termination of Transcription

This process is catalyzed by several enzymes, with Fcp1 acting on serine 2 (Archambault et al., 1998) and SCP1 acting on serine 5 (Meinhart et al., 2005). Recent findings from various laboratories have proposed a model of RNA Pol II recycling after it has transcribed a gene. This recycling involves the formation or preexistence of chromatin loops between the terminal and promoter regions of active genes. TFIIB, present at the promoter as a GTF, is capable of interacting with termination factors CstF and CPSF. This loop would facilitate rapid reinitiation of transcription on activated genes (Calvo and Manley, 2003; Singh and Hampsey, 2007).

III.5. Transcription Dynamics

Since the early studies on transcription, our understanding has evolved. Contrary to initial beliefs, the recruitment of factors involved in transcription is highly dynamic, occurring at two levels: proteins involved in transcription and its regulation (TFs and GTFs) exhibit rapid intranuclear mobility, and the recruitment of these proteins to their promoters is also dynamic, and in some cases, even cyclic. The literature on the first of these processes is extensive, encompassing various cell and protein models and different spatial-temporal resolutions. To illustrate this point, I have chosen a few examples related to the two main underlying questions in this issue.

III.5.1. Protein Dynamics

Transcription of a gene may require the precise recruitment of regulatory proteins and components of the transcription machinery (Metivier et al., 2003; Sims et al., 2004; Rochette-Egly, 2005; Gorski et al., 2008)(figure 55). However, considering that specific binding sites for TFs are rare within the genome compared to the number of non-specific binding sites, the

question arises of how a TF can quickly find and bind to a specific site. Initial studies on the genome suggested that both the genome and the proteins within it were relatively static and that interactions between TFs and their binding sites occurred randomly through simple diffusion (Gorski et al., 2006). However, this hypothesis wasn't entirely consistent with observations of intranuclear protein mobility using techniques like FRAP (Fluorescence Recovery After Photobleaching). An alternative model, known as facilitated diffusion, was proposed (Hager et al., 2009; Normanno et al., 2012). This model describes a dynamic behavior of TFs in the nucleus with two key features.

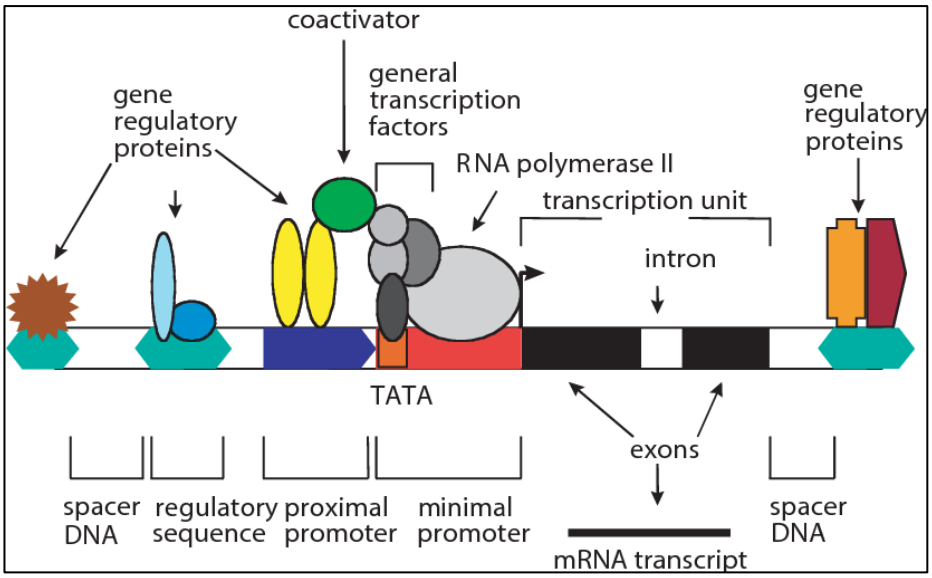

Figure 55: Protein dynamics for transcription (J. Villard et al., 2004)

The first feature involves free diffusion in space without requiring energy, during which TFs do not interact with DNA. This allows TFs to rapidly explore the entire nucleus, at speeds ranging from 0.5 to 5 $\mu m^2/s$, depending on the sizes of the proteins and their DNA-binding capabilities (Gorski et al., 2006). The second feature is non-specific binding of TFs to DNA, followed by exploration of the surrounding genome region over approximately fifty base pairs to locate a target sequence ("sliding" and "hopping"; Hager et al., 2009). It is now established that during their search for target sequences, TFs exhibit high dynamism.

III.5.2. Recruitment to Promoters

Our understanding of TFs' presence, such as transcription factors (TFs) or RNA Pol II, bound to their target sequences largely comes from experiments like ChIP (Chromatin Immunoprecipitation). While ChIP has provided substantial data, it doesn't offer real-time insights into processes like transcription. Over the last fifteen years, new techniques based on microscopy have been developed, allowing the analysis of protein dynamics in living cells.

Prior in vitro work or studies on fixed cells suggested that once the DNA/TF complex was formed, it was highly stable, with lifetimes on the order of several hours for certain factors like the glucocorticoid receptor (GR) (Perlmann et al., 1990). However, FRAP (Fluorescence Recovery After Photobleaching) studies conducted a decade later on live cells revealed that this binding is, in fact, very dynamic (McNally et al., 2000). Similar dynamics have been observed for other TFs, such as the progesterone receptor (Rayasam et al., 2005) and estrogen receptors (Sharp et al., 2006).

One of the most well-documented examples of gene transcription dynamics is regulated by estrogen (E2). The traditional view of E2-stimulated transcription was that the estrogen receptor (ER) binds to its response element at the promoter of its target genes and remains associated with that promoter as long as the estrogen signal is present (Hahn, 1998; Berk, 1999). However, initial studies by two research groups (Shang et al., 2000; Métivier et al., 2003) demonstrated that transcription co-activators mediated by ER, such as SRC-1, TIF2, GRIP1, AIB1, CBP, p300, and pCAF, along with ER itself, are not static throughout transcription. Instead, these ChIP-based studies revealed that ER is recruited only 15 minutes after the E2 signal, this recruitment peaks at 30-45 minutes, and then decreases or becomes undetectable at around 75 minutes. Furthermore, this cycle repeats with similar time intervals. These findings highlighted a cyclic and transient recruitment of ER co-activators during gene activation, an oscillatory process also described for other TFs such as androgen receptors (Kang et al., 2002), vitamin D receptors (Vaisanen et al., 2005), thyroid hormone receptors (Liu et al., 2006), and retinoic acid receptors (Bruck et al., 2009). It's important to note that these studies, unlike single-cell imaging techniques, characterize events at the level of cell populations and do not determine the residence times of the followed proteins. The observed oscillatory behaviors are likely a result of rapid hit-and-run binding events of proteins to DNA and the detection of these binding events occurring in a variable number of cells (Lemaire et al., 2006; Hager et al., 2009; Stavreva et al., 2012).

VI. Transcription at enhancers

Enhancers, located on DNA, are elements capable of activating transcription from a distance by interacting with the promoter (Geyer et al., 1990; Sanyal et al., 2012) (figure 56). Among other functions, they facilitate the recruitment of specific cellular transcription factors (TFs), RNA Polymerase II (RNA-PII), and factors involved in transcription initiation regulation, such as Mediator. The connection between an enhancer and a specific promoter occurs through chromatin looping (Blackwood and Kadonaga, 1998; Bulger and Groudine,

1999; de Laat et al., 2008). This operating model has been confirmed through 3C experiments (Dekker et al., 2002; de Wit and de Laat, 2012), exemplified in genes within the β-globin locus where the LCR containing multiple enhancers coordinates contact with genes in that locus over time (Tolhuis et al., 2002). In general, the formation of these loops between enhancers and regulated gene promoters requires different proteins depending on the cell type and genes (Vakoc et al., 2005; Jing et al., 2008; Kim et al., 2009).

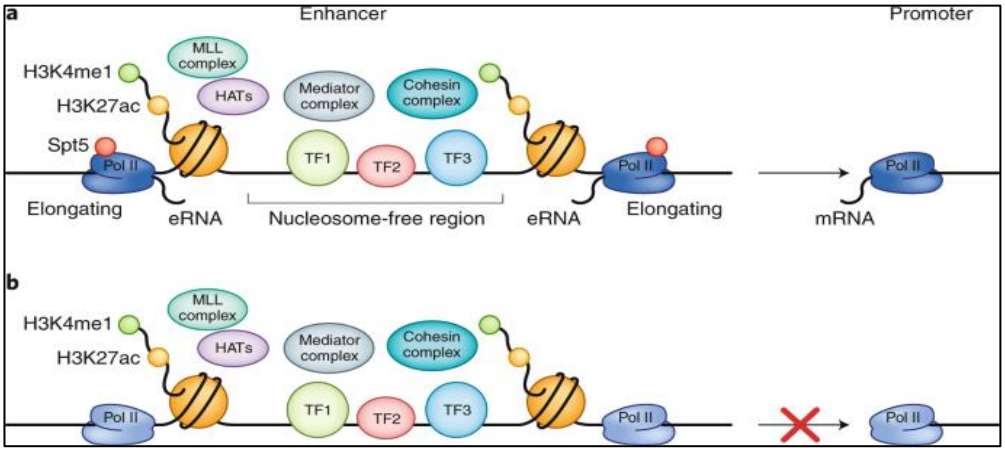

Figure 56 : Enhancer–promoter interactions and transcription (Higgs DR et al., 2020)

Enhancers are found in regions with low nucleosome density and are enriched with histone variants like H2A.Z and H3.3, whose incorporation destabilizes nucleosome-DNA interactions (Jin and Felsenfeld, 2007; Mito et al., 2007; Jin et al., 2009), as well as certain histone marks like H3K4me1 (Bernstein et al., 2002; Heintzman et al., 2007; Koch et al., 2007), H3K27ac, or H3K27me3, depending on their active or inactive state, respectively (Creyghton et al., 2010). H3K9me1/me2 and me3 modifications may also be present. Enhancers are also characterized by the presence of proteins such as p300 or CBP, which, through their HAT activities, facilitate the recruitment of a portion of the transcription machinery (Merika et al., 1998).

The advent of RNA-seq and ChIP-seq techniques has provided clear evidence of transcription within intergenic regions, resulting in regulatory RNAs (Birney et al., 2007; Prasanth and Spector, 2007). These transcripts are generally low in abundance, polyadenylated, and non-spliced (De Santa et al., 2010), and have been identified at cis-regulatory elements like the β-globin locus control region (LCR), where they contribute to maintaining an open chromatin state (Ashe et al., 1997; Gribnau et al., 2000). The development of the GRO-seq (global nuclear run-on sequencing) technique (Core et al., 2008) has expanded these observations of extragenic transcription to the level of enhancers. Specifically, this technique revealed rapid RNA synthesis (within 10 minutes of treatment) at enhancers recruiting the estrogen receptor (ER)

(Hah et al., 2011). The production of these enhancer RNAs (eRNAs) (Kim et al., 2010) introduces a new level of transcriptional regulation, as these eRNAs can exert positive or negative effects on the stability of local chromatin organization at the enhancer, the stability of the mRNA produced at the other end of the loops connecting enhancers to regulated gene promoters, and more.

IV.1. Repression by Polycomb

Proteins Just as gene activation is a highly intricate and finely regulated process, gene repression follows a similarly complex pattern. Polycomb group (PcG) proteins have been identified as repressive factors for homeotic genes in Drosophila. Indeed, in both Drosophila and vertebrates, the protein complexes formed by PcG play a regulatory role in numerous targets, primarily genes involved in development and cellular differentiation. In Drosophila, there exist several PcG complexes: PRC1, PRC2, PhoRC, dRAF, and PR-DNB (Beisel and Paro, 2011). Among these, only PRC1 and PRC2 are conserved in vertebrates, but their composition varies based on cell type and developmental stage. Both complexes are recruited to sequences known as PcG responsive elements (PREs), which lack identified consensus sequences. However, in vertebrates, these sequences are strongly correlated with a high CpG density (Ku et al., 2008; Mohn et al., 2008). The repressive activity of these complexes occurs through post-translational modifications of histones associated with inactive chromatin (Bantignies and Cavalli, 2011).

For instance, the PRC2 complex, through its subunit E(z), deposits characteristic marks such as H3K27me3, which serves as a recruitment platform for PRC1. PRC1, in turn, is responsible for ubiquitin mark deposition on H2AK119 through its subunits RING1B and BMI1 (Cao et al., 2005). The presence of this post-translational modification is correlated with the inhibition of RNA-Pol II transcription elongation (Stock et al., 2007; Zhou et al., 2008). Lastly, the high CpG density in PREs is associated with cooperation between the PcG systems and cytosine methylation, which would further establish/maintain stable repression of certain genes (Ku et al., 2008; Mohn et al., 2008)(figure 57).

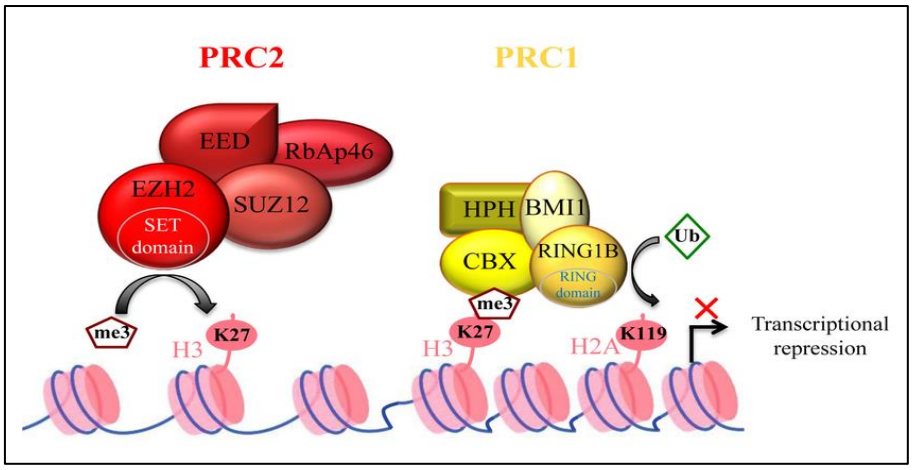

Figure 57: Polycomb complex-mediated transcription repression (uploaded by Jérôme Moreaux).

IV.2. Repression by p53

The P53 is a notably crucial protein with a fundamental role in cellular integrity maintenance: over 50% of human cancers exhibit a mutation or deletion in the p53 gene (Beckerman and Prives, 2010). This protein possesses the ability to coordinately regulate several hundreds of genes by binding to DNA sequences situated within the proximal promoter, the first intron, or even further downstream on the gene (Menendez et al., 2009). Fifteen percent of targets of this factor, involved in diverse cell-critical processes such as proliferation, cell cycle control, apoptosis... (Riley et al., 2008), undergo transcriptional repression, as seen in genes like survivin (Hoffman et al., 2002; Raj et al., 2008) or c-Myc (Ho et al., 2005). The repressive action of p53 can be attributed to several direct or indirect mechanisms (Ogbourne and Antalis, 1998). Notably, p53 could:Compete with transcription factors such as SP1 or ERF1 for binding to their sites, thereby obstructing chromatin access for the transcription machinery (Budhram-Mahadeo et al., 1999; Hoffman et al., 2002)(figure 58).

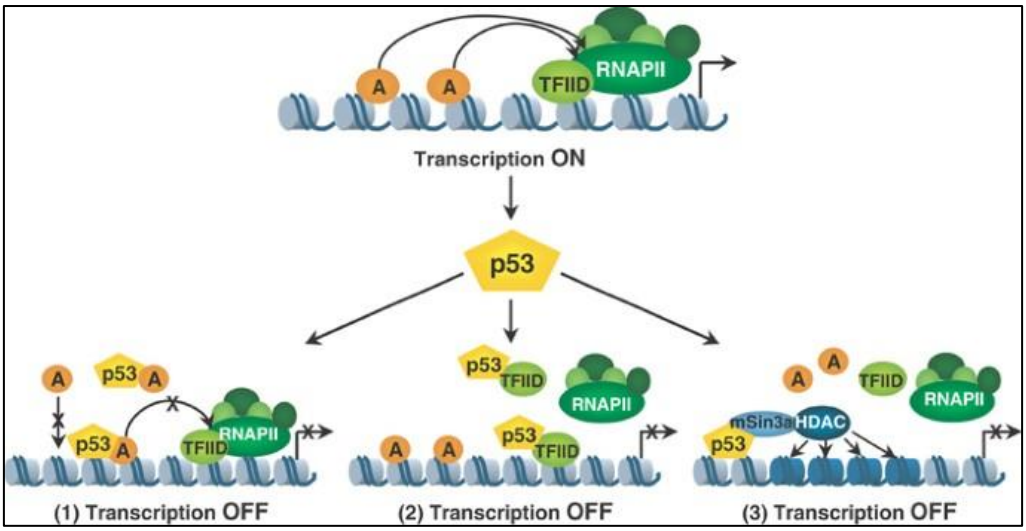

Figure 58: Transcriptional repression mediated by the p53 (Ho J et al., 2003)

Actively recruit complexes capable of chromatin modification, including HDACs, as well as repressor complexes like Sin3a or HP1 (Nguyen et al., 2005). Sequester activator factors like the glucocorticoid receptor (GR), as the physical interaction between these two proteins abolishes the activating capacities of GR (Maiyar et al., 1997).

Inhibit gene transcription activity through non-coding RNAs (ncRNAs) of two types: microRNAs (miRNAs) that bind to the 3' untranslated region of an RNA, leading to its degradation, or through long non-coding intergenic RNAs (lincRNAs) (Rinn and Huarte, 2011).

IV.3. Others transcriptional regulators and complexes

These are others examples of transcriptional regulators and complexes that can bind to enhancer regions to modulate gene expression. Each of them plays specific roles in various cellular processes and contributes to the intricate network of gene regulation.

IV.3.1. NF-kappaB (Nuclear Factor-kappa B)

NF-kappaB is a transcription factor complex that is involved in the regulation of immune and inflammatory responses. It plays a critical role in activating genes associated with immune response pathways. NF-kappaB binding sites are often found in enhancer regions of genes related to inflammation.

The NF-kappaB complex is typically composed of a family of transcription factors (figure 59), including RelA (p65), RelB, c-Rel, p50, and p52 subunits. These subunits can form homo- or

heterodimers that bind to DNA and regulate gene expression. In its inactive state, NF-kappaB is usually sequestered in the cytoplasm by a protein called IκB (Inhibitor of kappa B) (Hayden, M. S et al., 2012). Activation of NF-kappaB is triggered by various signaling pathways, such as those initiated by proinflammatory cytokines (e.g., TNF-alpha, IL-1β) or pathogen-associated molecular patterns (PAMPs) recognized by Toll-like receptors (TLRs). Upon activation, the IκB kinase (IKK) complex is activated, leading to the phosphorylation and subsequent degradation of IκB proteins (Oeckinghaus, A et al., 2009). This releases NF-kappaB subunits from their inhibitory complexes, allowing them to translocate into the nucleus, bind to DNA at specific enhancer and promoter regions, and regulate target gene expression.

NF-kappaB regulates the expression of a wide range of target genes that are critical for immune and inflammatory responses. These genes include cytokines (e.g., IL-6, IL-8, TNF-alpha), chemokines (e.g., CXCL1, CCL2), cell adhesion molecules (e.g., ICAM-1, VCAM-1), and enzymes involved in the production of inflammatory mediators (e.g., cyclooxygenase-2, inducible nitric oxide synthase) (LawrenceT et al., 2009).

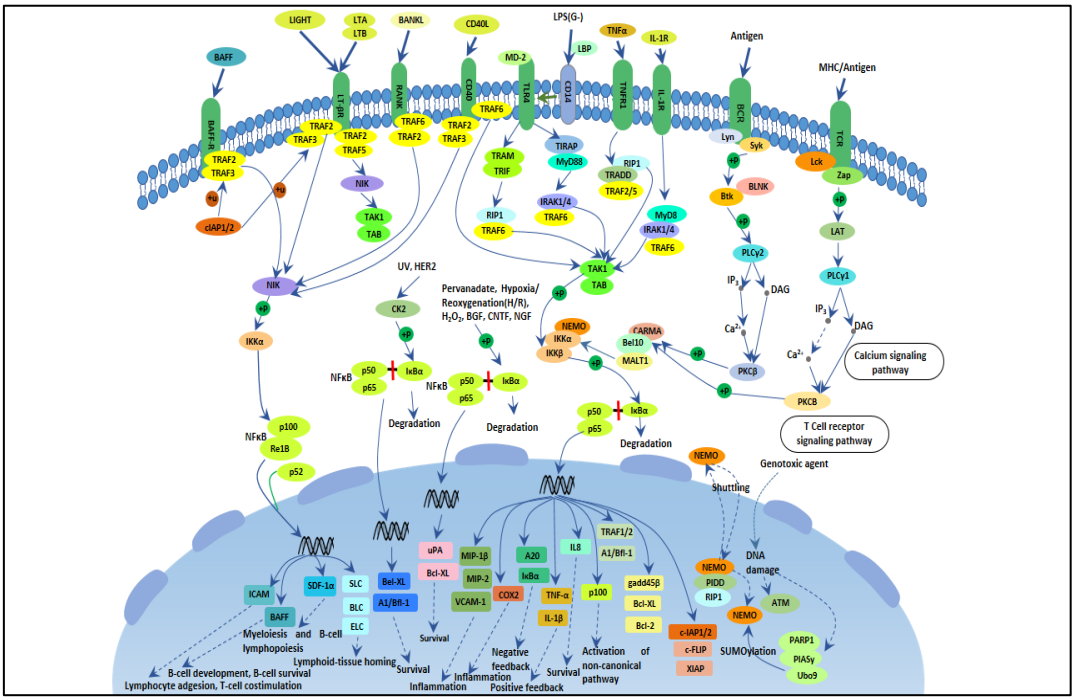

Figure 59: NF-kappa B signaling pathway (uploade Cusabio).

NF-kappaB binding sites are frequently found in the enhancer regions of genes related to inflammation. Enhancers are DNA sequences that can be located far from the promoter region of a gene but still exert control over its transcription (Perkins et al., 2012). NF-kappaB binding

to these enhancer regions is a critical step in initiating the transcriptional activation of genes involved in immune and inflammatory responses (Hayden MS et al., 2008).

These enhancer-bound NF-kappaB complexes interact with other transcription factors and coactivators to create a complex regulatory network that fine-tunes the expression of target genes in response to various signals, such as infections, tissue damage, and other stressors.

IV.3.2. STAT (Signal Transducer and Activator of Transcription)

The STAT family of transcription factors is involved in transmitting signals from cytokines and growth factors (Figure 60). These factors are crucial for mediating cellular responses to various environmental cues and are often involved in developmental processes and immune responses.

The STAT family consists of seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. STAT proteins contain several functional domains, including a DNA-binding domain, a coiled-coil domain for protein-protein interactions, and an SH2 (Src homology 2) domain that mediates phosphorylation-dependent protein interactions (Darnell Jr et al., 1997).

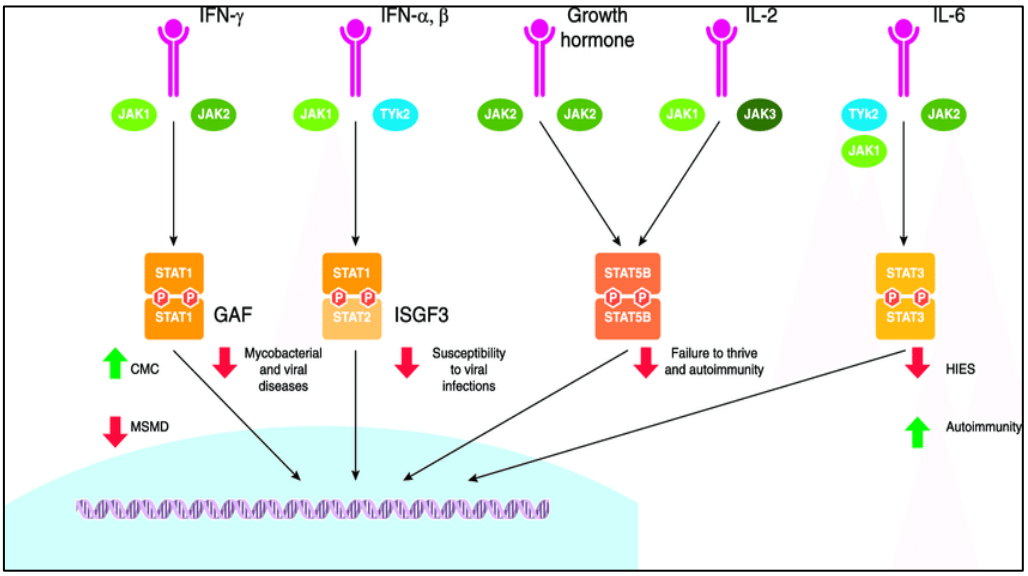

Figure 60: STAT signaling pathways (uploaded by Mauro Giacomelli)

Activation of STAT proteins typically involves the binding of cytokines or growth factors to their respective cell surface receptors. These binding triggers receptor activation and the subsequent activation of receptor-associated kinases, such as Janus kinases (JAKs) in the case of many cytokine receptors (Levy DE et al., 2002). The activated kinases phosphorylate tyrosine residues on the cytoplasmic tail of the receptor, creating docking sites for STAT

proteins. Once recruited to the receptor, STAT proteins are phosphorylated on specific tyrosine residues by the activated kinases, leading to their dimerization via SH2 domain interactions (O'Shea JJ et al., 2012).

Phosphorylated STAT dimers translocate to the nucleus, where they bind to specific DNA sequences known as STAT response elements (SREs) in the promoter regions of target genes. This binding often leads to the activation of transcription and subsequent changes in gene expression. STATs can act as both activators and repressors of gene transcription, depending on the specific cellular context and the target genes involved (Ihle et al JN et al., 2001).

Involvement in Development and Immune Responses: The STAT family is closely linked to developmental processes and immune responses (Schindler et al., 1995). For instance:

STAT3: It is involved in mediating the effects of many cytokines and growth factors, playing critical roles in cell proliferation, survival, and differentiation. STAT3 is essential for immune responses, tissue regeneration, and various developmental pathways.

STAT5: This family member is involved in mediating signals from cytokines such as interleukin-2 (IL-2) and growth hormone. STAT5 is crucial for regulating cell growth, differentiation, and survival, particularly in immune cells and mammary gland development.

STAT6: It is primarily associated with responses to IL-4 and IL-13, cytokines involved in allergic and anti-parasitic responses. STAT6 is essential for promoting Th2 immune responses and is implicated in diseases such as asthma.

IV.3.3. AP-1 (Activator Protein 1)

AP-1 is a transcription factor complex composed of proteins from the Jun and Fos families. It regulates gene expression in response to a variety of stimuli, including growth factors, cytokines, stress, and radiation. AP-1 is involved in processes such as cell proliferation, differentiation, and apoptosis (figure 61).

The AP-1 transcription factor complex is formed through the dimerization of proteins from the Jun and Fos families. The Jun family includes proteins like c-Jun, JunB, and JunD, while the Fos family includes proteins like c-Fos, FosB, Fra-1, and Fra-2 (Shaulian E et al., 2002; Hess J et al., 2004; Eferl R et al., 2003). These proteins contain basic leucine zipper (bZIP) domains that mediate their dimerization and DNA binding. Different combinations of Jun and Fos proteins form various heterodimeric complexes, each with distinct regulatory properties.

AP-1 activation is initiated by various extracellular signals. Growth factors, cytokines, hormones, stress signals, and environmental factors can trigger signaling pathways that converge on AP-1 activation. These pathways often involve protein kinases, such as mitogen-activated protein kinases (MAPKs), which phosphorylate and activate Jun and Fos proteins (Chinenov R et al., 2001; Karin M et al., 2001).

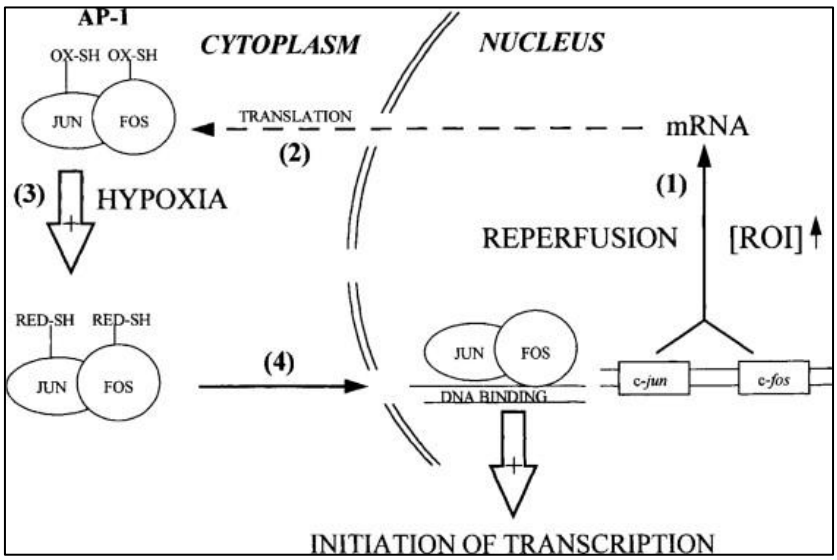

Figure 61: AP-1 Transcription Factor (Jawed S et al., 2000)

Activated AP-1 complexes bind to specific DNA sequences called AP-1 sites, located in the promoters or enhancers of target genes. The binding of AP-1 to these sites can result in the activation or repression of gene transcription, depending on the specific cellular context, the composition of the AP-1 complex, and the presence of other co-factors.

IV.3.4. MyoD

MyoD is a transcription factor that plays a key role in muscle development by converting non-muscle cells into muscle cells. It activates muscle-specific genes by binding to enhancers and promoters that control muscle-specific gene expression.

MyoD is a master regulator of myogenesis, which is the process by which precursor cells, known as myoblasts, differentiate into mature muscle fibers. During muscle development, MyoD is expressed in response to cues from various signaling pathways, such as those involving growth factors like insulin-like growth factor (IGF) and myogenic regulatory factors (Weintraub H et al., 1991; Tapscott SJ et al., 1998; Buckingham M et al., 2014) .

MyoD has the remarkable ability to "reprogram" non-muscle cells, such as fibroblasts, into muscle cells. This reprogramming involves inducing a muscle-specific gene expression program in these cells. By binding to enhancers and promoters of muscle-specific genes, MyoD activates the transcription of genes responsible for muscle cell differentiation, fusion, and maturation (Berkes CA et al., 2015) (figure 62).

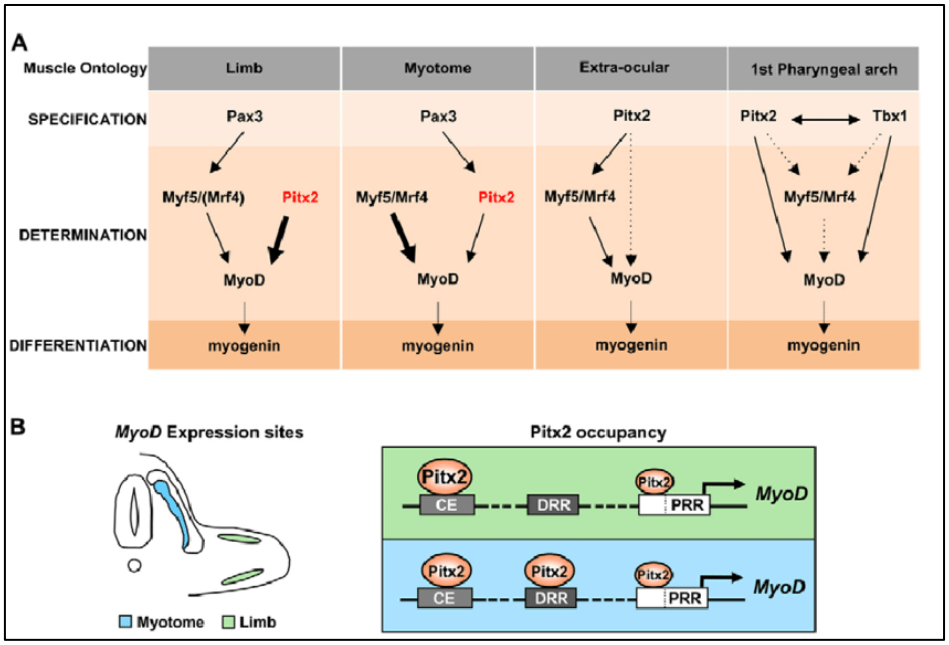

Figure 62: MyoD gene regulation (uploaded by Jacques Drouin).

MyoD binds to specific DNA sequences known as E-boxes in the enhancer and promoter regions of muscle-specific genes. This binding is facilitated by the basic helix-loop-helix (bHLH) domain of MyoD. Once bound, MyoD recruits co-activators and other transcriptional machinery to promote the activation of these genes. This results in the expression of proteins necessary for muscle structure and function, such as myosins and myogenic regulatory factors.

MyoD's activity leads to the fusion of myoblasts into multinucleated structures called myotubes. Myotubes subsequently mature into functional muscle fibers, which contract in response to neuronal signals.

IV.3.5. Estrogen Receptor (ER)

ER is a nuclear hormone receptor that binds to estrogen and regulates gene expression in response to hormonal signals. It plays a critical role in the development and maintenance of the female reproductive system and has implications in breast cancer.

ER belongs to the nuclear hormone receptor superfamily, which includes receptors for various hormones such as thyroid hormone, retinoids, and glucocorticoids. These receptors act as ligand-activated transcription factors, which means they are located in the cell nucleus and regulate gene expression upon binding to their specific ligands (Levin ER et al., 2005; Mangelsdorf DJ et al., 1995; McDonnell DPet al., 1997) (figure 63).

ER exists in two main isoforms, ERα (alpha) and ERβ (beta), both of which are encoded by separate genes. Estrogen, a steroid hormone, serves as the primary ligand for ER. When estrogen binds to ER, the receptor undergoes conformational changes that enable it to form dimers and interact with specific DNA sequences called estrogen response elements (EREs) located in the enhancer or promoter regions of target genes.

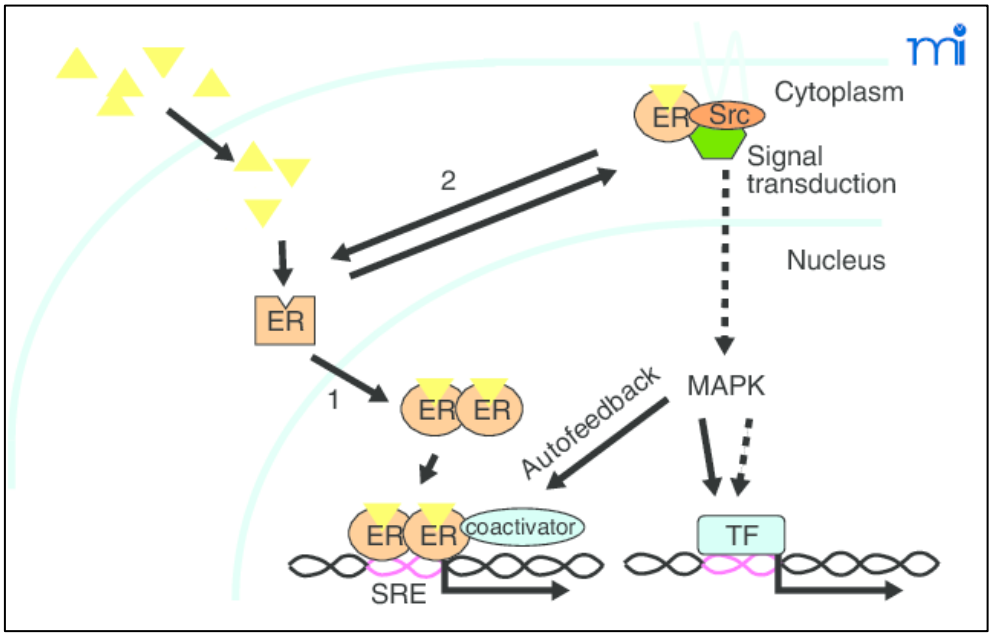

Figure 63: Actions of the estrogen receptor (ER);
estrogenic ligands (triangles) activate ER as a transcription factor (uploaded by Viroj Boonyaratanakornkit)

Upon binding to EREs, ER dimers recruit co-activator or co-repressor proteins and other transcriptional machinery to regulate the expression of target genes. ER-mediated gene

regulation is context-dependent, meaning it can either enhance or suppress gene transcription based on the specific genes involved and the presence of other co-factors (Ali S et al., 2002).

ER is critical for the development and function of the female reproductive system. It contributes to the growth of the uterus and regulation of the menstrual cycle. ER also plays a role in the development of secondary sexual characteristics, such as breast development and regulation of bone density (Nilsson S et al., 2011). ER's involvement in breast tissue makes it a critical factor in breast cancer development. Many breast cancers are classified based on their ER status, with tumors being either ER-positive (responsive to estrogen) or ER-negative (unresponsive to estrogen). ER-positive breast cancers can often be treated with hormone therapy that targets ER signaling to inhibit tumor growth.

IV.3.6. Androgen Receptor (AR)

Similar to ER, AR is a nuclear hormone receptor that responds to androgens (such as testosterone) and regulates gene expression. It is important for the development and maintenance of male reproductive tissues (figure 64).

Upon binding to AREs, AR dimers recruit co-activator or co-repressor proteins and other transcriptional machinery to regulate the expression of target genes (Heinlein CA et al., 2004; McEwan IJ et al., 2012). AR-mediated gene regulation is tissue-specific, contributing to the development and maintenance of male reproductive tissues, including the testes, prostate, and seminal vesicles.

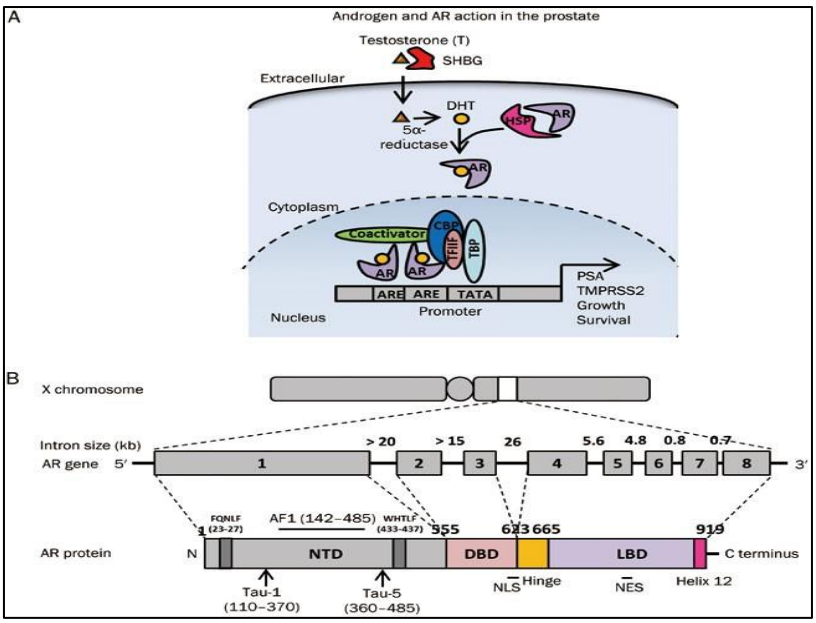

Figure 64: Androgen receptor structure (Tan MHE et al., 2015)

IV.3.7. CREB (cAMP Response Element-Binding Protein)

CREB is a transcription factor that responds to signals generated by cyclic AMP (cAMP). It is involved in many cellular processes, including learning and memory, and can activate gene expression by binding to CRE sites in enhancers.

CREB is closely tied to the cAMP signaling pathway. When cells receive certain extracellular signals, such as the binding of hormones like adrenaline or neurotransmitters like dopamine, an increase in intracellular cAMP levels is triggered. cAMP binds to and activates protein kinase A (PKA), which phosphorylates CREB at a specific site, serine 133. Phosphorylation of CREB at serine 133 is a critical step in its activation. Once phosphorylated, CREB forms a complex with its co-activator, CREB-binding protein (CBP), and binds to cAMP response elements (CREs) in the promoter or enhancer regions of target genes. CREs are specific DNA sequences recognized by the CREB-CBP complex (Mayr B et al., 2001; Lonze BE et al., 2002 ; Carlezon JR et al., 2005). CREB's binding to CREs leads to the activation or repression of target gene transcription, depending on the specific genes involved and the context of the cellular response. CREB is involved in regulating genes that are essential for processes like cell survival, synaptic plasticity, learning and memory, and metabolism.

IV.3.8. HIF (Hypoxia-Inducible Factor)

HIF is a transcription factor complex that responds to changes in oxygen levels. It plays a crucial role in adapting cells to hypoxic (low oxygen) conditions by regulating the expression of genes involved in angiogenesis and metabolism.

IV.3.9.YY1 (Yin Yang 1)

YY1 is a transcription factor with diverse roles in gene regulation. It can function both as a repressor and an activator of gene expression and is involved in a wide range of processes, including development, differentiation, and cell cycle regulation.

IV.3.10.C/EBP (CCAAT/Enhancer Binding Protein)

C/EBP transcription factors are involved in the regulation of genes related to cellular differentiation, inflammation, and metabolism. They play crucial roles in various tissues, including the liver and adipose tissue.

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