Gene regulation

Lecture 2: Chromatin structure and function

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Notes:

* A list of contact details

* Journal club schedule (practical)

* Exam next week

Chromatin:

*Why do we have to study chromatin?

Definition:

It is the combination between DNA and histones.

Function:

Packaging DNA into a small volume to fit in the cell.

* Allow mitosis and meiosis

*Control gene expression and DNA replication

- Strengthen DNA to protect it from damage.

Chromatin Organization:

Euchromatin: DNA wraps around histone proteins forming a structure known as nucleosome.

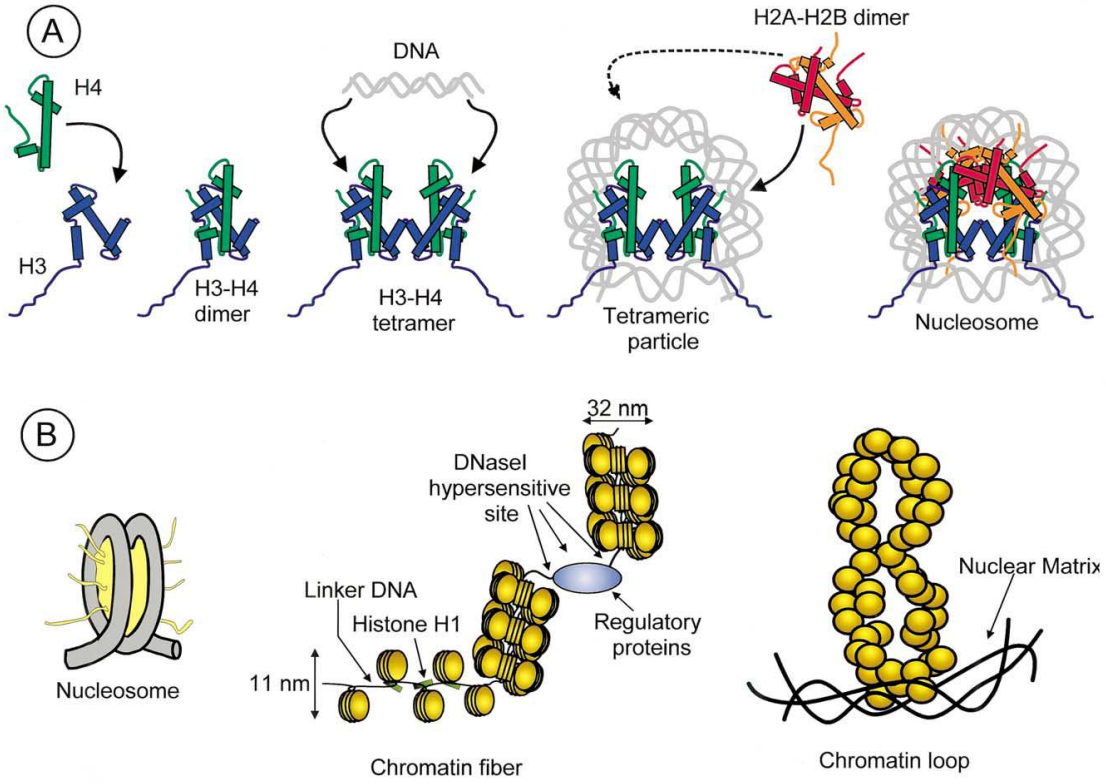
Heterochromatin: Multiple nucleosomes wrap into a fibre consisting of nucleosome arrays.

Higher level DNA packaging: represents the most compact form of DNA packaging (metaphase chromosome).

Exercise: Compare between Eu and heterochromatin in terms of chemical modifications.

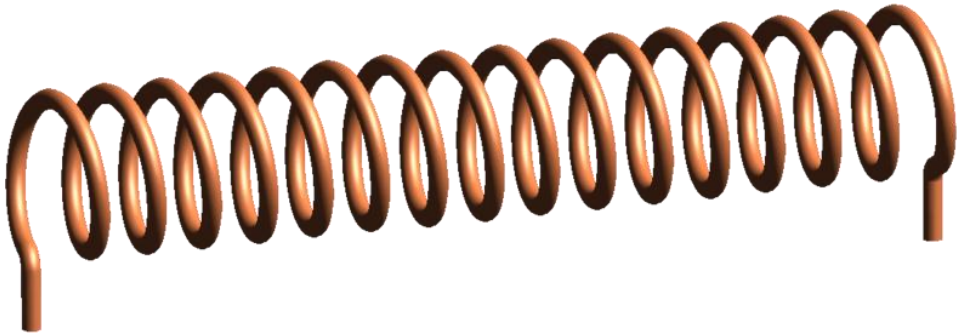
Chromatin structure

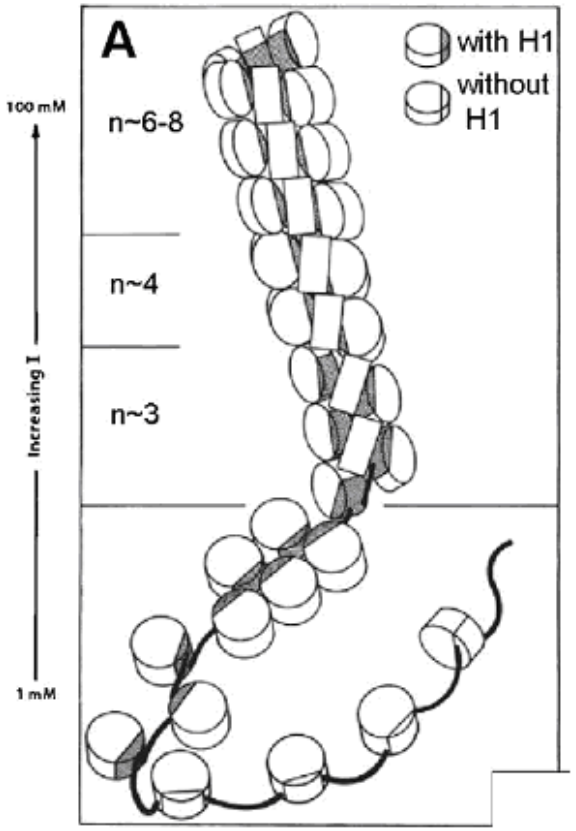
Nucleosome: 146 base pairs (bp) of DNA coiled around a core consisting of a histone octamer (H2A, H2B, H3, and H4).



Chromatin structure

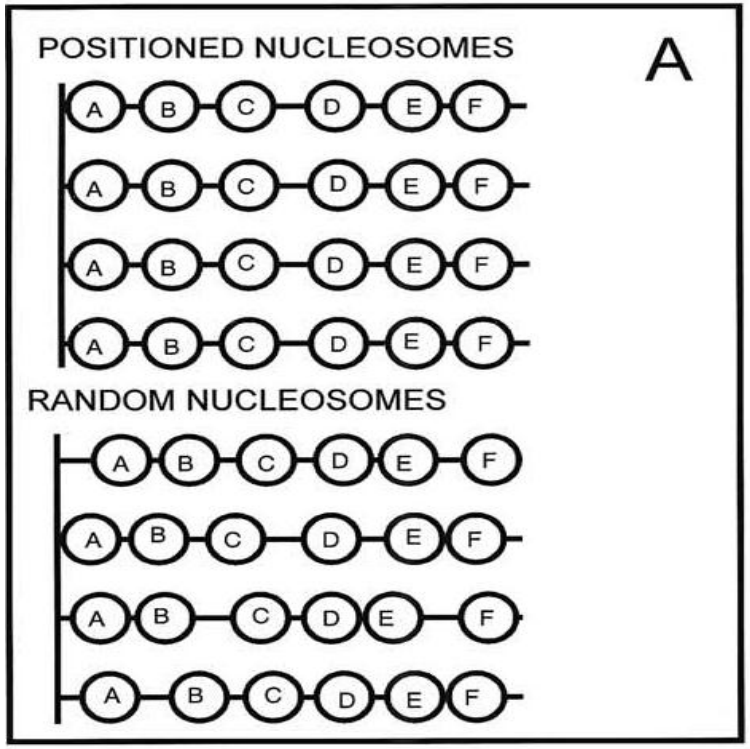
Chromatin fibers:





Chromatin structure

Nucleosome positioning:



Chromatin structure

Nucleosome modulation:

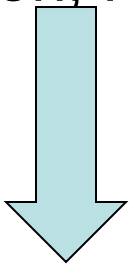
Definition: Substitution of one of the histones for a variant counterpart.

*Histone H2A.Z ⟹ marker for the active chromatin

* Phosphorylated Histone H2AX ⟹ DNA double strand breaks

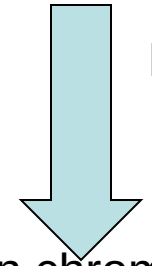
Chromatin Function

DNA transcription, replication, repair and/or recombination



Require

Chromatin accessibility

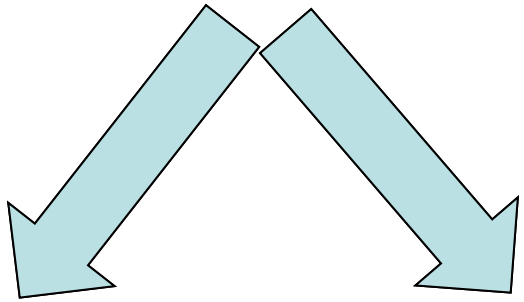


Requires

Alterations in chromatin structure
(Chromatin remodelling)

Chromatin Function

Chromatin remodeling



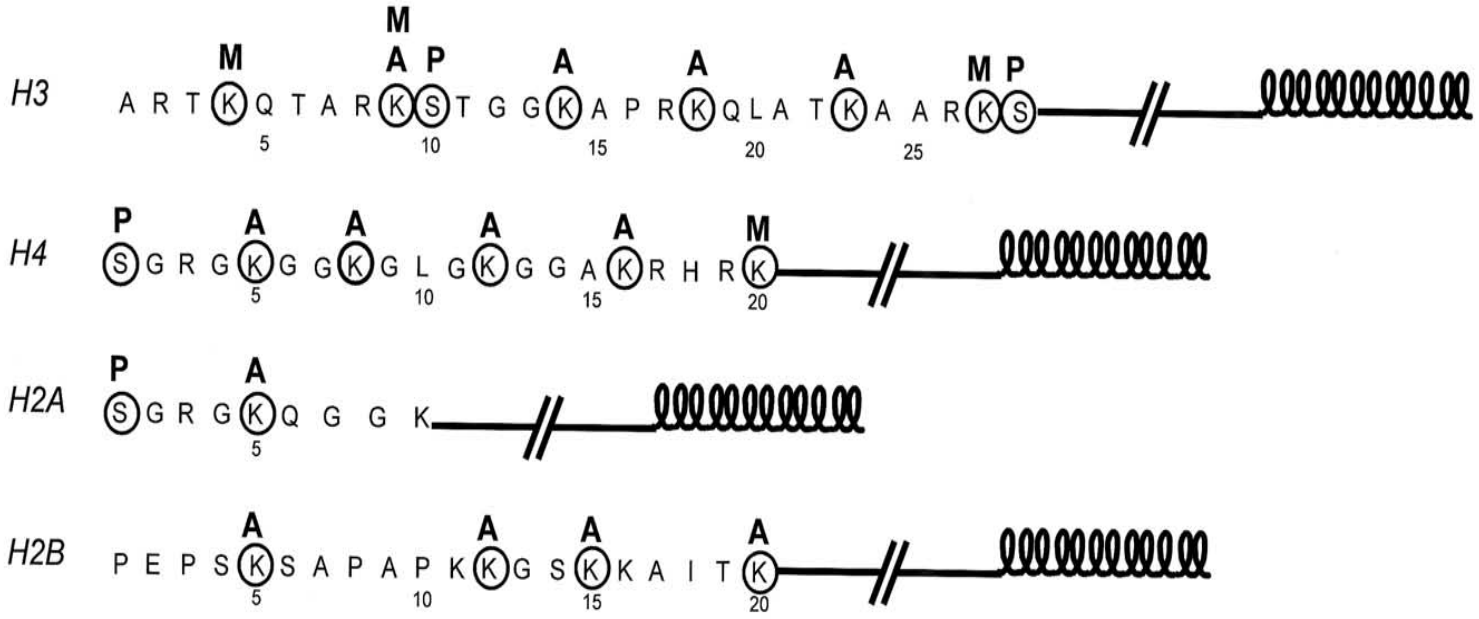
Histone modifications

ATP-dependent chromatin remodeling complexes

Chromatin Function

Posttranslational modification of histones

(Acetylation, methylation, phosphorylation, poly-ADP ribosylation, and ubiquitination of histone amino termini) ⇒ Affinity of Histones to DNA



Chromatin function

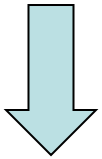
Histone code: It is a code formed by a combination of the positioning and modification of the histones.

* Histones code is called epigenetic ‘memory’ that is passed from mother cell to daughter cell and form epigenome.

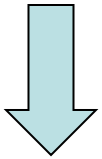
Chromatin function

Histone acetylayion

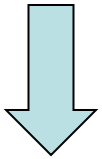
Addition of acetyl groups to lysines in N-terminus of core histones.



Charge neutralization



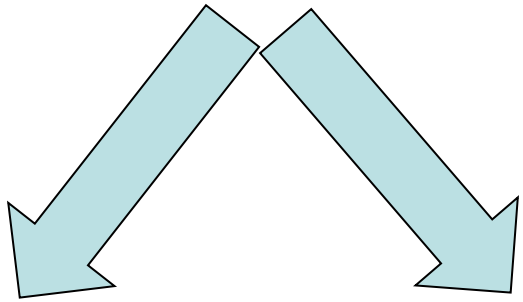
Opened chromatin



Active transcription

Chromatin function

Histone acetylayion



Histone acetytransferases (HATS)	Histone deacetylases (HDACS)
*GNAT	18 mammalian HDACs
*MYST	*ClassI HDACs (HDAC1, -2, -3 and -8)
p300/CBP	*ClassII HDACs

Table 1
Human enzymes involved in DNA methylation, histone acetylation and poly-ADP-ribosylation of histone and non-histone proteins

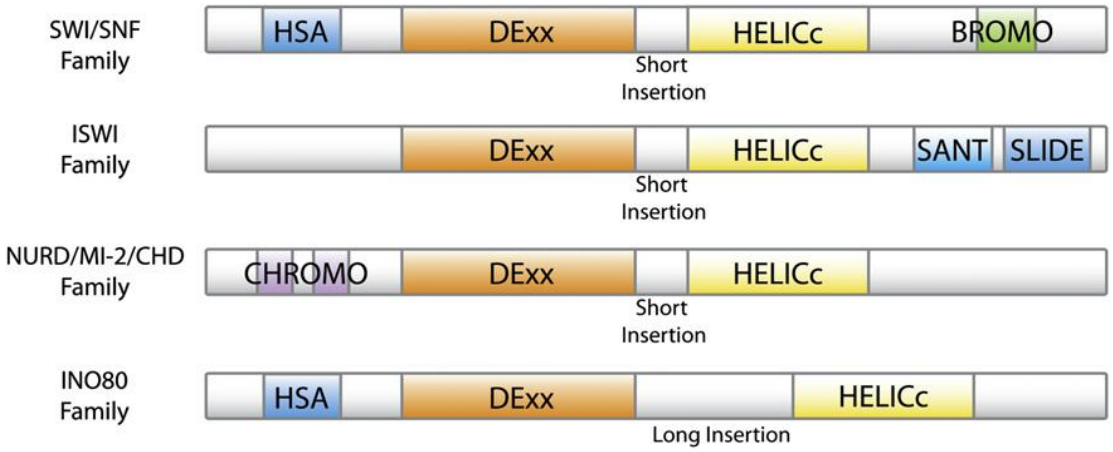
DNA methylation		Histone acetylation		Poly-ADP-ribosylation	
DNMTs [17,237]	DNA demethylases [17]	HATs families [3]	HDACs [39,84,129]	PARPs [174]	PARG [174]
DNMT1	MBD2	GNAT	Class I: HDAC1, HDAC2, HDAC3, HDAC8	PARP-1	
				PARP-2	
				PARP-3	
DNMT2	5-MCDG				
DNMT3A		P300/CBP	Class II (*IIa*): HDAC4, HDAC5, HDAC7, HDAC9	vPARP	PARG
DNMT3B	G/T MMR enzyme			Tankyrase-1	
DNMT3L	MBD4	MYST	Class II (*IIb*): HDAC6, HDAC10	Tankyrase-2	
			Class III: SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, SIRT7	TiPARP	
			Class IV: HDAC11		

DNMT: DNA methyltransferases; MMR: mismatch repair; MBD: methyl CpG-binding domain; meCs: methyl cytosines; HAT: histone acetyltransferases; GNAT: GCN5-related *N*-acetyltransferases; CBP: CREB-binding protein; MYST: named for the founding members of this HAT family MOZ, Ybf2/Sas3, Sas2, and Tip60; HDACs: histone deacetylases; SIRT: sirtuins; PARP: poly-ADP-ribose polymerases; PARG: poly-ADP-ribose-ribose glycohydrolase.

Chromatin function

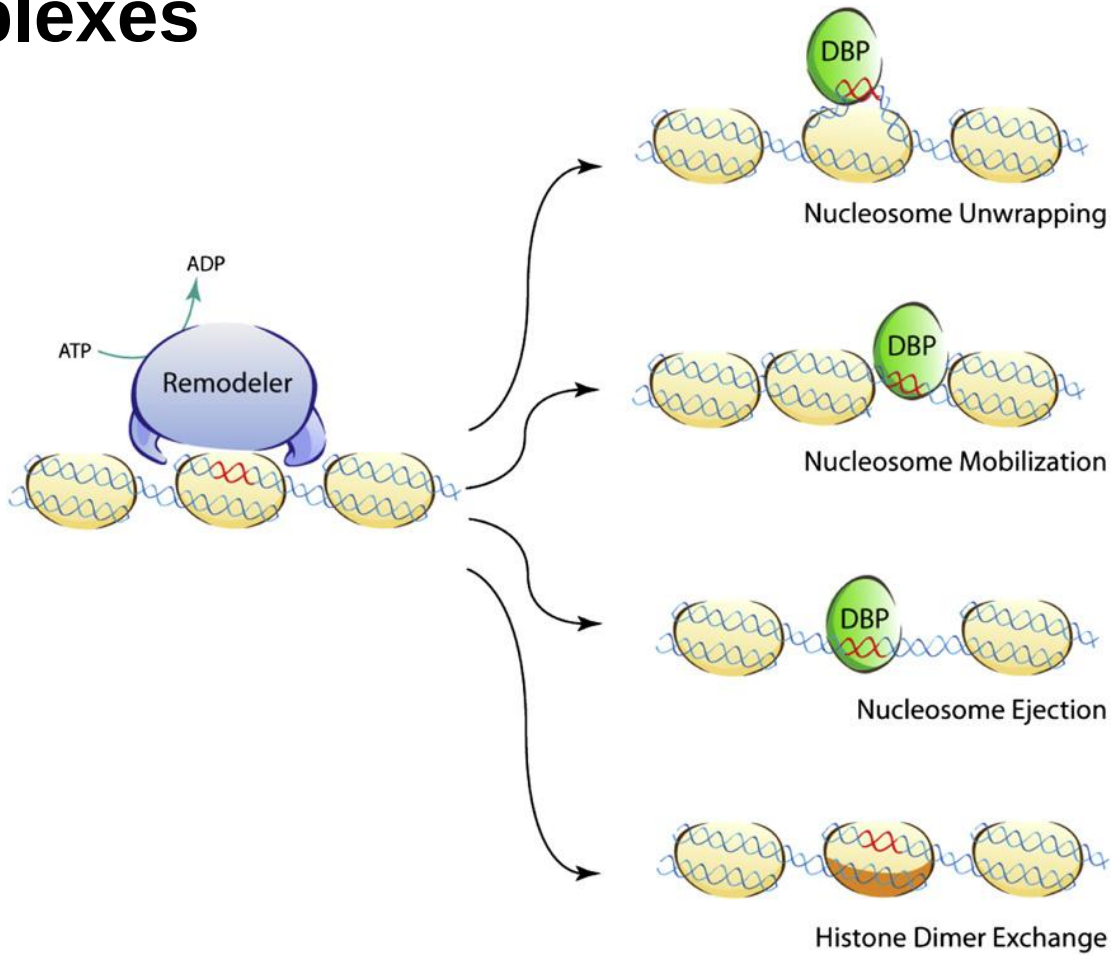
ATP-dependent chromatin remodeling complexes

*Bind DNA and use the energy from ATP hydrolysis to move the histone octamers
*Recognize Histone modifications and recruit transcription factors
*Large (>1 MDa) multi-component complexes
* 4 different families



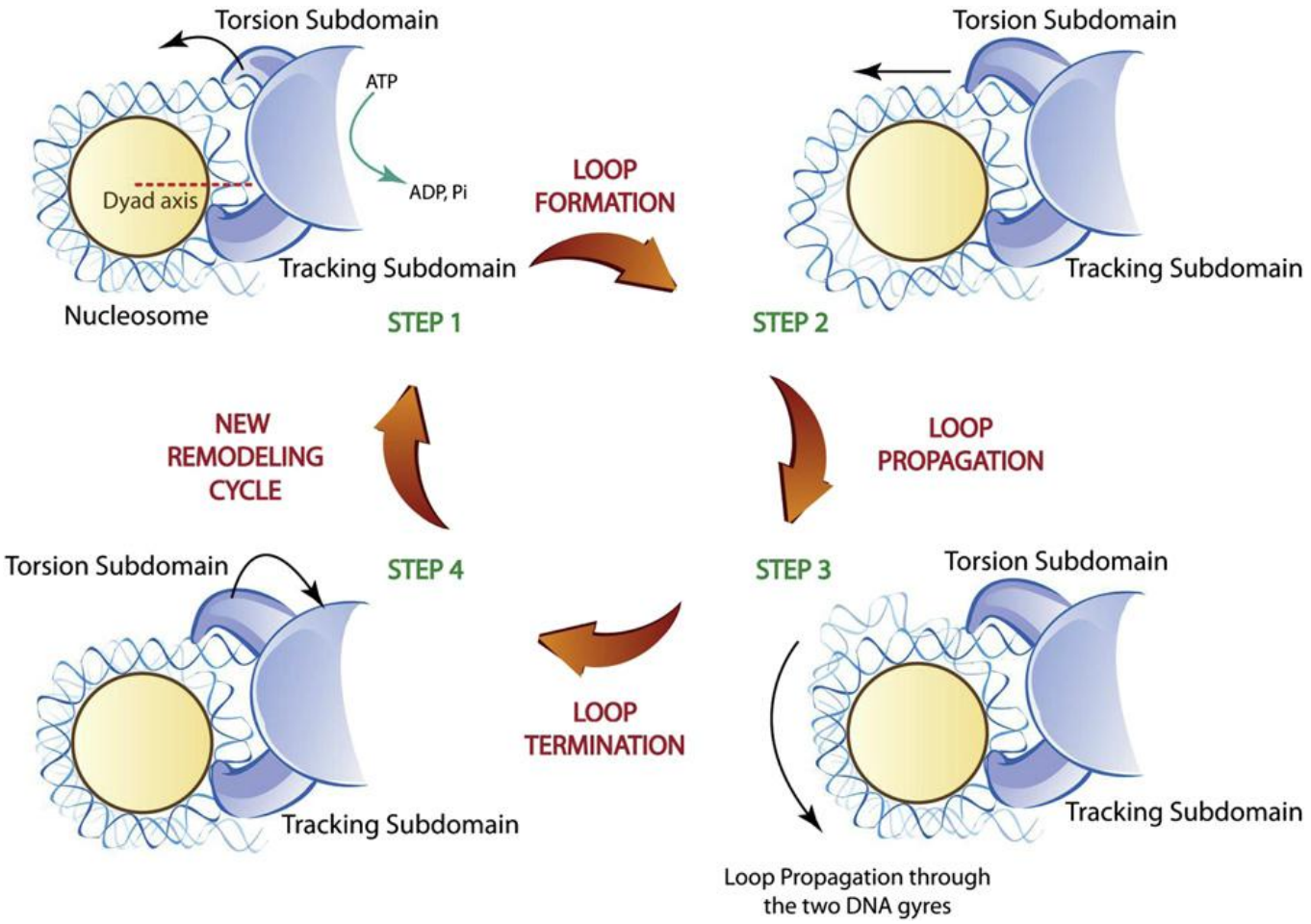
Chromatin function

ATP-dependent chromatin remodeling complexes



Chromatin function

ATP-dependent chromatin remodeling complexes



Chromatin function

Chromatin remodeling and diseases

Histone acetylation	
Histone hypoacetylation	Prostate
HATs over-expression	Breast, ovarian
PCAF	
Mutation	Ovarian, colorectal
P300	
Missense or truncating mutation	Colorectal, gastric
Translocation	Leukemia
CBP	
Mutation or deletion	Lung
Translocation	AML
MOZ/MYST3	
Translocation	AML
HDAC1 over-expression	Gastric Prostate Colon Breast
HDAC2 over-expression	Gastric
HDAC6 over-expression	Breast (ERα-positive)
HDAC10 reduced expression	Lung
SIRT7 over-expression	Thyroid

Epigenetic therapies: HDACs inhibitors

References and further readings

1- Morales V, etal. (2001) **Chromatin structure and dynamics: Functional implications.** Biochimie 83:1029−1039

2- Daban J. (2011) **Electron microscopy and atomic force microscopy studies of chromatin and metaphase chromosome structure.** Micron 42: 733–750

3- Lafon-Hughes L, etal. (2008) **Chromatin-remodelling mechanisms in cancer**. Mutation Research 658:191–214

4- Tang L, etal. (2010) **Structure and function of SWI/SNF chromatin remodeling complexes and mechanistic implications for transcription.** Progress in Biophysics and Molecular Biology 102: 122e128

5- Quina A, etal. (2006) **Chromatin structure and epigenetics**. Biochemical pharmacology 72: 1563– 1569


Questions