

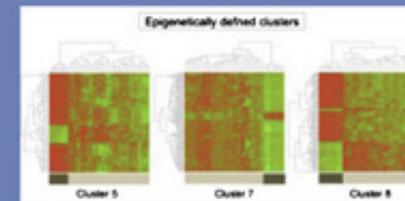
Différentes approches à l'étude d'un génome

R. Redon, C. Dina,
P. Lidenbaum
S. Le Scoarnec



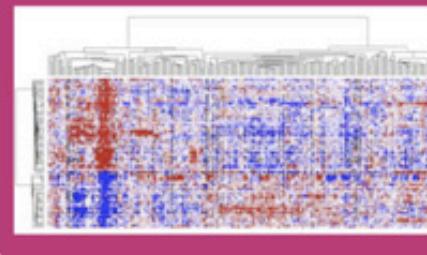
C. Cario-Toumaniantz

Epigenomics



C. Cario-Toumaniantz

Transcriptomics



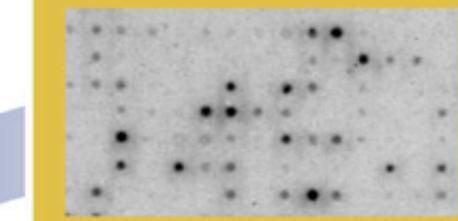
Pharmacogenomics,
Metabolomics,
Clinical observations
Physiology...



Patient

G. Toumaniantz

Proteomics

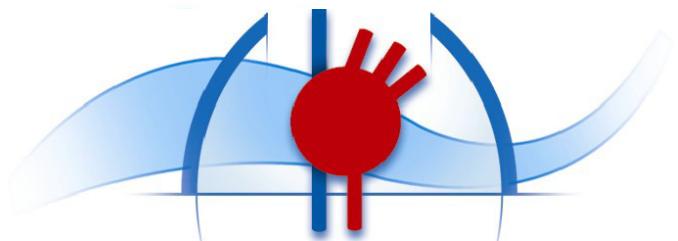


**Disease characterization,
Medication choice and
appropriate dosing**

L'Epigénétique

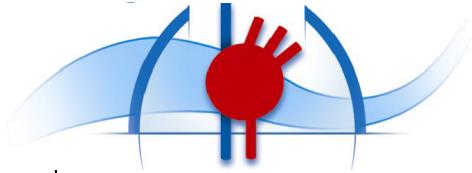
*Chrystelle
Cario-Toumaniantz*

l'Institut du thorax



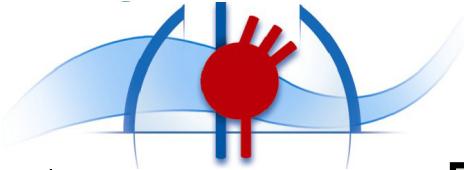
2013



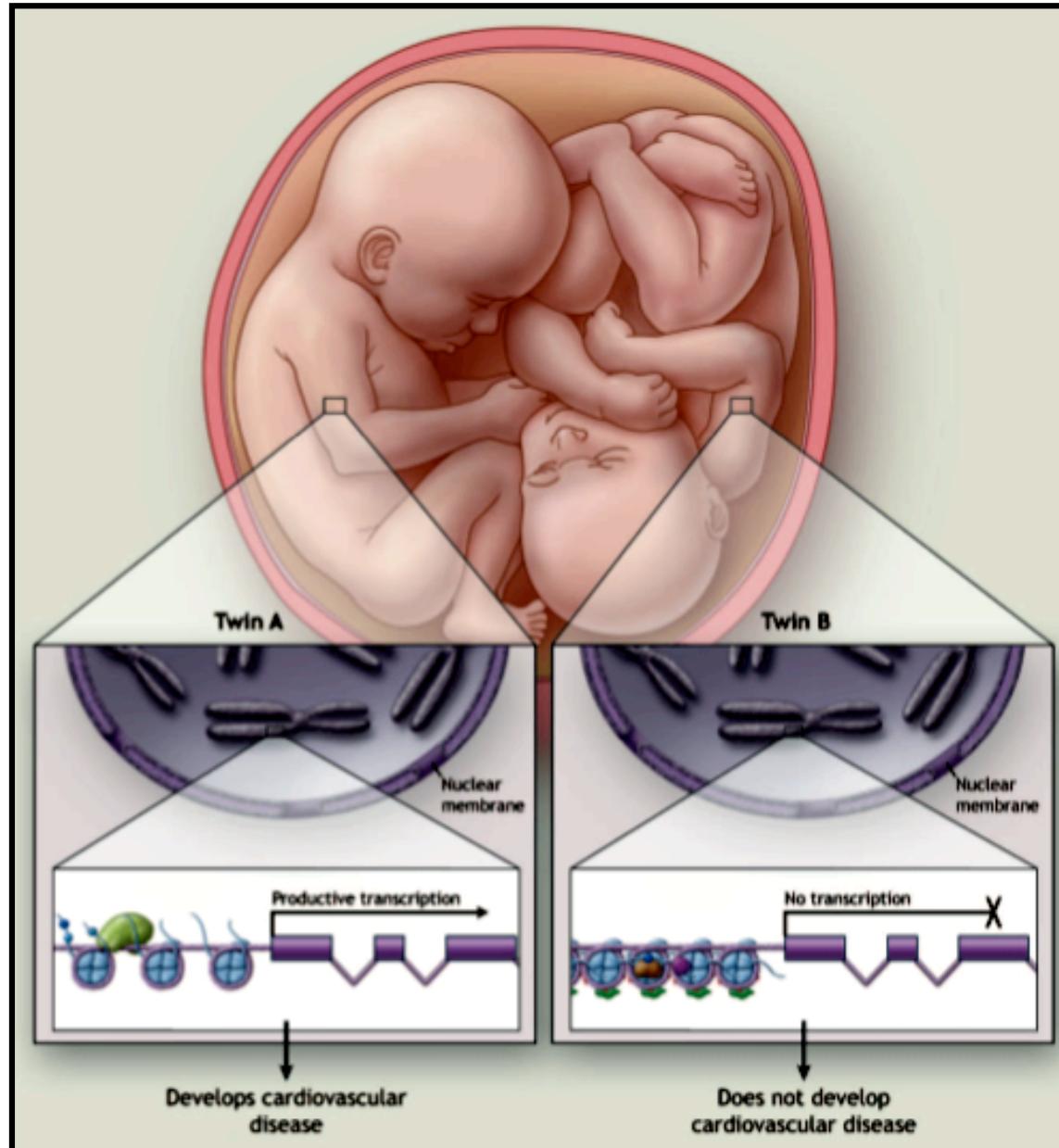


L'épigénétique

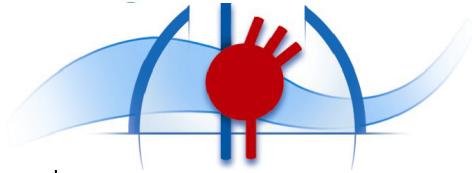
I - Introduction



Introduction



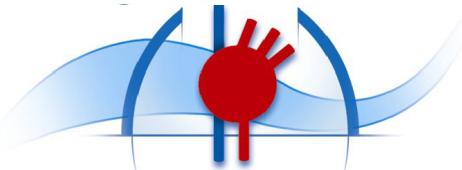
...serm



L'épigénétique

I – Introduction

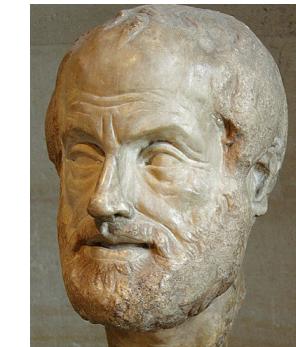
II - Historique



Historique

350 av JC : Aristote, épigenèse

L'embryon se développe progressivement en devenant de plus en plus complexe sous l'influence de forces extérieures



15^{ème}, 16^{ème}, 17^{ème} : théories pré-formation/épigenèse

Girolamo Fabrici et William Harvey, soutiennent l'épigenèse

17^{ème}-18^{ème} : Théorie pré-formationiste prédominante

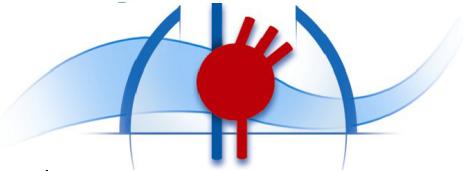
Malpighi, Wolff

19^{ème} : Théorie cellulaire

Scheilder, Schawnn, Virchow, Von Baer, Hertwing, Strasburger, Kolliker, Mendel, Darwin, Flemming

Début 20^{ème} : Début de la génétique/confrontation avec les embryologistes

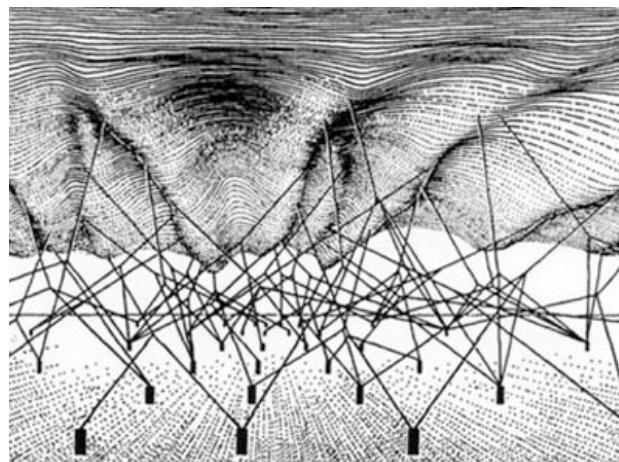
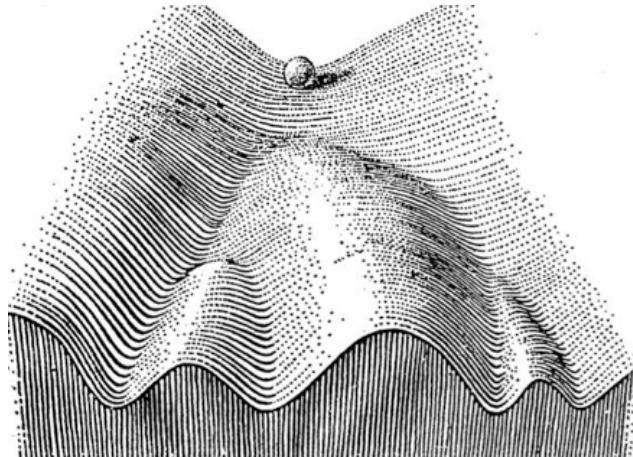
Comment l'information génétique est-elle différemment exploitée au cours de la différentiation cellulaire ?

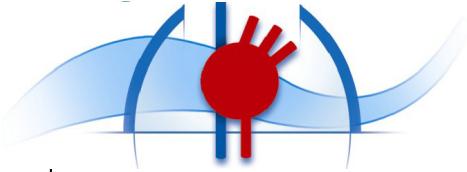


Historique

1942 : Conrad Waddington, épigénétique

comment les génotypes induisent les phénotypes au cours du développement ?



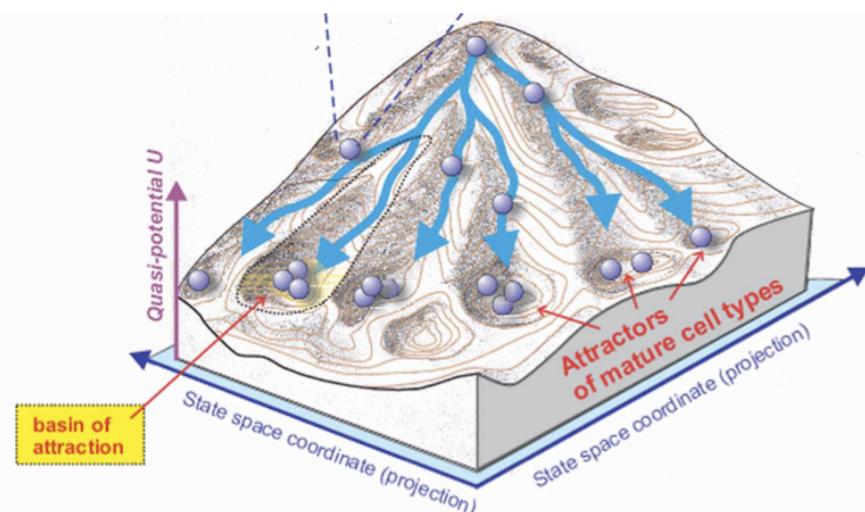
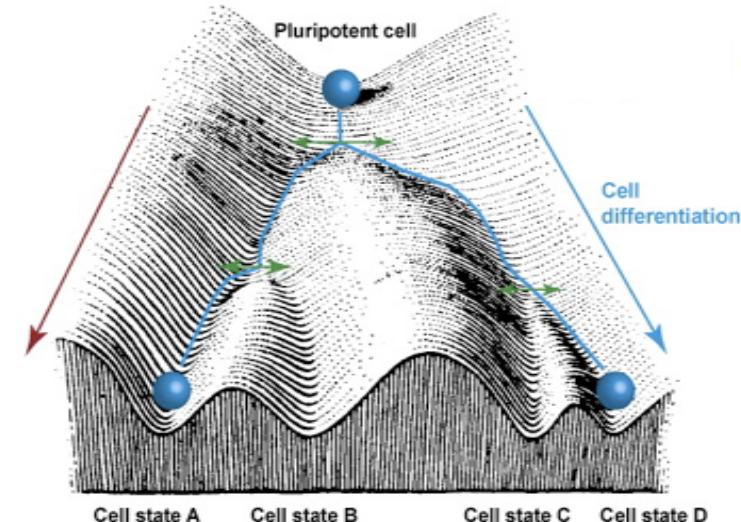
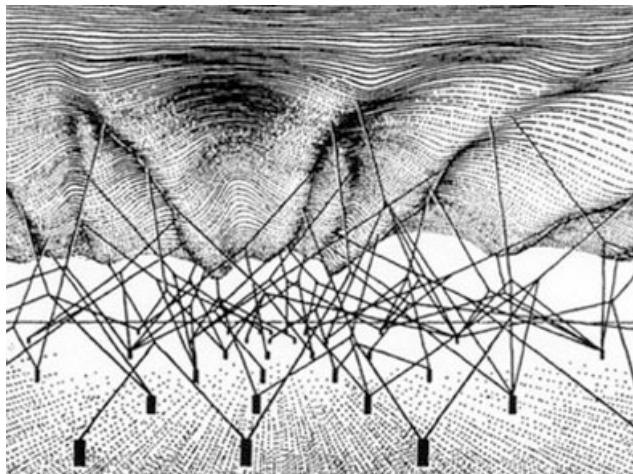
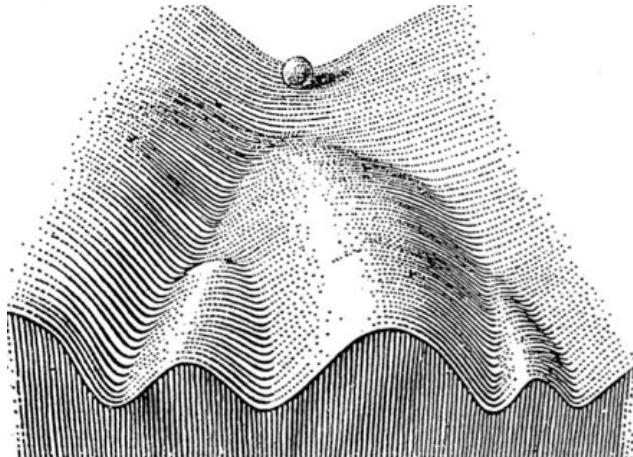


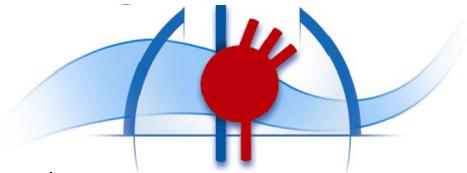
Historique



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Historique

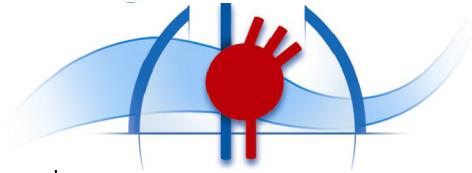
1970-80 : épigénétique et héritabilité

- Conservation de la spécialisation des cellules en culture ?
- Cellules souches et différenciation ?
- Inactivation du chromosome X ?
- Phénomènes de transmission non-Mendélien ?

1975 : Riggs *et al.*, Holliday *et al.*, méthylation de l'ADN, redéfinition de l'épigénétique

Etude des changements de la fonction des gènes qui sont transmissibles au cours de la mitose et/ou de la méiose et qui ne peuvent pas être expliquer par des modifications de la séquence de l'ADN



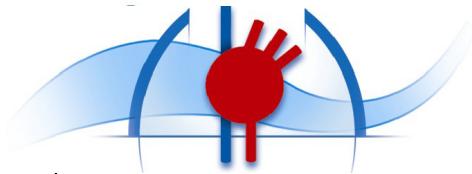


L'épigénétique

I – Introduction

II – Historique

III – Définition et rappels

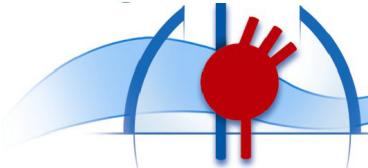


Définition

L'épigénétique correspond à des modulations hérétés d'expression de gènes qui interviennent sans qu'il y ait de modification dans la séquence d'ADN

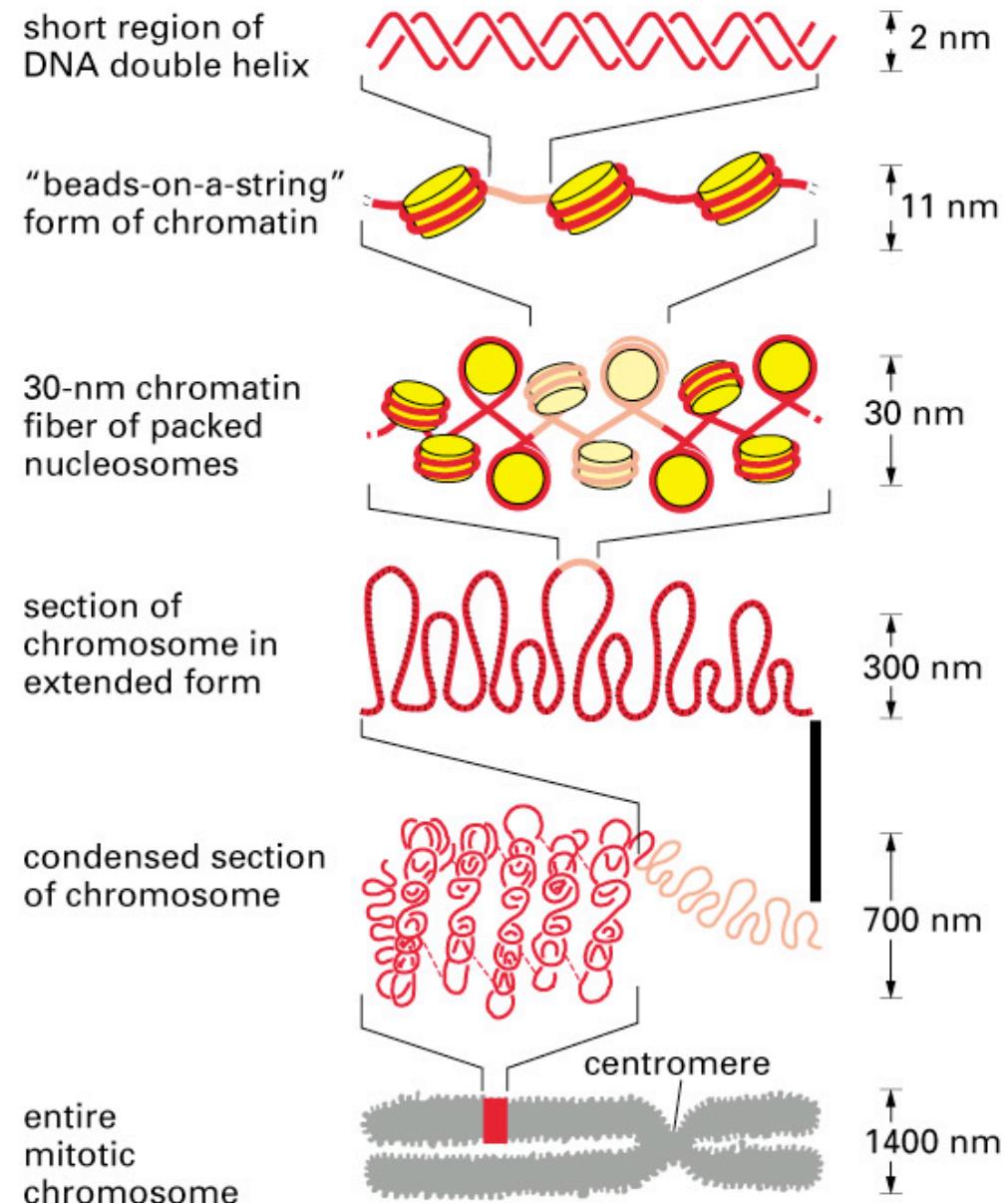
Ces modifications ne peuvent pas être imputées à des modifications de séquences d'ADN (mutations, gains et pertes de matériel chromosomique, translocations chromosomiques)

Ces modifications peuvent être réversibles.

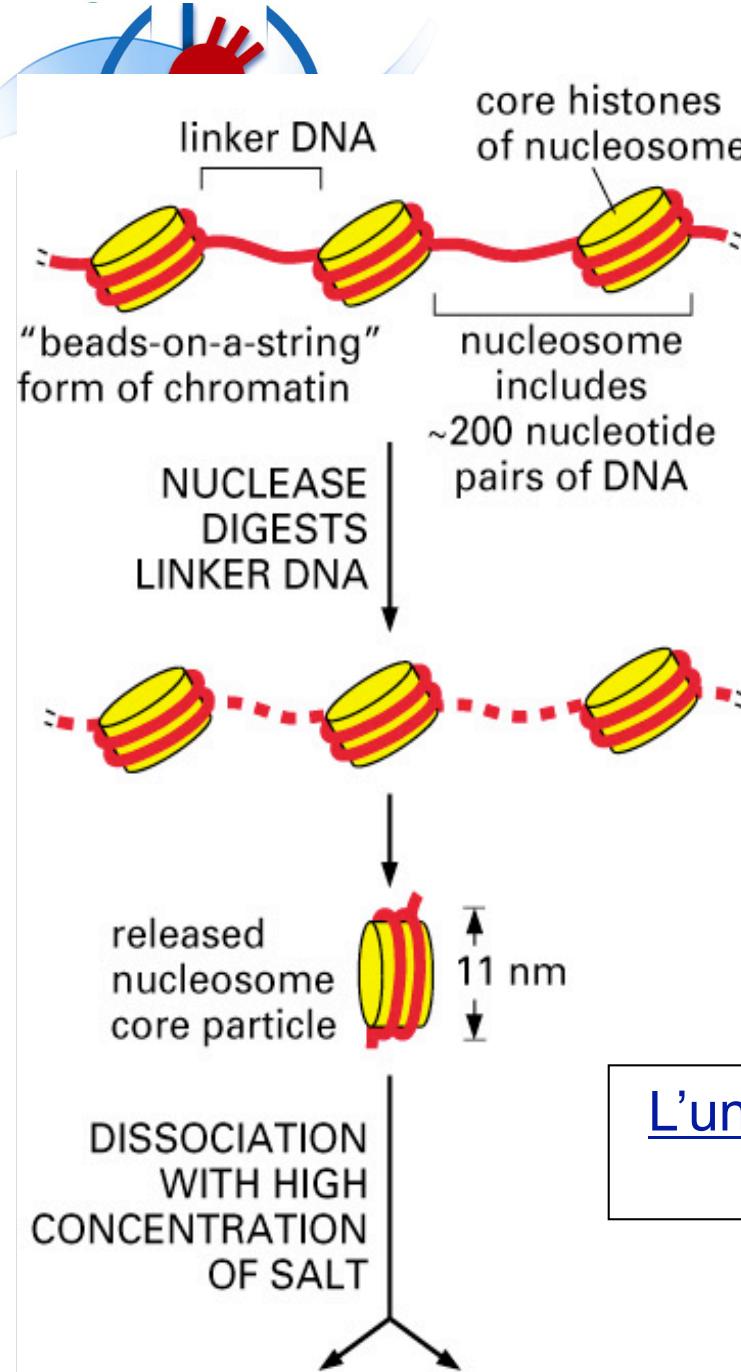


Rappels

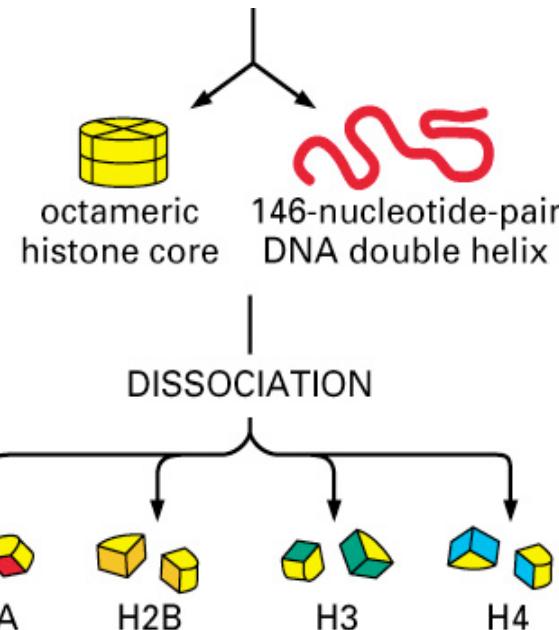
Différents niveaux
d'organisation
structurale avant
d'accéder à l'ADN au
sein du noyau



NET RESULT: EACH DNA MOLECULE HAS BEEN
PACKAGED INTO A MITOTIC CHROMOSOME THAT
IS 10,000-FOLD SHORTER THAN ITS EXTENDED LENGTH

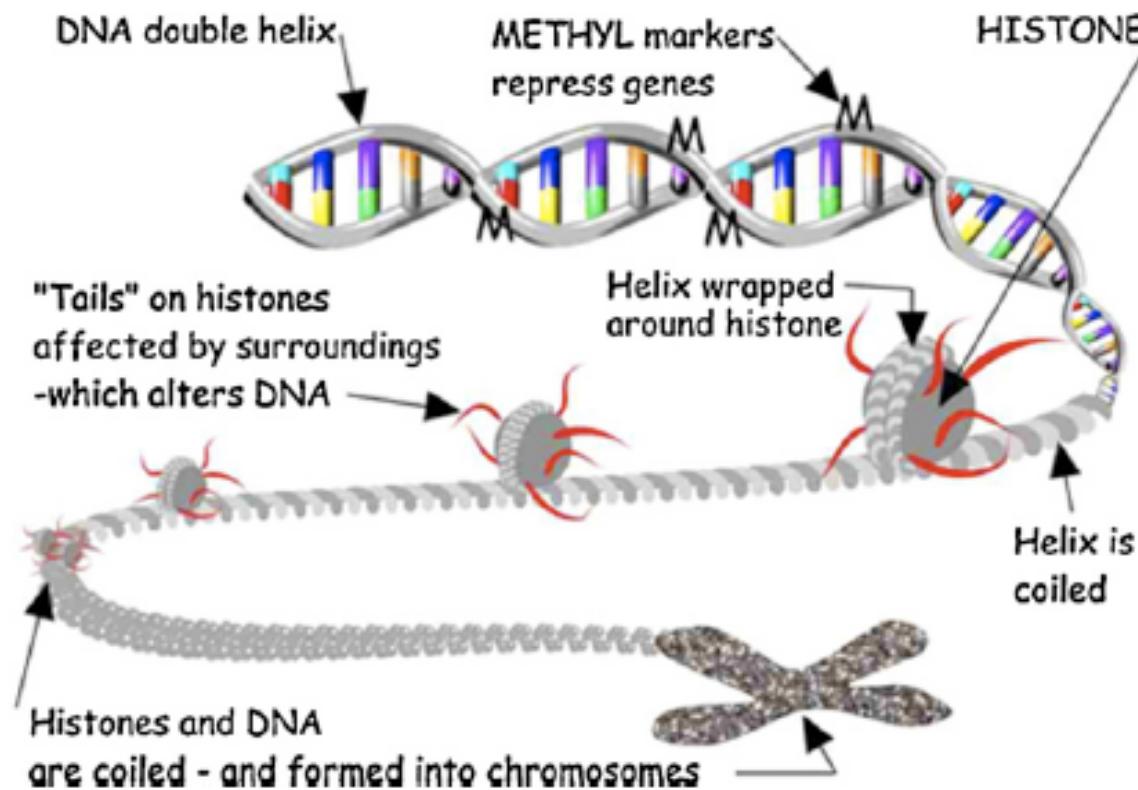


Rappels

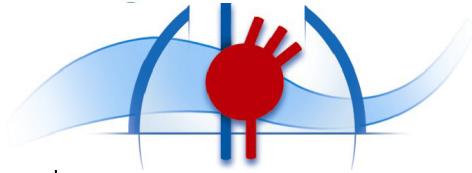


L'unité de base de la chromatine est
le nucléosome

Mécanismes des modifications épigénétiques



- **Modification de l'ADN** : La méthylation de l'ADN
- **Modifications de la structure de la chromatine/des protéines** :
Modifications des Histones/réorganisation du nucléosome
- **Implication des ARNs non-codants**



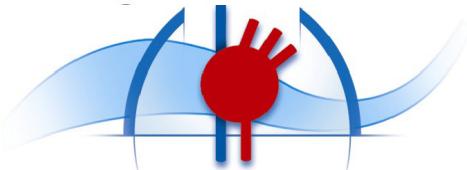
L'épigénétique

I – Introduction

II – Historique

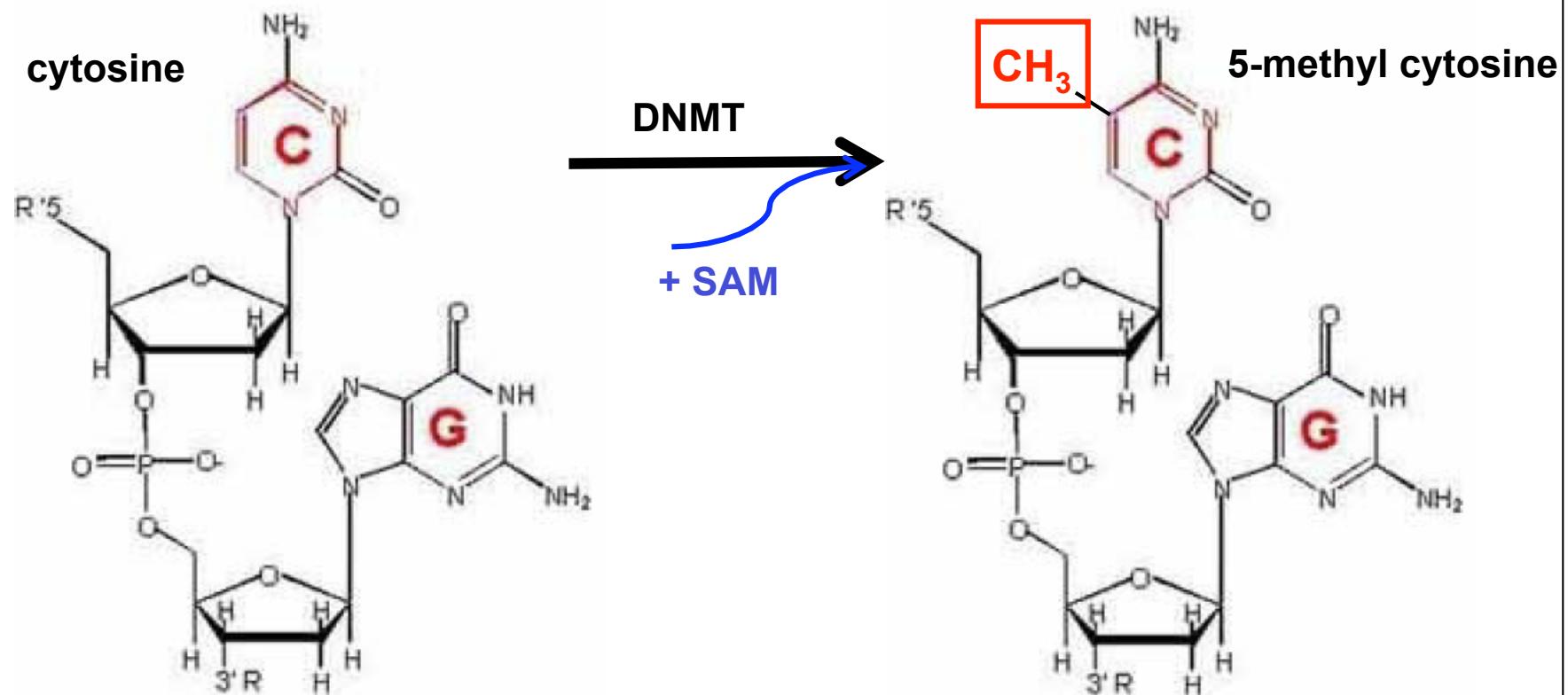
III – Définition et rappels

IV – Modifications de l'ADN : la méthylation



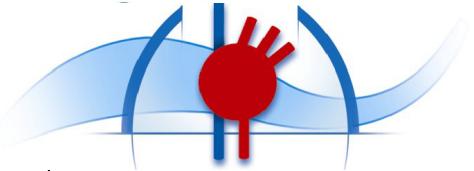
La méthylation de l'ADN

- Les gènes transcriptionnellement inactifs = souvent méthylés
- Eucaryotes : cibles de méthylation = résidus cytosine précédant une guanine

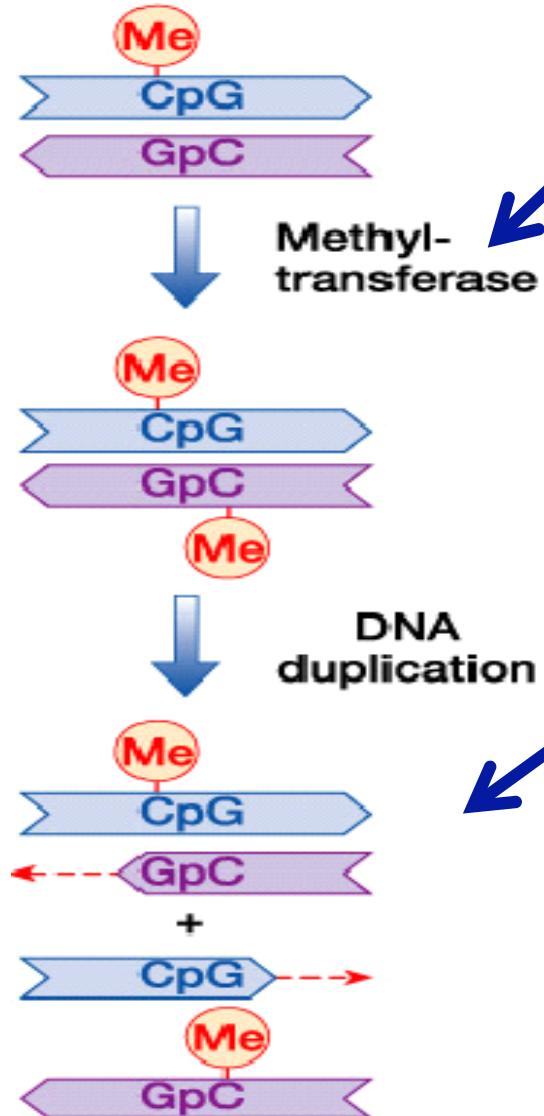


Les sites de méthylation sont les dinucléotides CpG chez les vertébrés

DNMT = DNA MethylTransferase, SAM = S-adenosyl Méthionine = donneur de CH₃



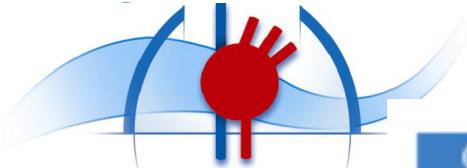
La méthylation de l'ADN



Méthylation due aux Cytosine methyl transferases ou DNA methyl transferases .
Substrat préférentiel de dnmt1 = cibles à demi-méthylées

Lors de la synthèse de nouveau brin d'ADN, le profil de méthylation sera conservé à l'image des brins parents

La DNA (cytosine-5) méthyltransférase 1 ou DNMT1 est une enzyme qui maintient la méthylation et qui coordonne la répression des gènes en partenariat avec les histones déacétylases.

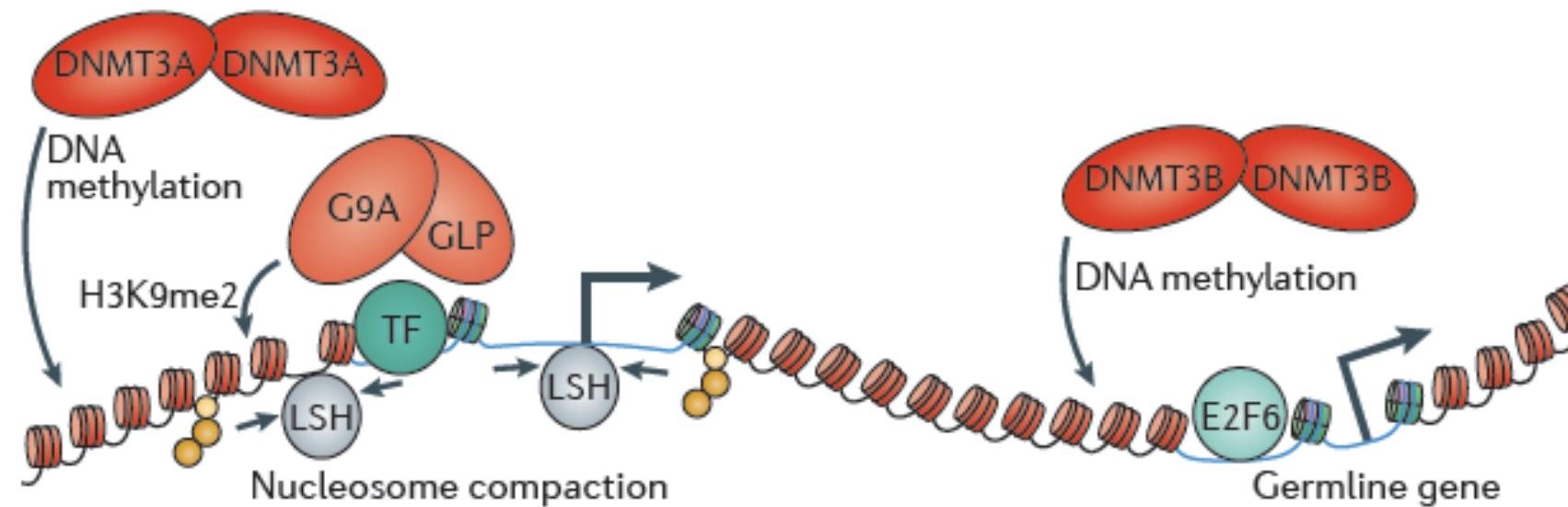


Les DNA MéthylTransférases

Category	Gene
DNMTs	<i>DNMT1</i>
	<i>DNMT3A</i>
	<i>DNMT3B</i>

= DNA méthyltransférase de maintenance

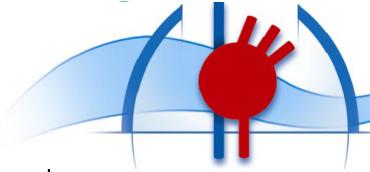
} = De Novo méthyltransférases



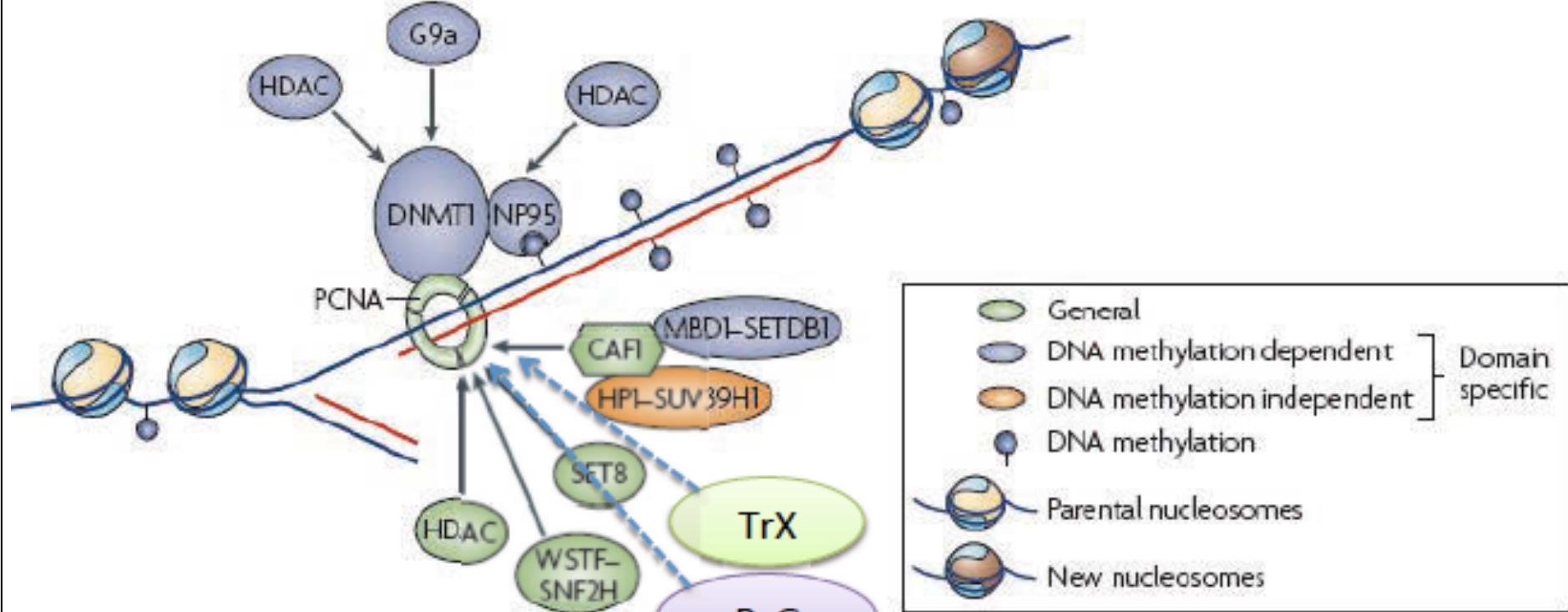
DNMT = DNA MethylTransferase,

TF = transcription Factor

LSH = chromatin remodeler, H3K9 (G9A+GLP) = histone méthyltransferase

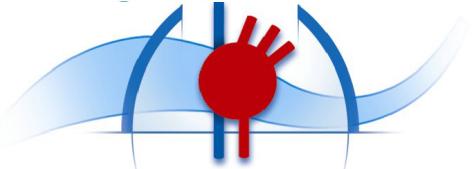


Le complexe de DNA MéthylTransférase 1



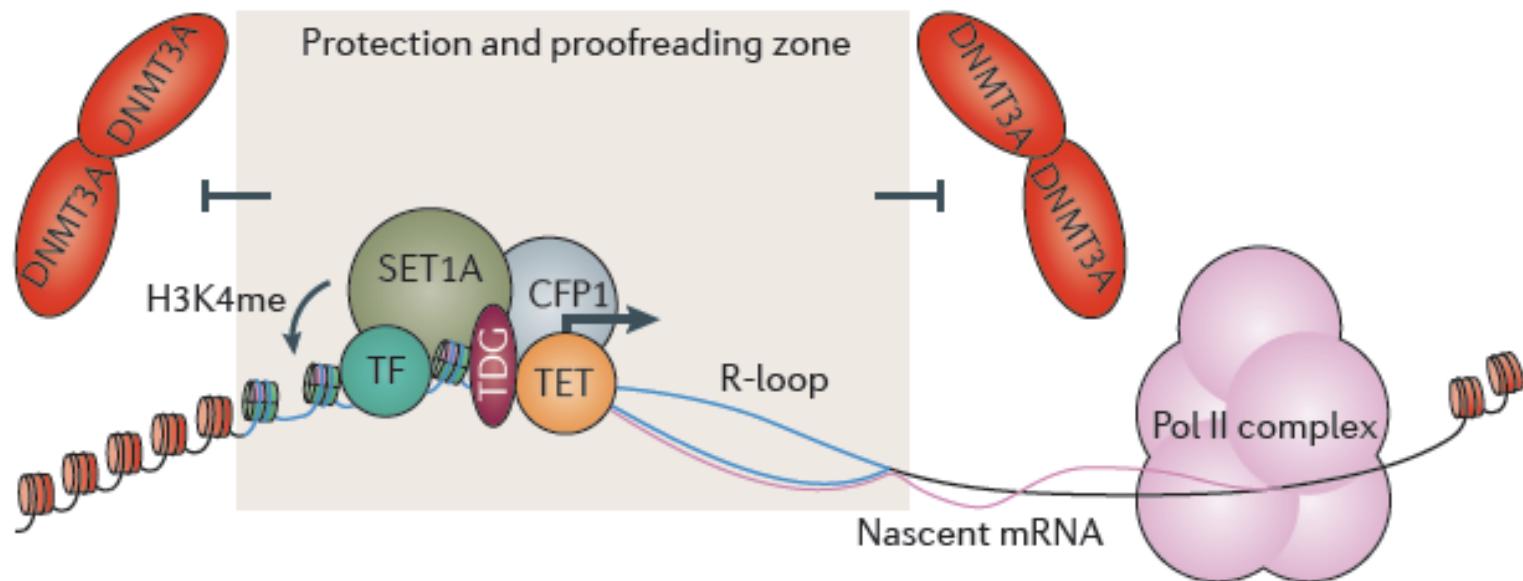
DNMT = DNA MethylTransferase,

PCNA = proliferating cell nuclear antigen



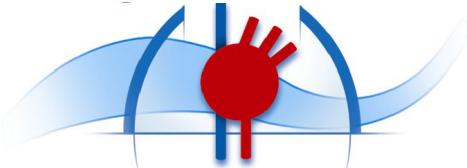
La DéMéthylation de l'ADN

Processus passif



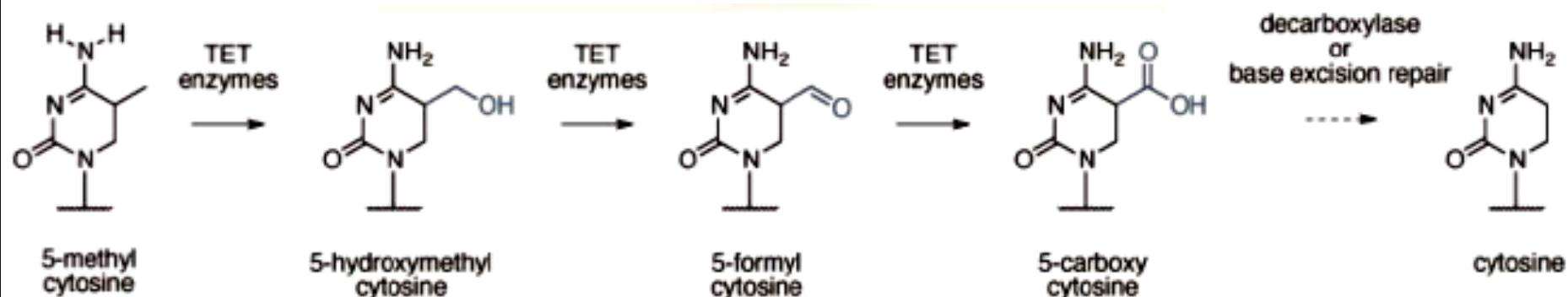
DNMT = DNA MethylTransferase,

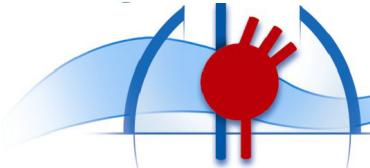
PCNA = proliferating cell nuclear antigen



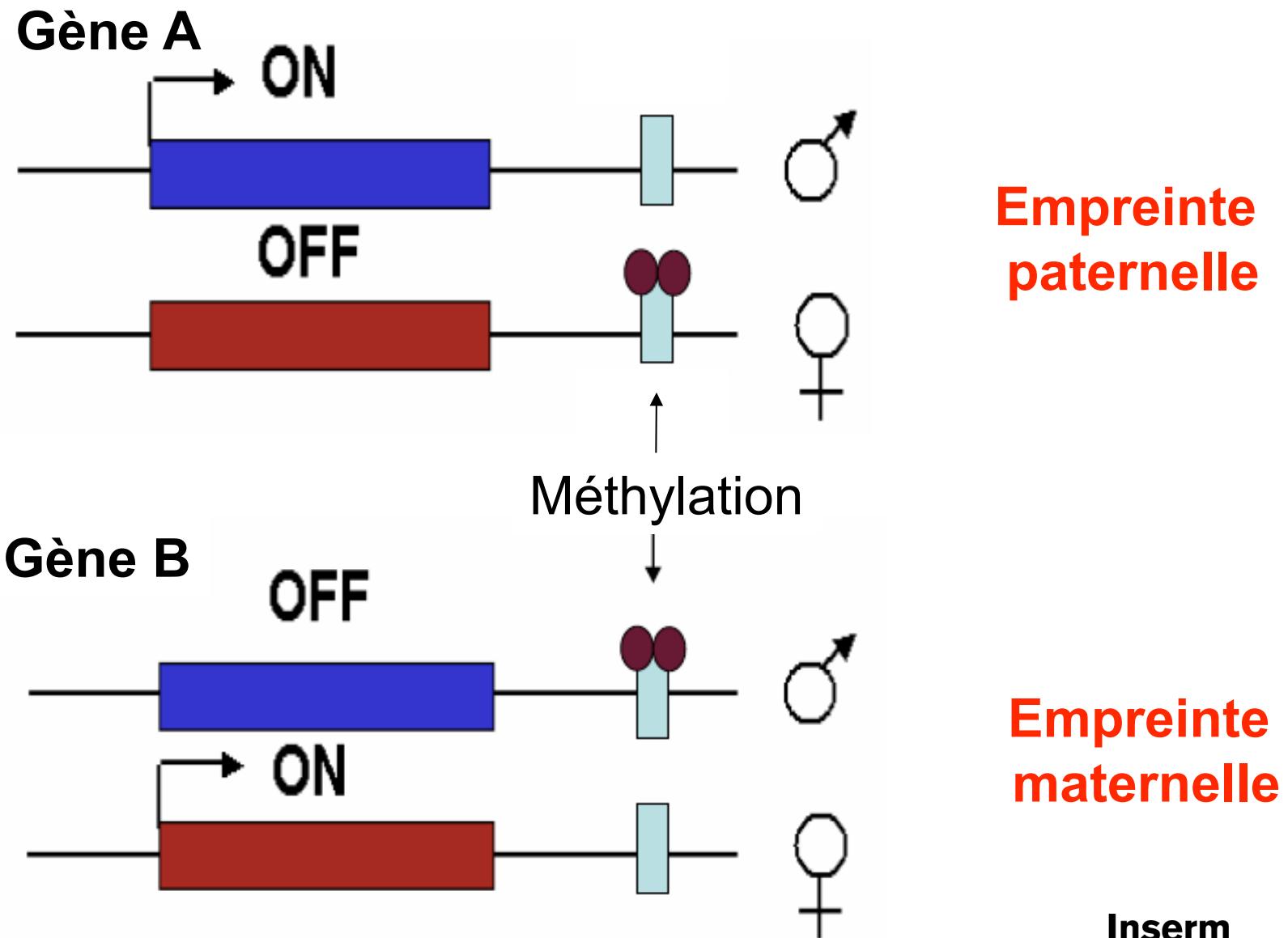
La DéMéthylation de l'ADN

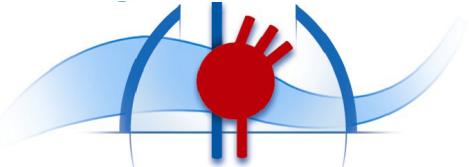
Processus actif





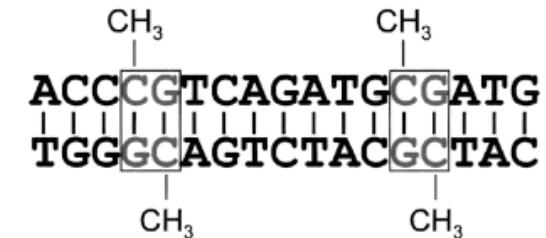
La méthylation de l'ADN et l'empreinte parentale





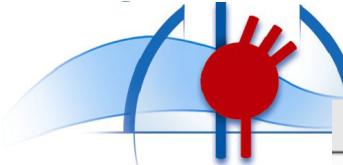
Méthylation abérantes et pathologies

- Hypométhylation --> instabilité génétique, surexpression de gènes oncogénique
- Hyperméthylation des îlots CpG --> inactivation de certains gènes comme des gènes suppresseurs de tumeurs → recherche des profils de méthylation dans certaines pathologies



Génés inhibés par méthylation dans les cancers

Cell cycle	RB1, INK 4a, INK4b, p14 ARF
Signal transduction	APC, LKB1/STK11, RASSF1
Apoptosis	DAPK, caspase-8
DNA repair	MGMT, BRCA1, MLH1
Carcinogen metabolism	GSTP1
Hormonal response	ER, PR, RAR
Metastasis	E-cadherin, VHL

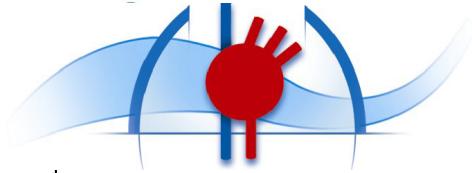


Méthylation abérantes et pathologies

Table 1: Associations between epigenetic modifications and human diseases and conditions

Disease/condition	Gene	Biological process	Disease/condition	Gene	Biological process
Cancer					
Bladder	Multiple genes	Hypermethylation ²⁰	Schizophrenia	<i>RELN</i>	Hypermethylation ^{46,47}
Brain (glioma)	<i>RASSF1A</i>	Hypermethylation ^{28,29}	Bipolar disorder	<i>11p?</i>	Unknown ⁴⁸
Brain (glioblast)	<i>MGMT</i>	Hypermethylation ³⁰	Memory formation	Multiple genes	Hypo-, hypermethylation ²⁹
Breast	<i>BRCA1</i>	Hypermethylation ³¹	Lupus	Retroviral DNA	Hypomethylation ³⁰
Breast	Multiple genes	Hypermethylation ^{32,33}	Cardiovascular		
Cervix	<i>p16</i>	Hypermethylation ³⁴	Atherosclerosis	Multiple genes	Hypo-, hypermethylation ^{39,51}
Colon	Multiple genes	Hypermethylation ²⁰	Homocysteinemia	Multiple genes	Hypomethylation ³²
Colorectal	L1 repeats	Hypomethylation ³⁵	Vascular endothelium	<i>eNOS</i>	Hypomethylation ³³
Esophagus	<i>CDH1</i>	Hypermethylation ²⁰	Imprinting and pediatric syndromes		
Head/neck	<i>p16, MGMT</i>	Hypermethylation ²⁰	PWS or AS	15q11-q13	Imprinting ⁵⁴
Kidney	<i>TIMP-3</i>	Hypermethylation ²⁰	BWS	11p15	Imprinting ⁵⁵
Leukemia	<i>p15</i>	Hypermethylation ²⁰	SRS	Chromosome 7	Imprinting ⁵⁶
Liver	Multiple genes	Hypermethylation ³⁶	UPD14	14q23-q32	Imprinting ⁵⁷
Lung	<i>p16, p73</i>	Hypermethylation ²⁰	PHP, AHO, MAS	20q13.2	Imprinting ⁵⁸
Lymphoma	<i>DAPK</i>	Hypermethylation ²⁰	Rett syndrome	<i>MECP2</i>	Mutation ⁵⁹
Myeloma	<i>DAPK</i>	Hypermethylation ³⁷	ICF syndrome	<i>DNMT3B</i>	Mutation ⁶⁰
Ovary	<i>BRCA1</i>	Hypermethylation ³⁸	ATRX	ATRX	Chromatin structure ⁶¹
Ovary	<i>Sat2</i>	Hypomethylation ³⁹	FraX	Triplet repeat	Silencing ⁶²
Pancreas	<i>APC</i>	Hypermethylation ²⁰	FSHD	3.3 kb repeat	Chromatin structure ⁶³
Pancreas	Multiple genes	Hypomethylation ⁴⁰	Reproductive		
Prostate	<i>BRCA2</i>	Hypermethylation ^{20,41}	Ovarian teratoma	No paternal genome	Imprinting ⁶⁴
Rhabdomyosarcoma	<i>PAX3</i>	Hypermethylation ⁴²	CHM	No maternal genome	Imprinting ⁶⁵
Stomach	<i>Cyclin D2</i>	Hypomethylation ⁴³	BiCHM	Maternal genome	Imprinting ⁶⁵
Thymus	<i>POMC</i>	Hypomethylation ⁴⁴	Aging	Chromatin	Hypo-, hypermethylation ⁶⁶
Urothelial	Satellite DNA	Hypomethylation ⁴⁵			
Uterus	<i>hMLH1</i>	Hypermethylation ²⁰			

Note: PWS = Prader-Willi syndrome; AS = Angelman syndrome; BWS = Beckwith-Wiedemann syndrome; SRS = Silver-Russell syndrome; UPD14 = uniparental disomy 14; PHP = pseudohypoparathyroidism; AHO = Albright hereditary osteodystrophy; MAS = McCune-Albright syndrome; ICF = immunodeficiency, centromeric instability and facial anomalies; ATRX = α -thalassemia/mental retardation syndrome, X-linked; FraX = Fragile X syndrome; FSHD = facioscapulohumeral muscular dystrophy, CHM = complete hydatidiform mole, BiCHM = familial biparental CHM.



L'épigénétique

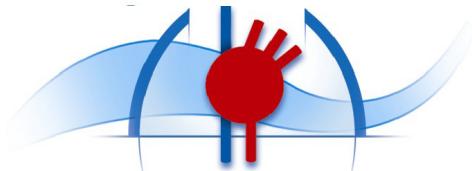
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III – Définition et rappels

IV – Modifications de l'ADN : la méthylation

V – Modifications de la structure de la chromatine/des protéines



L'épigénétique

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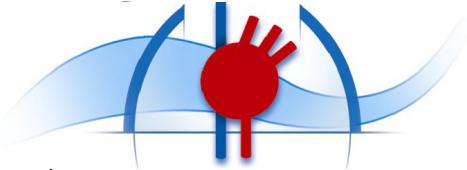
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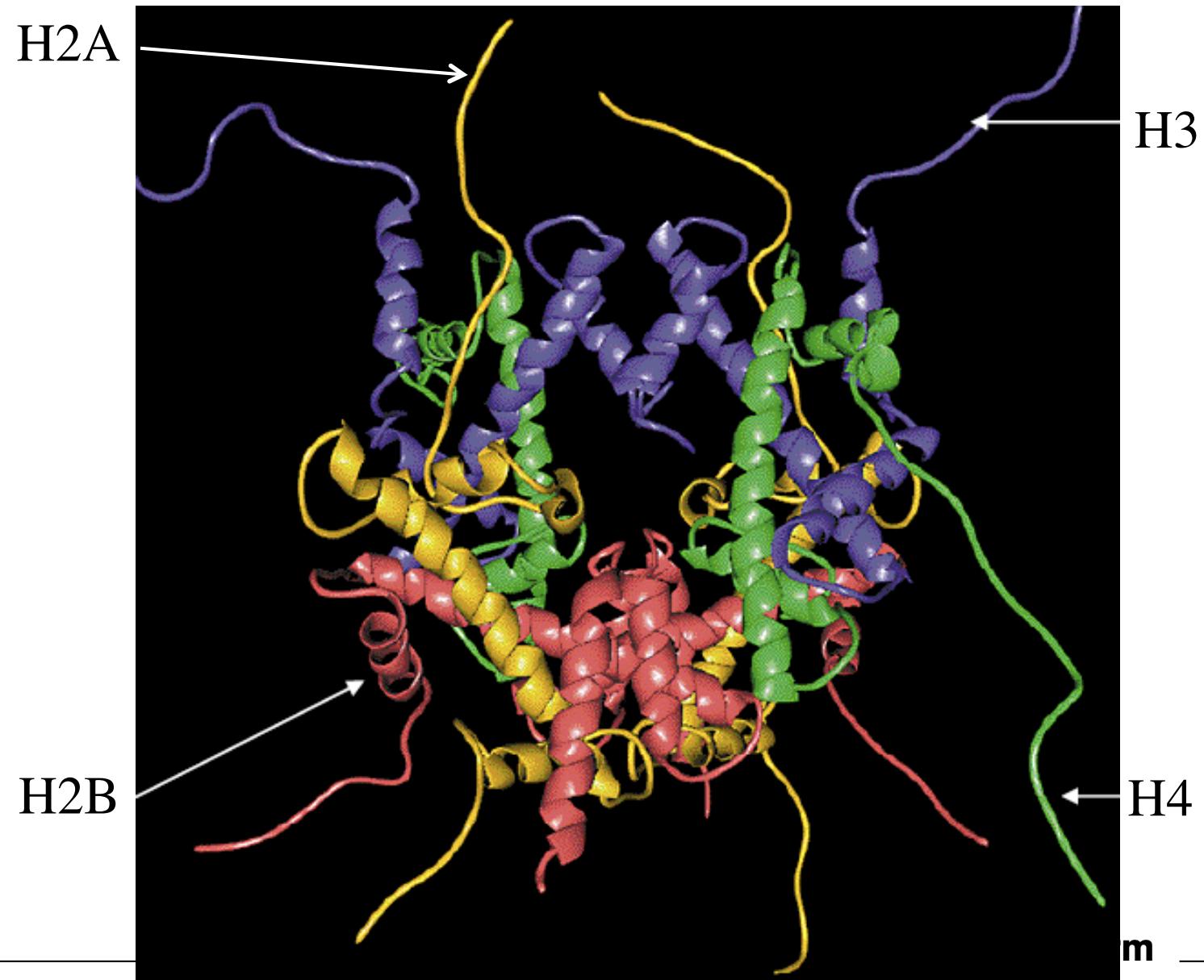
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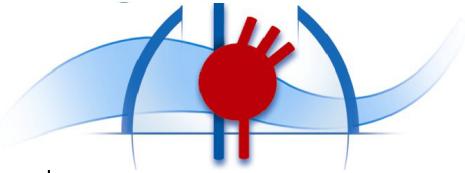
V – Modifications de la structure de la chromatine/des protéines

- Modifications des histones/réorganisation du nucléosome

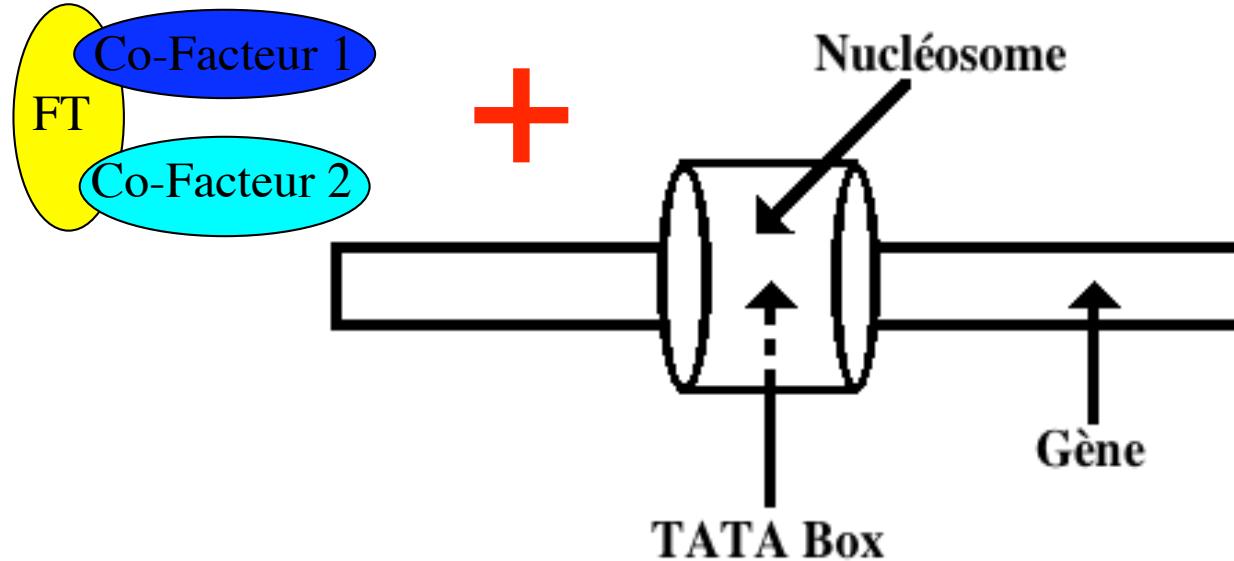


Cristallographie des histones



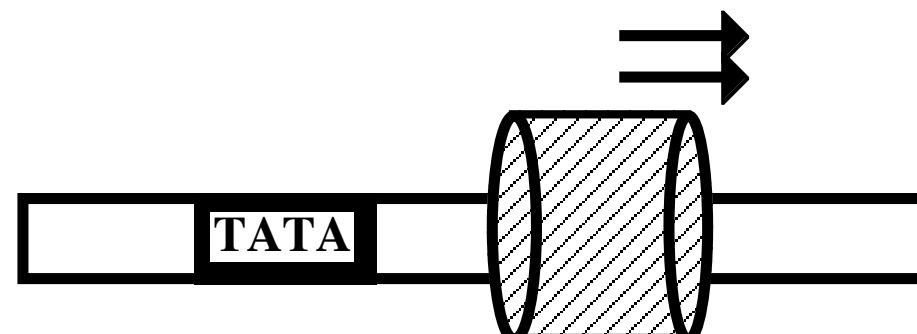


Initiation de la transcription



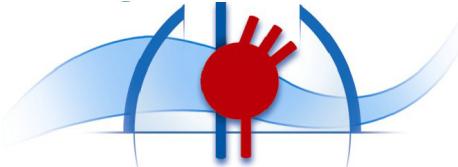
1. Déstabilisation du Nucléosome

→ Structure Moins Rigide

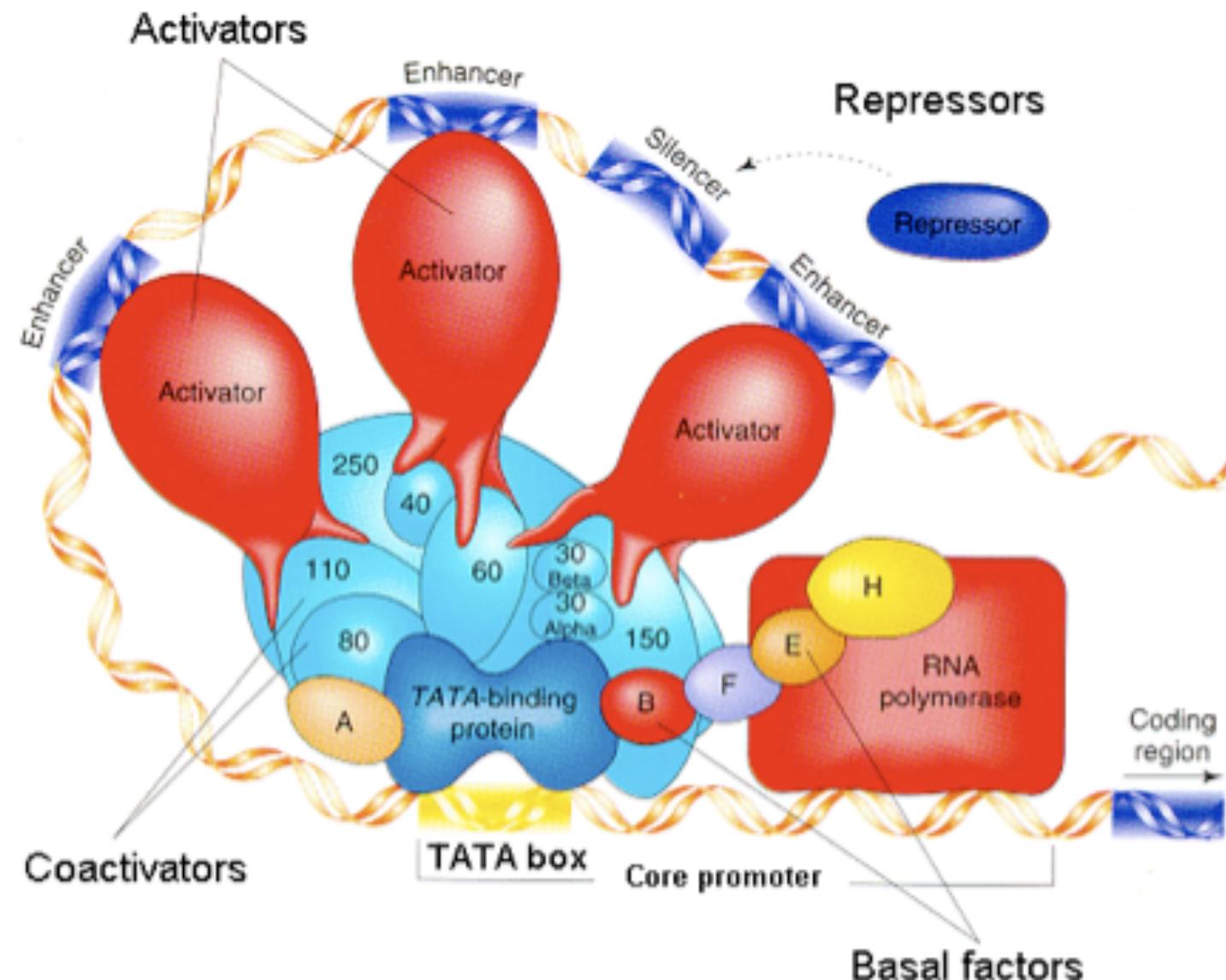


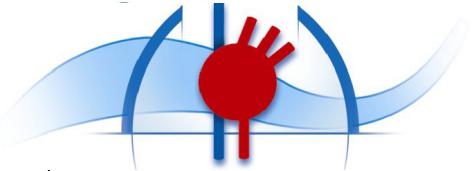
2. Déplacement du Nucléosome

→ TATA Box Accessible



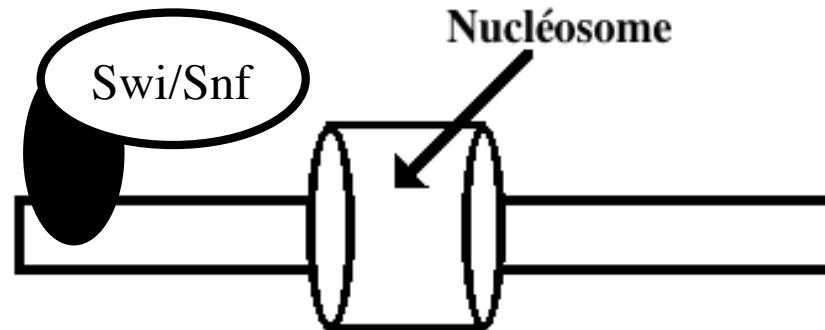
Le complexe d'initiation de la transcription



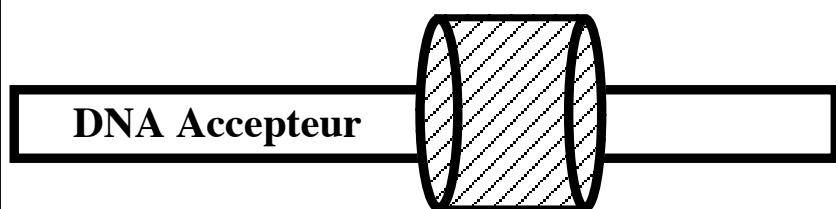


Déplacement du nucléosome

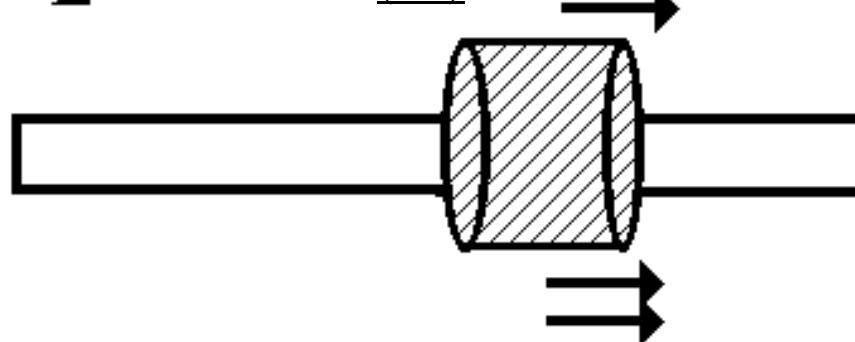
SWI/SNF



Transfert du Nucléosome
(trans)

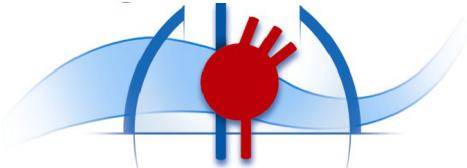


Déplacement du Nucléosome
(cis)



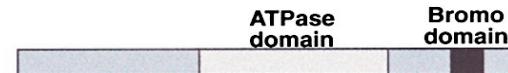
Le Déplacement du Nucléosome est un Processus qui Dépend de 1 'ATP

→ Après Fixation sur l'ADN, le Complexe
Hydrolyse des Quantités Importantes d'ATP

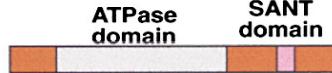


Les complexes de remodelage

SWI2/SNF2 family



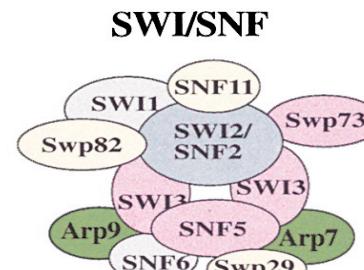
ISWI family



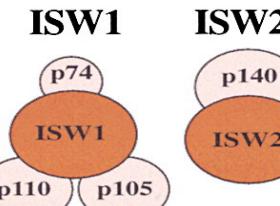
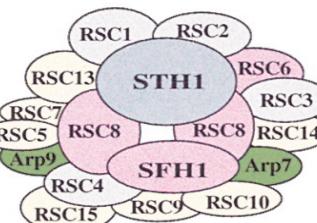
Mi-2 family



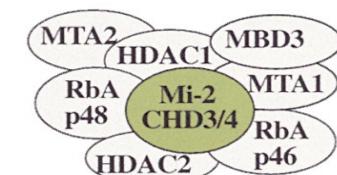
Yeast



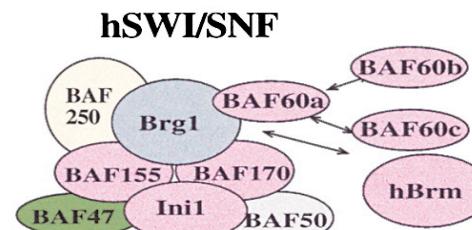
RSC



NuRD



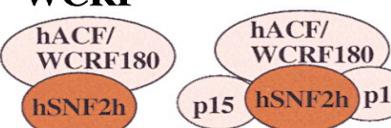
Human



RSF



hACF/ WCRF

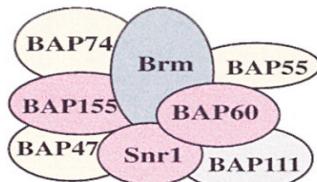


hCHRAC



Drosophila

dSWI/SNF



NURF

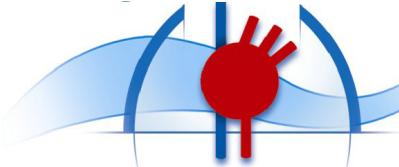


CHRAC

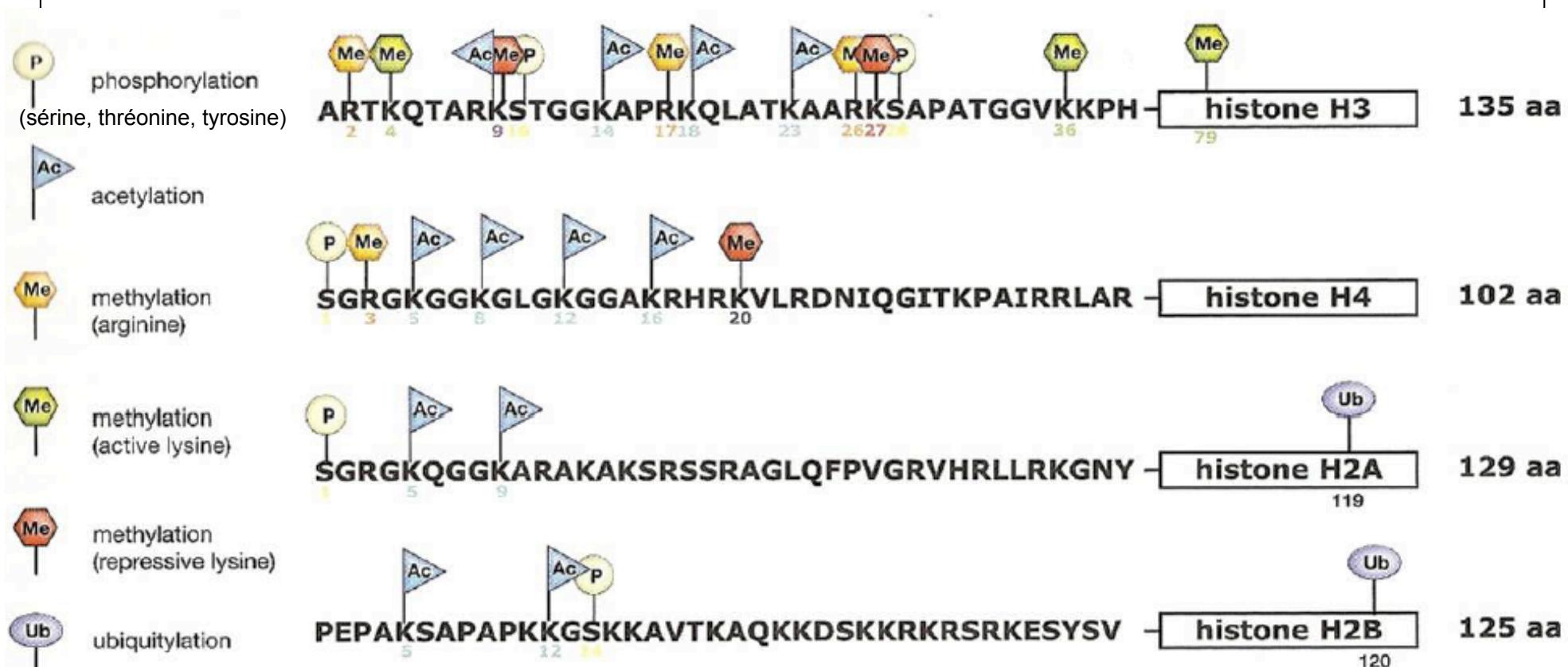


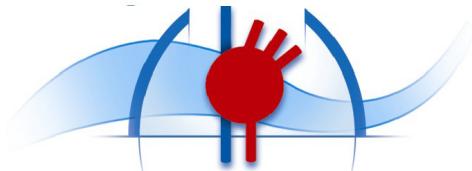
ACF





Modifications de la structure de la chromatine : modifications des histones





L'épigénétique

I – Introduction

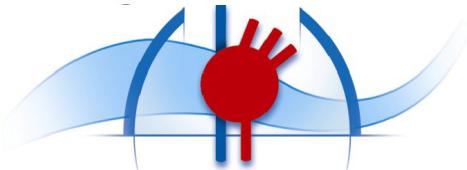
II – Historique

III – Définition et rappels

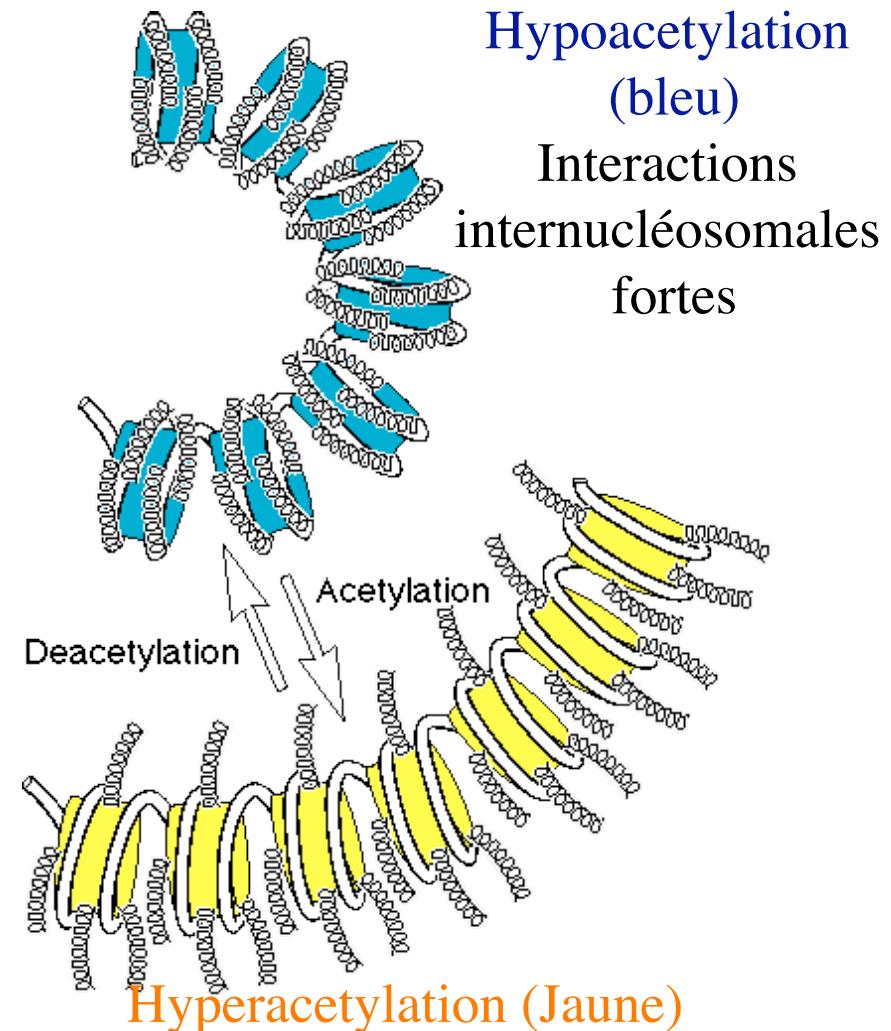
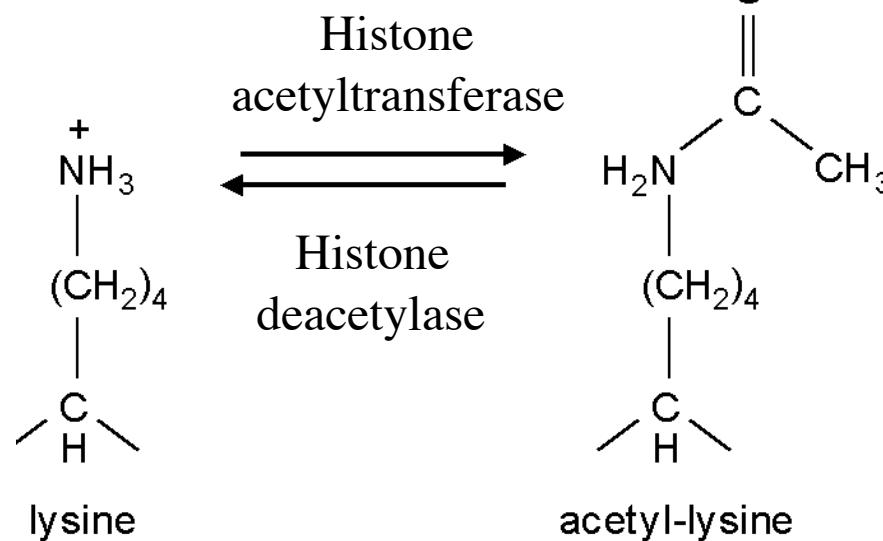
IV – Modifications de l'ADN : la méthylation

V – Modifications de la structure de la chromatine/des protéines

- Modifications des histones/réorganisation du nucléosome
- L'acétylation des histones



L'acétylation des histones



L'acétylation a 2 fonctions :

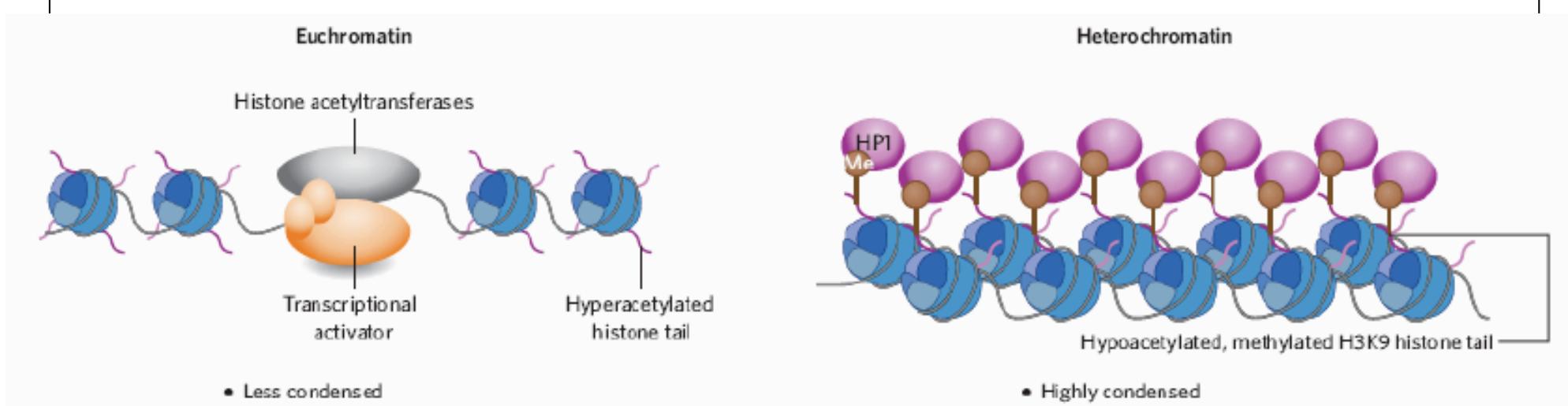
- 1) Neutraliser les charges positives des résidus lysine
- 2) Déstabiliser les interactions entre les queues d'histone et les protéines de structure

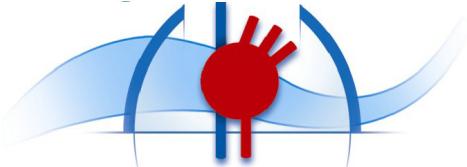
Interactions internucléosomales faibles :
 Les queues d'histone ne contiennent pas d'ADN, qui sont ainsi accessibles pour les facteurs de transcription



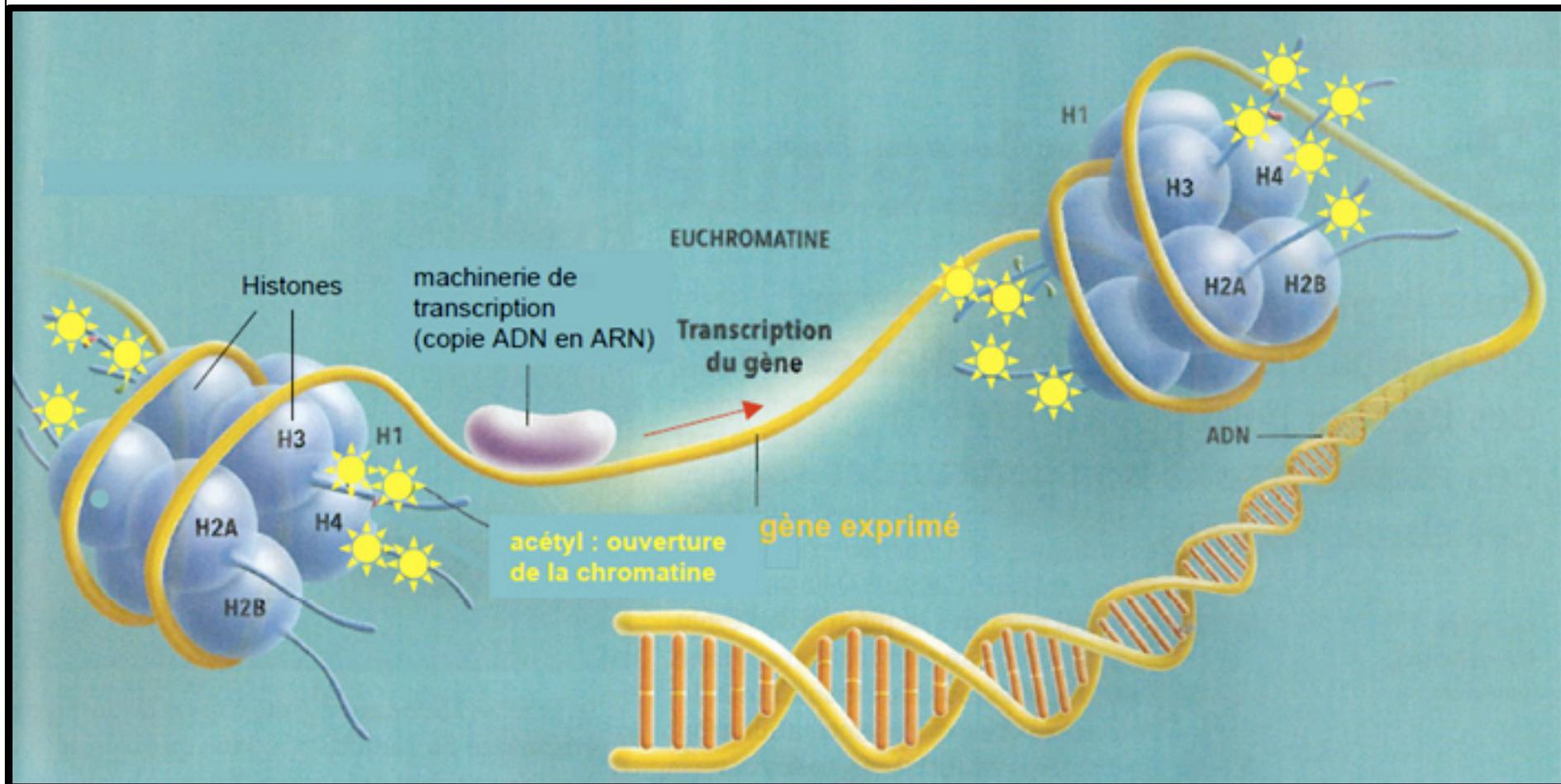
L'acétylation des histones

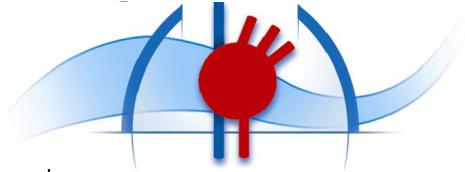
- 1) Acétylation des histones au niveau des zones portant des gènes transcriptionnellement actifs
- 2) Acétylation = modification des résidus lysine au sein des histones →
 - réduction des charges positives et diminution de l'interaction avec l'ADN
 - ADN est plus accessible pour l'ARN polymérase II
- 3) Les enzymes qui permettent l'acétylation des histones sont recrutées pour participer à l'activation de la transcription des gènes
- 4) Les enzymes qui enlèvent les groupements acétyl des histones sont recrutées en parallèle pour la méthylation de l'ADN. Déacetylation/gènes inactifs





L'acétylation des histones





Acétylases et déacétylases

La famille des acétylases

GNATs (Gcn5-related acetyltransferase)

Hat1 (Substrates: H2A, 4)
 Gcn5 and Gcn5L (H2B, H3 K9/K14, c-Myc)
 Elp3 (H3, 4)
 Hpa2 (H3, 4)
 PCAF (H3, 4, c-Myc, GATA2)

MYST (MOZ, Ybf2/Sas3, Sas2,

Esa1 (H2A, 4)
 Tip60 (H2A, 4, c-Myc, AR)
 MOF (H2A, 3, H4 K16)
 MOZ
 Sas3 (H3, 4)
 Sas2 (H4 K16)

P300/CBP

P300/CBP (H2A, 2B, 3, 4, p53, p65, AR, ER)

General transcription factor HATs

TAF250 (H3, 4)
 TFIIC (H2A, 3, 4)

Nuclear hormone related HATs

SRC1 (H3, 4)
 SRC3/ACTR (H3, 4)

La famille des déacétylases

Class I (Rpd3 homologs)

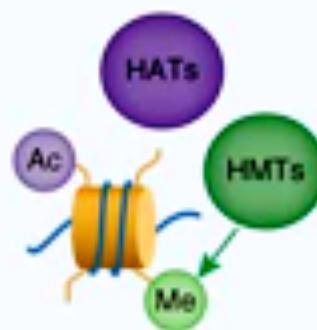
HDAC1 (Substrates: H2A, 2B, 3, 4, AR, ER, SHP, YY1)
 HDAC2 (H2A, 2B, 3, 4, GR, YY1)
 HDAC3 (H2A, 2B, 3, 4, GR, SHP, GATAI, YY1)
 HDAC8 (H2A, 2B, 3, 4)
 HDAC11 (H2A, 2B, 3, 4)

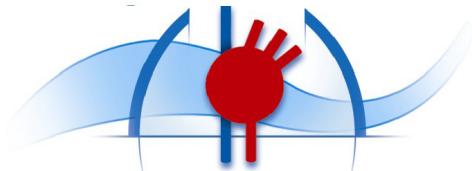
Class II (Hdal homologs)

IDAC4 (H2A, 2B, 3, 4, GATAI)
 IDAC5 (H2A, 2B, 3, 4, GATAI)
 IDAC6 (H2A, 2B, 3, tubulin, SHP)
 IDAC7 (H2A, 2B, 3, 4)
 IDAC9 (H2A, 2B, 3, 4)
 IDAC10 (H2A, 2B, 3, 4)

Class III (Sir2 homologs - Sirtuins)

SIRT1
 SIRT2
 SIRT3
 SIRT4 (non-histone proteins)
 SIRT5 (tubulin, p65, p53)
 SIRT6
 SIRT7





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- La méthylation des histones



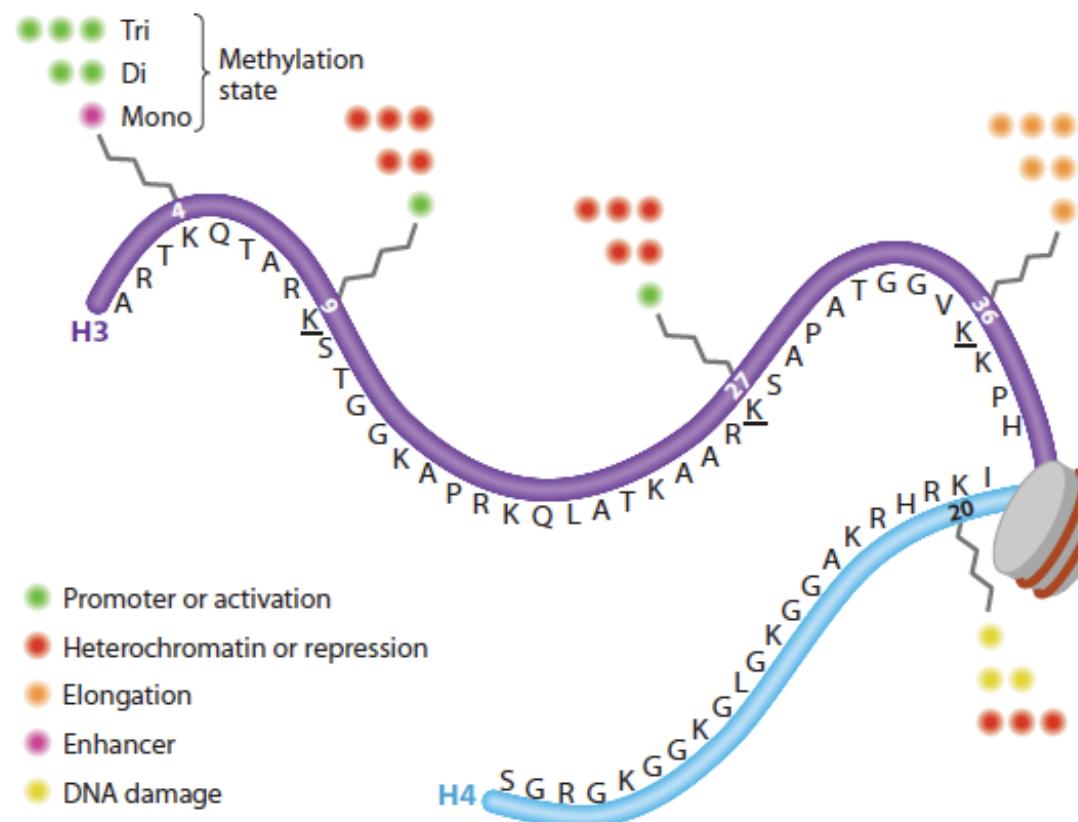
La méthylation des histones

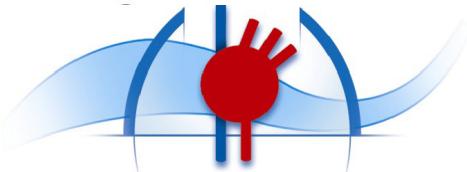
1) Méthyltransférases ciblent certains résidus arginine et lysine de l'histone

2) La méthylation des arginines = activation transcriptionnelle

La méthylation des lysines = répression transcriptionnelle mais dépend du degré de méthylation et de la position des lysines

3) La méthylation des histones interagit avec la méthylation de l'ADN





L'épigénétique

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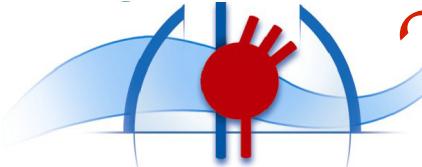
II – Historique

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IV – Modifications de l'ADN : la méthylation

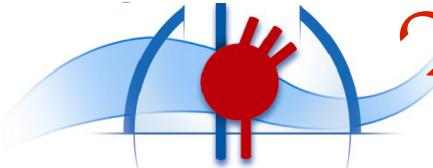
V – Modifications de la structure de la chromatine/des protéines

- Modifications des histones/réorganisation du nucléosome
- L'acétylation des histones
- La méthylation des histones
- Autres modifications

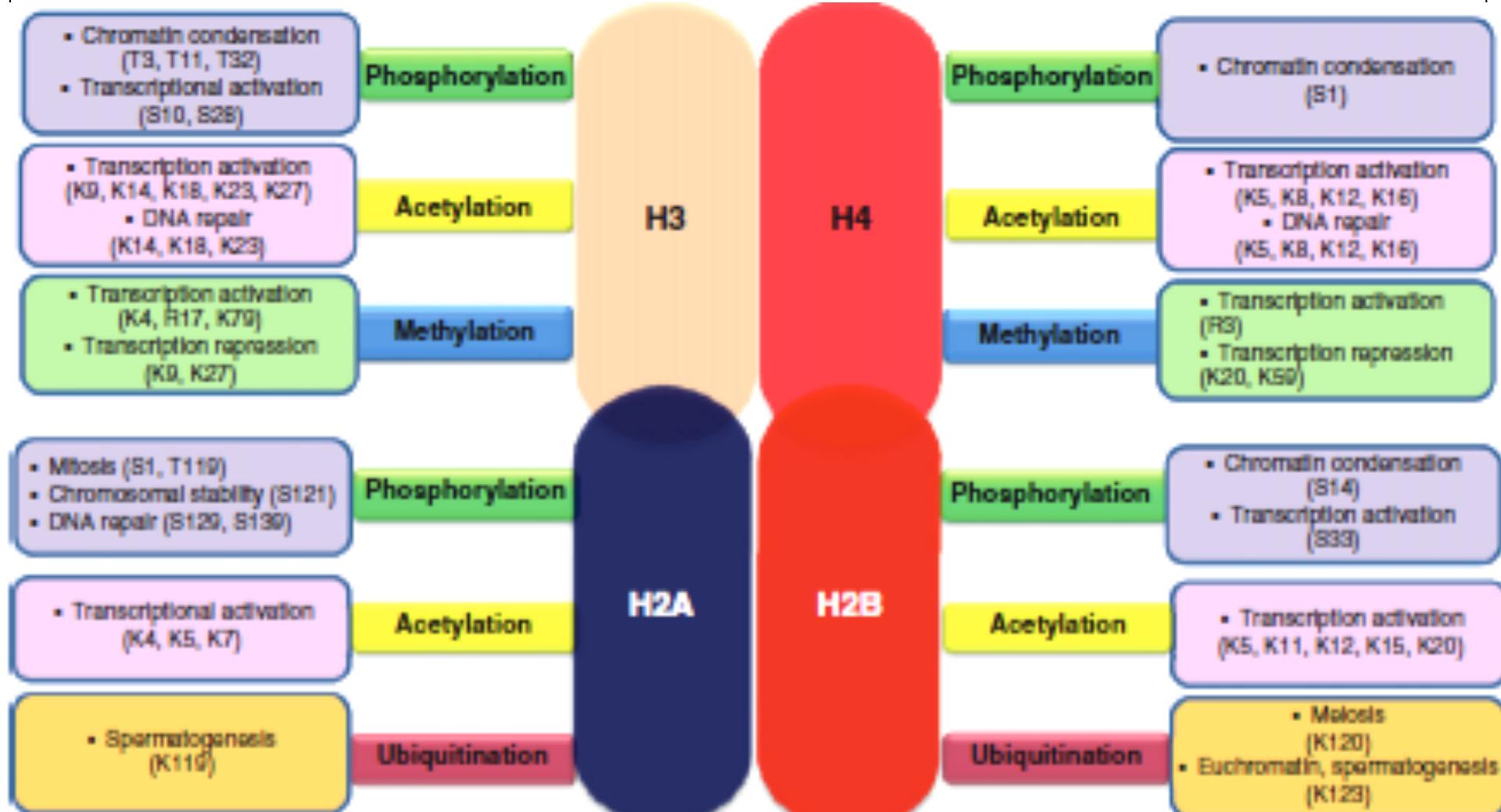


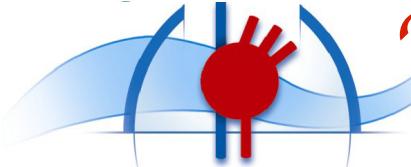
Modifications de la structure de la chromatine : Autres modifications des histones

Chromatin modification	Residue modified	Modifier	Cofactors
Histone methylation	Lysine	SET domain HMTs	SAM
	Arginine	PRMT	SAM
Histone demethylation	Lysine, arginine	Jumonji family	Oxygen, α -ketoglutarate, Fe(II)
	Lysine	LSD	FADH
Histone <i>O</i> -linked glycosylation	Serine, threonine, tyrosine	OGT	UDP-GlcNAc
Histone acetylation	Lysine	HAT	Acetyl-CoA
Histone deacetylation	Lysine	Sirtuins	NAD ⁺
		HDAC	None
Histone ubiquitylation	Lysine	RING finger E3 ligases	ATP
Histone sumoylation	Lysine	SUMO E3 ligases	ATP
Histone ADP-ribosylation	Glutamine	PARP	NAD ⁺
Histone deimination	Arginine	PADI4	Ca ²⁺
Histone isomerization	Proline	Prolyl-isomerase	None
Histone phosphorylation	Serine, threonine, tyrosine	Kinases	ATP
Histone clipping	Histone H3 N-terminal tail	Cathepsin-L	
Histone crotonylation	Lysine	Not identified	Crotonyl-CoA



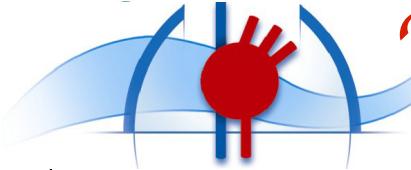
Modifications de la structure de la chromatine : modifications des histones





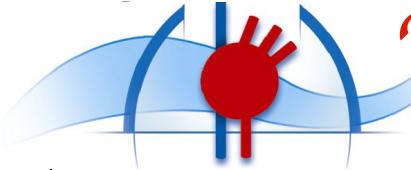
Modifications de la structure de la chromatine : modifications des histones : le code histone 1

PTM	Position	Enzyme			Function	Recognized by	Reversed by		
		S.c.	D.m.	Mammals			S.c.	D.m.	Mammals
Lys Acetylation	H2AK4	Esa1	Tip60 [173]	TIP60, P300/CBP, HBO1 [174-176]	Transcription activation		Rpd3 [177]		
	H2AK5	[172]							
	H2AK7	Esa1 [172]			Transcription activation		Rpd3, Hda1 [177]		
	H2BK11	Gcn5		P300/CBP, ATF2 [175, 179]					
	H2BK12	[178]							
	H2BK16	Gcn5, Esa1		P300/CBP, ATF2 [175, 179]	Transcription activation		Rpd3, Set3, Hda1, Hos2, Hst1 [193, 194]	dHDAC1 [185]	SIRT1/6 [186]
	H2BK15	[178]							
	H3K9	Gcn5, Rtt109 [180, 181]	dGcn5 [182]	SRC1, PCAF [175, 183]					
	H3K14	Gcn5, Hpa2, Esa1, Elp3, Sas2, Sas3 [172, 178, 180, 187-190]	dGcn5, Taf1, dCBP [182, 191]	P300/CBP, TAF1, hGCN5, PCAF, MOZ, MORF, TIP60, SRC1, HBO1 [174, 175, 183, 191, 192]	Bromo, PHD [193, 194]				
	H3K18	Gcn5 [180]	dCBP	P300/CBP [175, 195]					
	H3K23	Gcn5, Sas3 [178, 190]		P300/CBP [175]					
	H3K27	Gcn5, Rtt109 [178, 196]	dCBP [197]		PH, (Snf5) [200, 201]			Sir2 [199]	SIRT1/2/6 [199, 203]
	H3K36	Gcn5 [198]							
	H3K56	Rtt109 [51]	dCBP [199]	P300/CBP [199]					
	H4K5	Esa1	Hat1, dCBP	HAT1, TIP60, P300, HBO1 [174, 204]	Transcription activation	Bromo [205]	Rpd3, Set3, Hos2, Hst1 [177, 184, 206]		
	H4K8	Esa1, Elp3, Gcn5 [188]	dCBP	TIP60, P300, HBO1 [174, 204]		Bromo [205]			
	H4K12	Hat1, Esa1, Hpa2 [187]		TIP60, P300, HBO1 [174, 204]					
	H4K16	Sas2, Esa1 [172, 189]	Mof, Atac2 [207, 208]	hMOF, TIP60, ATF2 [174, 179, 209]		Bromo [210]	Sir2 [211]	Sir2 [199]	SIRT1/2 [186, 212]



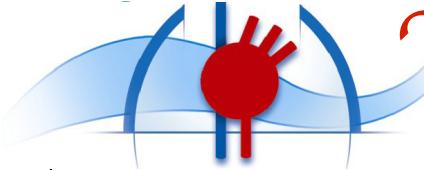
Modifications de la structure de la chromatine : modifications des histones : le code histone 2

Lys Methylation	H3K4	Set1 [55]	Trx, Trr, Ash1, Set1 [213-216]	SET1, NSD2-3, SET7/9, MLL1-4, SMYD3, ASH1L [217-220]	Transcription activation	PHD, Chromo, WD40, ADD, Tudor, MBT, Zf-CW [68, 73, 74, 221-225]	Jhd2 [226]	Lid, Su(var)3-3 [227, 228]	LSD1, AOF1, JARID1A-D [229-231]
	H3K9		Su(var)3-9, Ash1, G9a [215, 232, 233]	SUV39H1/2, G9a, Eu-HMT1, SETDB1, RIZ1, ASH1 [232, 234-237]	Silencing	PHD, Chromo, Tudor, WD40, Ankyrin [223, 238-241]	Rph1 [242]	dKDM4B [243]	LSD1, JHDM2A/B, JMJD2A-D, KIAA1718, PHF8 [244-248]
	H3K23					Chromo [249]			
	H3K27		E(z) [250]	EZH1/2, NSD2-3, G9a [217, 234, 251]	Silencing	Chromo, WD40 [240, 252]			
	H3K36	Set2 [113]	Set2, Mes4, Ash1 [253-255]	SETD2-3, NSD1-3, SMYD2, ASH1L, SETMAR [254, 256-258]	Transcription elongation	Chromo, PHD, PWWP [128, 259, 260]	Jhd1, Rph1, Gis1 [242, 261, 262]	dKDM4A/B [243]	JHDM1A/B, JMJD2A-C [246, 263]
	H3K79	Dot1 [92]	Crappa [109]	DOT1L [93]		Tudor [112]			
	H4K20		Pr-set7, Suv4-20, Ash1 [215, 264-266]	ASH1L, NSD1, Pr-SET7, SUV4-20H, NSD2 [257, 264, 265, 267, 268]	Transcription activation/repression	Tudor, MBT, PWWP, WD40 [70, 224, 269]			KIAA1718, PHF8 [247, 248]
Arg Methylation	H3R2me2a H3R2me2s	? [270]		PRMT6 PRMT5/7 [86, 271]	Transcription repression/activation	WD40 [86]			JMJD6 [272]
	H3R8			PRMT5 [273]	Transcription repression				PAD4 [274]
	H3R17			CARM1 [195]	Transcription activation				PAD4 [274]
	H3R26			CARM1 [276]					
	H4R3	Rmt1 [91]		PRMT1, PRMT5 [273, 277]	Transcription activation	Tudor, ADD, (p300/PCAF) [275, 278, 279]			JMJD6, PAD4 [272, 274]
Phosphorylation	H2BS10 H2BS14	Ste20 [280]		MST1 [281]	Apopotosis				
	H3S10	Snf1, Ipl1 [282, 283]	Jil1, Aurora B [284, 285]	MSK1/2, IKK α , PKB, RSK2, PIM1, Aurora B, JNK [286-291]	Transcription activation, mitosis, meiosis	(Gcn5), 14-3-3 [292, 293]	Glc7 [283]	PP2A [294]	

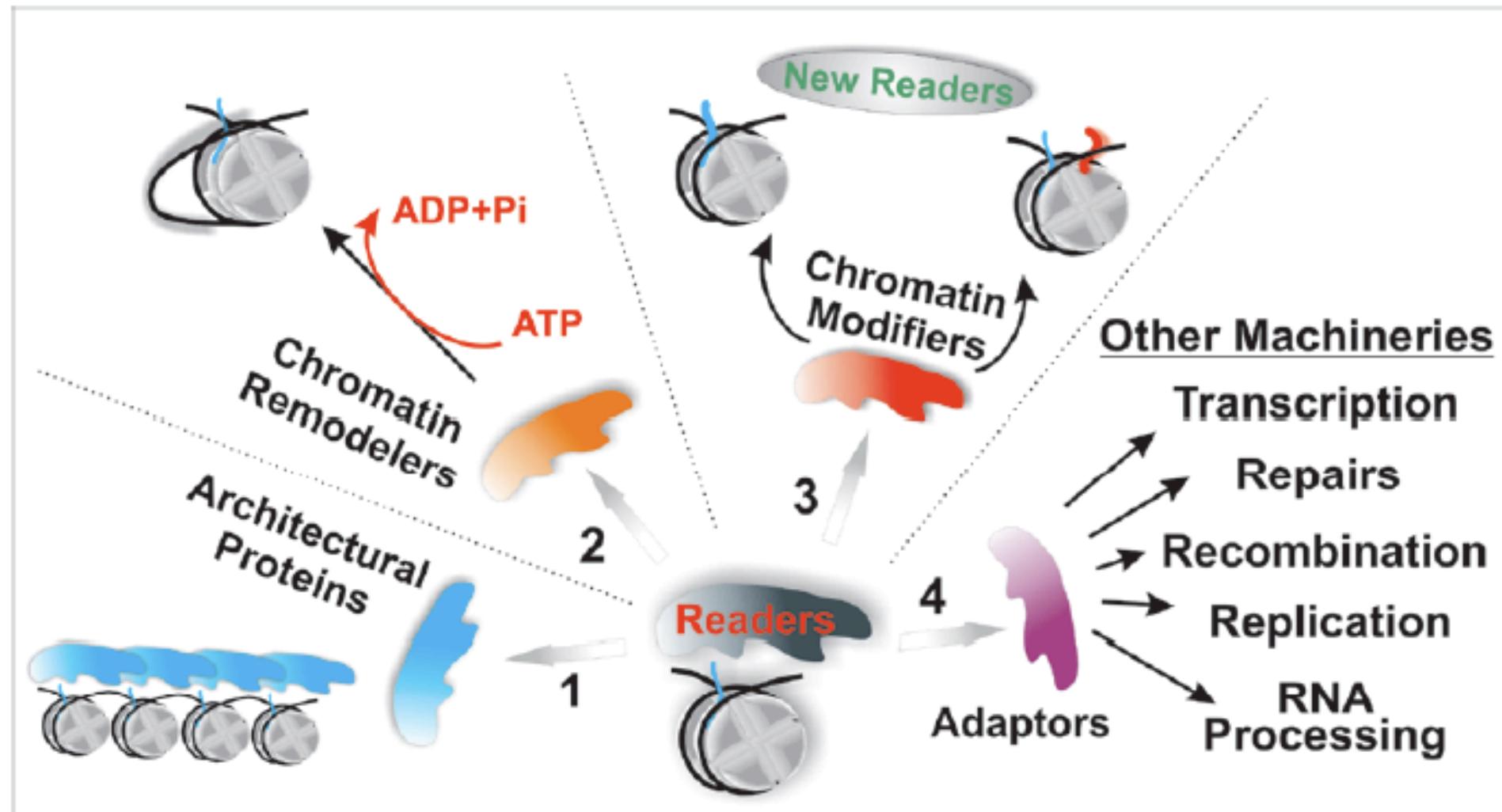


Modifications de la structure de la chromatine : modifications des histones : le code histone 3

Ubiquitination	H2AK119		Ring1B [295]	Ring1B, 2A-HUB [296, 297]	Transcription repression			Calypso [298]	USP3, USP16, USP21, USP22, 2A-DUB [299-303]
	H2BK123 H2BK120	Rad6, Bre1 [58, 304]	Rad6, Bre1 [305, 306]	HR6A/B, RNF20/40, UbcH6 [307, 308]	Transcription activation	(Cps35) [85]	Ubp8, Ubp10 [309, 310]	Nonstop, Scrawny, USP7 [311-313]	USP3, USP22 [299, 314]
Sumoylation	H2AK126	Ubc9, Siz1, Siz2 [315]			Transcription repression				
	H2BK6/7								
	H2BK16/K17								
	H4K5 K8 K12 K16 K20	Ubc9, Siz1, Siz2 [315]		UBC9					



Modifications de la structure de la chromatine : Fonctions des readers



Primary Modification

Further Modification

Secondary Modification