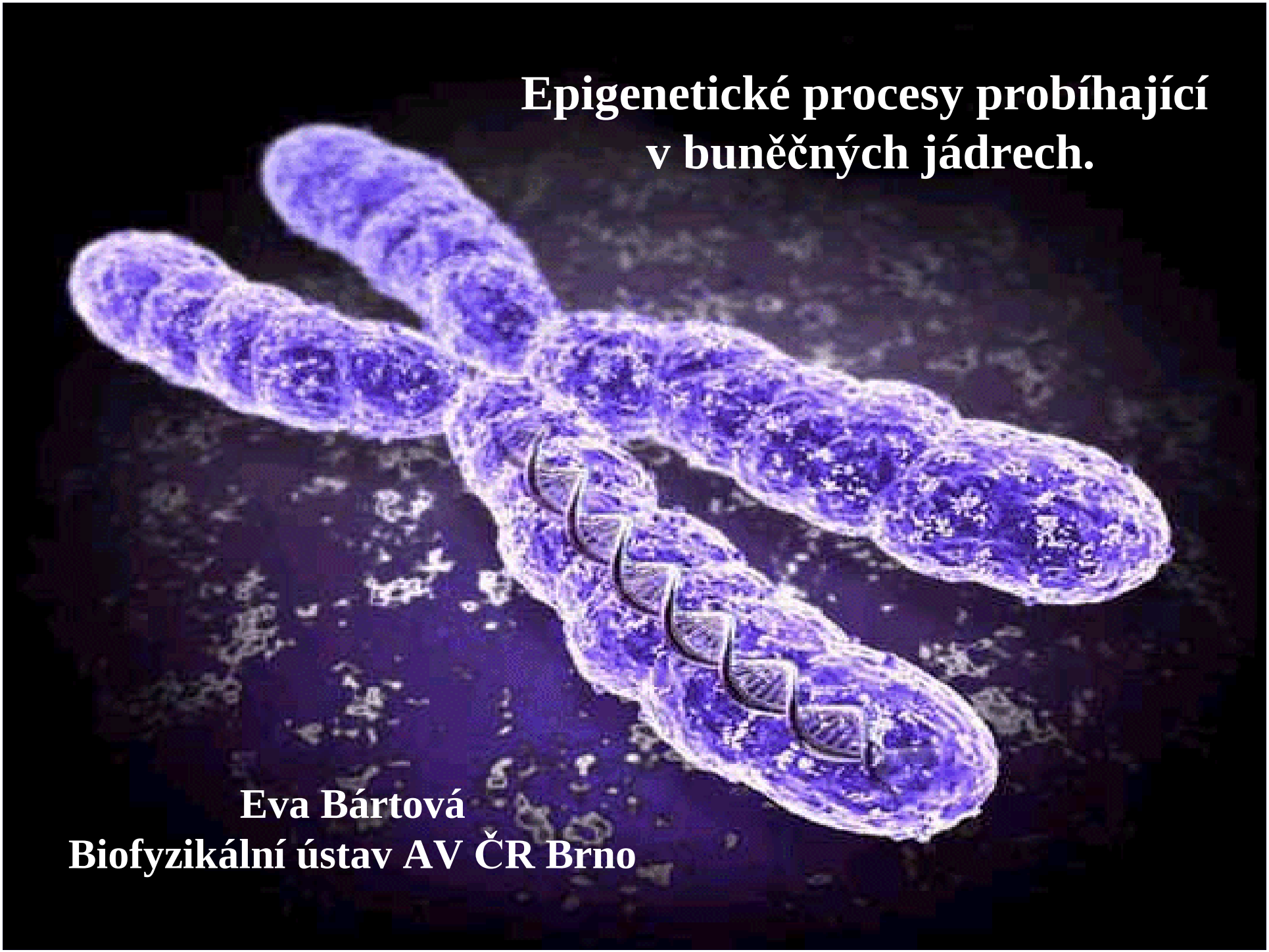
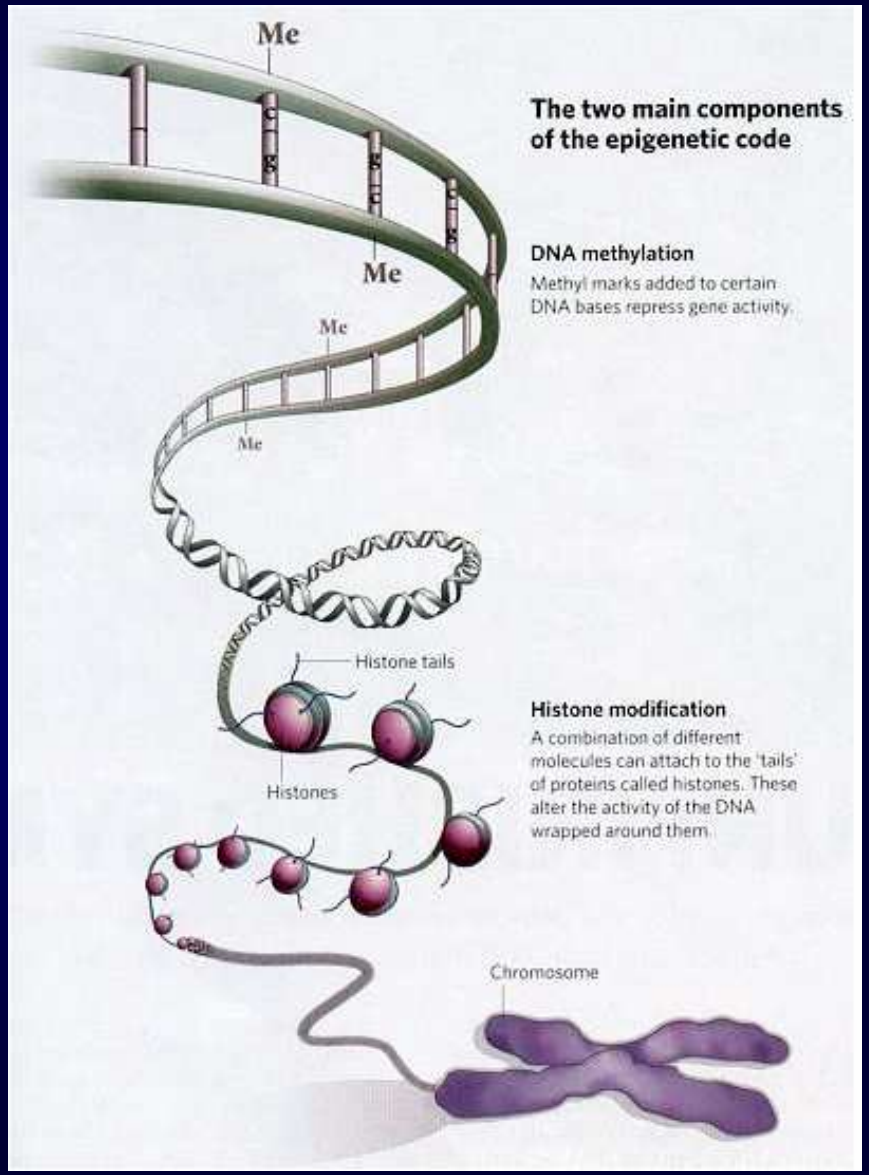
Epigenetické procesy probíhající v buněčných jádrech.



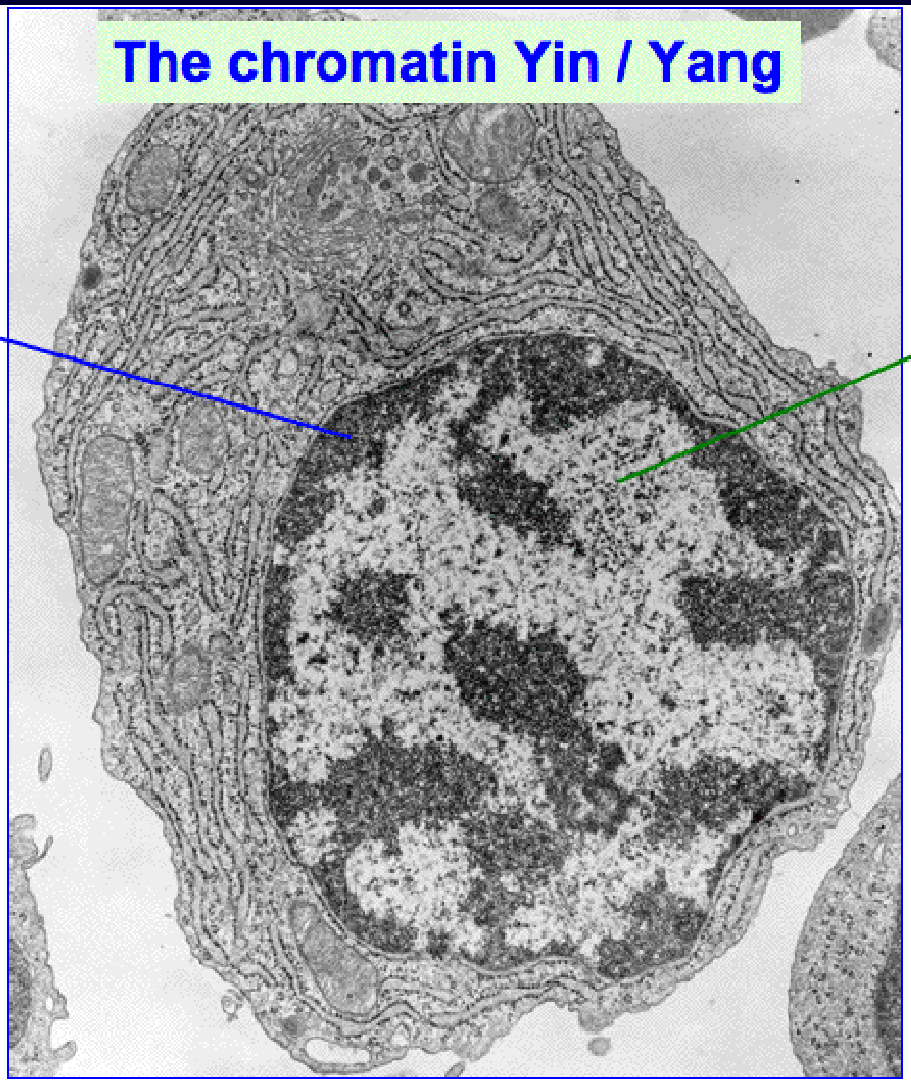
Eva Bártová
Biofyzikální ústav AV ČR Brno

What is epigenetics ?

Epigenetics refers to heritable changes in the phenotype that occur irrespective of alterations in the DNA sequences.



The chromatin Yin / Yang



Heterochromatin

- Heavily condensed
- Gene poor
- Silent genes
- Late replicating
- DNA hypermethylated
- Rich in histone H1
- Histones have repressive post translational marks

Euchrochromatin

- Less condensed
- Gene rich
- Active genes
- Early replicating
- DNA hypomethylated
- Poor in histone H1
- Histones have specific, activating post translational marks

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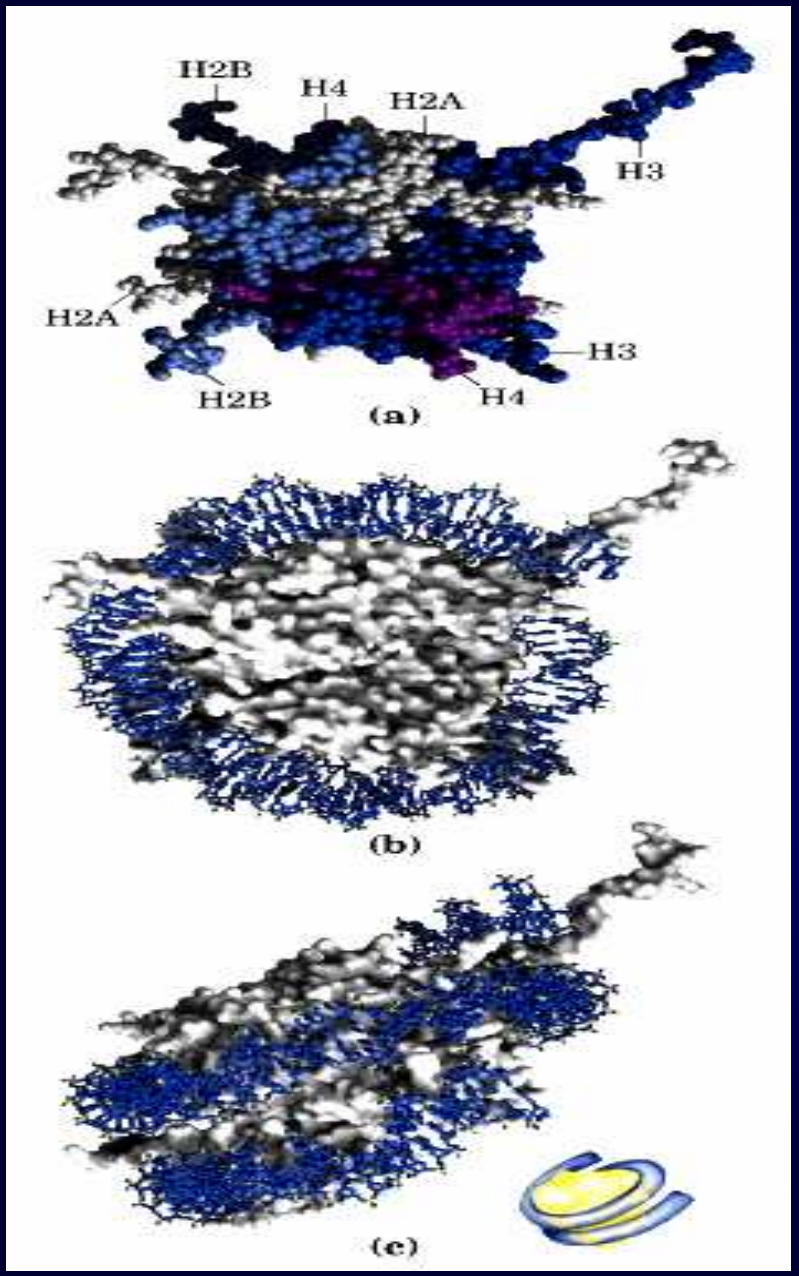
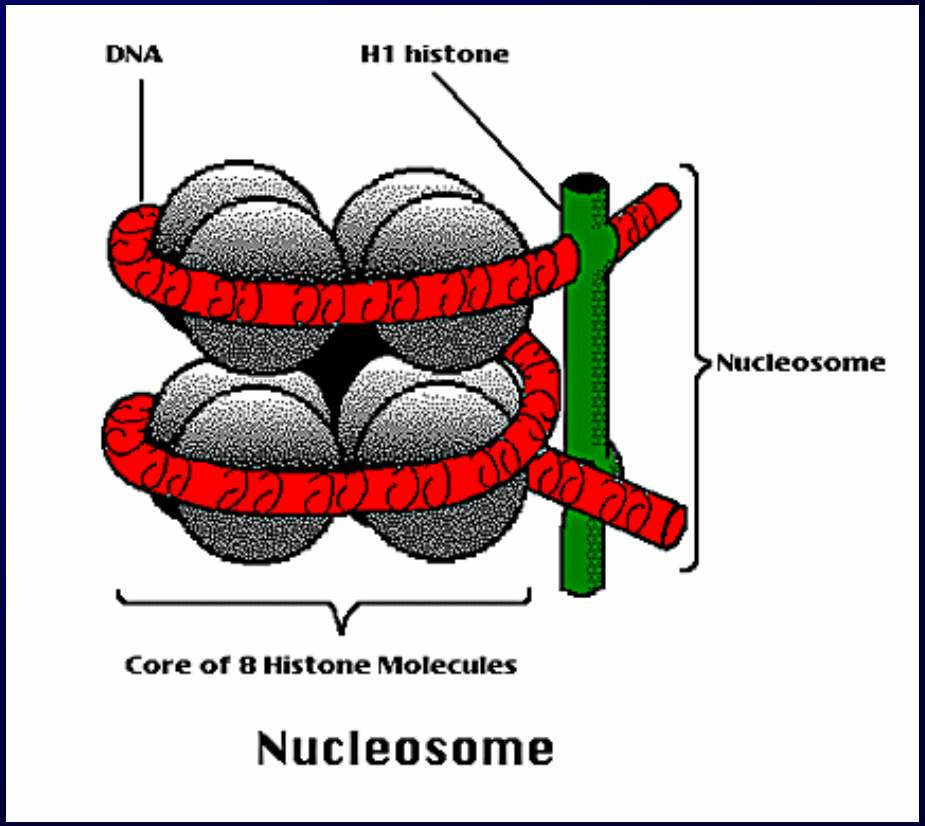
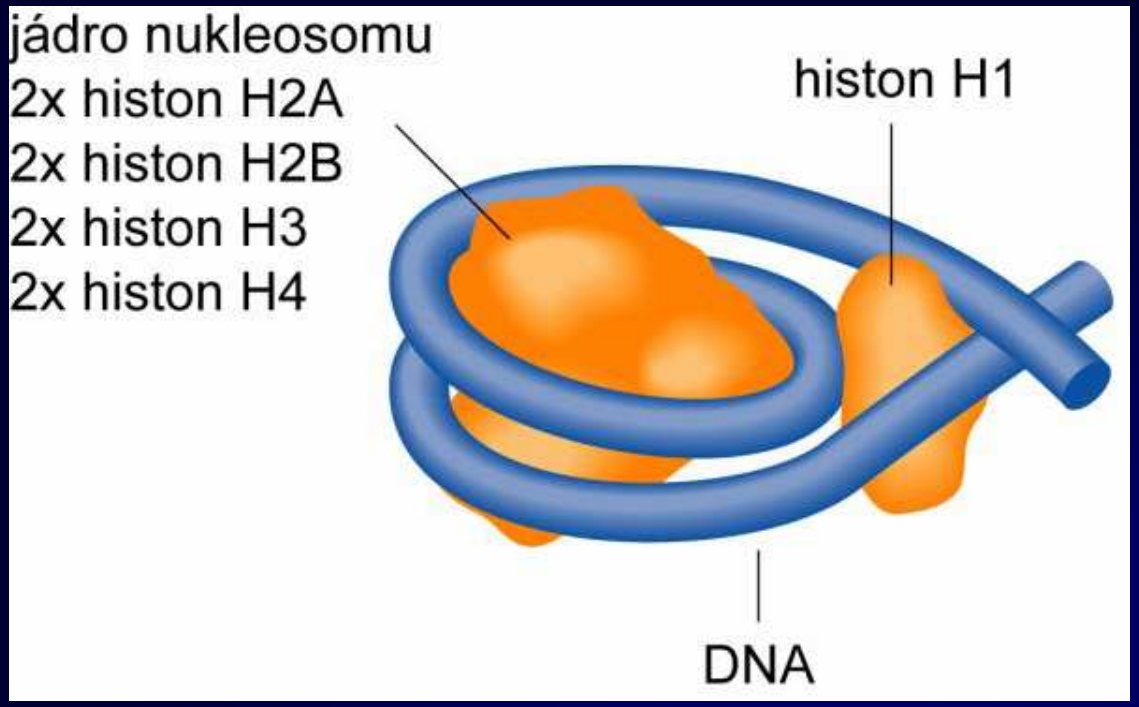
Cavalli Lab



N-koncové oblasti histonů H2A, H2B H3a H4 (délka 16-44 aminokyselin nejsou součástí jádra nukleosomu, ale vybíhají do stran (volné konce). V linkerové oblasti – H1: funkce na kondenzaci chromatinu vyššího řádu.

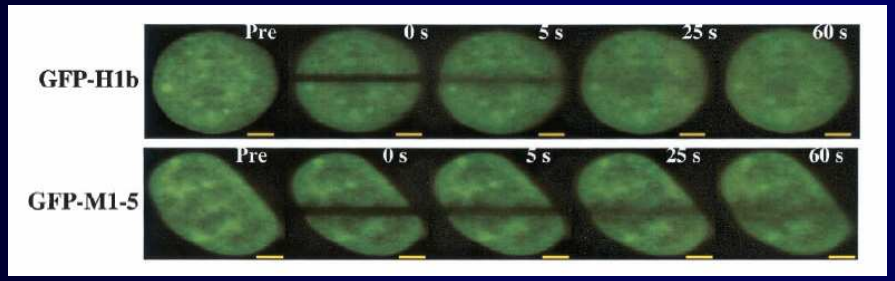




1. **Buňka může existovat i bez významně redukovaného množství H1.**
2. **H1 varianty nejsou hlavní determinanty buněčného fenotypu.**
3. **Funkce H1 variant je nejenom při utlumení transkripční aktivity ale také při její aktivaci (může snižovat nebo i zvyšovat expresi specifických genů.**
4. **H1 hraje důležitou úlohu v kondensaci chromatinu. Spíše je důležitý pro stabilizaci nukleosomů než pro vlastní řízení kondenzace chromatinu.**
5. **Experimentálně navozená redukce H1 vede ke zkrácení linkerové DNA**

The linker histone H1 is involved in maintaining higher-order chromatin structures and displays dynamic nuclear mobility, which may be regulated by posttranslational modifications. H1 tail phosphorylation play in important role.

Using the technique of fluorescence recovery after photobleaching, Contreres et al., 2003 observed that the mobility of a GFP-wild-type H1 fusion protein is dependent on Cdk2 activity. GFP-H1 mobility was decreased in cells with low Cdk2 activity but not in the cells with bloked phophorylation of H1. Blocking the activity of Cdk2 by p21 expression decreased the mobility of GFP-H1. These data suggest that CDK2 phosphorylates histone H1 in vivo, resulting in a more open chromatin structure by destabilizing of nucleosomes.

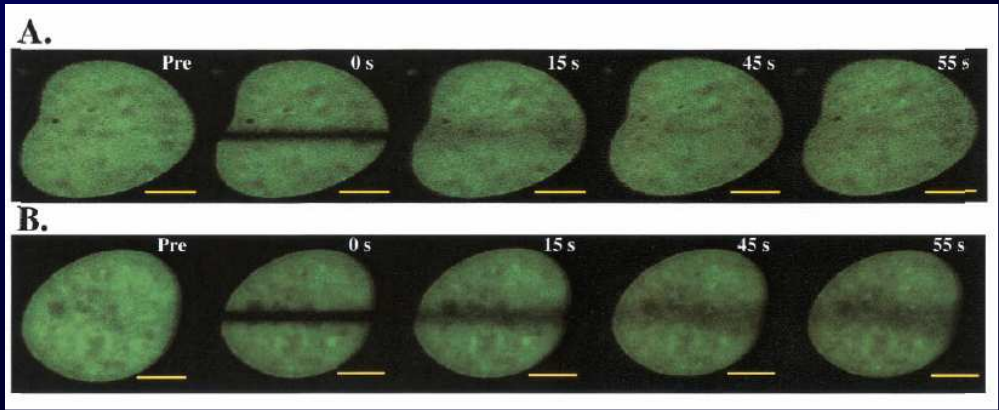


GFP-M1-5: five cyclin-dependent kinase phosphorylation consensus sites were mutated from serine or threonine residues into alanines

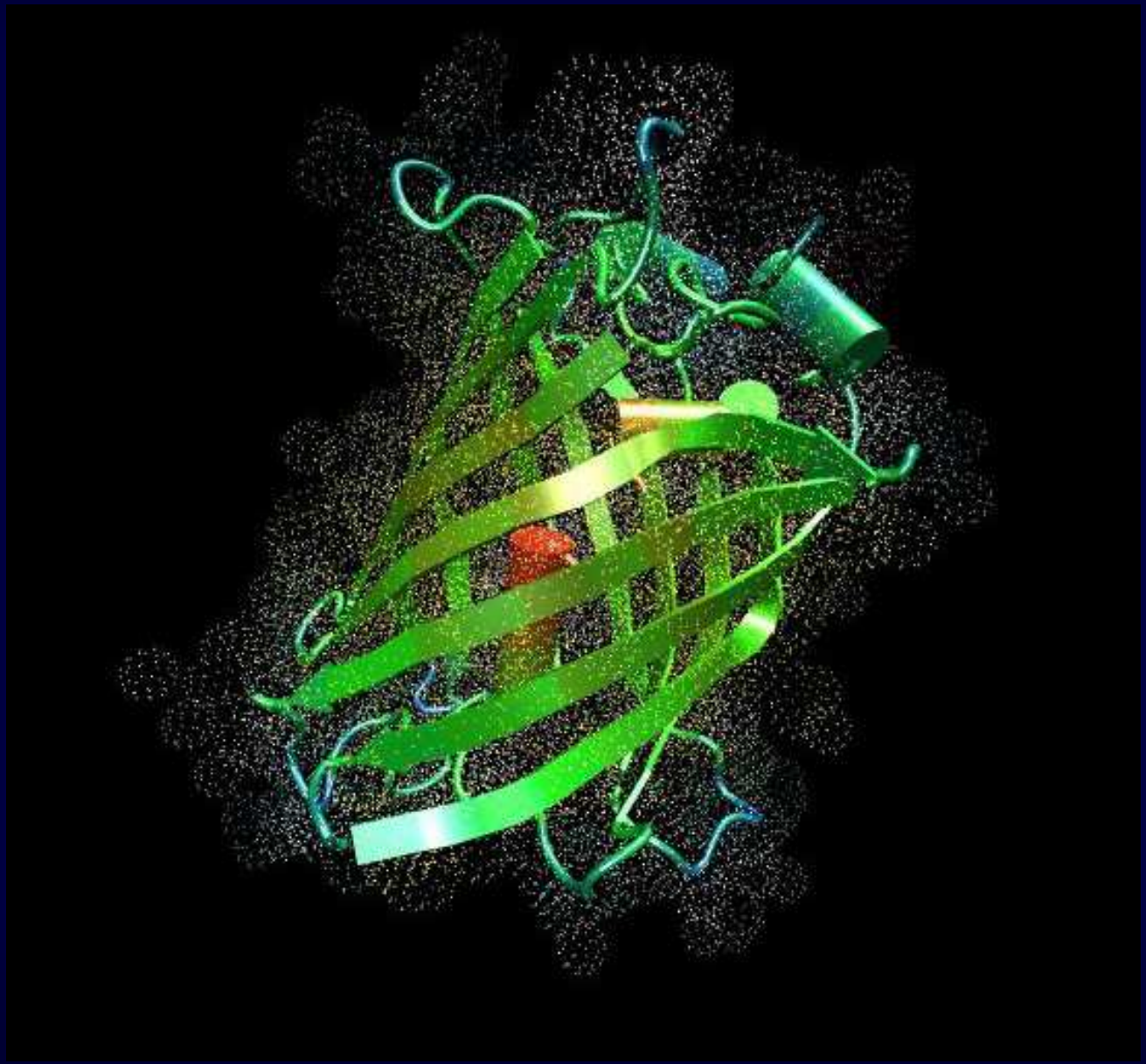
Overexpression p21

GFP-H1b

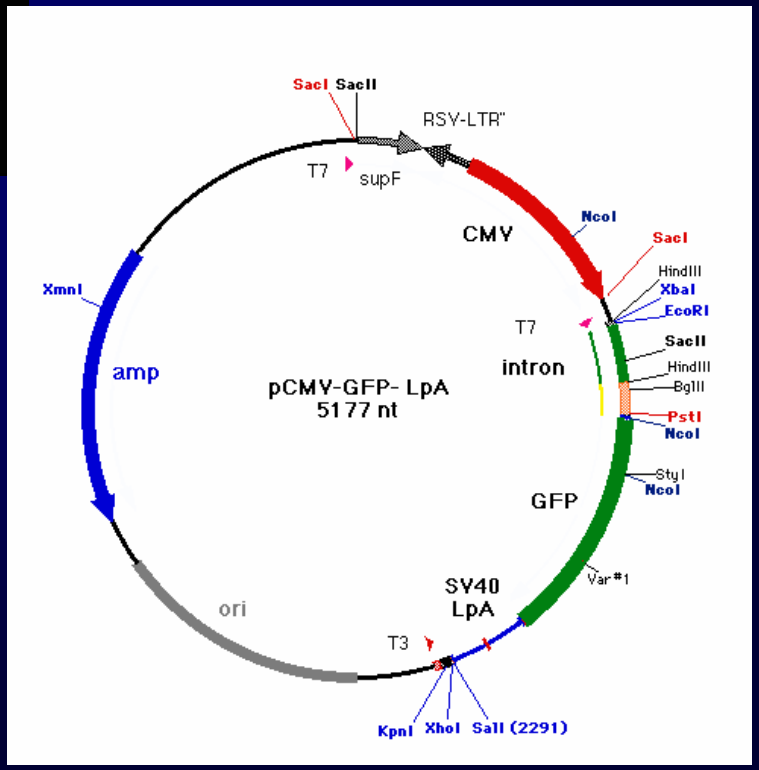
GFP-M1-5



GFP



Pacific jellyfish, *Aequoria victoria*



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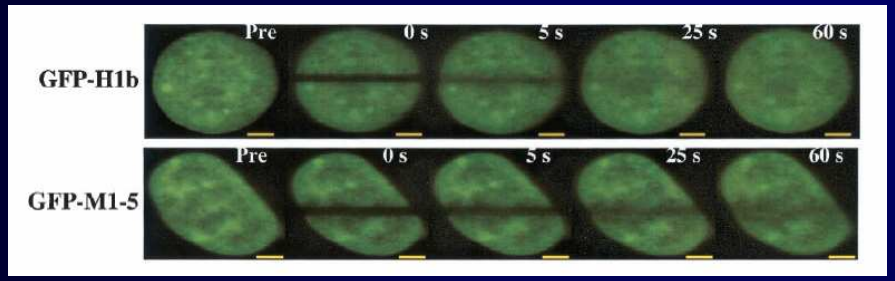

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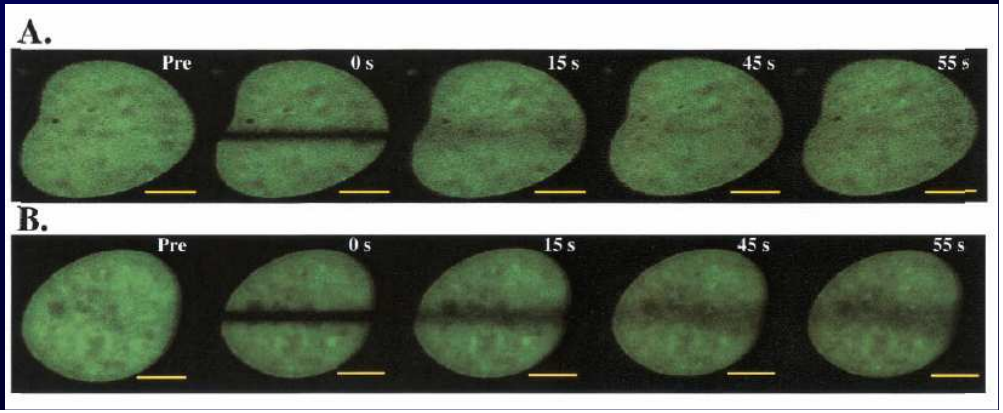
GFP-H1b

GFP-M1-5



Varianty histonů

H1: varianty $H1^o$, H5 a testis-specific varianta H1. varianty H1 se různě uplatňují během buněčného cyklu, diferenciace a vývoje. RA diferenciace myších F9 je doprovázena zvýšenou transkripci histonu $H1^o$.

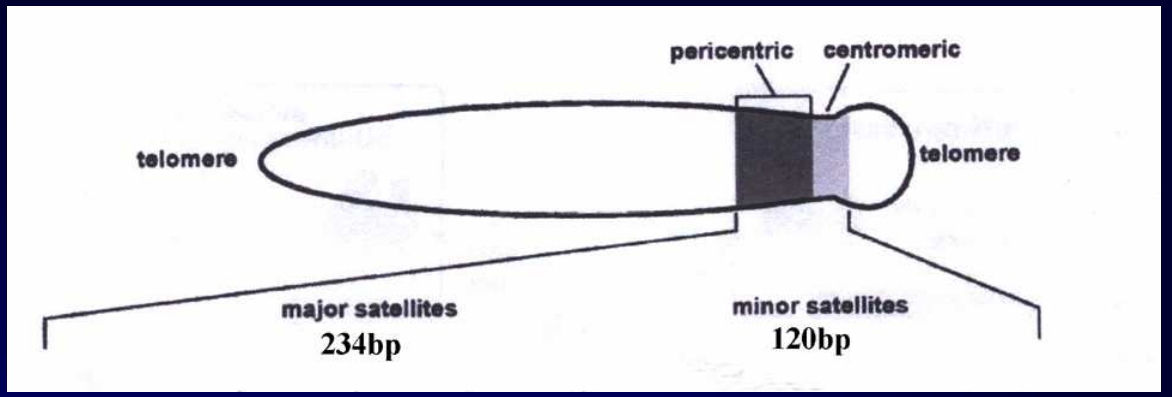
H2A: H2A.X, H2A.Z, MacroH2A, H2A-Bbd, H2AvD, H2A.X. varianta H2A.Z je konzervativní během evoluce. Macro H2A se vyskytuje u Xi, zatímco H2A-Bbd u Xa chromosomu a autosomů. H2A.Z se vyskytuje v intergenických oblastech.

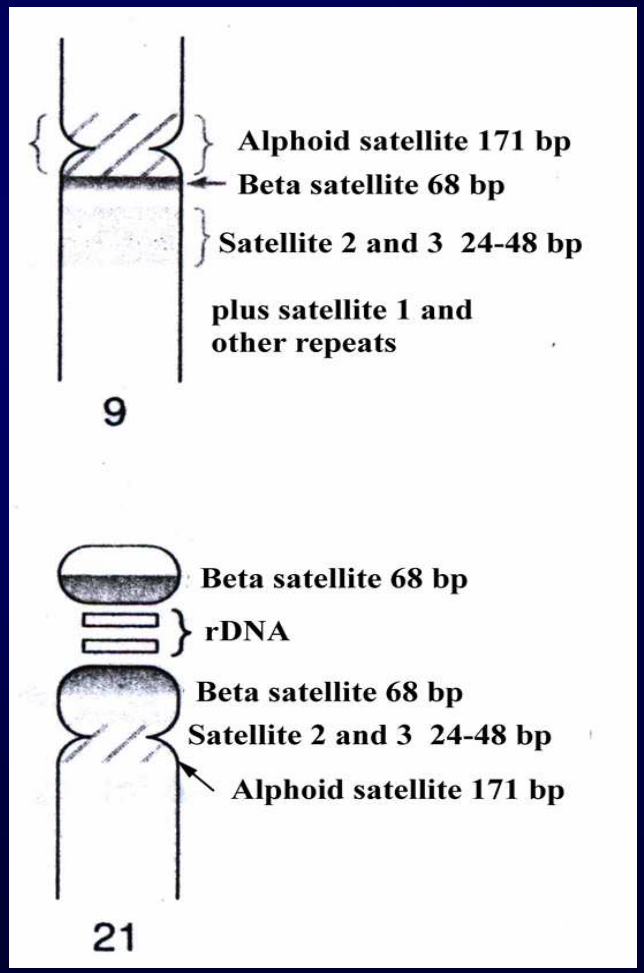
H2B: nemá varianty, uplatňuje se při regulaci kondenzace chromatinu, represi transkripce a během gametogeneze, H2B je zodpovědný za uspořádání chromatinu u spermií.

Varianty histonů

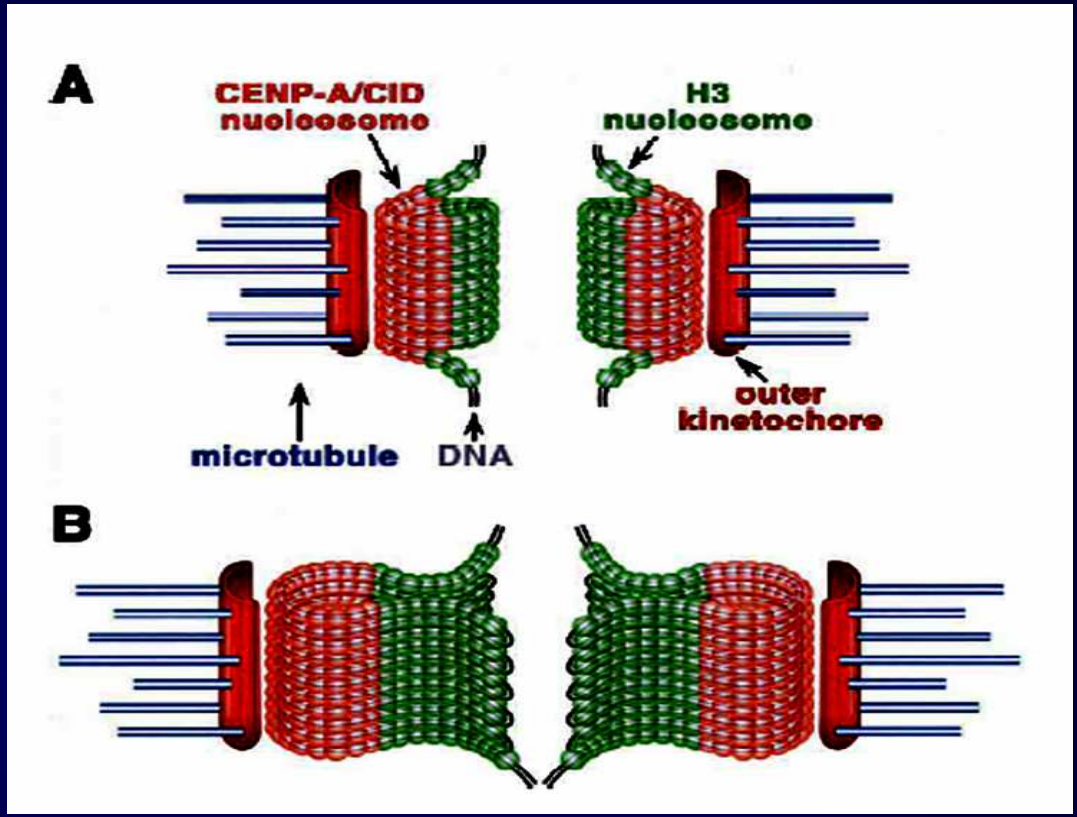
H3: existují dvě hlavní

Varianty H3.3 a centromerické varianty H3 (cenH3) = CENP A: jsou zodpovědné za vazbu kinetochoru a segregaci sesterských chromatid u eukaryot





Varianty histonů H3: **phosphorylation of CENP-A on Ser-7 is essential for kinetochore function. Overexpression of CENPA plays an important role for aneuploidy in colorectal cancers.**



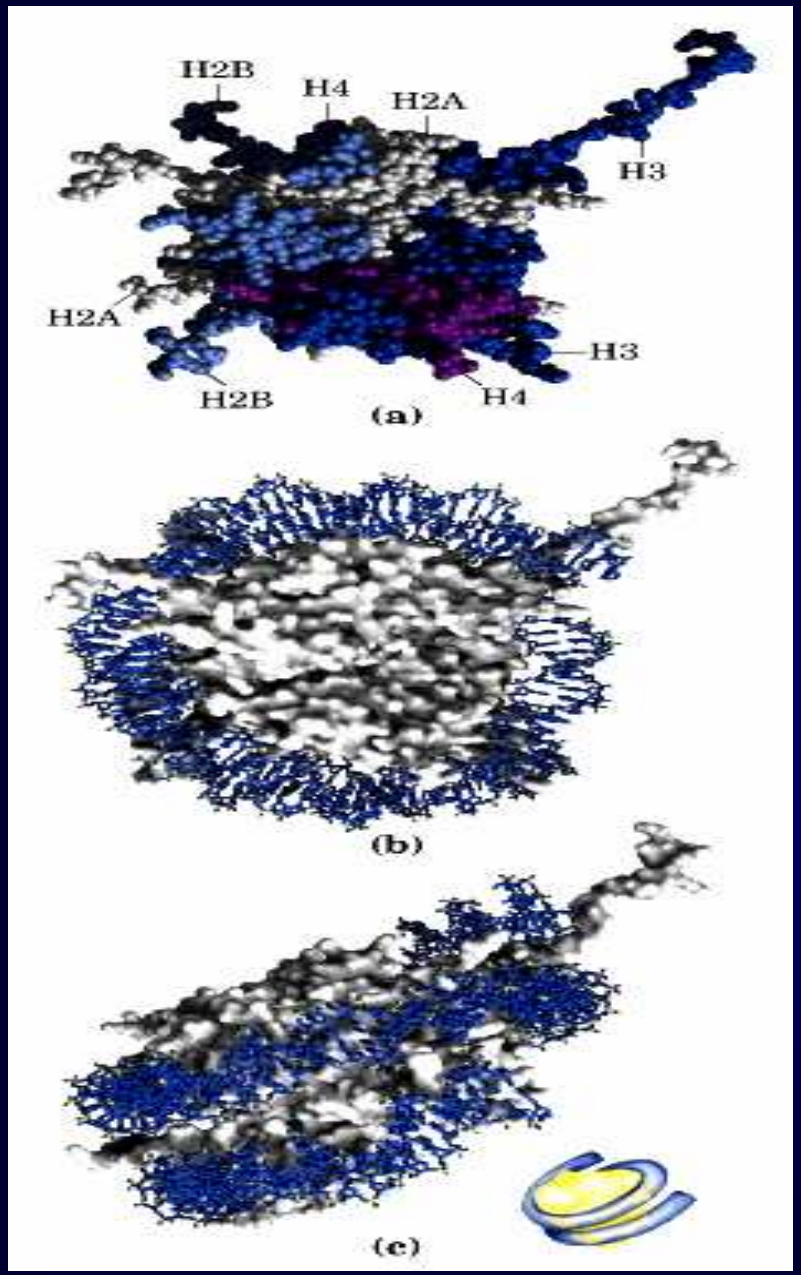
Varianty histonů H4: **většina genů kódujících hlavní histonové proteiny jsou exprimovány během S fáze buněčného cyklu. V případě H4, geny jsou konstitutivně exprimovány během buněčného cyklu. Pro H4 nejsou známy žádné varianty.**

Chemické modifikace histonů

- **Dynamická struktura chromatinu je přímo ovlivněná postranslačními modifikacemi amino-konců histonů**

- **Typy histonových modifikací:**
  a) acetylace,
  b) methylace,
  c) fosforylace,
  d) polyadenylace,
  e) ubiquitinace

- **Methylace histonů byla objevena již před 30 lety.**



Vztah mezi acetylací a metylací histonů: acetylace histonů je katalyzována histon acetyl-transferázami (HATs) a odstraňo-vána histon deacetylázami (HDACs). HDACs odstraní acetyl-skupinu, která je nahrazena methyl skupinou za účasti HMTs (Suv39H1- human, Clr4 – S.pombe)

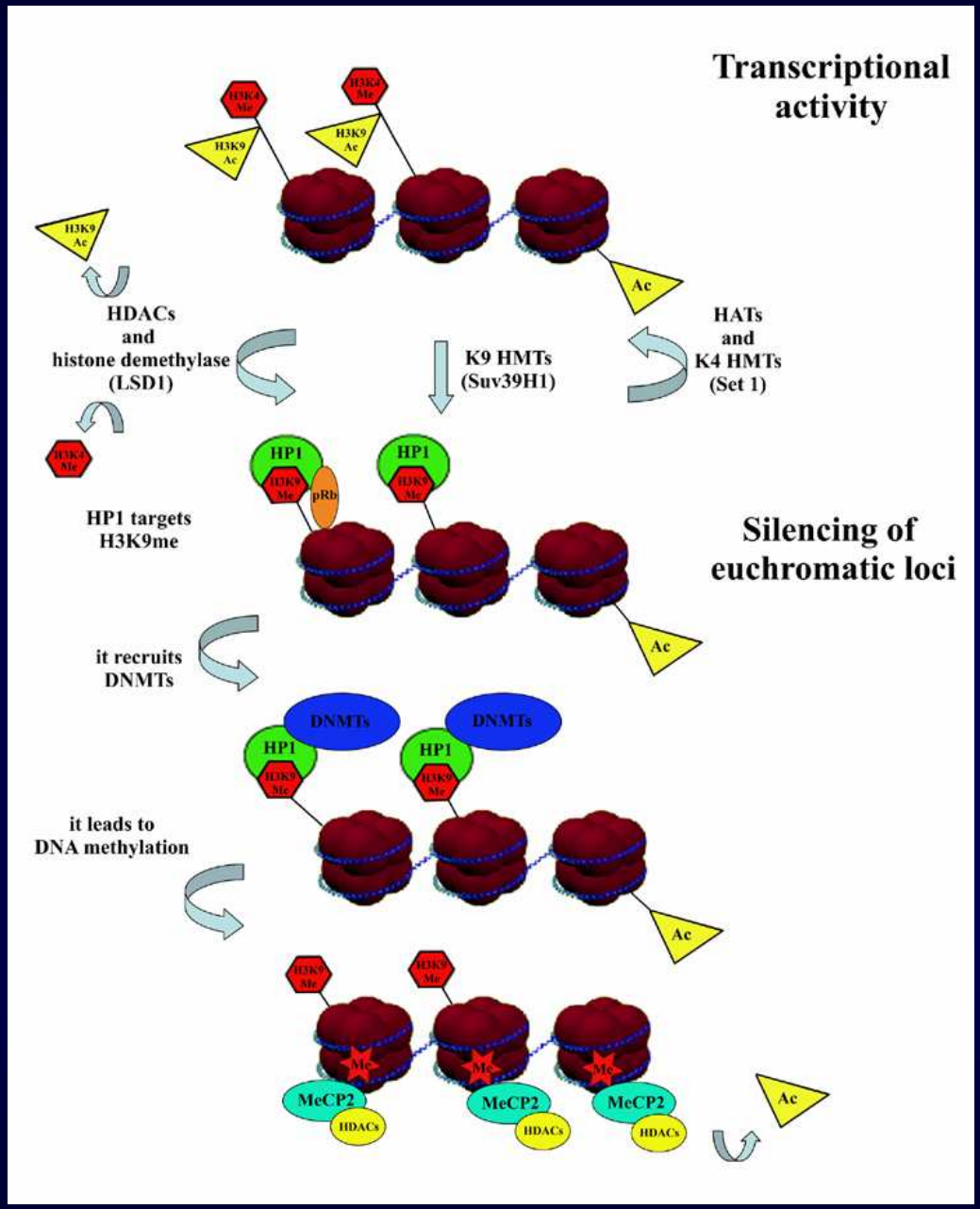
2004: Objev demethylace histonů za účasti amin oxidasy LSD1 (KIAA0601) (Shi et al., Cell 2004). LSD1 specificky demethyluje H3 (K4), epigenetickou modifikaci zodpovědnou za transkripční aktivitu.

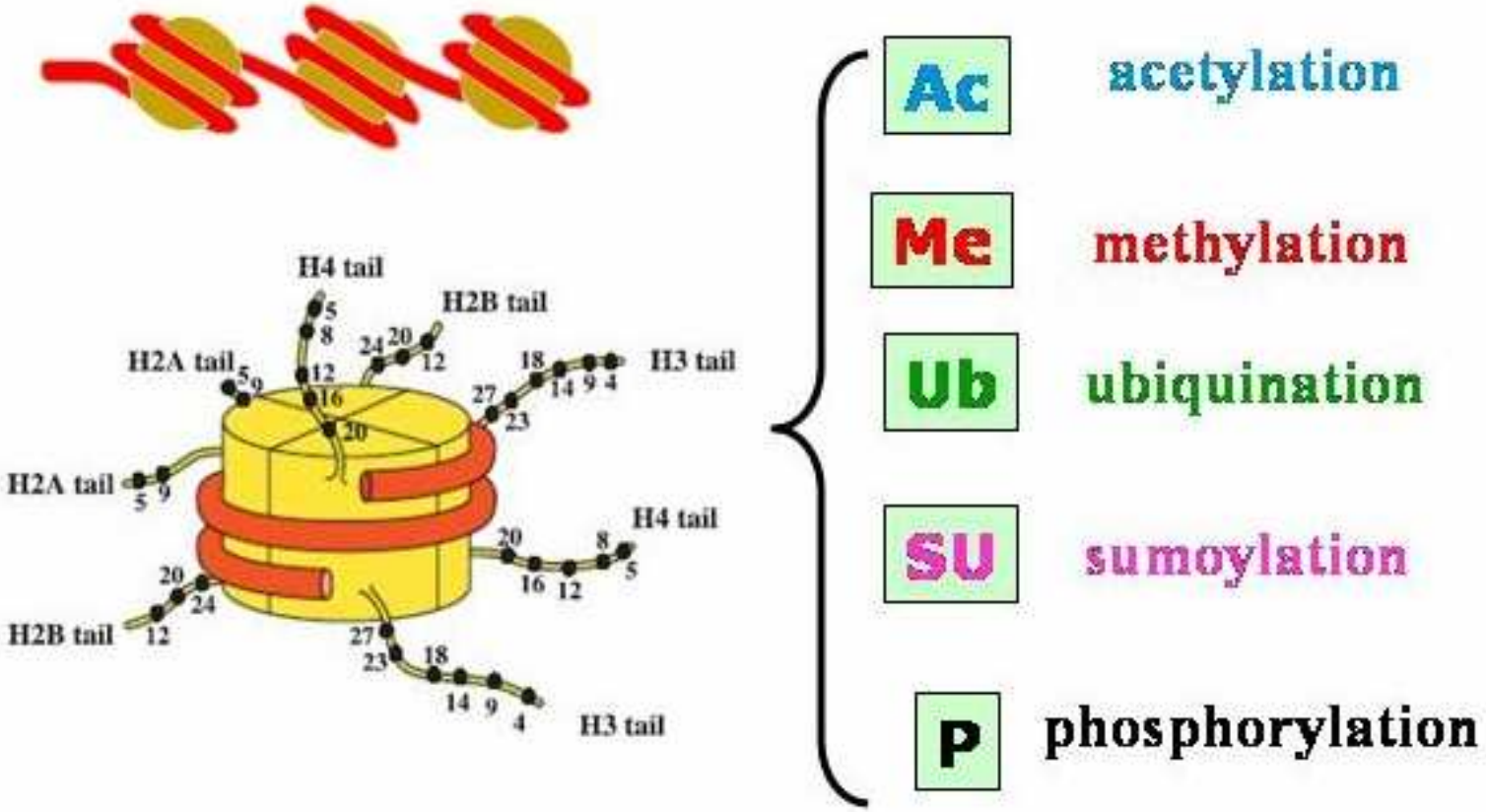
HATs: HAT1, PCAF, CBP/p300, TFIIC90 (according Allis et al., 2007)

HDACs: Class I, II, III

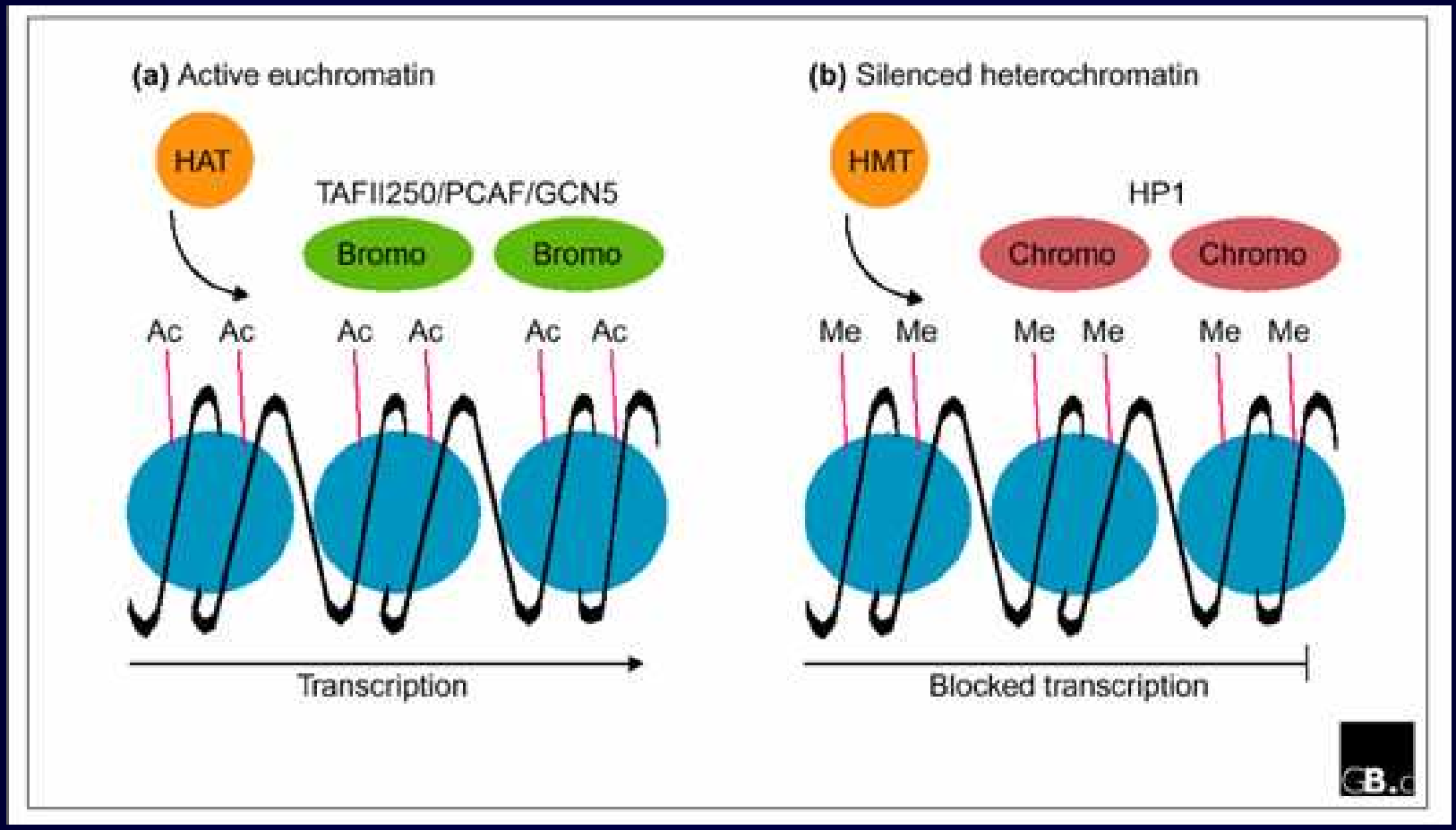
HMTs: Suv39H1, G9a, MLL1, Set 1, Set 2

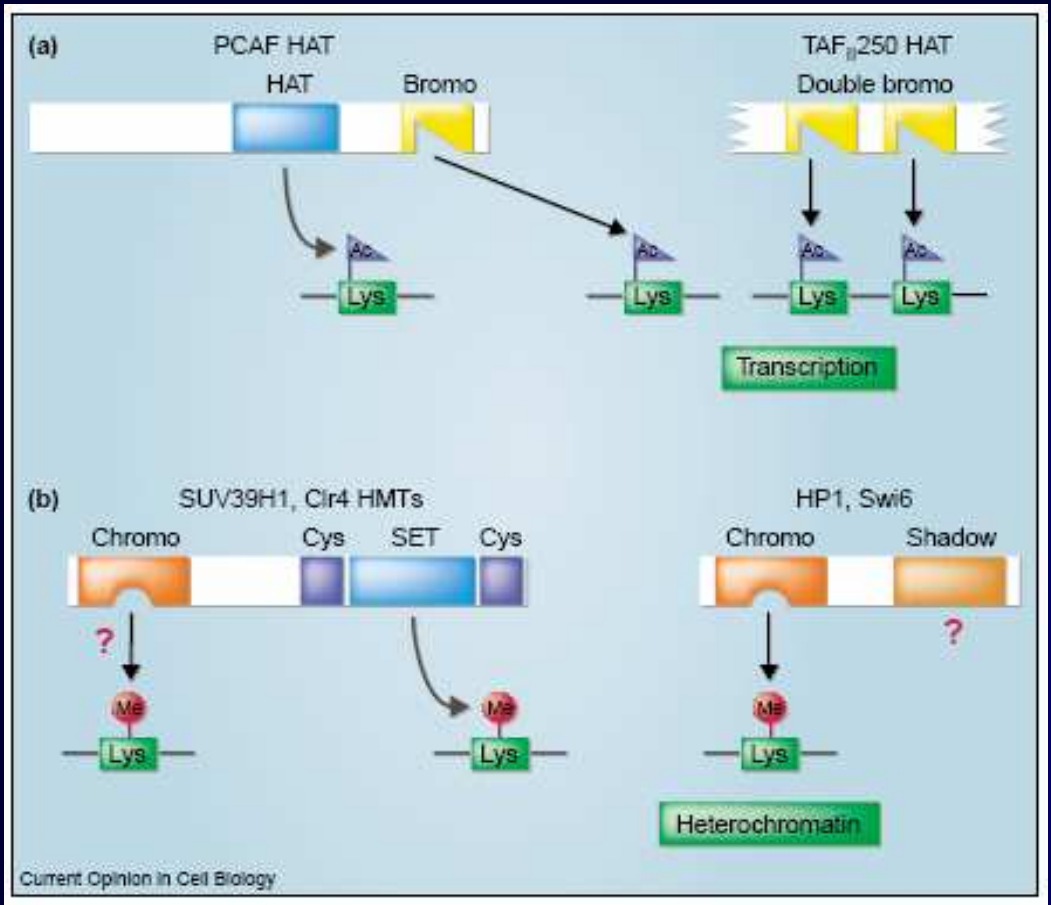
Demethylases: LSD1, JHDM1a, JHDM2a, JMJ D2B


Transcriptional activity
H3K4 Me
H3K9 Ac
H3K4 Me
H3K9 Ac
H3K9 Ac
Ac
HDACs and histone demethylase (LSD1)
K9 HMTs (Suv39H1)
HATs and K4 HMTs (Set 1)
H3K4 Me
HP1
H3K9 Me
pRb
HP1
H3K9 Me
HP1 targets H3K9me
Silencing of euchromatic loci
Ac
it recruits DNMTs
DNMTs
HP1
H3K9 Me
DNMTs
HP1
H3K9 Me
it leads to DNA methylation
Ac
H3K9 Me
H3K9 Me
Me
Me
Me
MeCP2
HDACs
MeCP2
HDACs
MeCP2
HDACs
Ac



The figure illustrates nucleosome models and major posttranslational modifications which play essential roles in gene expression regulation and disease processes

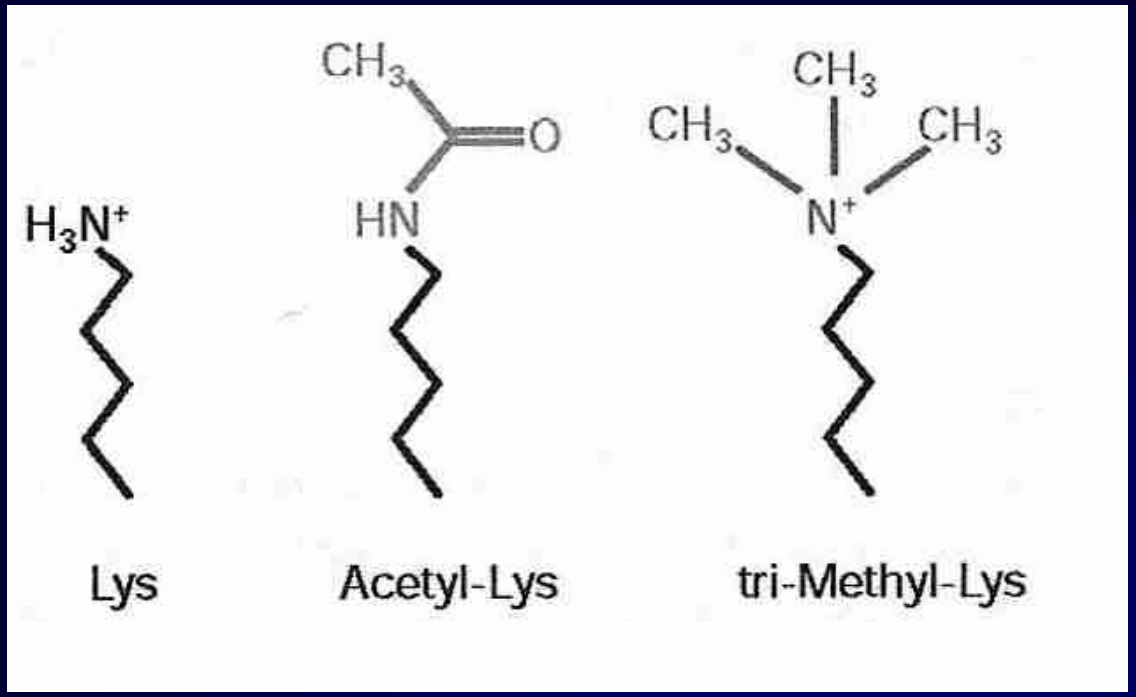

(a) Active euchromatin
HAT
TAFII250/PCAF/GCN5
Bromo
Bromo
Ac Ac Ac Ac Ac Ac
Transcription
(b) Silenced heterochromatin
HMT
HP1
Chromo
Chromo
Me Me Me Me Me Me
Blocked transcription

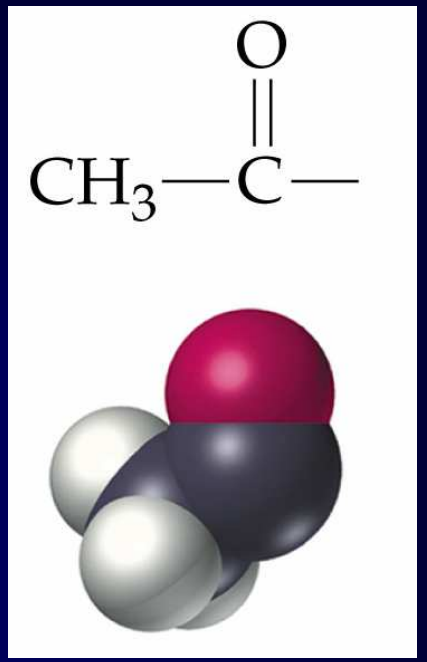


CD: protein-chromatin
CSD: protein-protein
HD: HP1-to-DNA and linker histones

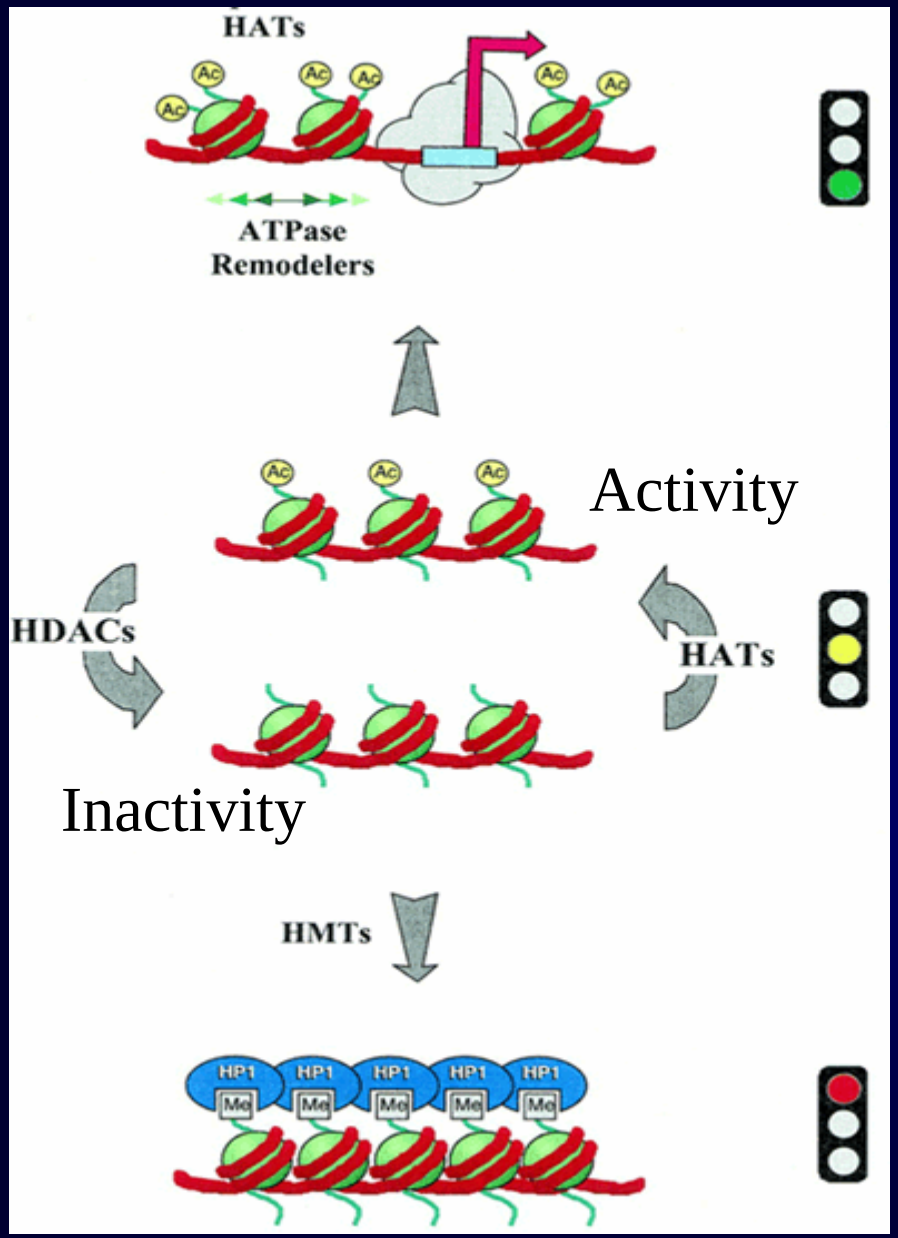
HMTs:

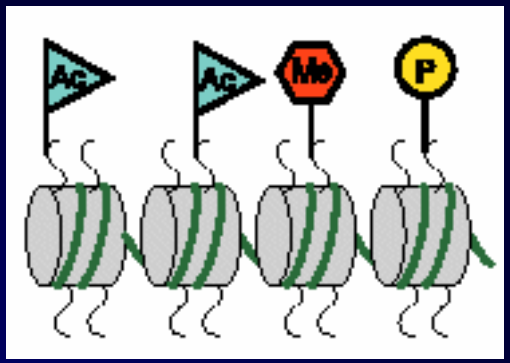
D. melanogaster: Su(var)3-9 je lokalizován v oblastech kondenzovaného chromatinu a je to klíčový regulátor v organizaci represivního chromatinu. homolog u S.pombe je Clr4 umyší SUV39h1 a u lidských buněk SUV39H1. Tyto HMTs specificky methylují H3(K9).

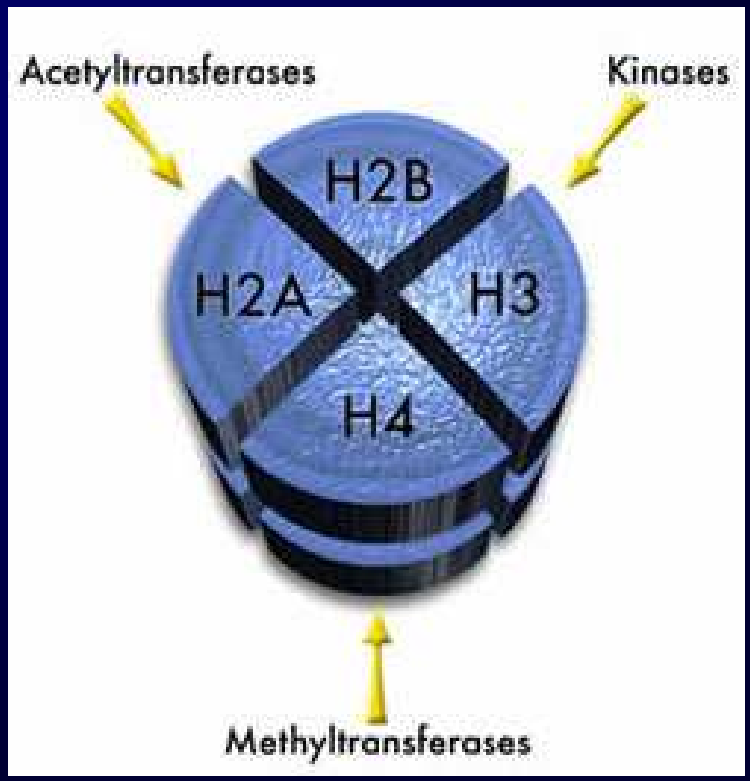




Primárním důsledkem histonových modifikací je snížení schopnosti histonových konců interagovat s dalšími složkami chromatinu, včetně DNA.

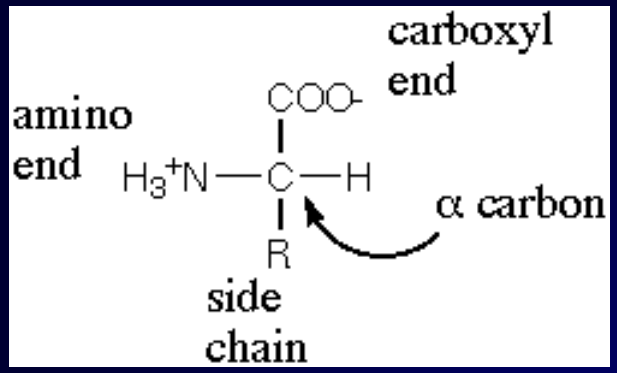


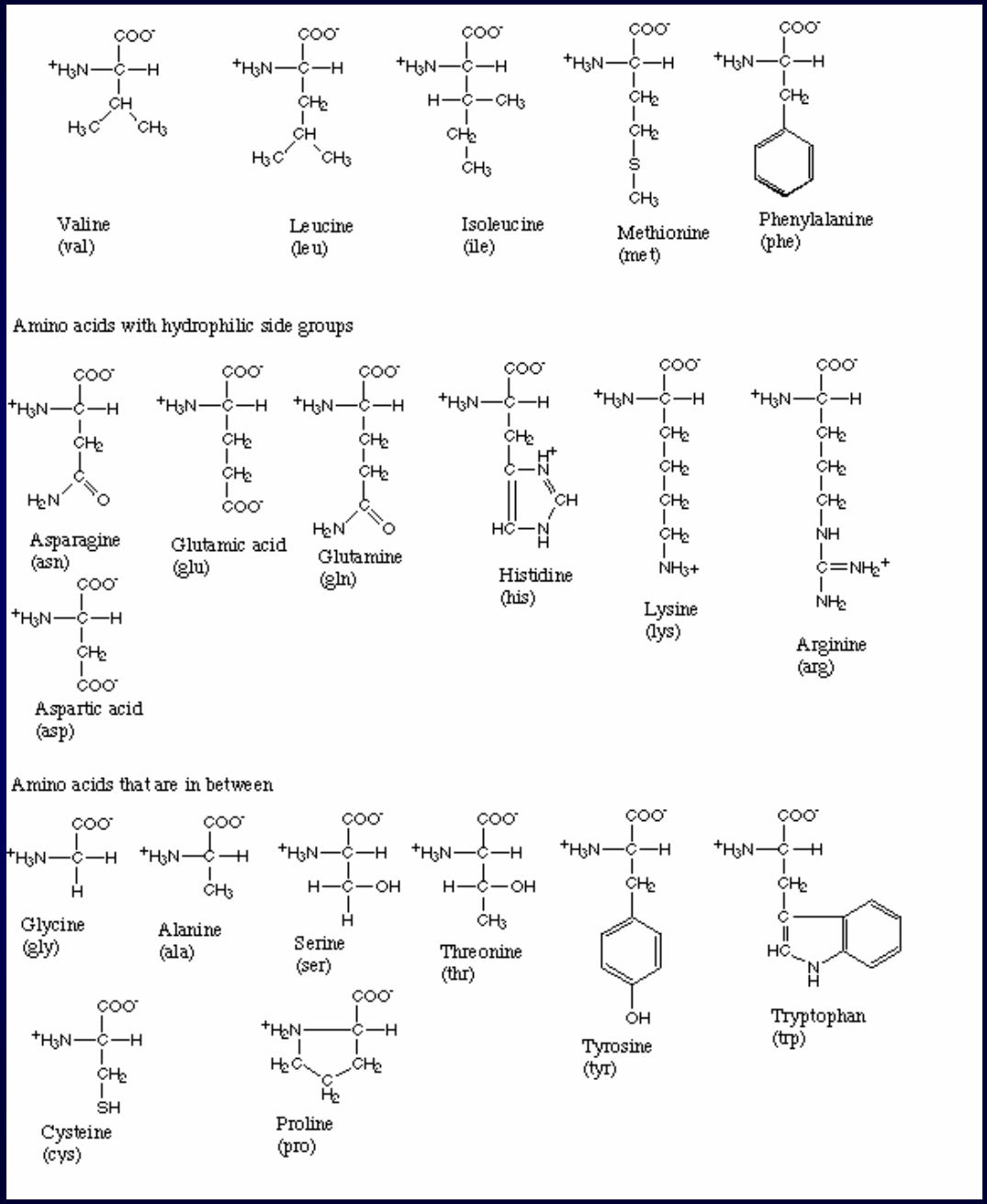


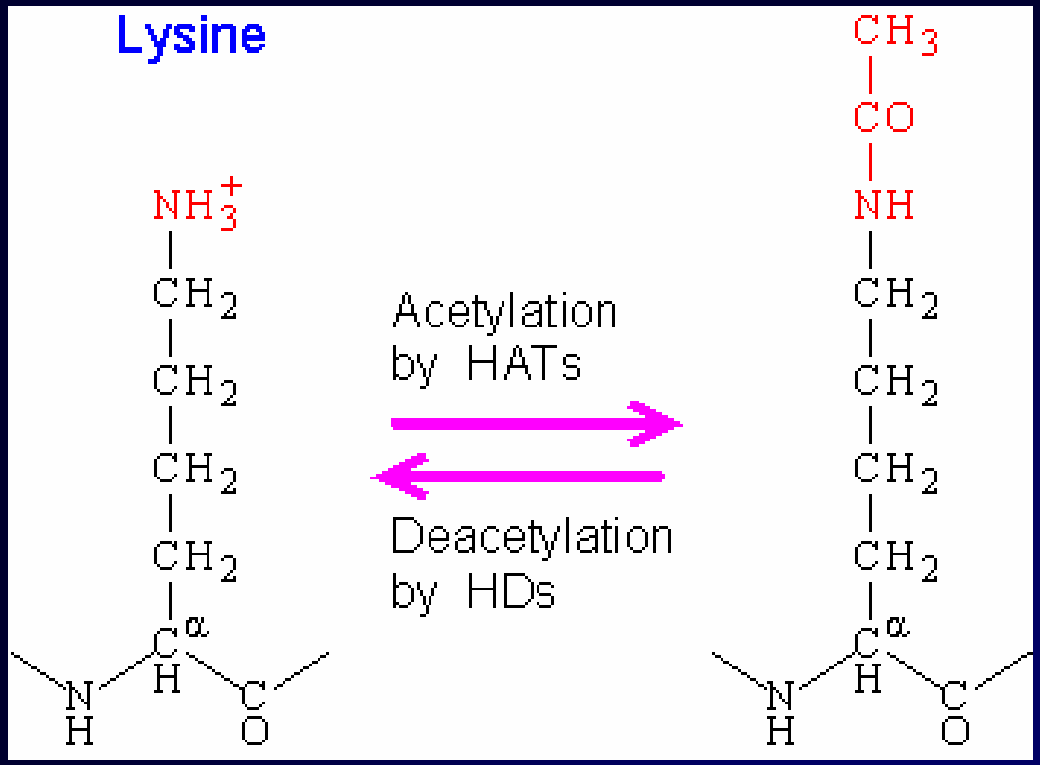


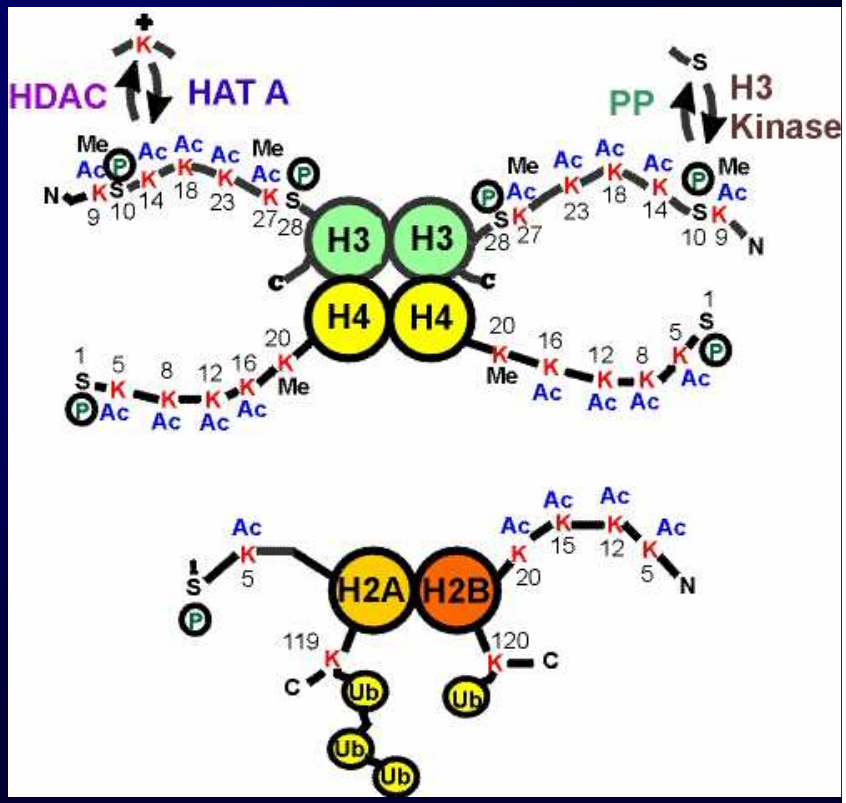
Ikaros, Helios

Amino acid

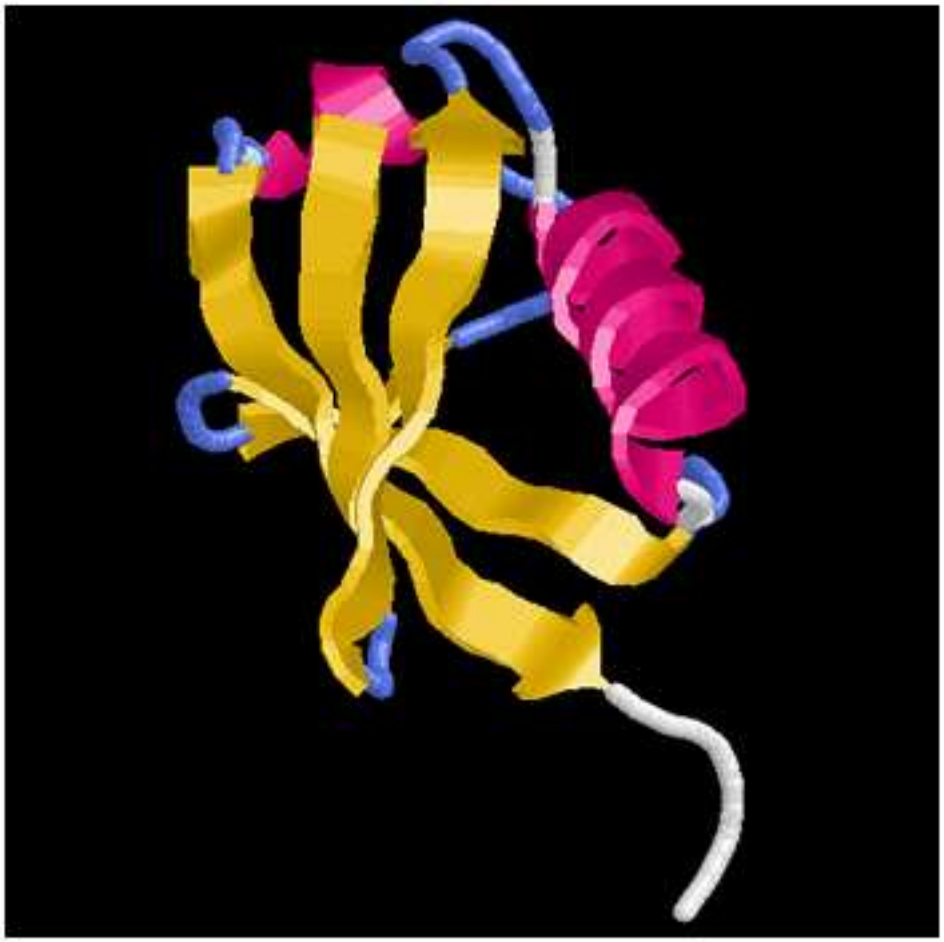

carboxyl
end
amino
end
COO-
H3+N
C
H
α carbon
R
side
chain

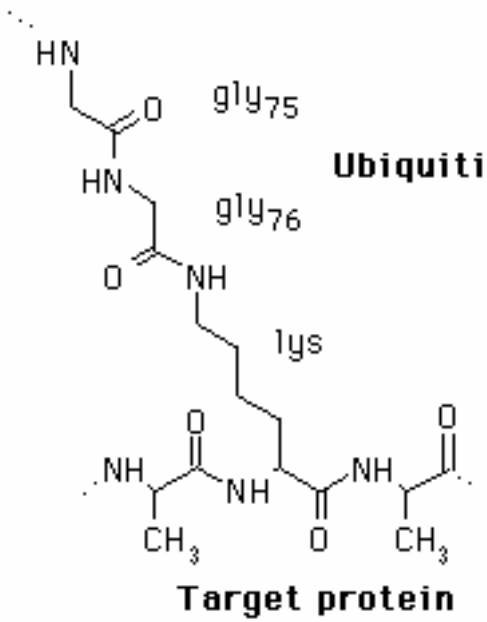

Valine
(val)
Leucine
(leu)
Isoleucine
(ile)
Methionine
(met)
Phenylalanine
(phe)
Amino acids with hydrophilic side groups
Asparagine
(asn)
Glutamic acid
(glu)
Glutamine
(gln)
Histidine
(his)
Lysine
(lys)
Arginine
(arg)
Aspartic acid
(asp)
Amino acids that are in between
Glycine
(gly)
Alanine
(ala)
Serine
(ser)
Threonine
(thr)
Tyrosine
(tyr)
Tryptophan
(trp)
Cysteine
(cys)
Proline
(pro)


Lysine
Acetylation
by HATs
Deacetylation
by HDs


HDAC
HAT A
PP
H3
Kinase
H3
H3
H4
H4
H2A
H2B
Ub
Ub
Ub
Ub

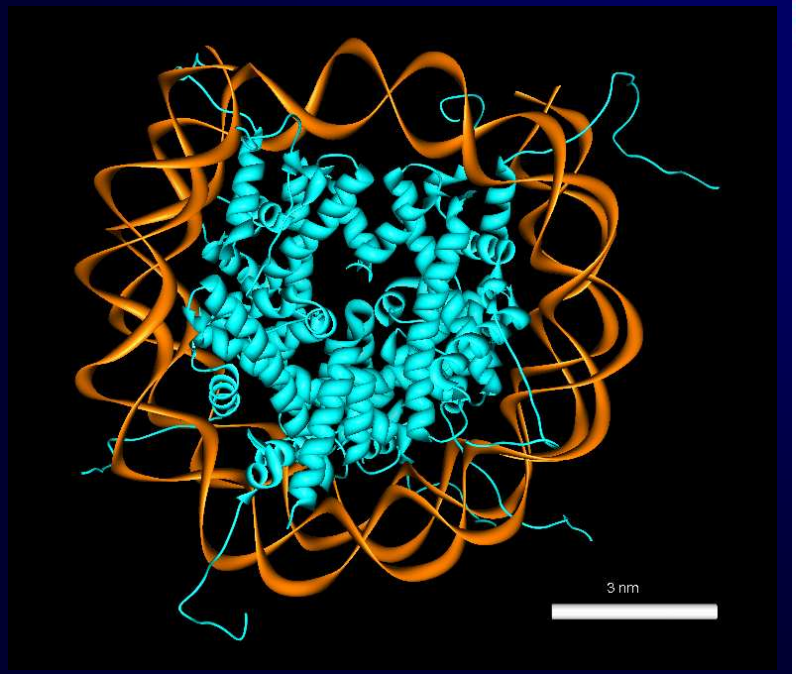
Ubiquitin structure





Ubiquitination of histones has been reported *in vivo* although the most prevalent ubiqutination occurs in H2A and H2B. One of the widely studied proteins that undergoes ubiquitination for its activity is p53.

Figure 9. Interplay between different post-translational modifications occurring on histone H3 and H4 amino-terminal tails. Residues that are known to be acetylated (Ac), methylated (Me), and phosphorylated (P) are indicated. Positive and negative affects are indicated.



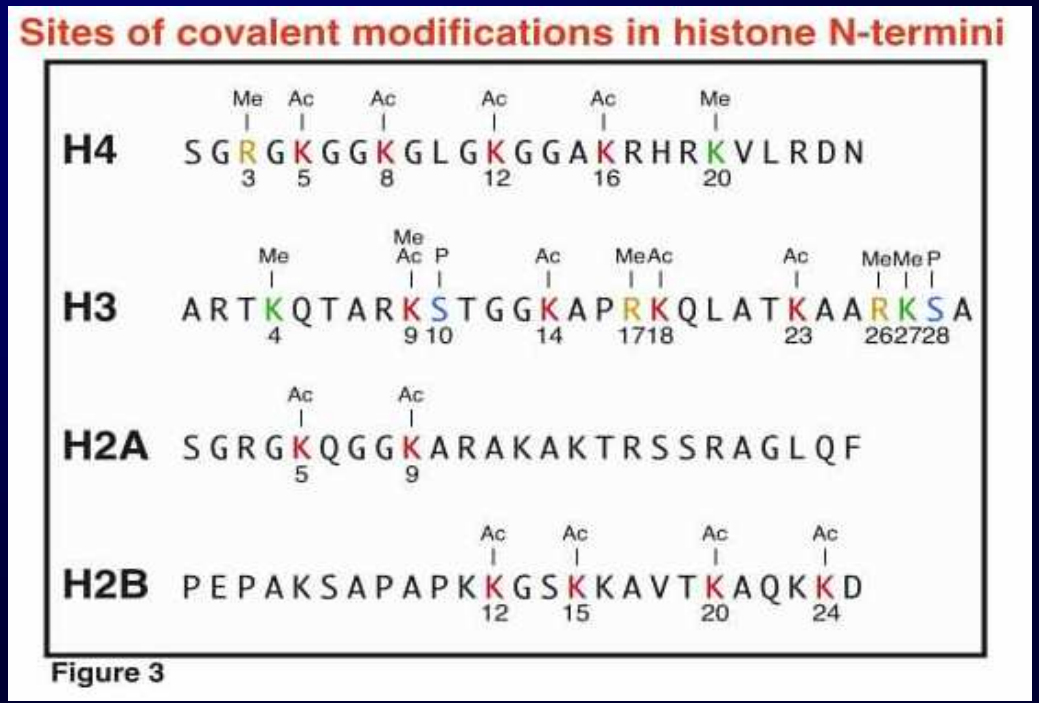
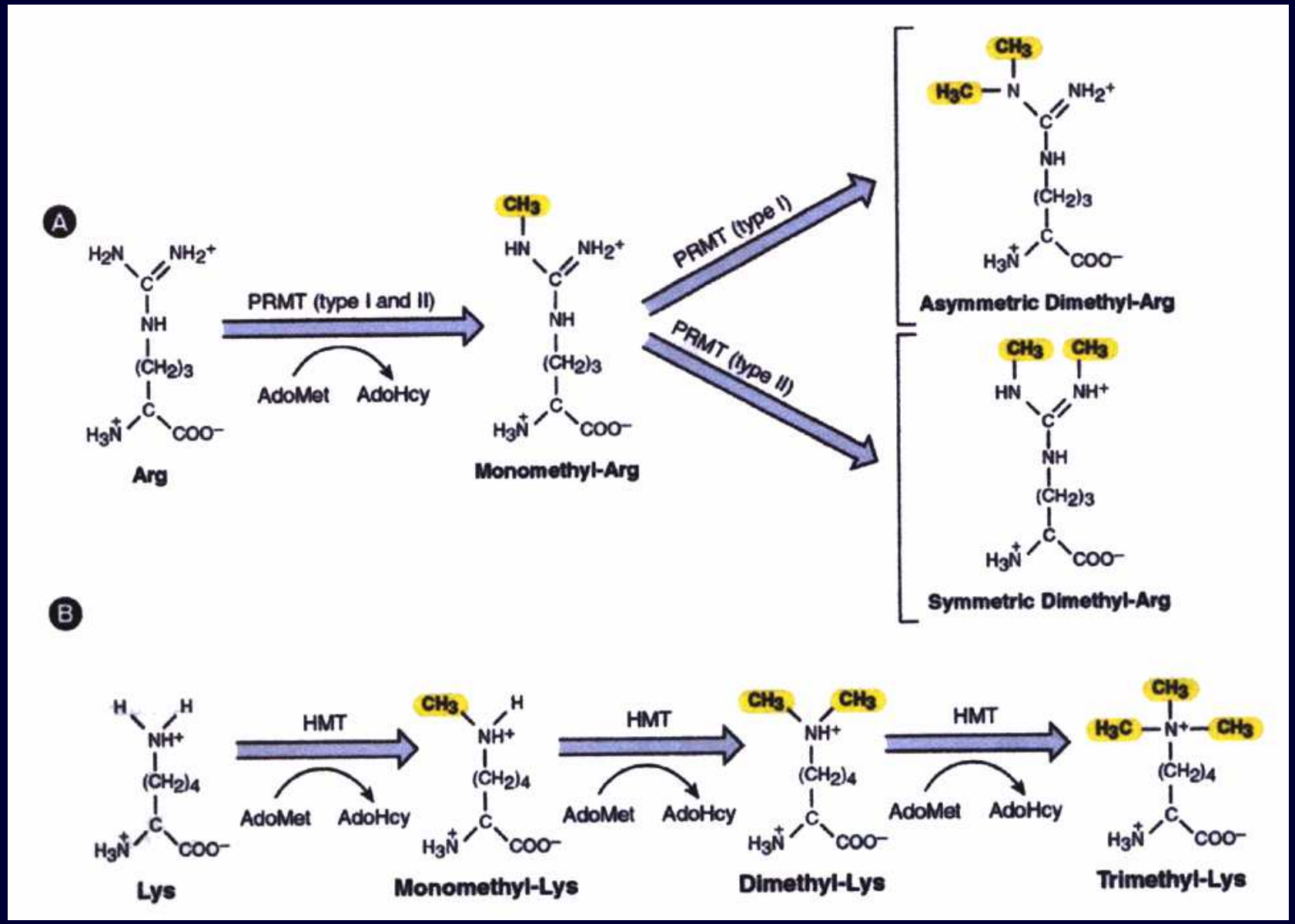
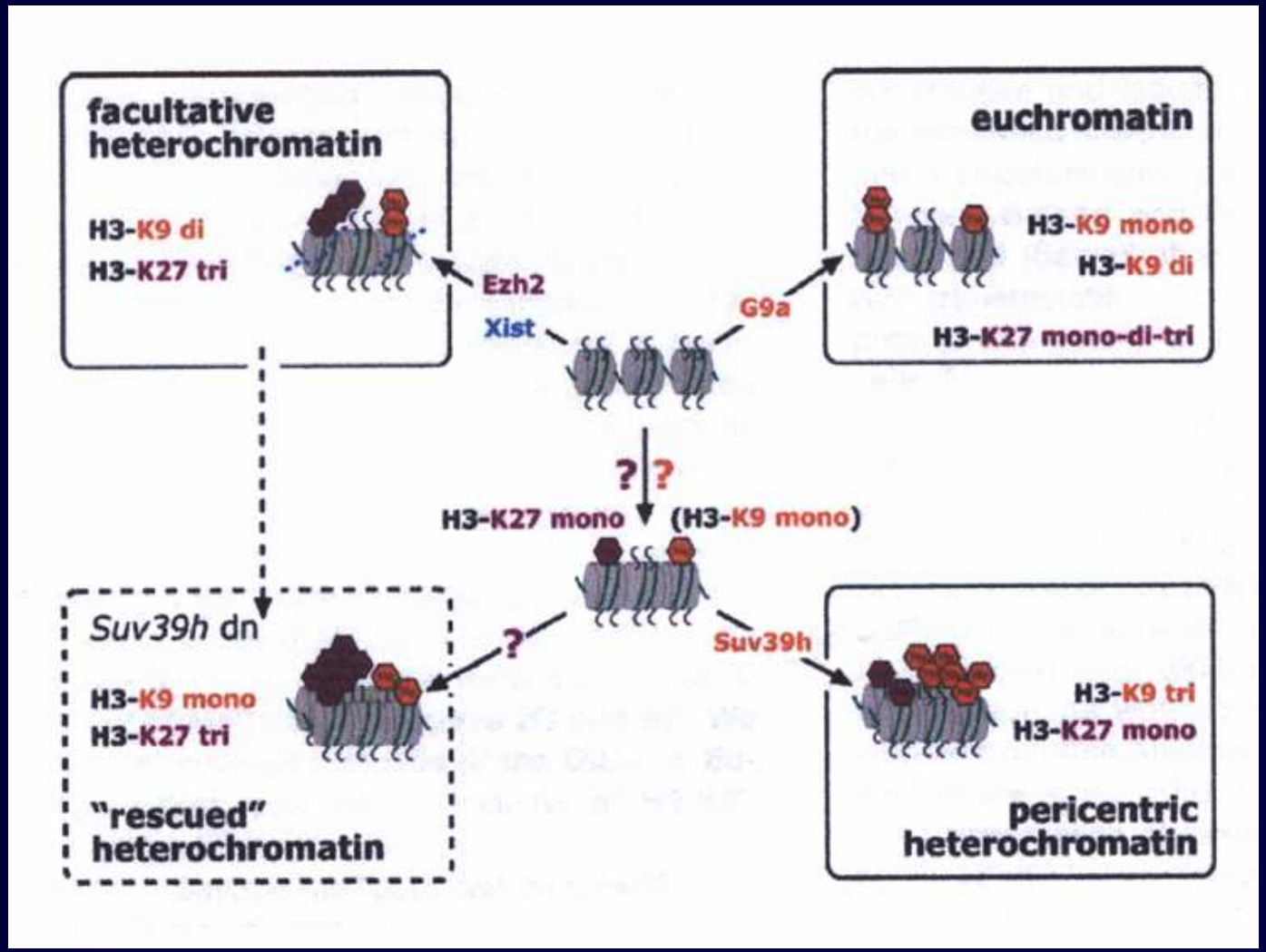


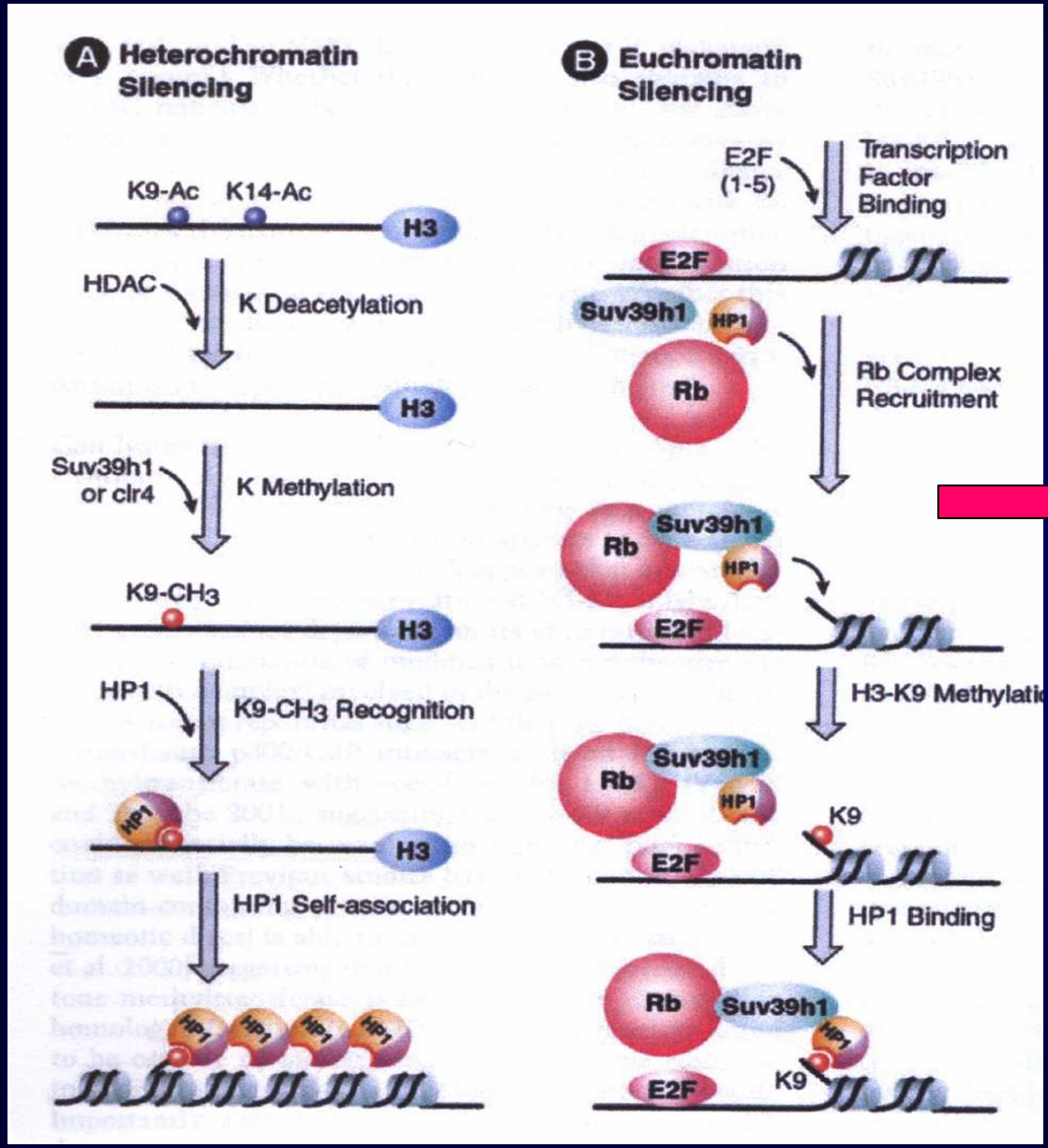
Figure 3

TRANSKRIPČNÍ AKTIVACE: H3-R2-Me, H3- Ac-K9, H3- K27-Me (Xi), H3-K36-Me, H3- K79-Me (telomeric silencing), H4-K20-Me (mitotic condensation)

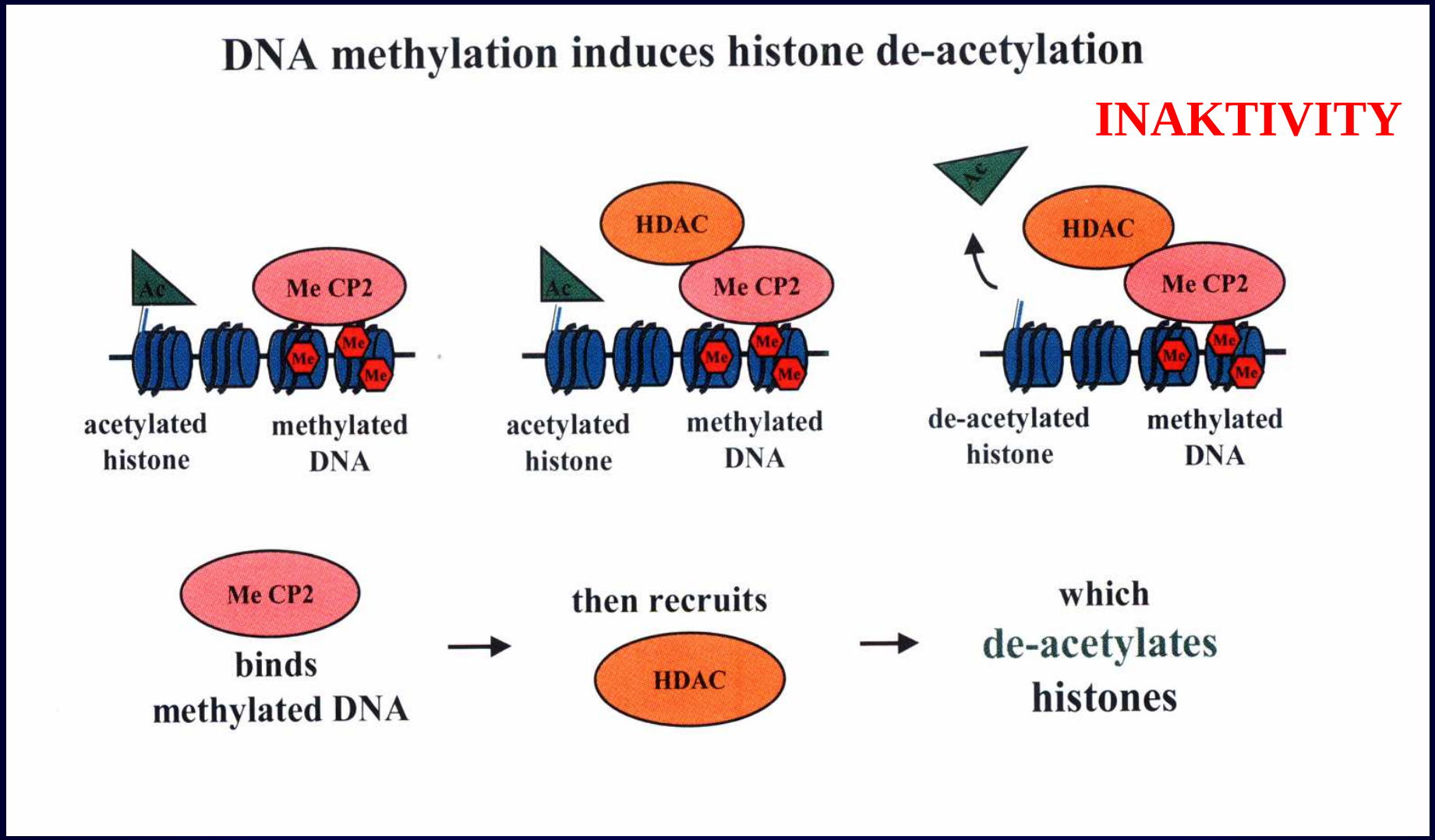
TRANSKRIPČNÍ INAKTIVACE: H3-Me-K9, H3-S10-P, H3-K17-Ac, H3- R-17-Me, H3-K18-Ac, H3-K23-Ac, H4-R3-Me, H4-K8-Ac,


A
PRMT (type I and II)
AdoMet
AdoHcy
Arg
Monomethyl-Arg
PRMT (type I)
PRMT (type II)
Asymmetric Dimethyl-Arg
Symmetric Dimethyl-Arg
B
HMT
AdoMet
AdoHcy
Lys
Monomethyl-Lys
Dimethyl-Lys
Trimethyl-Lys


facultative heterochromatin
H3-K9 di
H3-K27 tri
Ezh2
Xist
G9a
euchromatin
H3-K9 mono
H3-K9 di
H3-K27 mono-di-tri
? ?
H3-K27 mono
(H3-K9 mono)
Suv39h dn
H3-K9 mono
H3-K27 tri
"rescued" heterochromatin
?
Suv39h
H3-K9 tri
H3-K27 mono
pericentric heterochromatin

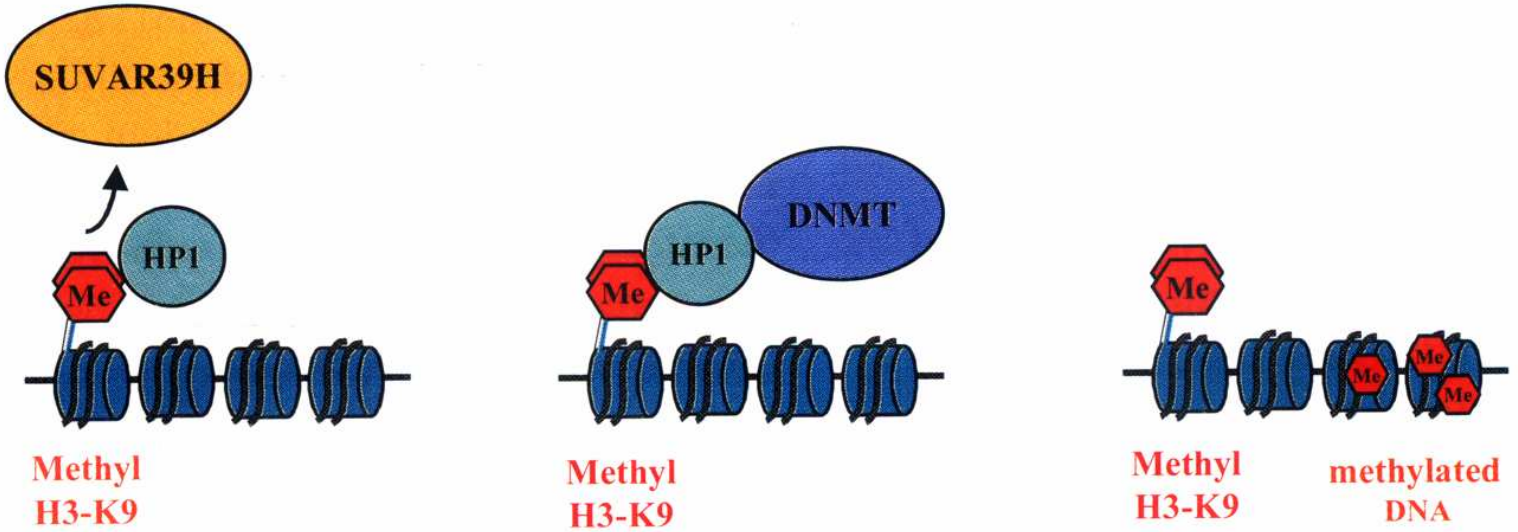


Repression of cyclin E promoter

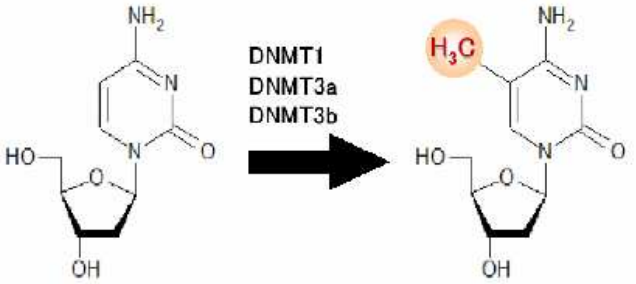


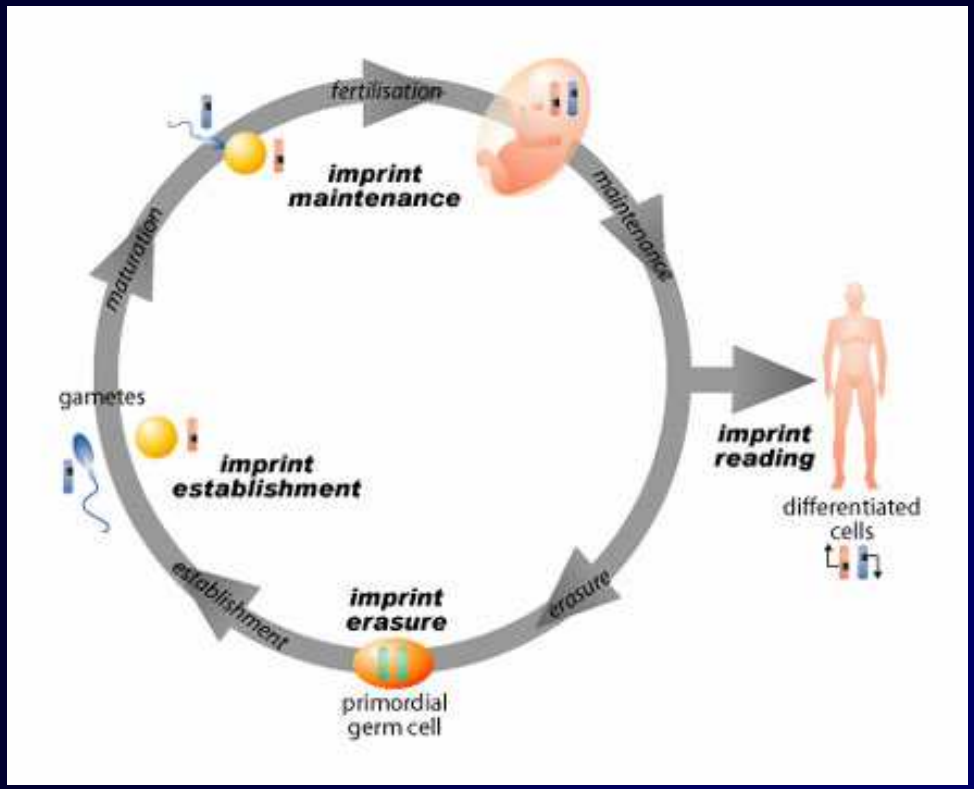
MeCP2: Methyl-CpG binding Protein, specifically binds to to methylated DNA

Histone H3-K9 methylation induces DNA methylation



HP1 **targets** Methyl H3-K9 → **then recruits** DNMT → **which methylates DNA**



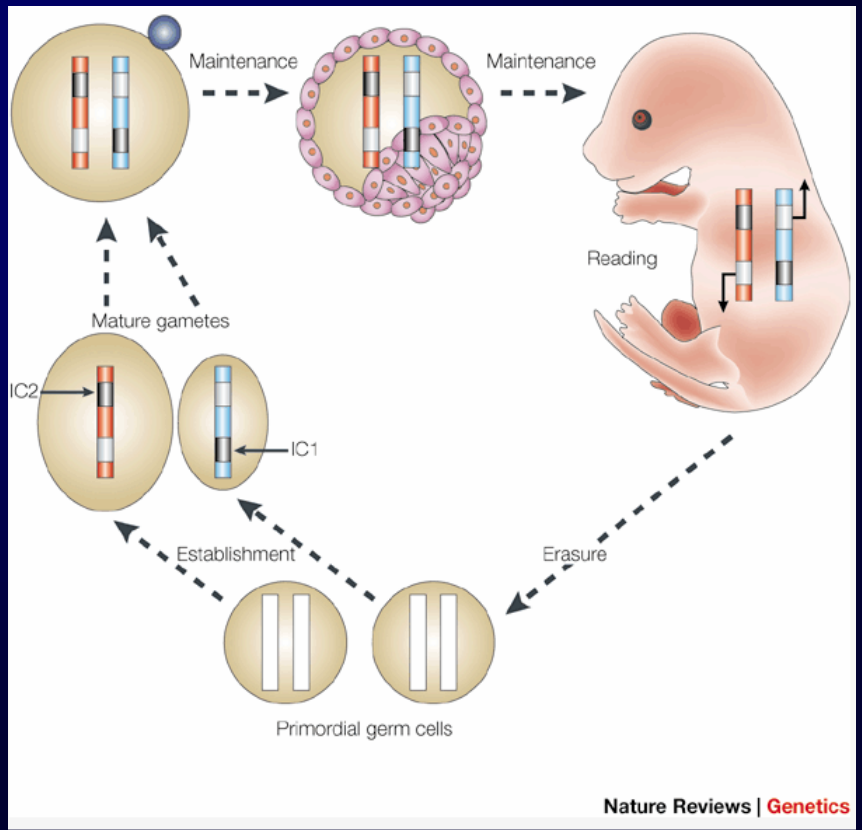


IMPRINTING

Myší embryo: samičí alela je zamethylována, nevyjadřuje se

Dospělý jedinec: obě alely jsou demethylovány

Gametogeneze: se obnoví původní stav
Platí pro gen IGF II.



ISSN1471-0056

Methylation state of centromeres

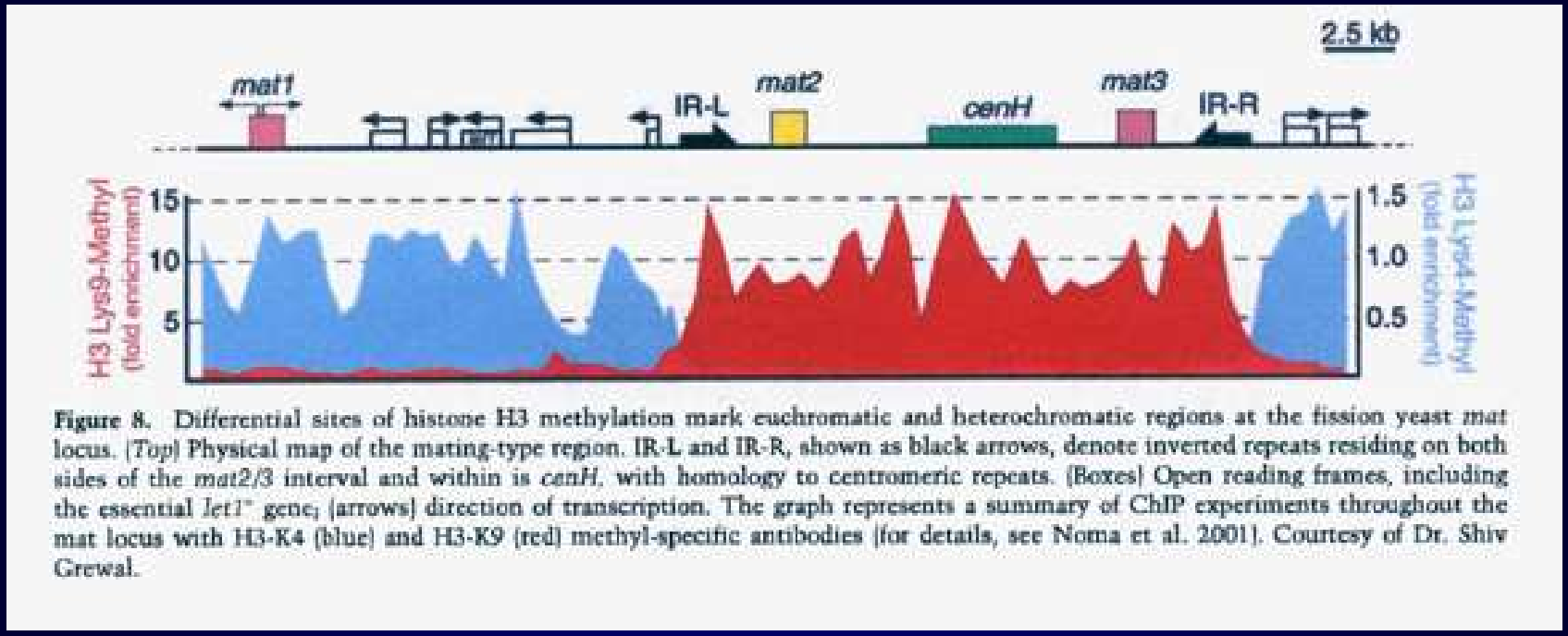
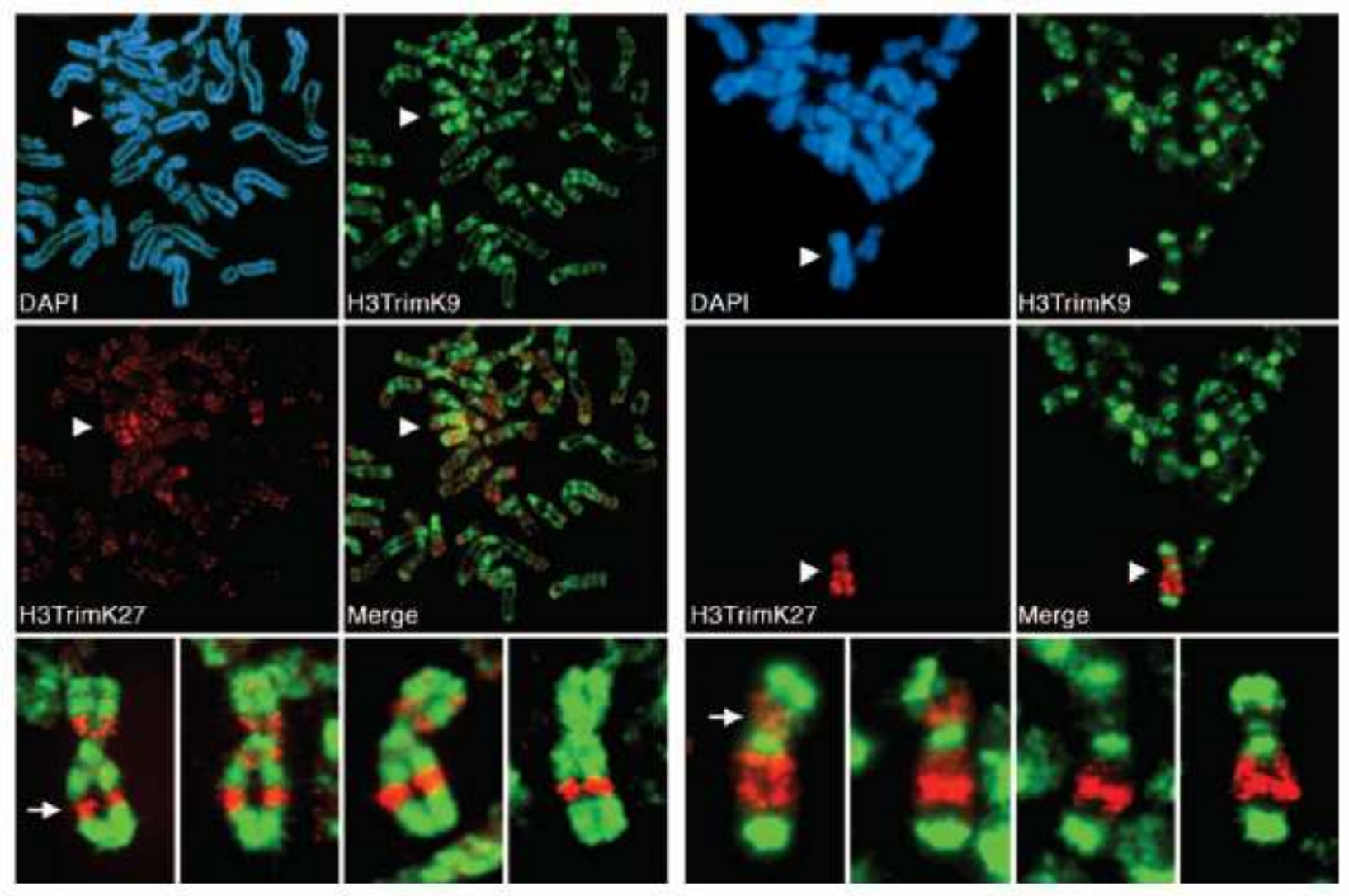


Figure 8. Differential sites of histone H3 methylation mark euchromatic and heterochromatic regions at the fission yeast *mat* locus. (*Top*) Physical map of the mating-type region. IR-L and IR-R, shown as black arrows, denote inverted repeats residing on both sides of the *mat2/3* interval and within is *cenH*, with homology to centromeric repeats. (Boxes) Open reading frames, including the essential *let1*$^+$ gene; (arrows) direction of transcription. The graph represents a summary of ChIP experiments throughout the mat locus with H3-K4 (blue) and H3-K9 (red) methyl-specific antibodies (for details, see Noma et al. 2001). Courtesy of Dr. Shiv Grewal.

•Methylation of H3(K9), H3(K27) and H3(K20) are associated with the repressive chromatin state whereas H3(K4), H3(K36) and H3(K79) methylations and/or histone acetylation have been correlated with active chromatin (summary Fischle et al., 2003; Lachner et al., 2003).

- Centromeric heterochromatin: mono- or di-meH3-K9
- Pericentric heterochromatin: tri-meH3K9
- Euchromatin: di-meH3-K4 and Acetylated
- Xi is α-4x-methyl H3(K9)

Inaktivace X chromosomu ve vztahu k epigenetickým modifikacím



Chadwick nad Willard, PNAS, 101, p.17450-17455

Inaktivace X chromosomu ve vztahu k epigenetickým modifikacím

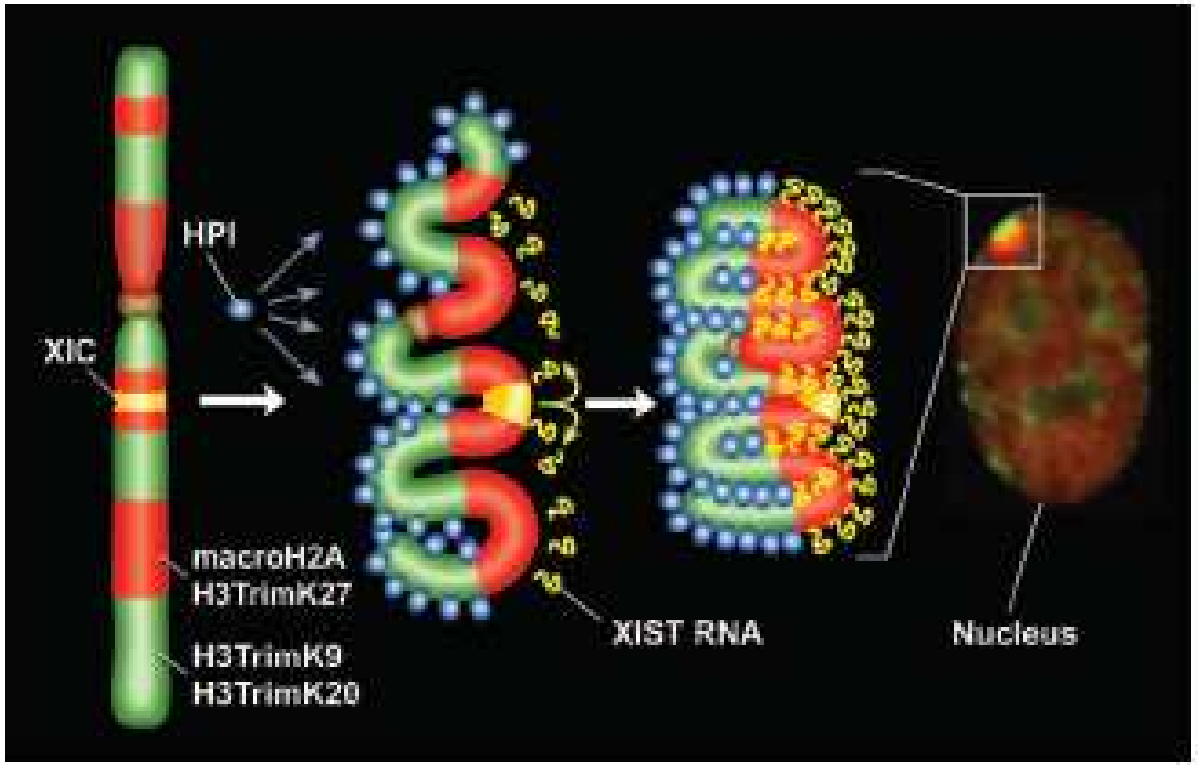
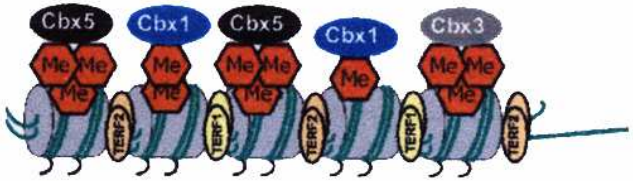


Fig. 4. Schematic model showing how heterochromatin of the Xi could transition between metaphase and interphase to be organized into the two nonoverlapping heterochromatin territories and to explain how XIST RNA could rapidly spread in cis outward from the X inactivation center (XIC) along only part of the Xi. See main text for details.

Methylation state of telomeres

Wild-type telomeres



3´

Normal-length telomeres

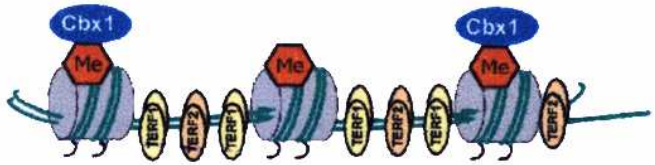
H3K9 (mono-, di- and trimethylated)

Cbx5, Cbx1, Cbx3

TERF1

TERF2

SUV39DN telomeres



3´

↓ H3K9 (di-, trimethylated)

↑ H3K9 (monomethylated)

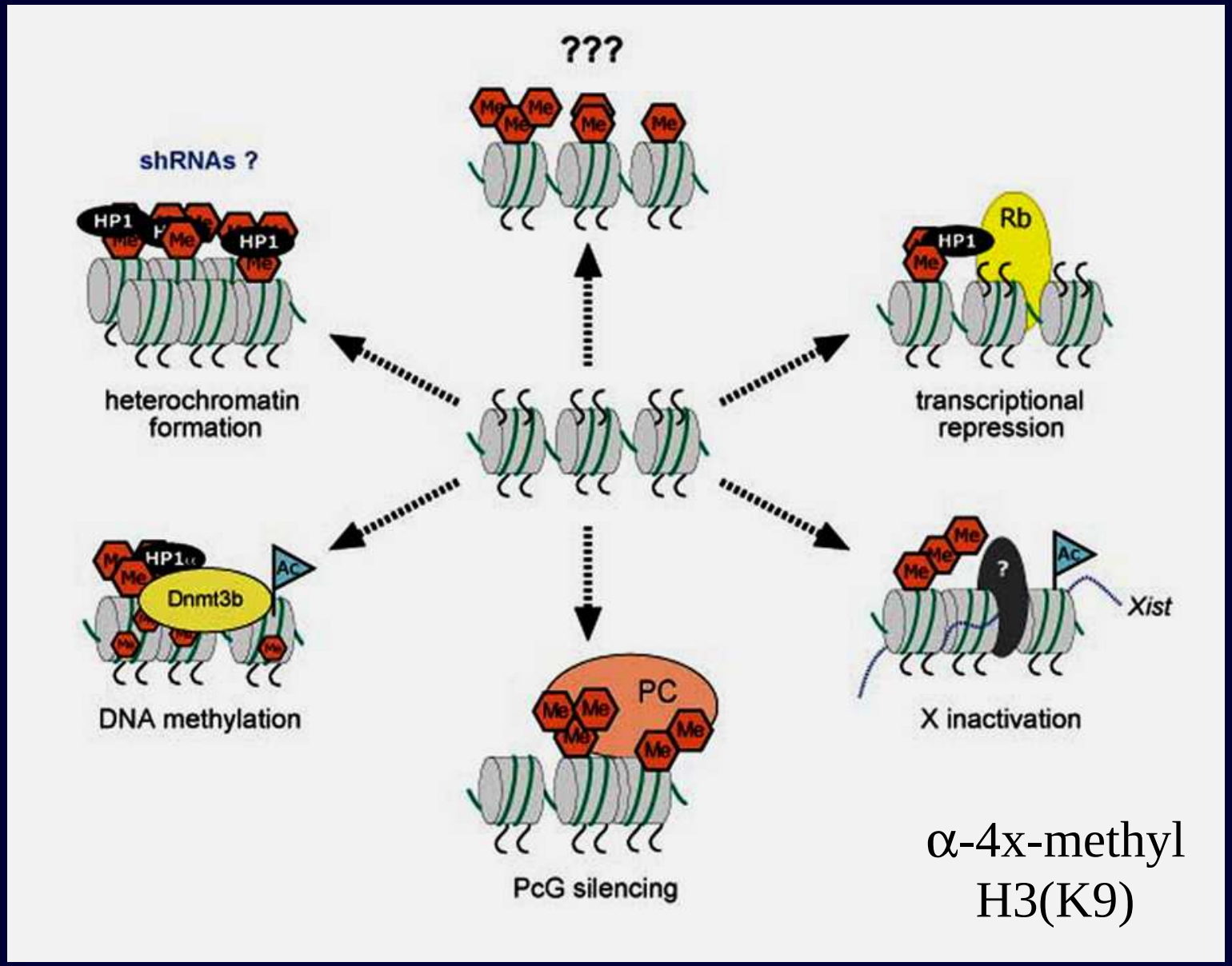
↓ Cbx5, Cbx3

↓ 50% decrease in Cbx1

Normal TERF2 binding

Slight increase in TERF1 binding

Abnormal telomere elongation



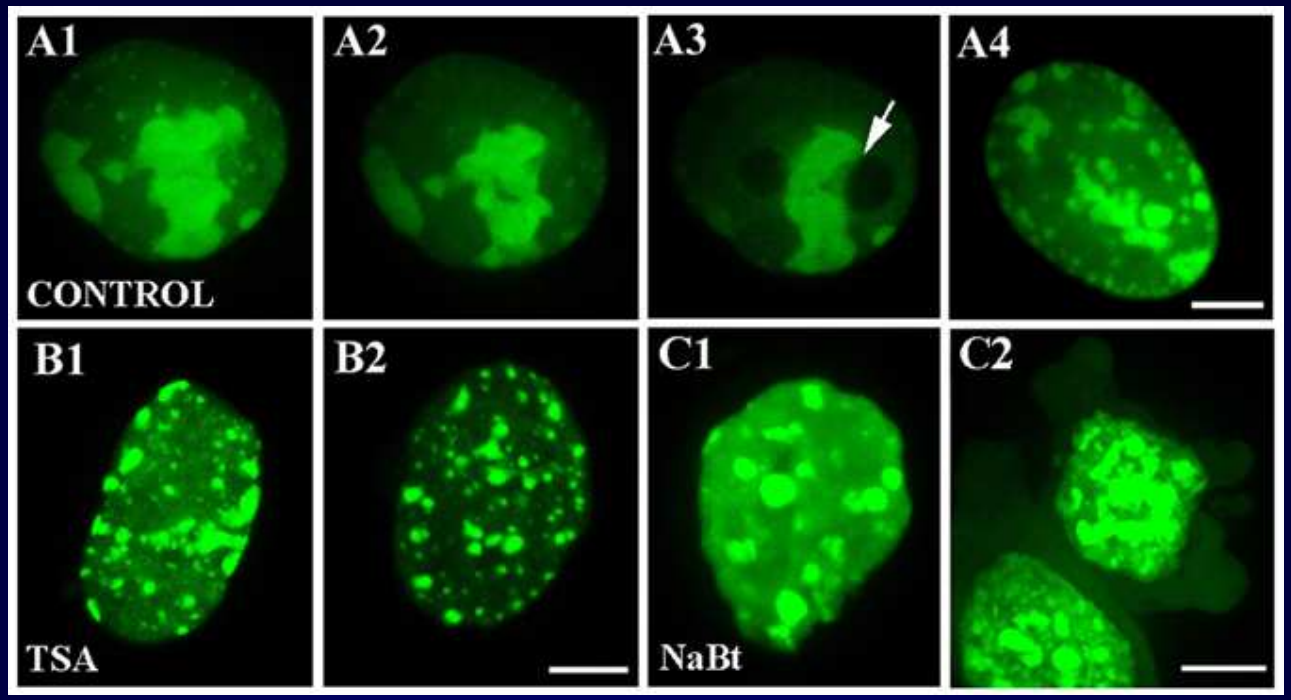
FAKULTATIVNÍ HETEROCHROMATIN

Polycomb group (PcG) proteins are highly conserved regulatory factors that were initially discovered in Drosophila. PcG genes are best known for their role in maintaining silent expression states of Hox genes during development, while trithorax group (trxG) proteins maintain Hox gene expression patterns in the appropriate spatial domains. PcG and trxG proteins are also involved in the regulation of normal cell proliferation, and their mutation has been linked to defects in stem cell fates and to cancer. They act by regulating chromatin structure and chromosome architecture at their target loci.

Year	Brief description of the main findings	Pubmed link
1978	Ed Lewis's founding Polycomb paper identifying a role for the *Pc* gene in the regulation of homeotic genes	go!
1985	Characterization of the *trithorax* gene as a regulator of homeotic gene expression Role of PcG proteins in the maintenance of homeotic gene expression, i.e. in the process of "cellular memory"	go! go!
1988	Antagonism between *Polycomb* and *trithorax* genes	go!
1989	Polytene chromosome binding pattern of Pc	go!
1991	Identification of Bmi-1, the first mammalian PcG gene Role of Bmi-1 in Cancer	go! go: a! b!
1992	Involvement of Trithorax in leukemia	go!
1993	Characterization of PREs in Drosophila Chromatin IP of Polycomb	go: a! b! c! go!
1994	Bmi-1 action as a bona fide mammalian PcG protein	go!
1997	Analysis of PcG proteins in plants PcG proteins and epigenetic regulation of gene expression by "cosuppression"	go! go!
1999	Purification of the PRC1 complex Role of PcG in cell proliferation	go! go!
2000	trxG proteins and histone acetylation	go: a! b!
2001	Link between PcG proteins and the basal transcriptional machinery PcG proteins and genomic imprinting in mammals	go: a! b! go!
2002	Characterization of the E(z)-Esc / PRC2 complex - Histone methyltransferase activity trxG proteins and histone methylation	go: a! b! c! d! go: a! b!
2003	Binding of the PC chromo domain to histone H3 methylated at Lysine 27 PcG proteins and X-inactivation Polycomb as a Sumo E3 protein	go: a! b! go: a! b! go!
2004	PRC1 proteins mediate histone ubiquitination Identification of a PRC3 complex related to PRC2 and identification of histone H1 methylation activity	go! go!
2005	Identification of a link between PcG proteins and DNA methylation Role for PcG proteins in the phenomenon of transdetermination in *Drosophila*	go: a! b! go: a! b!

2006: Genome-wide mapping of the down-stream target sites for PcG proteins

HP1 proteins

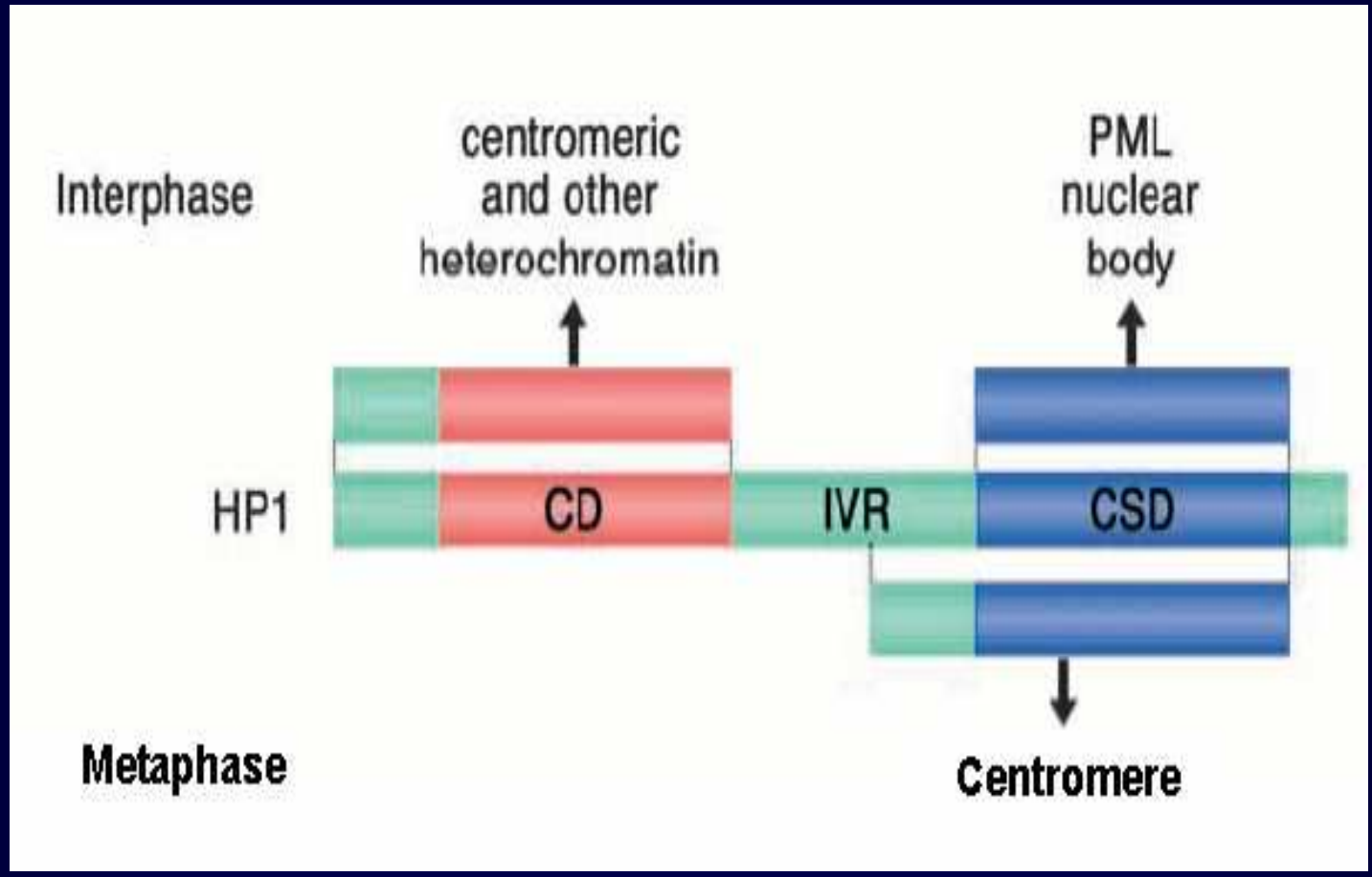


•**HP1 proteiny jsou hlavní složkou heterochromatinu a hrají důležitou úlohu při jeho tvorbě. HPs jsou mají vysokou afinitu k pericentromerickým a telometrickým oblastem chromosomů.**

• **HPs interagují s HMTs jako je SUV39h, která je zodpovědná za methylaci H3(K9).**

HP1 proteins:

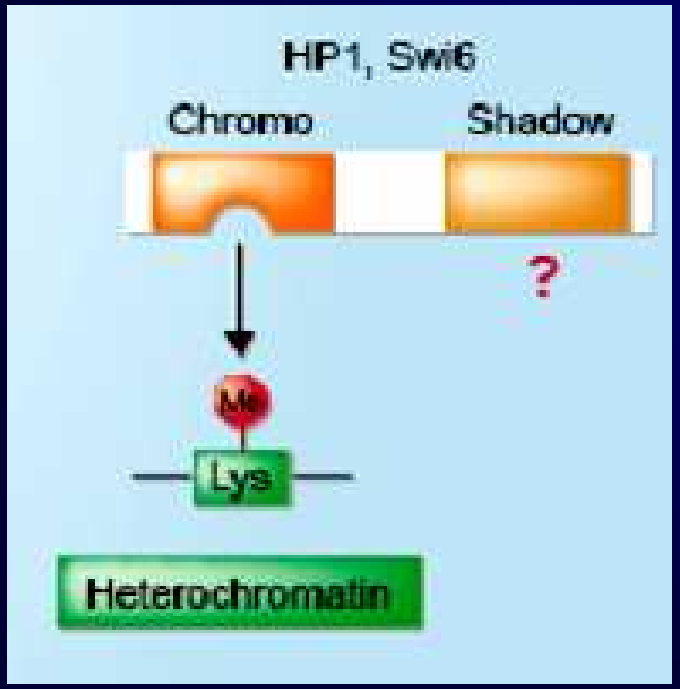
1. Heterochromatin protein (dHP1) was first identified in *Drosophila* and shown to localise to heterochromatin by antibody staining.
2. Mutation of HP1 gene decrease the effect of **PEV** (position effect variegation) on gene expression.
3. Null mutations of HP1 are lethal due to chromosome loss during cell division.
4. Homologous protein to HP1 are these of Polycomb group (Pc). Both Pc and HP1 share a common amino acid sequence of the chromodomain (chromatin modification) which is thought to mediate protein/protein interactions. This domain is highly conserved from yeast to man.
5. Three genes for mammalian HP1 have been identified: α, β, and γ.
6. To date only α and γ HP1 proteins have been identified in *Xenopus laevis*. We want to determine the role of HP1 proteins in *Xenopus* development.


Interphase
centromeric
and other
heterochromatin
PML
nuclear
body
HP1
CD
IVR
CSD
Metaphase
Centromere

HPs se skládají z vysoce konzervativních oblastí:

a) N-terminální chromodomény (CD)

b) strukturálně odvozené C-terminální chromo-shadow domény (CSD)



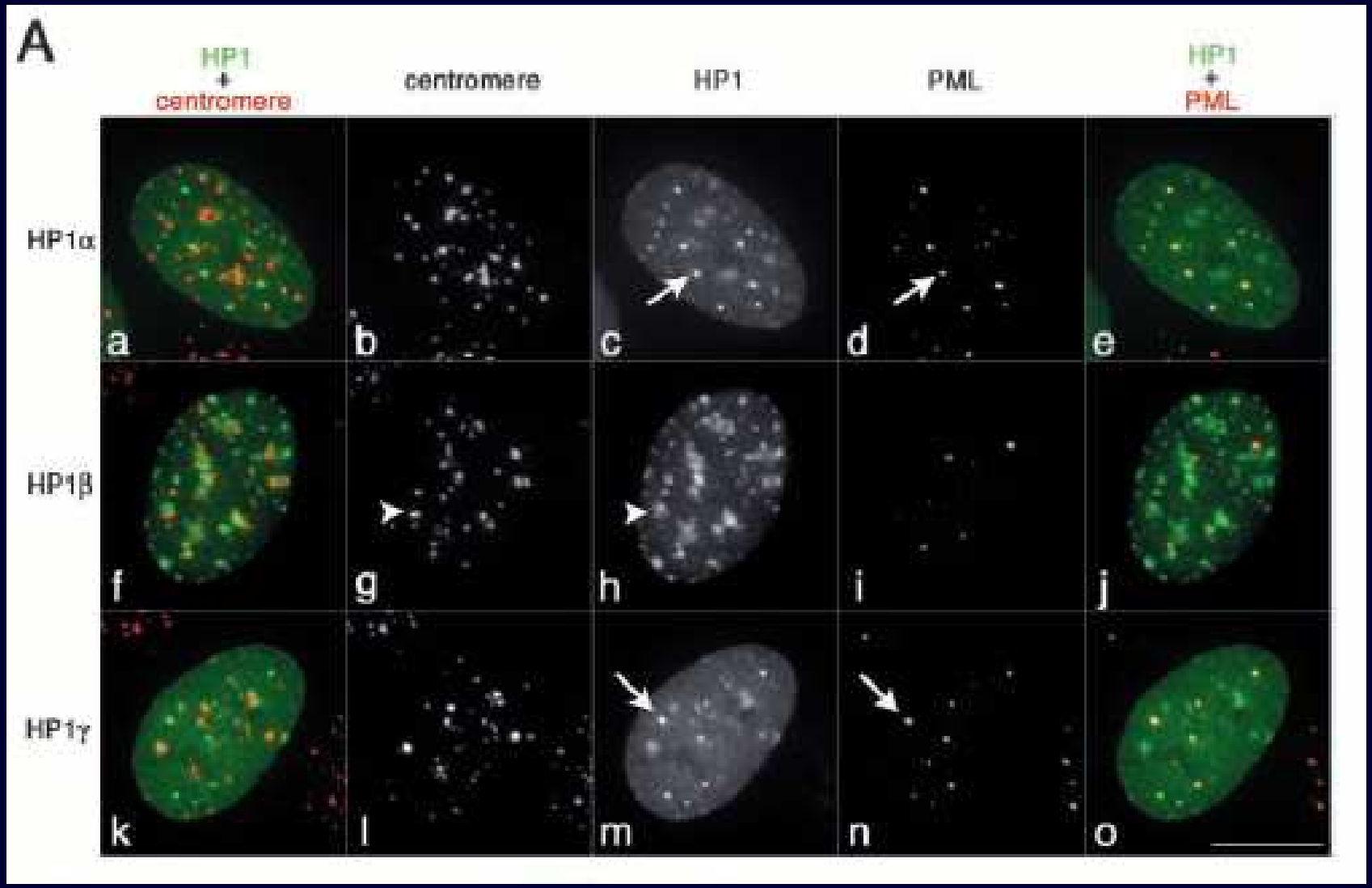
FUNKCE HPs

a) **Uspořádání chromatinu**

b) **Regulace transkripce**

c) **Optimální regulace délky telomer a zprostředkování procesu telomeric silencing**

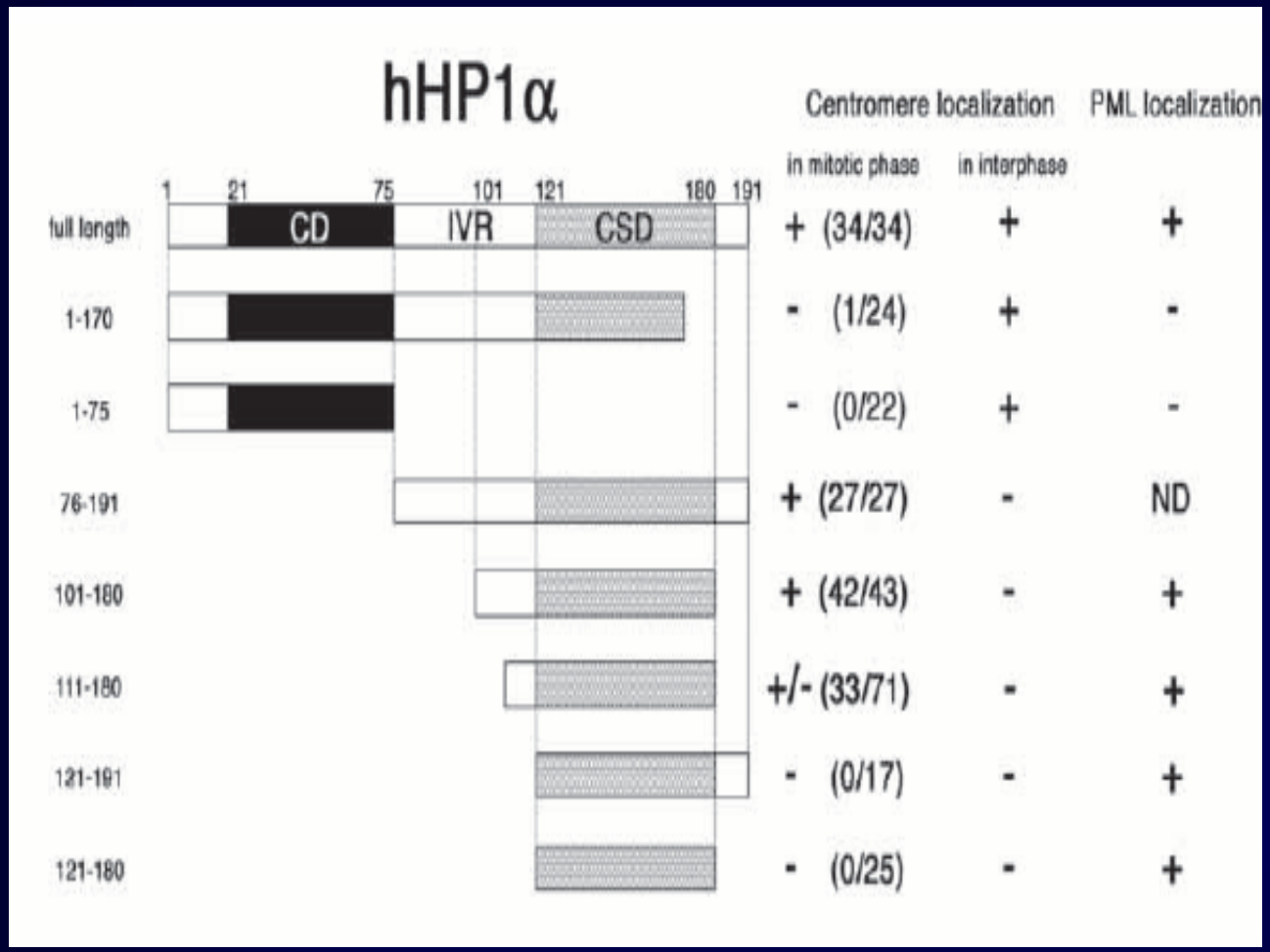
HP1 proteiny – v lidských buňkách jsou 3 sub-typy

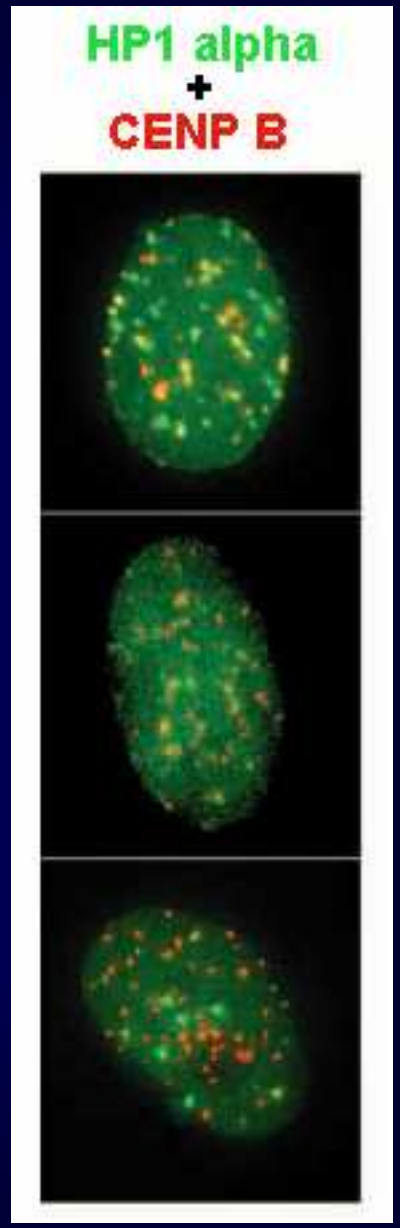


Hayakawa et al., 2003

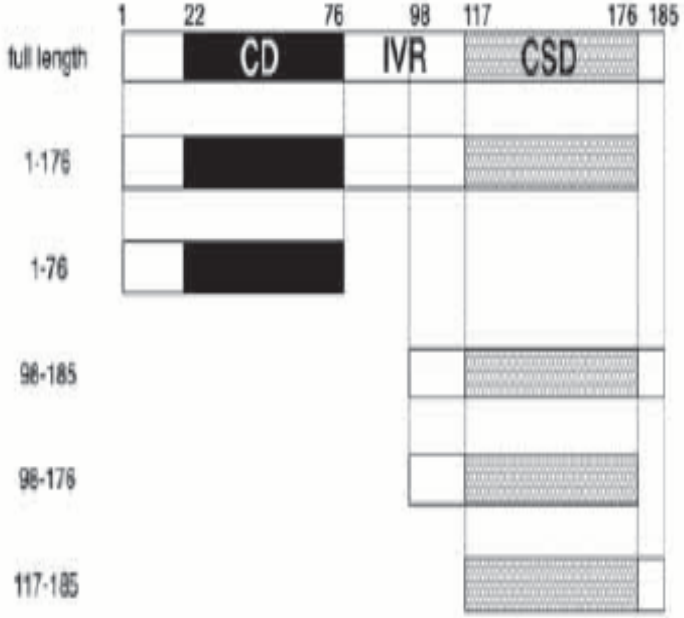
Savčí jádra obsahují 10-30 sférických struktur zvaných **PML bodies** (PODs, ND10 nebo Kremer bodies). Gen kódující PML je fúzován s genem kódujícím receptor pro kyselinu retinouvou a to u akutní promyelocytické leukemie (APL), Jde o translokaci t(15;17). PML bodies jsou cílem mnoha virů při časné infekci, jsou místem iniciace transkripce u virů.

PML bodies interagují s mnoha proteiny podobnými HDAC, které se však neshromažďují v PML bodies. PML jsou zahrnuty v řadě procesů jako je buněčný růst, apoptóza, imunitní odpovědi a regulace transkripce. PML jsou také místem degradace některých proteinů, asociují nejen s HP1, ale i se specifickými geny jako je p53 a jeho protein TP53. PML NBs obsahují nově syntetizovanou RNA, výsledkem je významná úloha PML bodies v regulaci genové exprese.

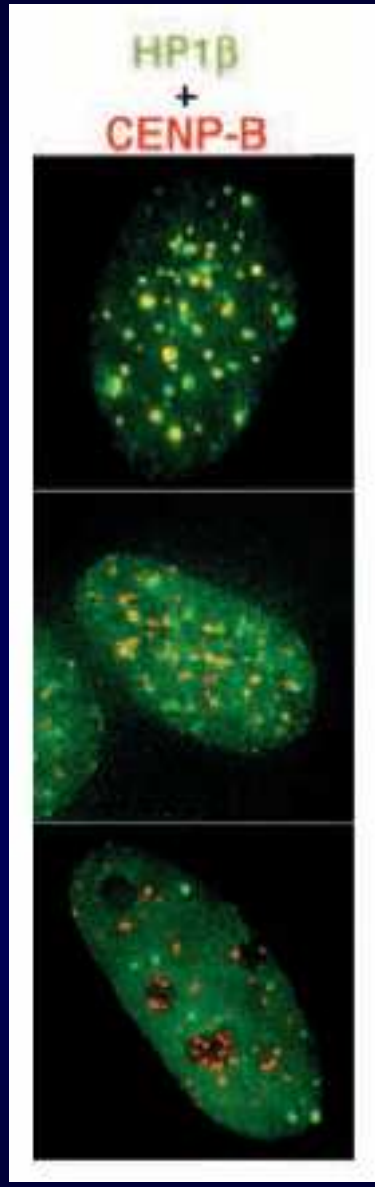

hHP1α
Centromere localization
PML localization
in mitotic phase
in interphase
1
21
75
101
121
180
191
CD
IVR
CSD
full length
+ (34/34)
+
+
1-170
- (1/24)
+
-
1-75
- (0/22)
+
-
76-191
+ (27/27)
-
ND
101-180
+ (42/43)
-
+
111-180
+/- (33/71)
-
+
121-191
- (0/17)
-
+
121-180
- (0/25)
-
+

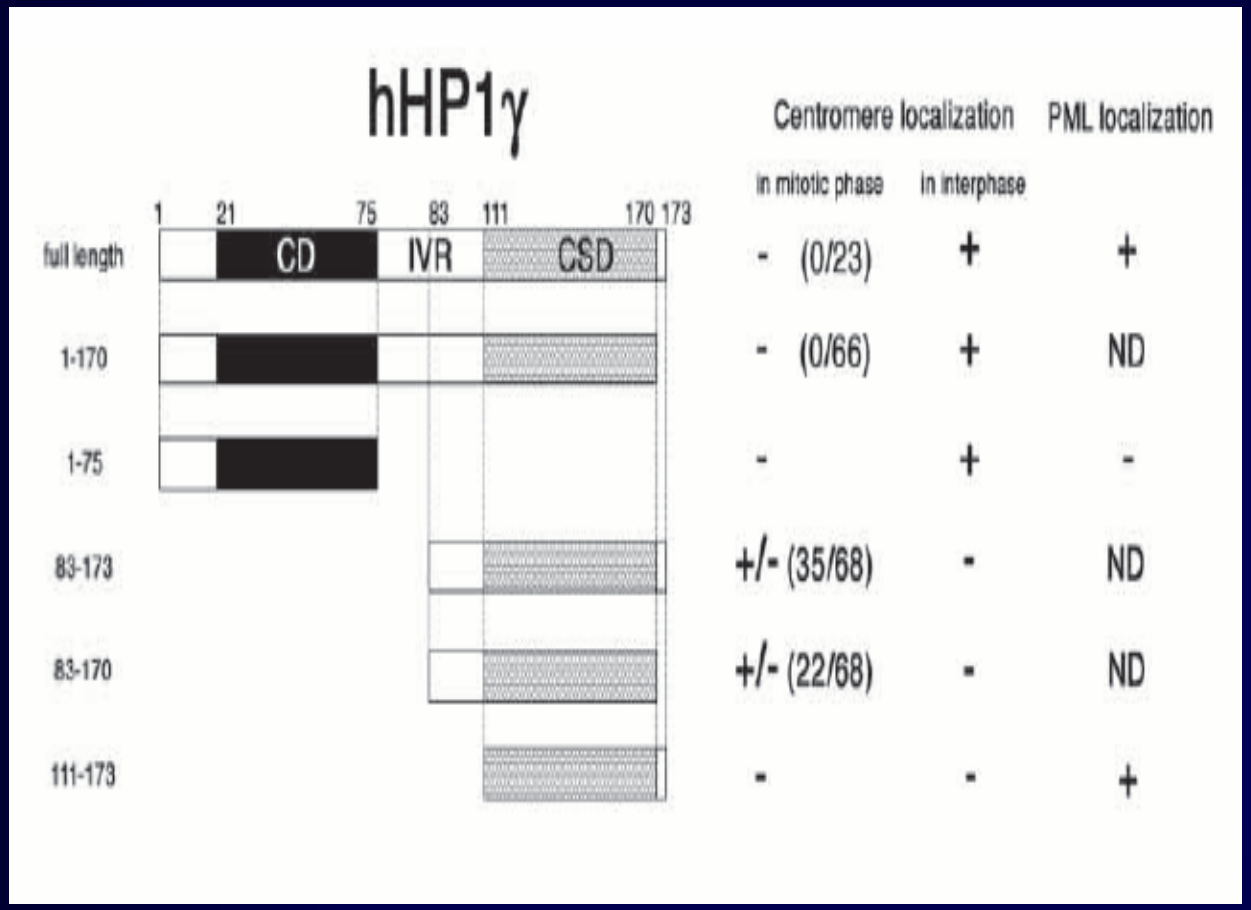

HP1 alpha
+
CENP B

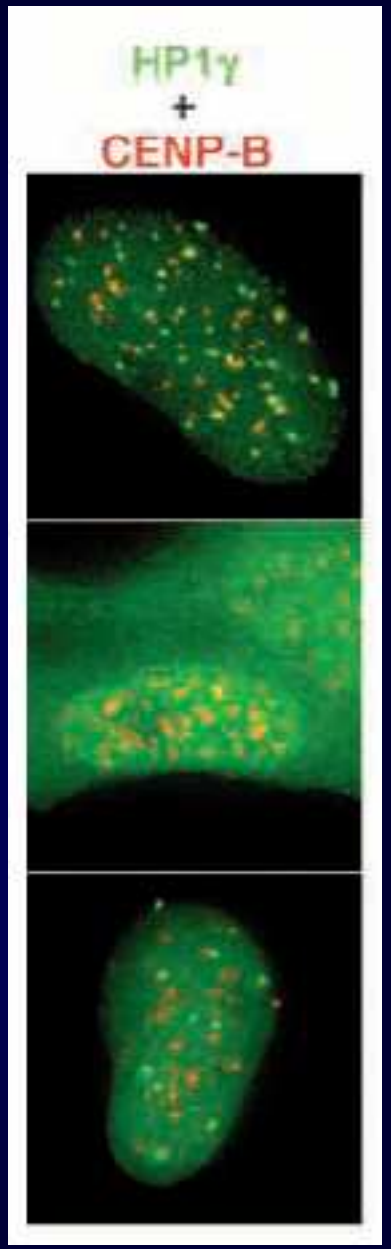
hHP1β



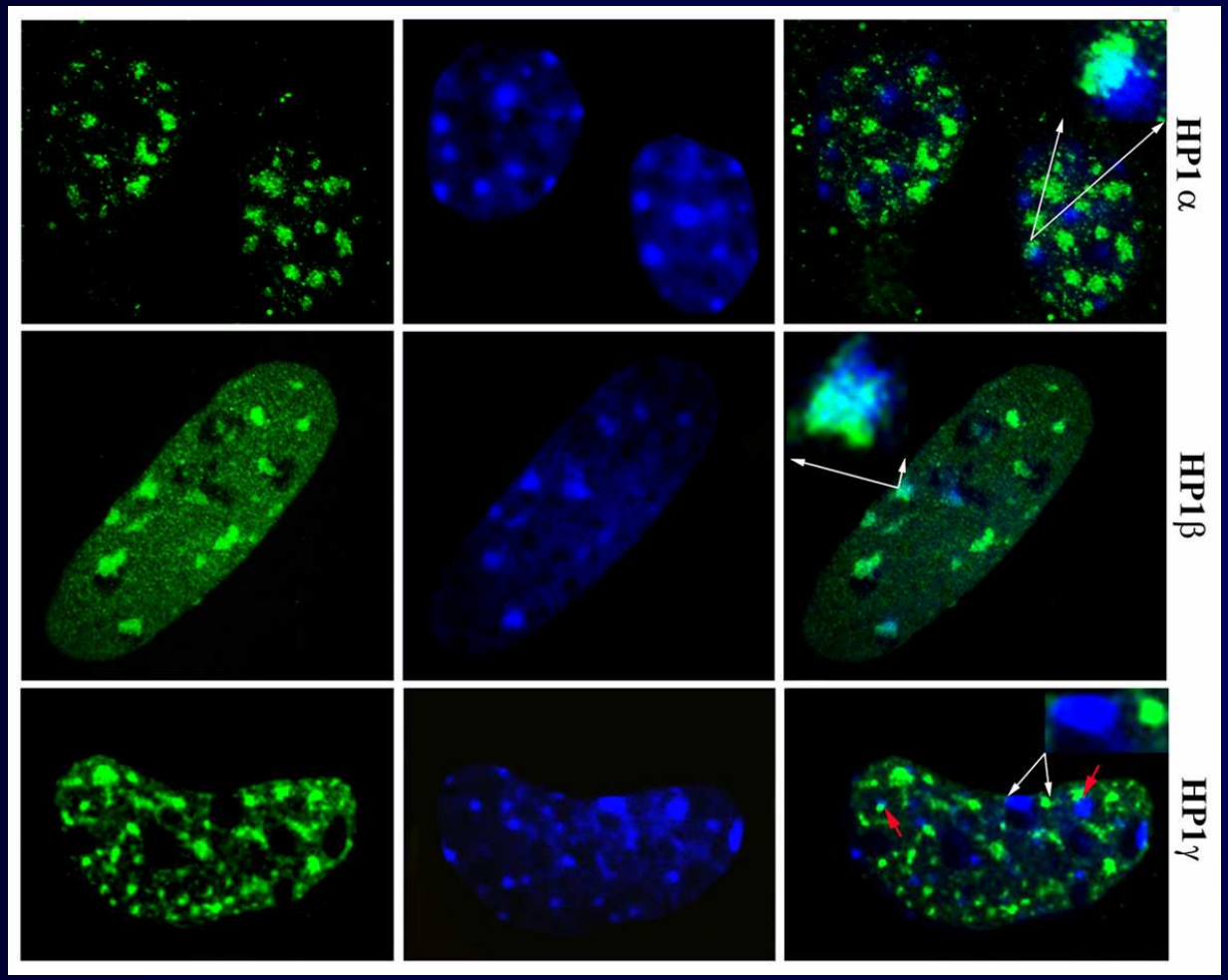
	Centromere localization		PML localization
	in mitotic phase	in interphase	
full length	- (0/23)	+	+
1-176	- (9/64)	+	ND
1-76	-	+	-
98-185	+/- (32/67)	-	ND
98-176	+/- (42/69)	-	ND
117-185	-	-	+



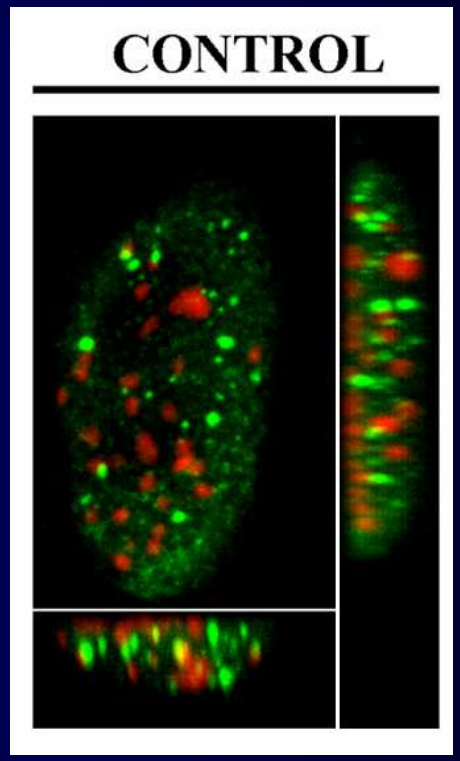

hHP1γ
1
21
75
83
111
170 173
CD
IVR
CSD
full length
1-170
1-75
83-173
83-170
111-173
Centromere localization
PML localization
in mitotic phase
in interphase
- (0/23)
+
+
- (0/66)
+
ND
-
+
-
+/- (35/68)
-
ND
+/- (22/68)
-
ND
-
-
+

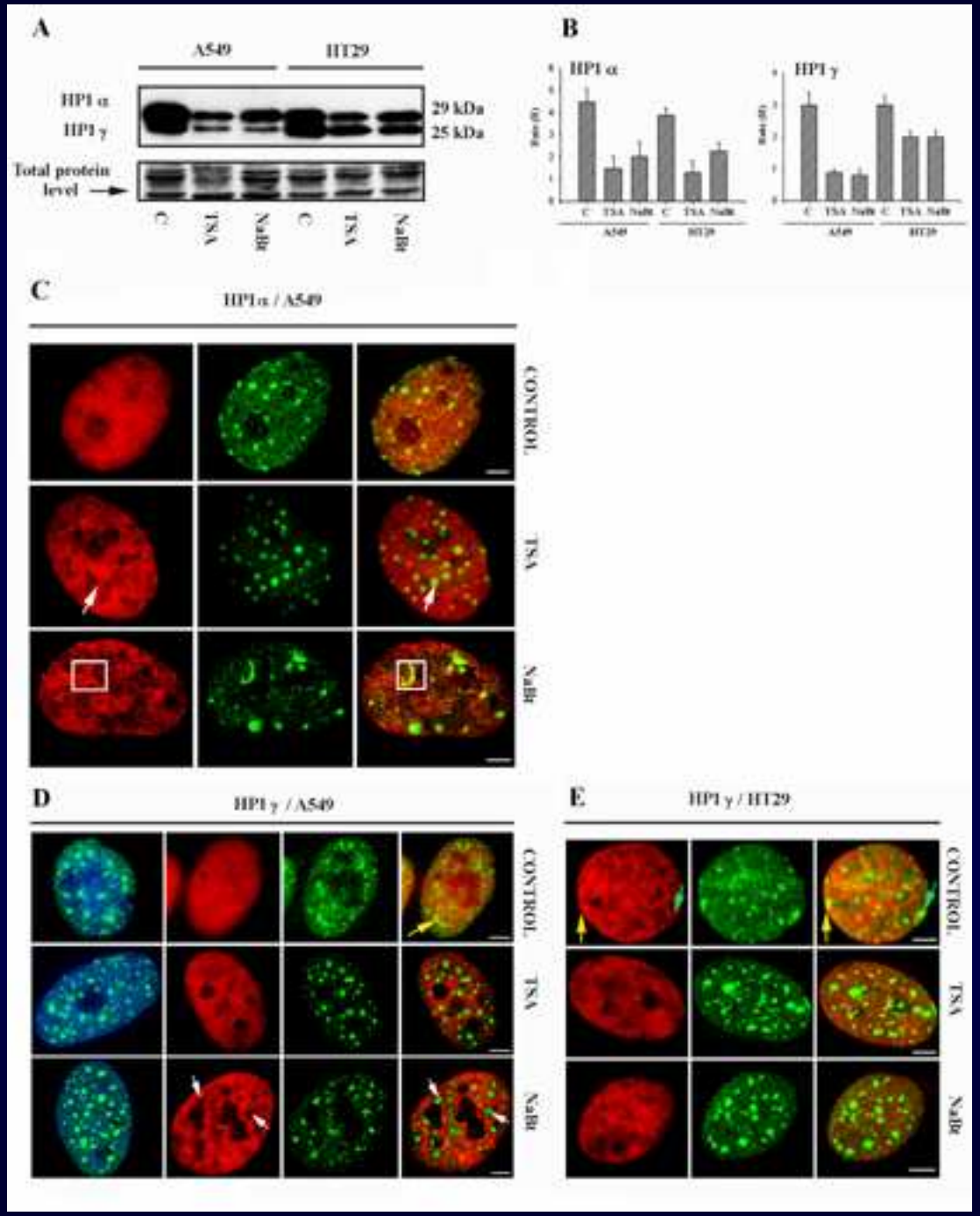

HP1γ
+
CENP-B

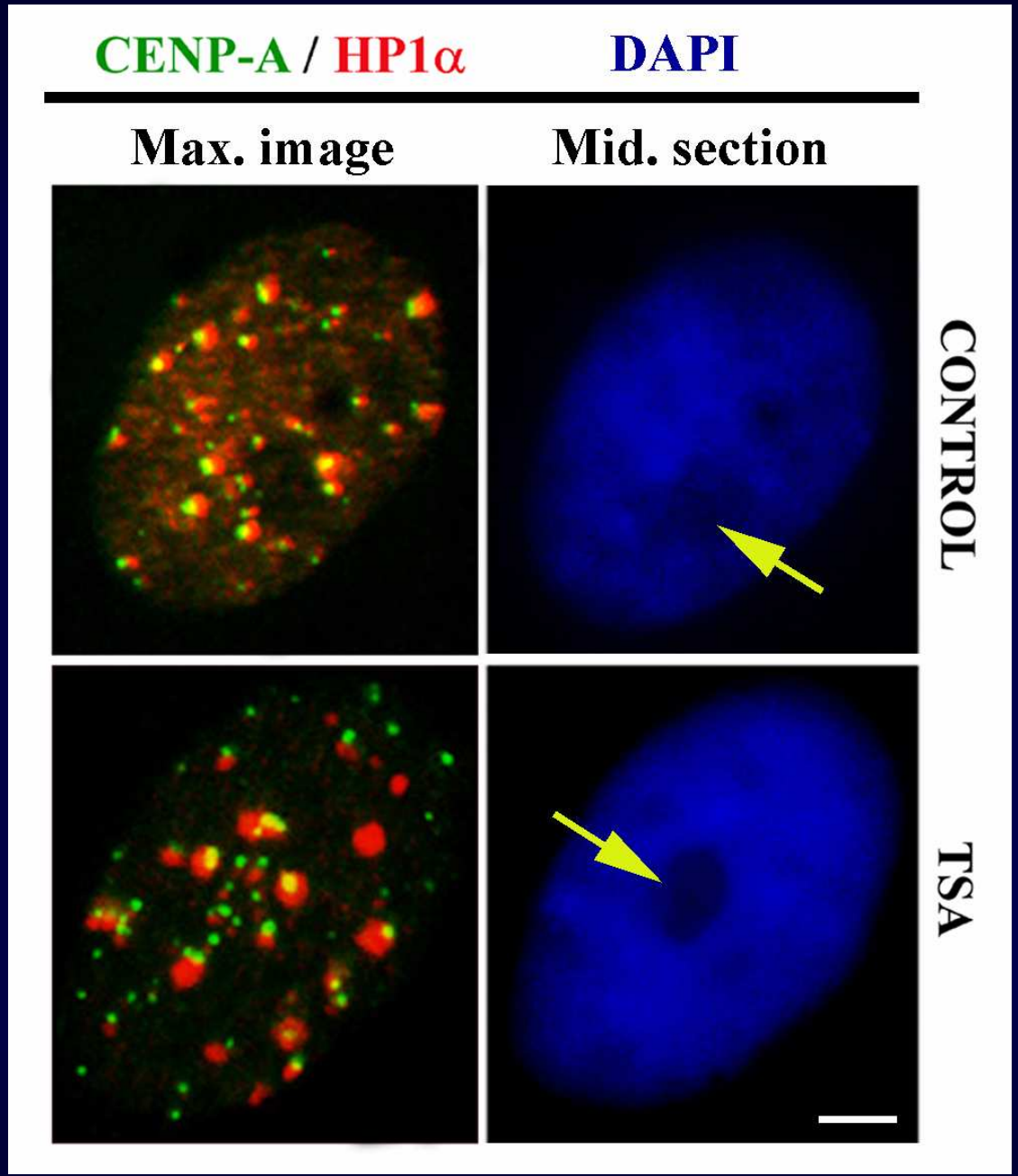
Neuronal cell differentiation of EC cells - HP1 proteins

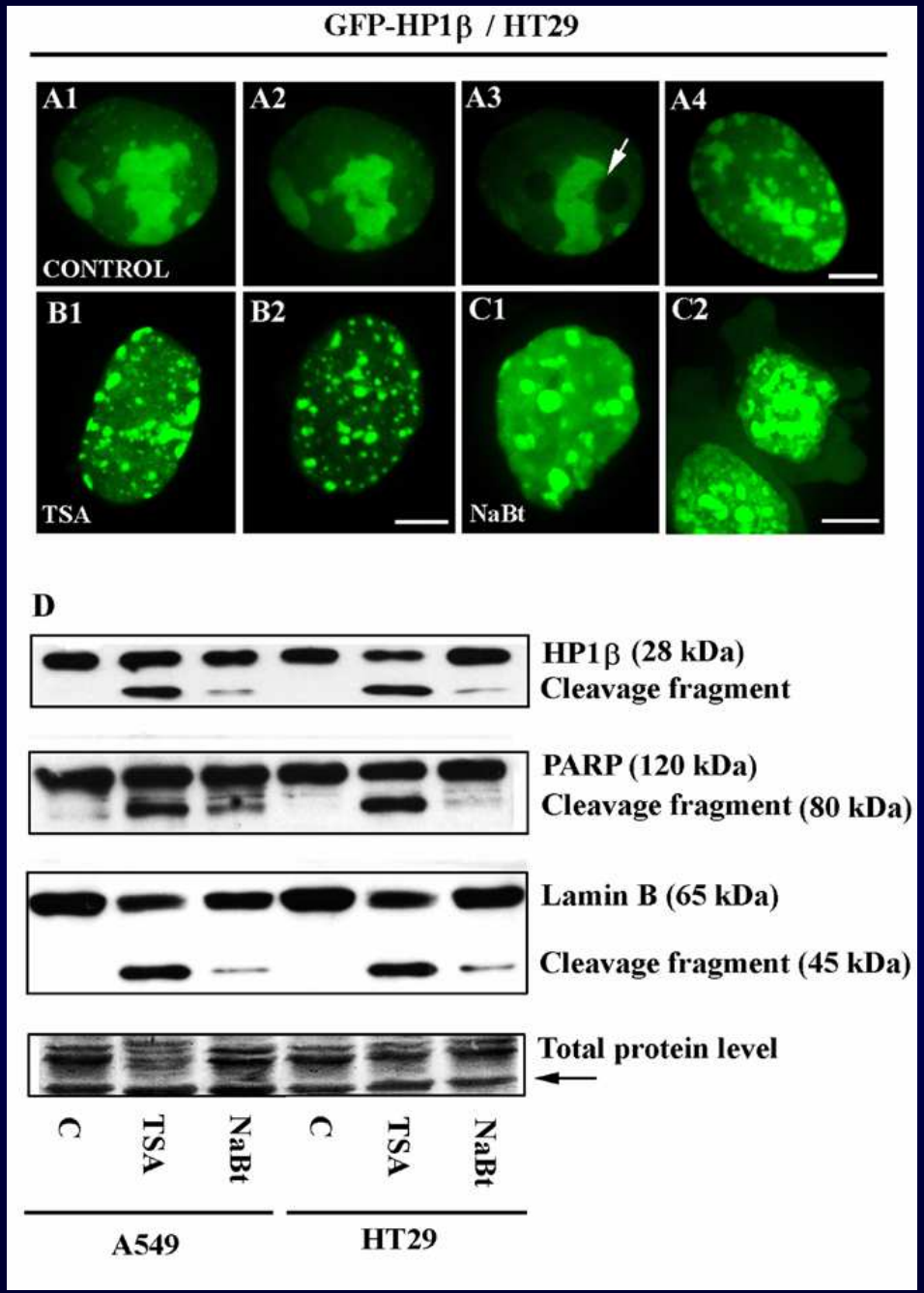


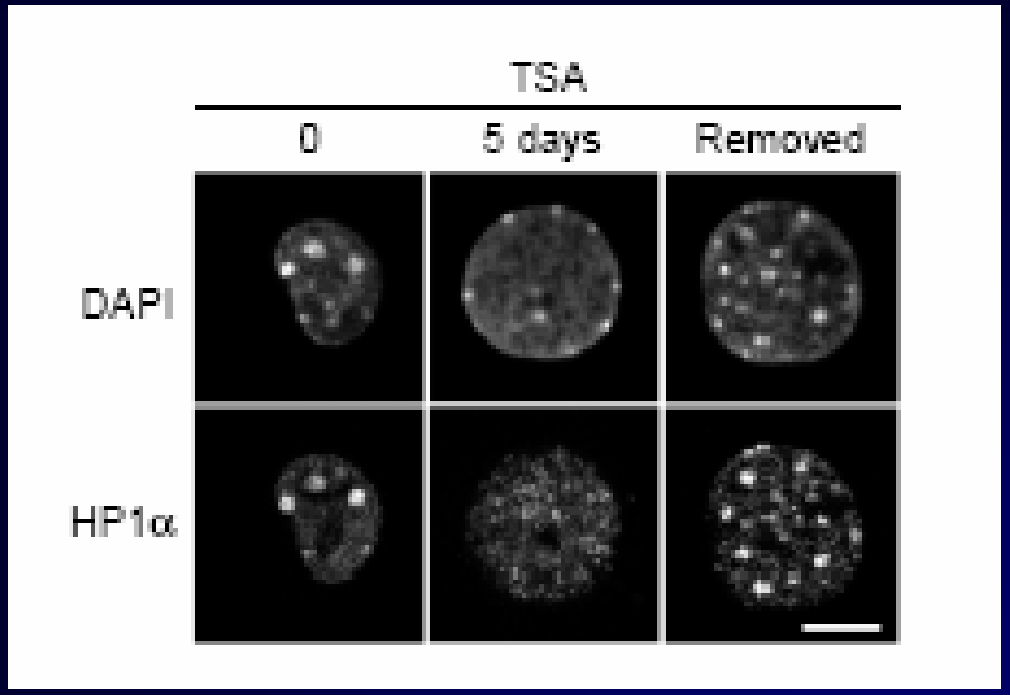
HP1α HP1β



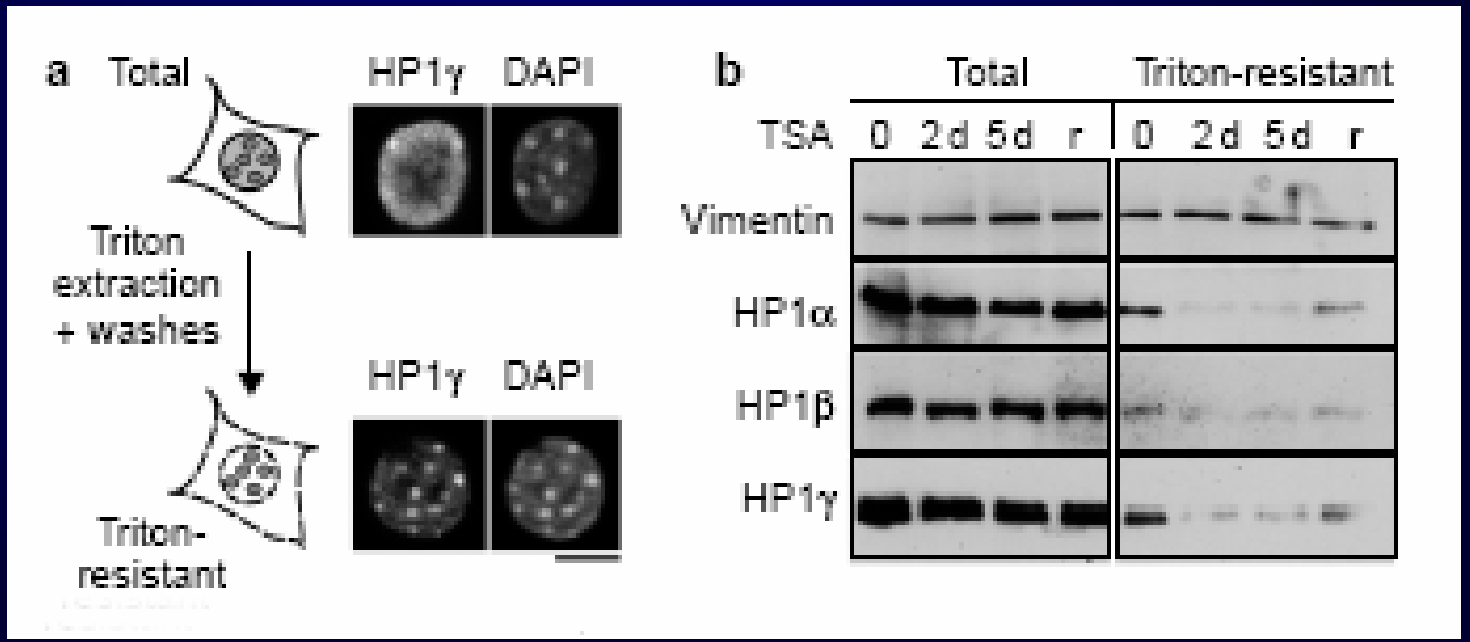

A
A549
HT29
HP1 α
HP1 γ
29 kDa
25 kDa
Total protein level
C
TSA
NaBt
B
HP1 α
HP1 γ
C
TSA
NaBt
A549
HT29
C
HP1α / A549
CONTROL
TSA
NaBt
D
HP1 γ / A549
CONTROL
TSA
NaBt
E
HP1 γ / HT29
CONTROL
TSA
NaBt


CENP-A / HP1α
DAPI
Max. image
Mid. section
CONTROL
TSA

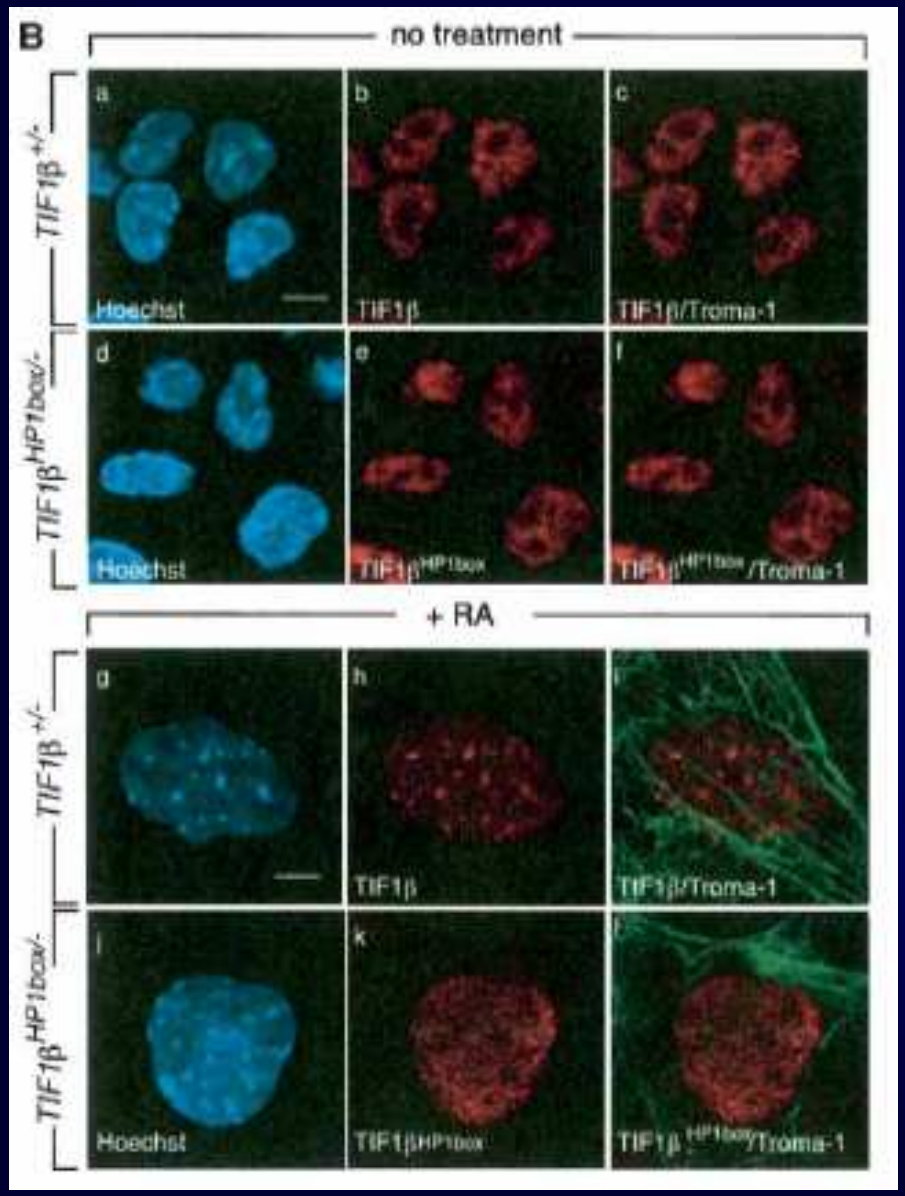

GFP-HP1β / HT29
A1
A2
A3
A4
CONTROL
B1
B2
C1
C2
TSA
NaBt
D
HP1β (28 kDa)
Cleavage fragment
PARP (120 kDa)
Cleavage fragment (80 kDa)
Lamin B (65 kDa)
Cleavage fragment (45 kDa)
Total protein level
C
TSA
NaBt
C
TSA
NaBt
A549
HT29

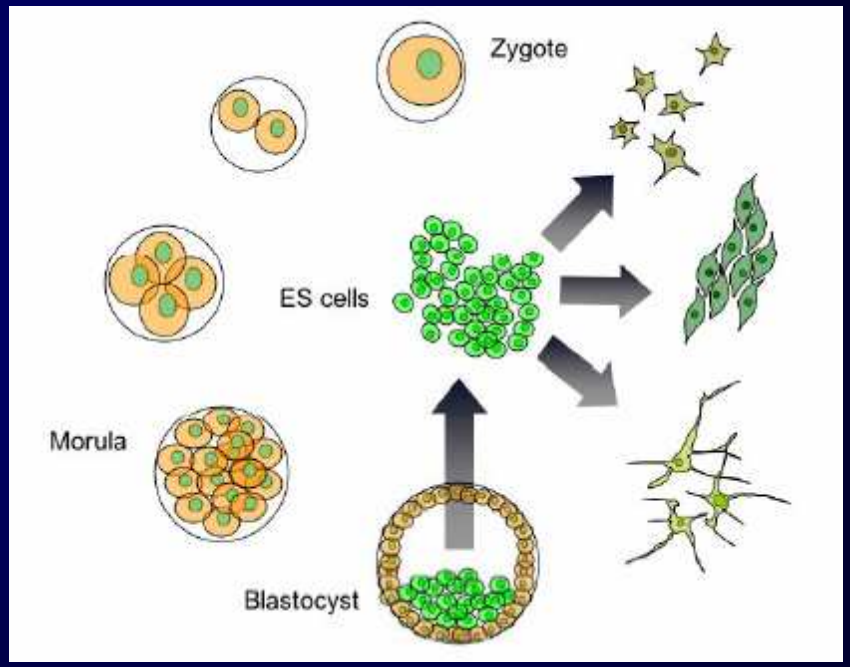


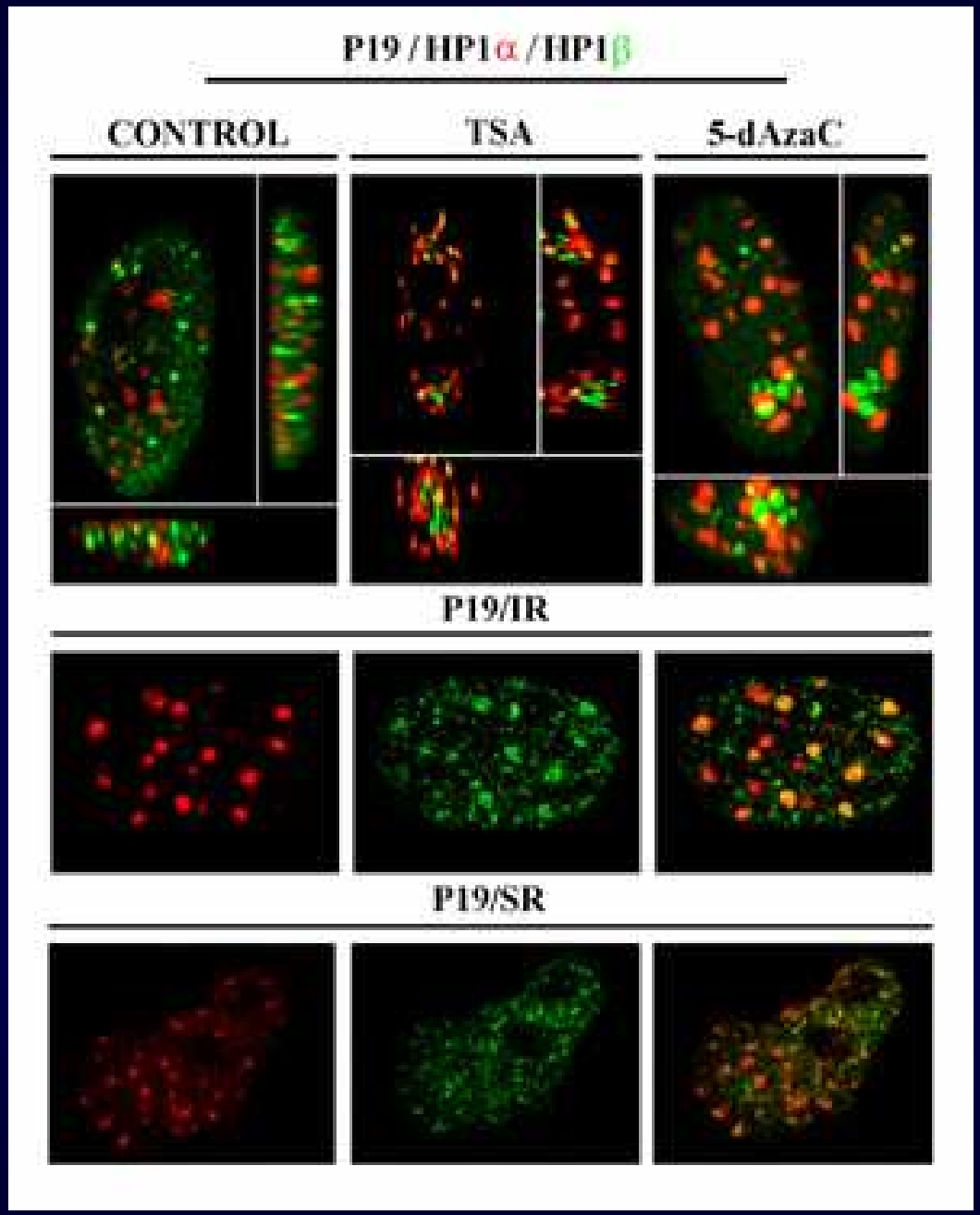
Taddei et al., 2001

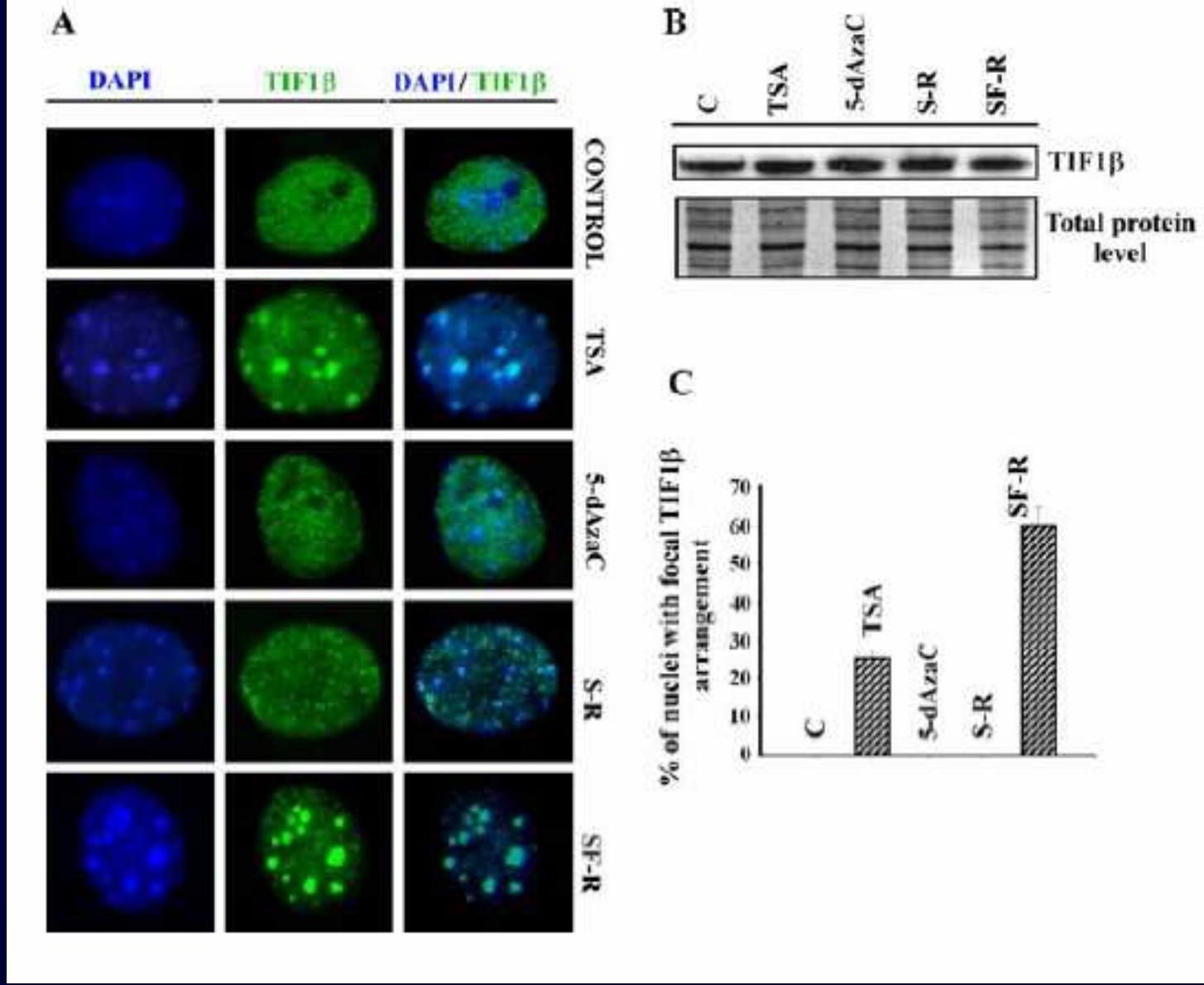


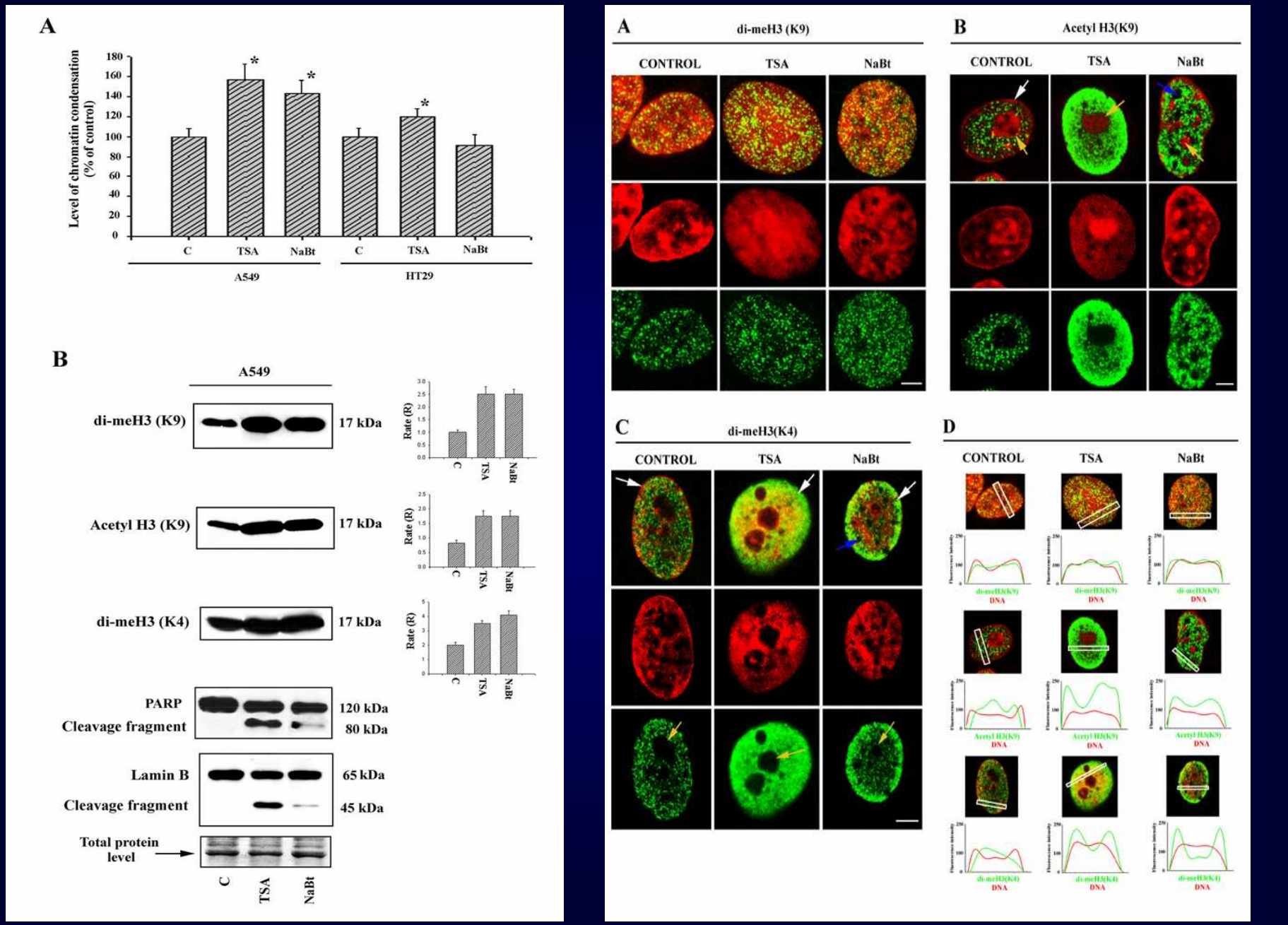
TIF1 beta and chromocentres and HP1 protein



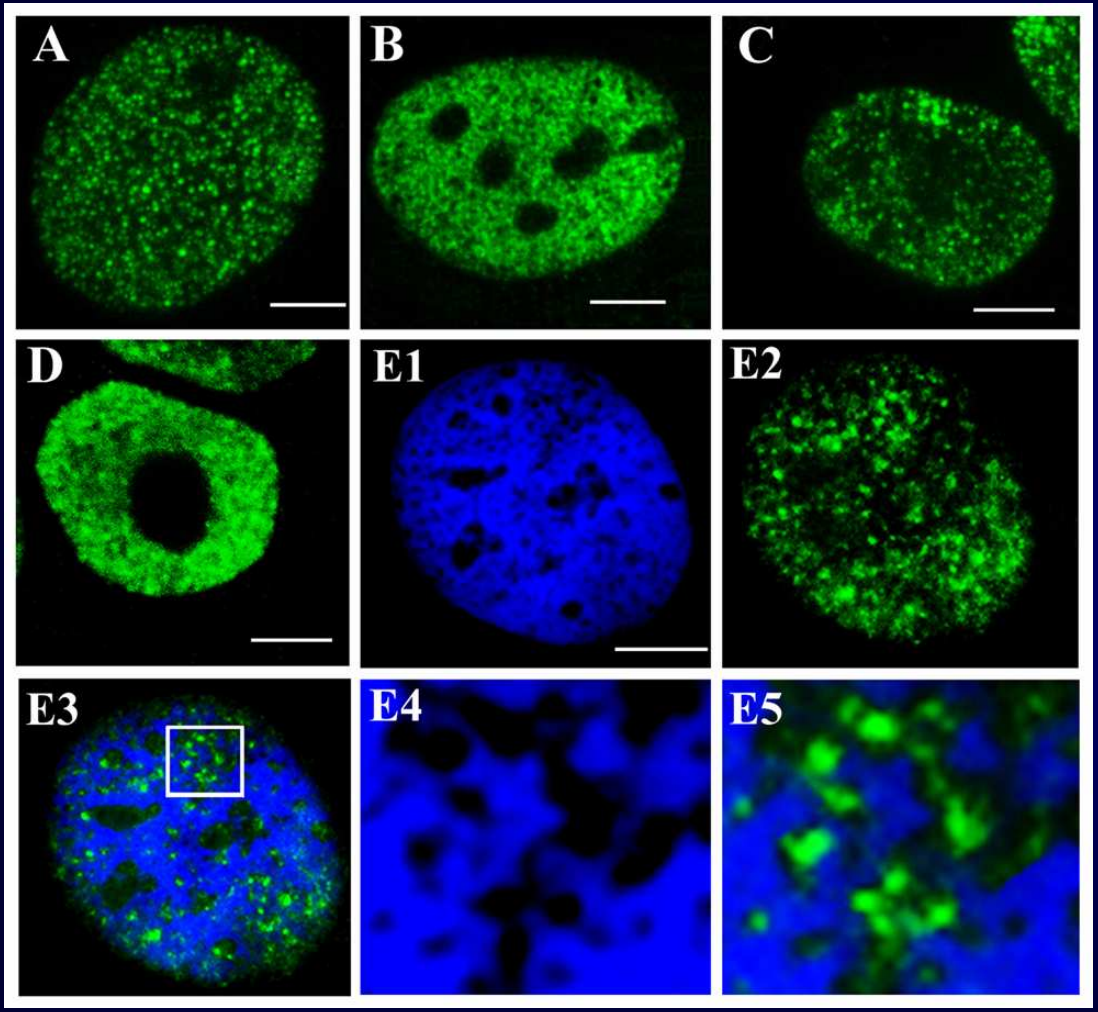



P19 / HP1α / HP1β
CONTROL
TSA
5-dAzaC
P19/IR
P19/SR

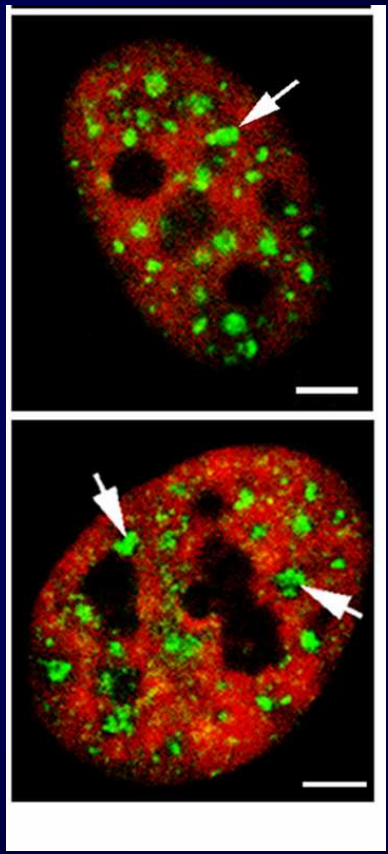

A
DAPI
TIF1β
DAPI/ TIF1β
CONTROL
TSA
5-dAzaC
S-R
SF-R
B
C
TSA
5-dAzaC
S-R
SF-R
TIF1β
Total protein level
C
% of nuclei with focal TIF1β arrangement
0
10
20
30
40
50
60
70
C
TSA
5-dAzaC
S-R
SF-R

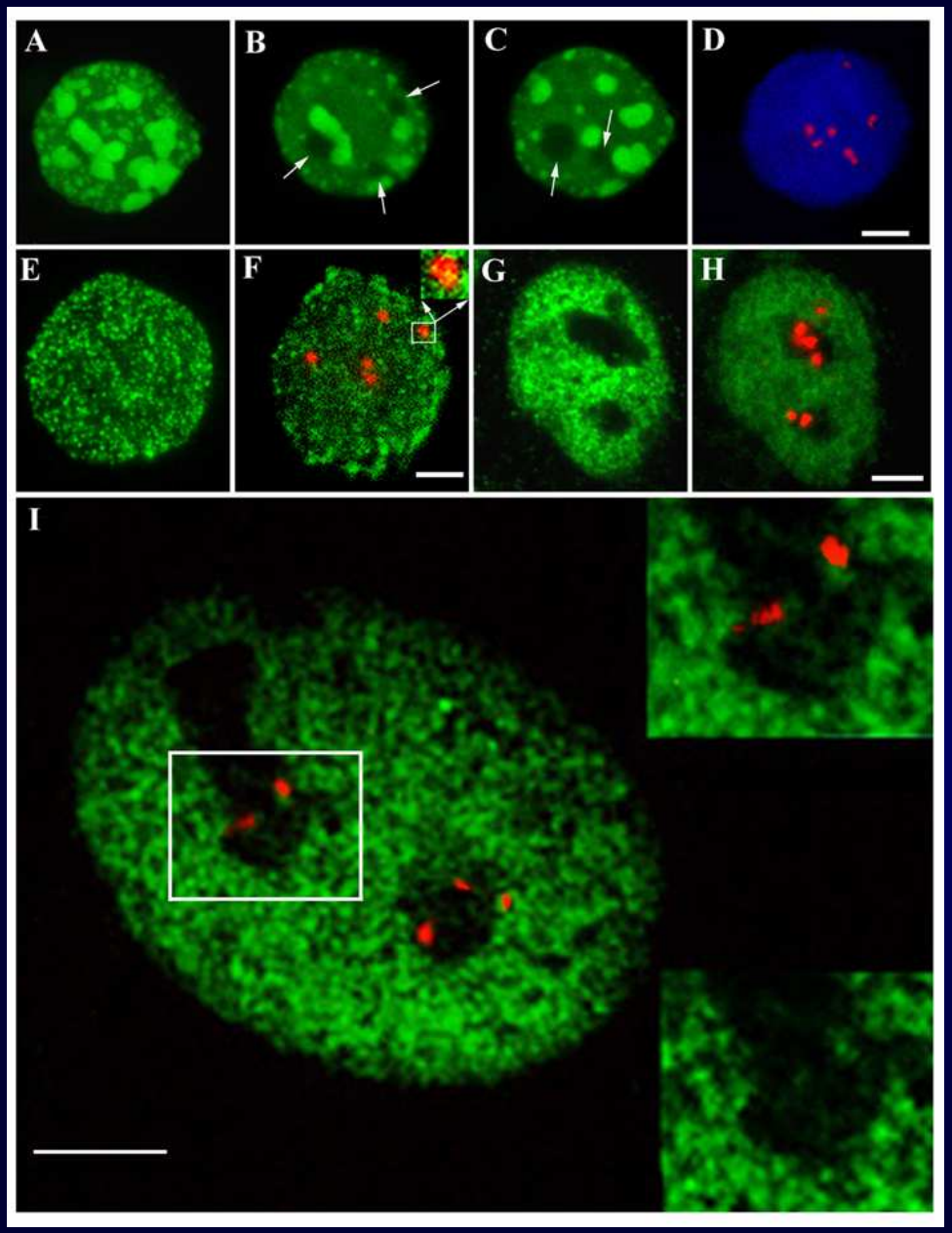

A
Level of chromatin condensation (% of control)
180
160
140
120
100
80
60
40
20
0
C
TSA
NaBt
C
TSA
NaBt
A549
HT29
B
A549
di-meH3 (K9)
17 kDa
Acetyl H3 (K9)
17 kDa
di-meH3 (K4)
17 kDa
PARP
Cleavage fragment
120 kDa
80 kDa
Lamin B
Cleavage fragment
65 kDa
45 kDa
Total protein level
Rate (R)
C
TSA
NaBt
A
di-meH3 (K9)
CONTROL
TSA
NaBt
B
Acetyl H3(K9)
CONTROL
TSA
NaBt
C
di-meH3(K4)
CONTROL
TSA
NaBt
D
CONTROL
TSA
NaBt
di-meH3(K9)
DNA
Acetyl H3(K9)
DNA
di-meH3(K4)
DNA

H3(K4) di-methylation and IC spaces



HP1

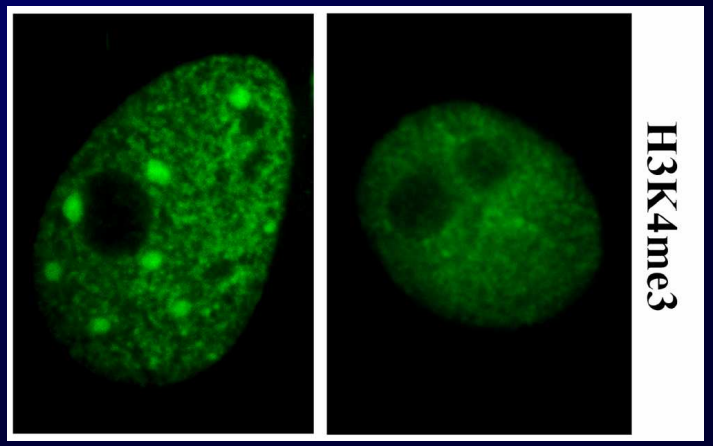




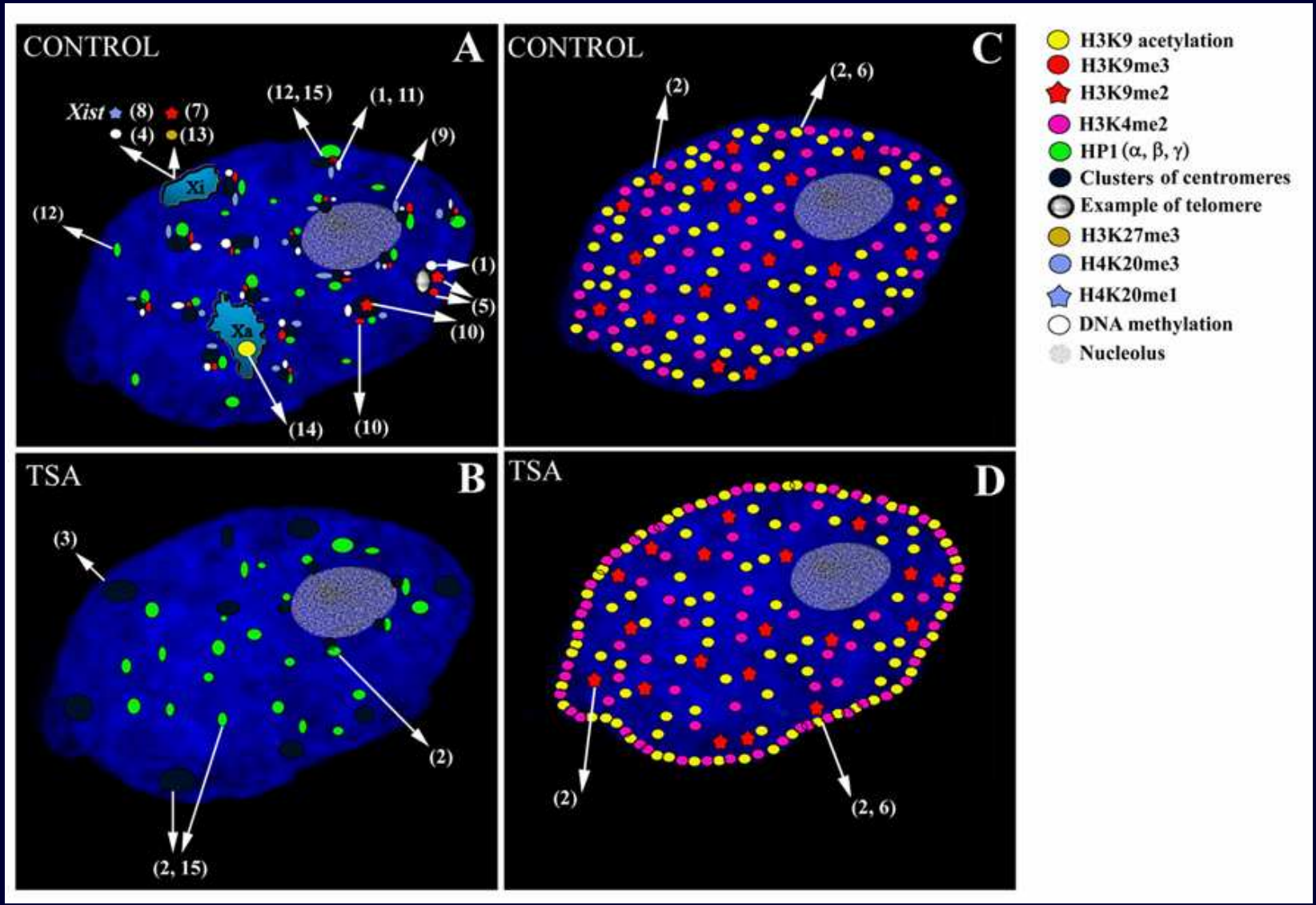
HP1α **Cen 14/22**

H3K9 me2

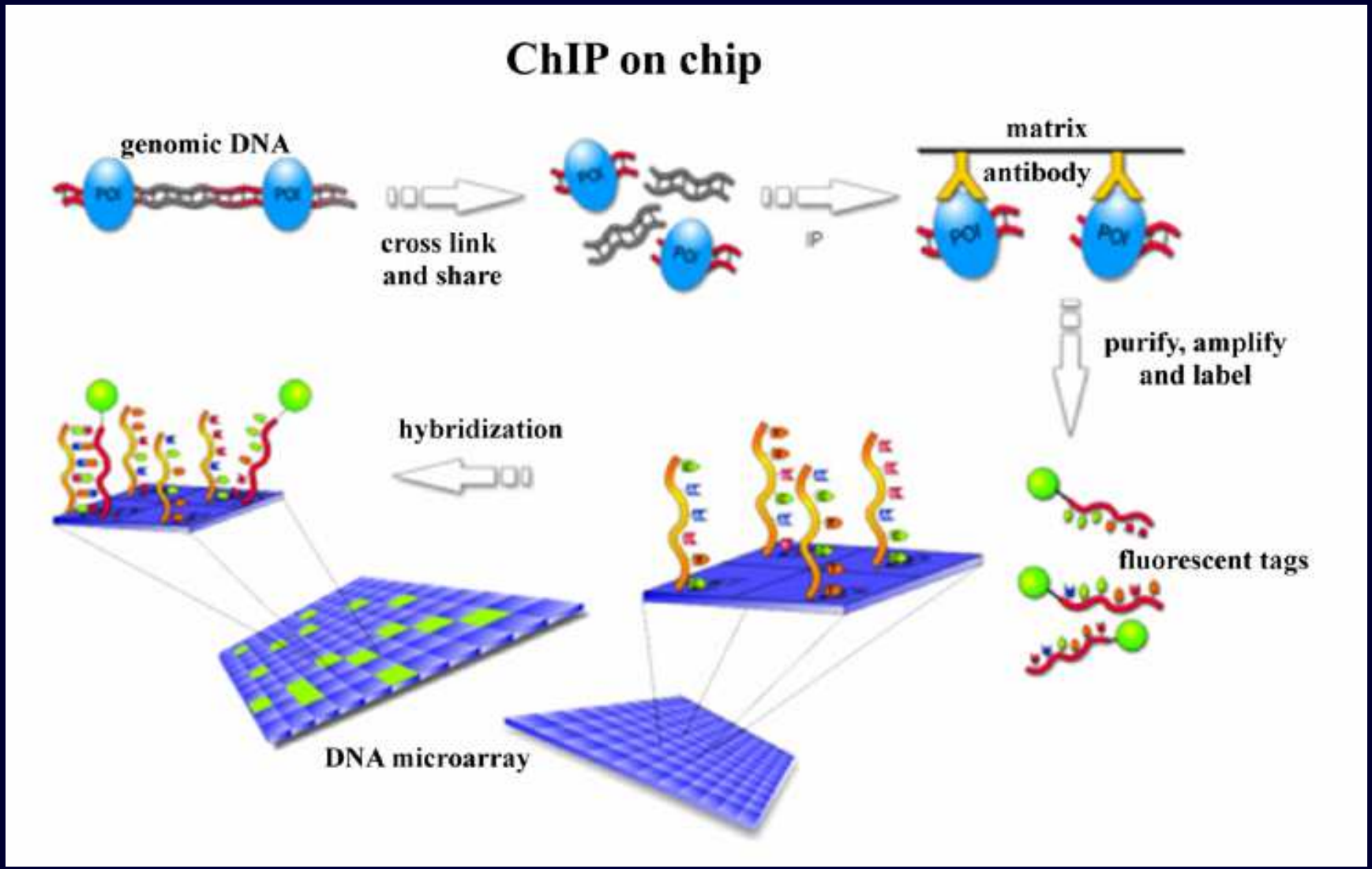
H3K4 me2

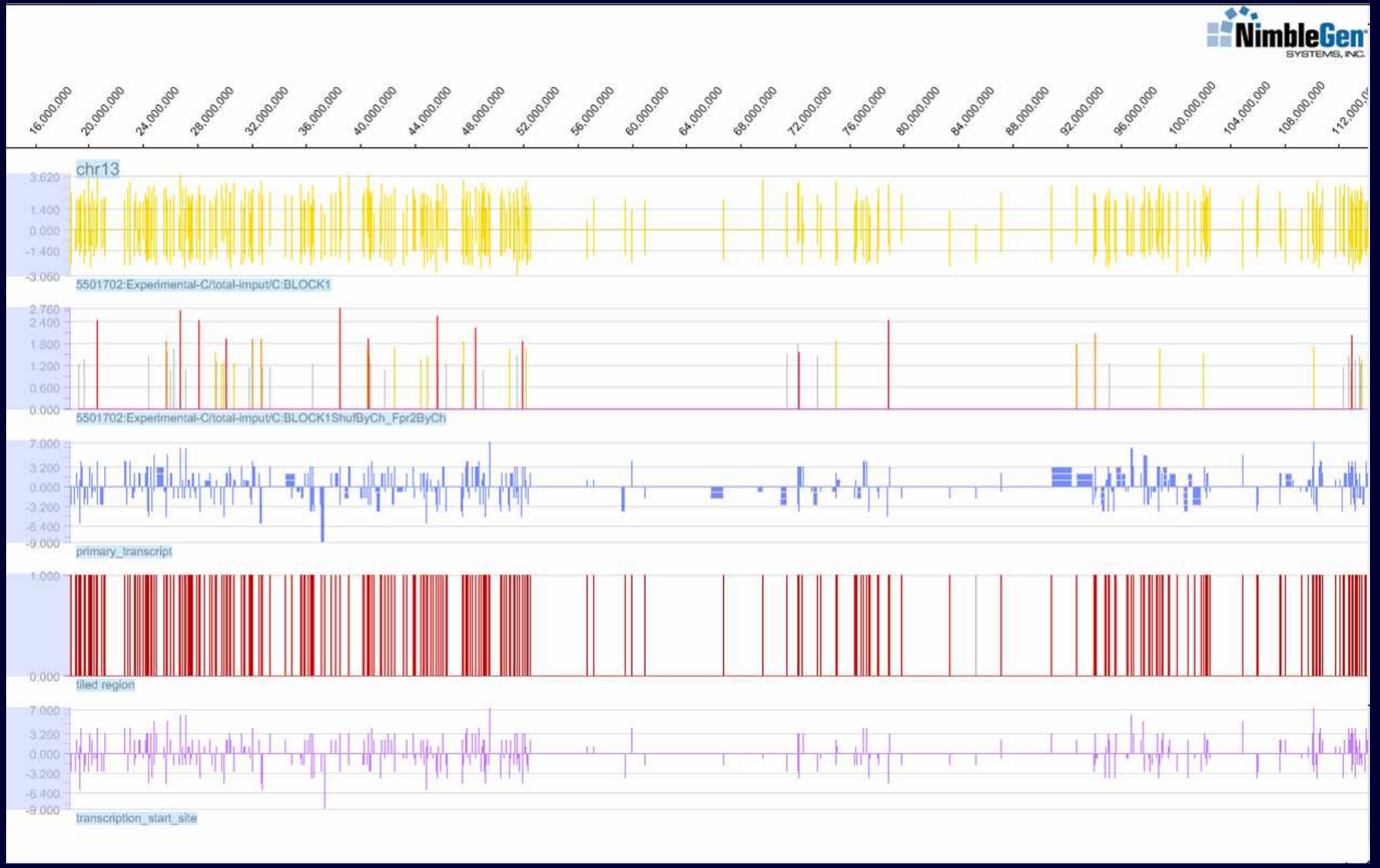


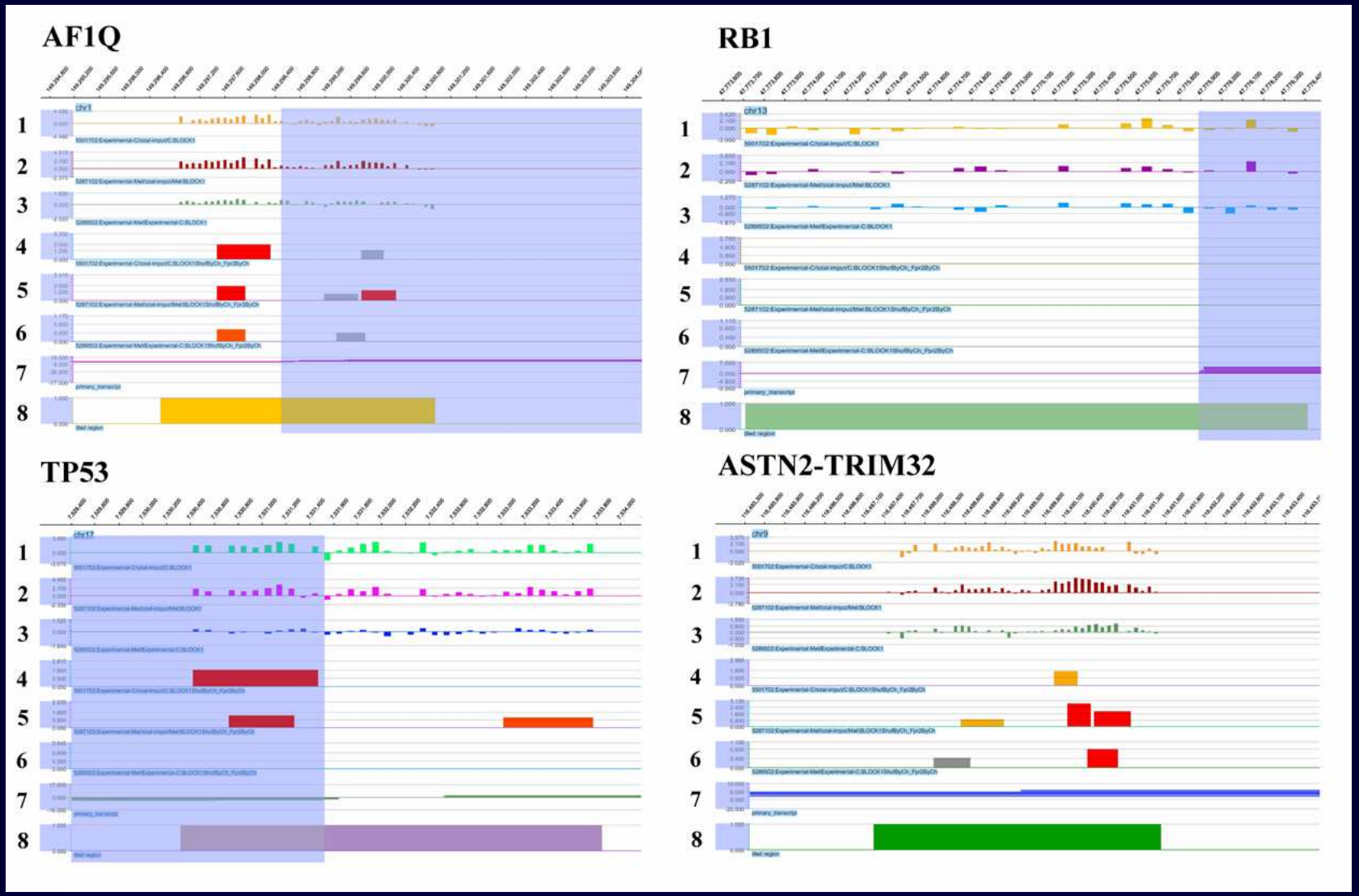
SHRNUTÍ


CONTROL
A
Xist (8) (7)
(4) (13)
(12,15)
(1, 11)
(9)
Xi
(12)
(1)
(5)
(10)
Xa
(14)
(10)
CONTROL
C
(2)
(2, 6)
TSA
B
(3)
(2)
(2, 15)
TSA
D
(2)
(2, 6)
H3K9 acetylation
H3K9me3
H3K9me2
H3K4me2
HP1 (α, β, γ)
Clusters of centromeres
Example of telomere
H3K27me3
H4K20me3
H4K20me1
DNA methylation
Nucleolus

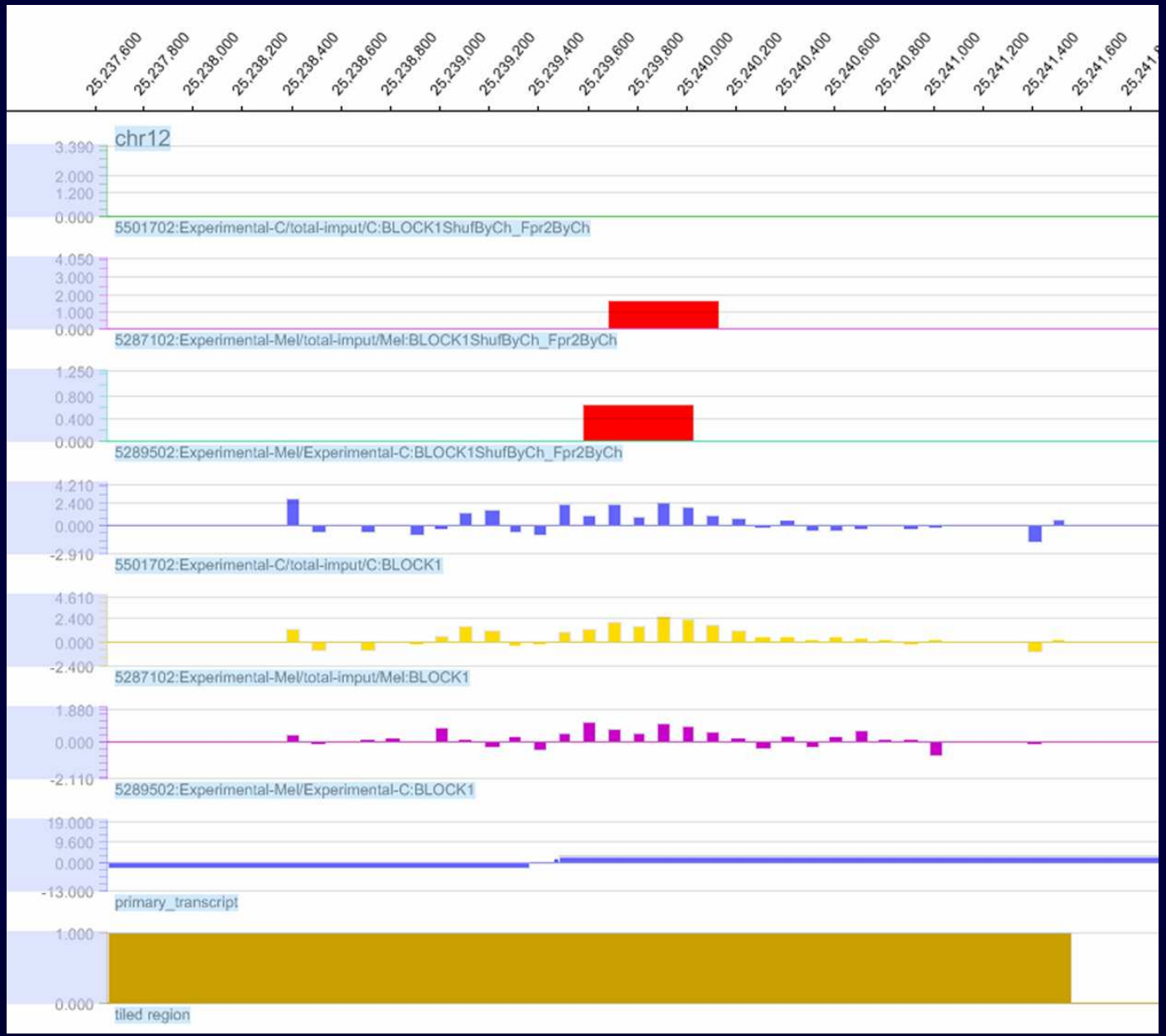
Ligation mediated PCR




NimbleGen
SYSTEMS, INC.
16,000,000
20,000,000
24,000,000
28,000,000
32,000,000
36,000,000
40,000,000
44,000,000
48,000,000
52,000,000
56,000,000
60,000,000
64,000,000
68,000,000
72,000,000
76,000,000
80,000,000
84,000,000
88,000,000
92,000,000
96,000,000
100,000,000
104,000,000
108,000,000
chr13
3.620
1.400
0.000
-1.400
-3.060
5501702:Experimental-C/total-imput/C:BLOCK1
2.760
2.400
1.800
1.200
0.600
0.000
5501702:Experimental-C/total-imput/C:BLOCK1ShufByCh_Fpr2ByCh
7.000
3.200
0.000
-3.200
-6.400
-9.000
primary_transcript
1.000
0.000
tiled region
7.000
3.200
0.000
-3.200
-6.400
-9.000
transcription_start_site


AF1Q
RB1
TP53
ASTN2-TRIM32

Cancer susceptibility gene 1



Shrnutí problematiky

1. Organizace chromatinu, struktura nukleosomů
2. Varianty histonů
3. Epigenetické modifikace histonů a jejich funkce
4. Epigenetické modifikace centromer, Xi a telomer
5. HP1 proteiny – struktura a funkce
6. Účinky HDACi
7. Methylace DNA versus methylace histonů