

EPIGENETIC INFORMATION

Definition: Epigenetic information is not encoded in the DNA sequence (A,T,G,C) but is transmissible during cell division

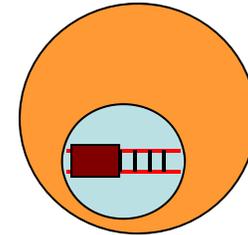
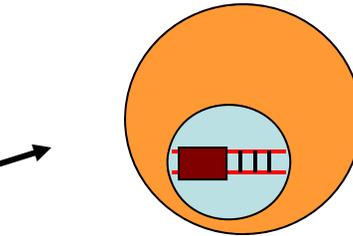
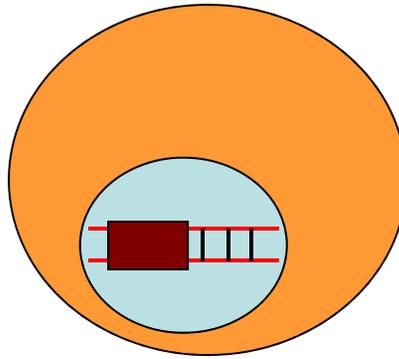
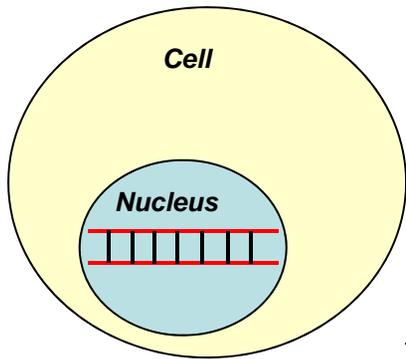
Mechanism: Epigenetic 'marks' chemically modify either one of the DNA bases, or the proteins with which the DNA is packaged within the nucleus

Effect: These marks serve to control patterns of gene expression, cell division, and other cell functions.

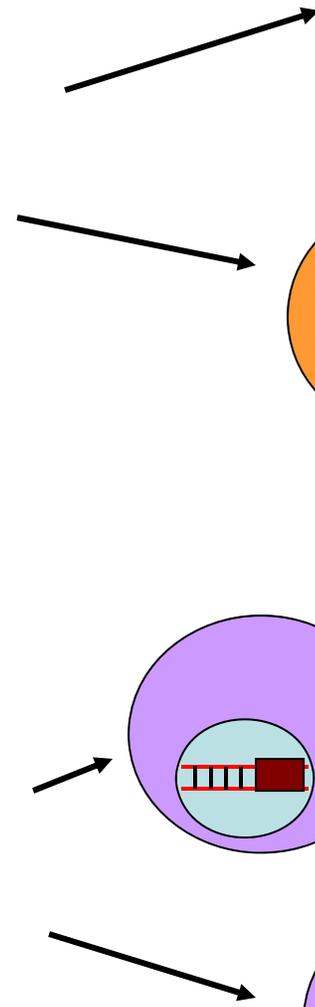
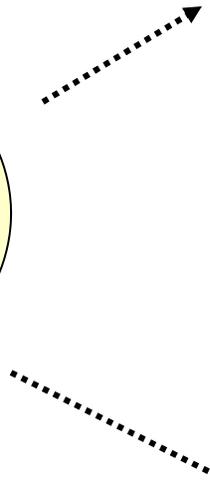
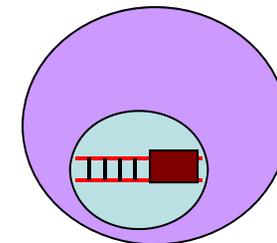
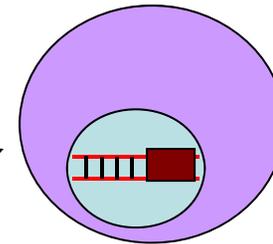
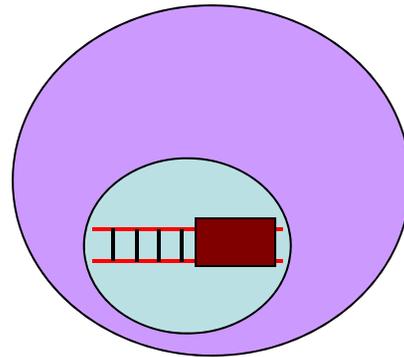
Defects in epigenetic mechanisms, like mutations, can have profound effects on cells and organisms

*DNA base sequence
remains the same*

*Cell properties
(phenotypes) change*



*Changes are
passed on to
daughter cells*



EPIGENETIC MARKS

What are they?

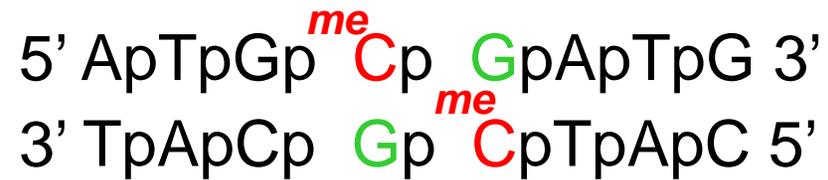
How are they propagated?

How do they work?

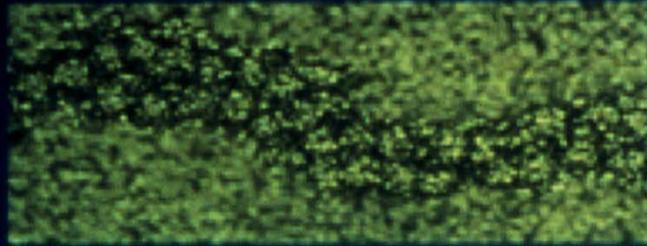
How are they initiated?

***EPIGENETIC MARKS:
Modify phenotype, propagate to daughter cells***

DNA methylation

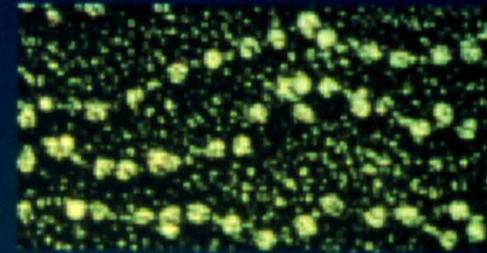


DNA in Eukaryotes is Packaged as Chromatin

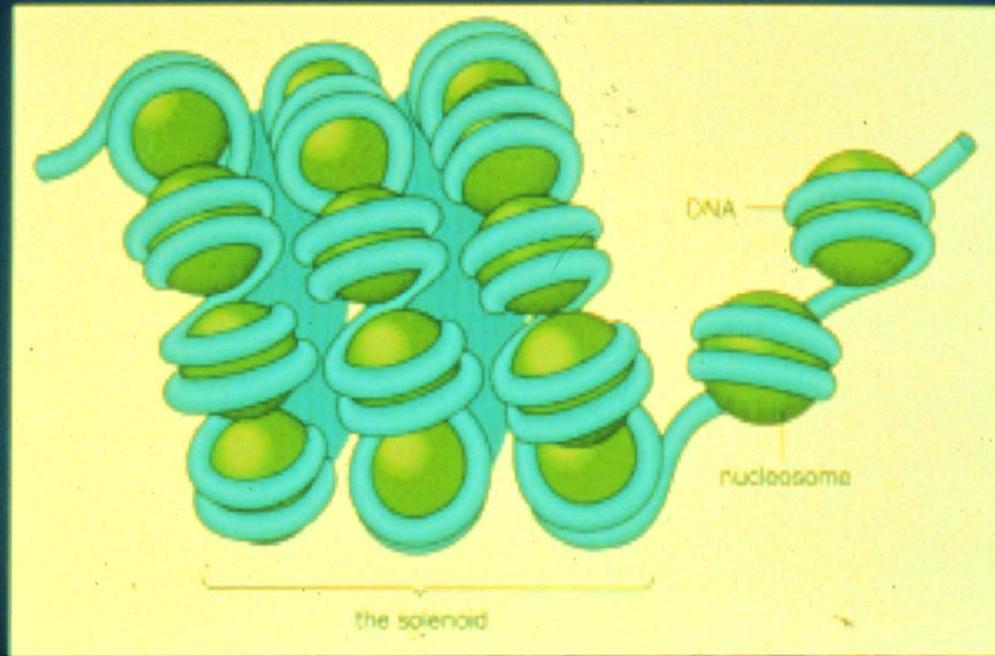


30 nm
chromatin fiber

Chromatin
fibers



10 nm
"beads on a string"



© 1998, Jakob Witt

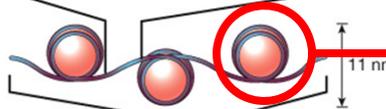
a

Short region of DNA double helix



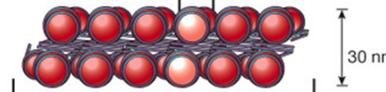
2 nm

"Beads on a string" form of chromatin



11 nm

30-nm chromatin fibre of packed nucleosomes



30 nm

Section of chromosome in an extended form



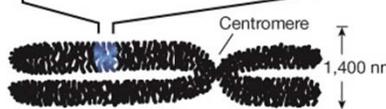
300 nm

Condensed section of chromosome



700 nm

Entire mitotic chromosome

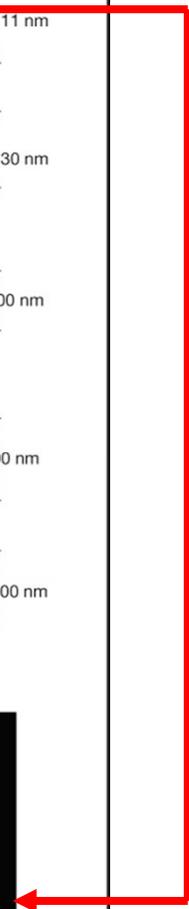
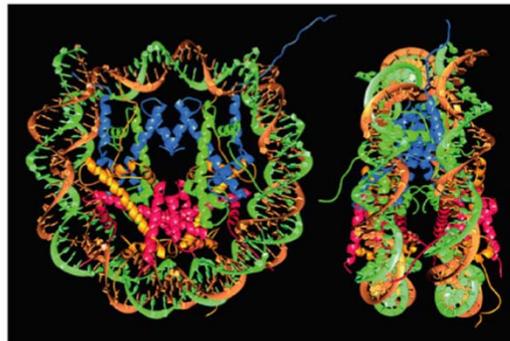


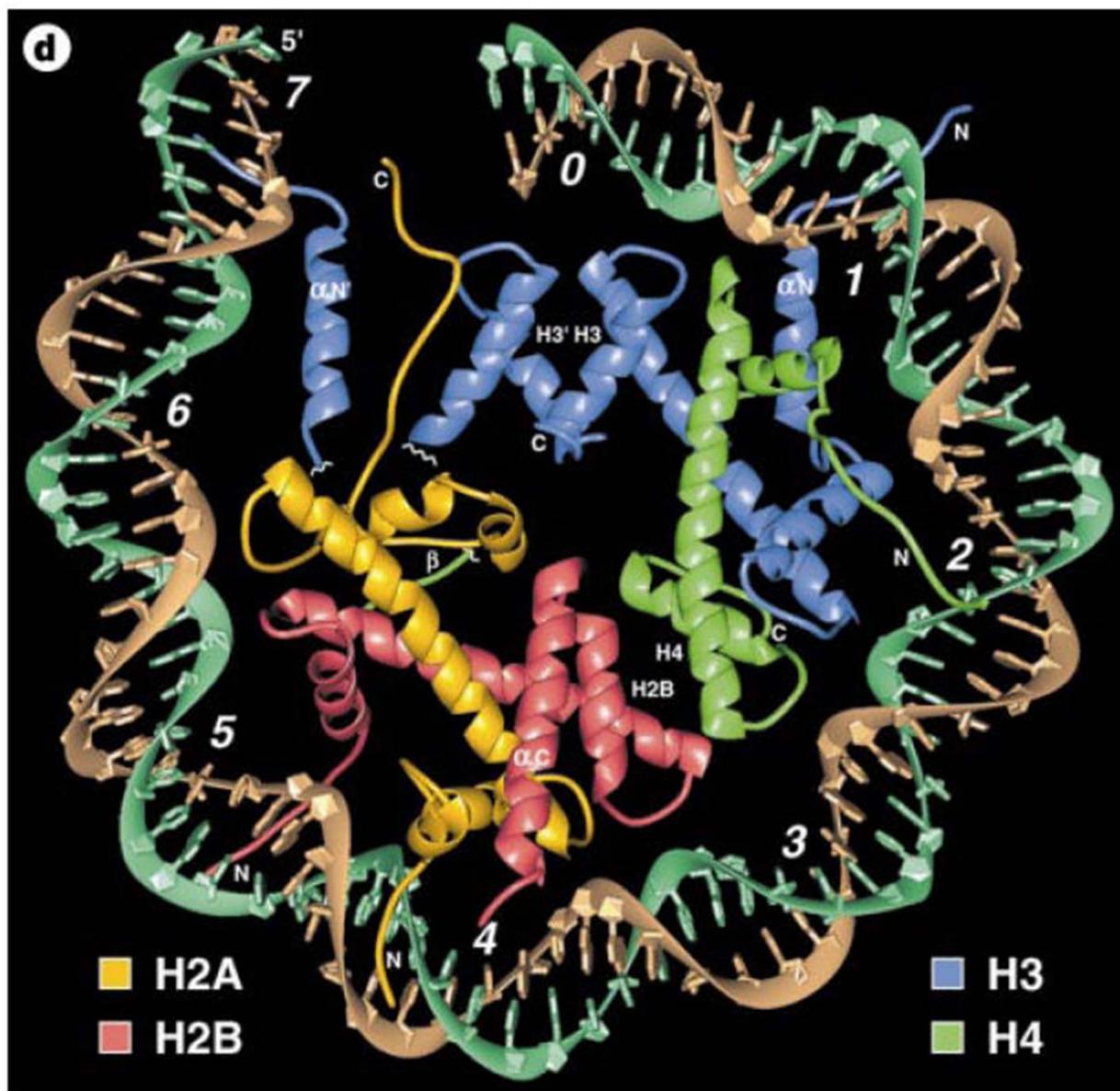
Centromere

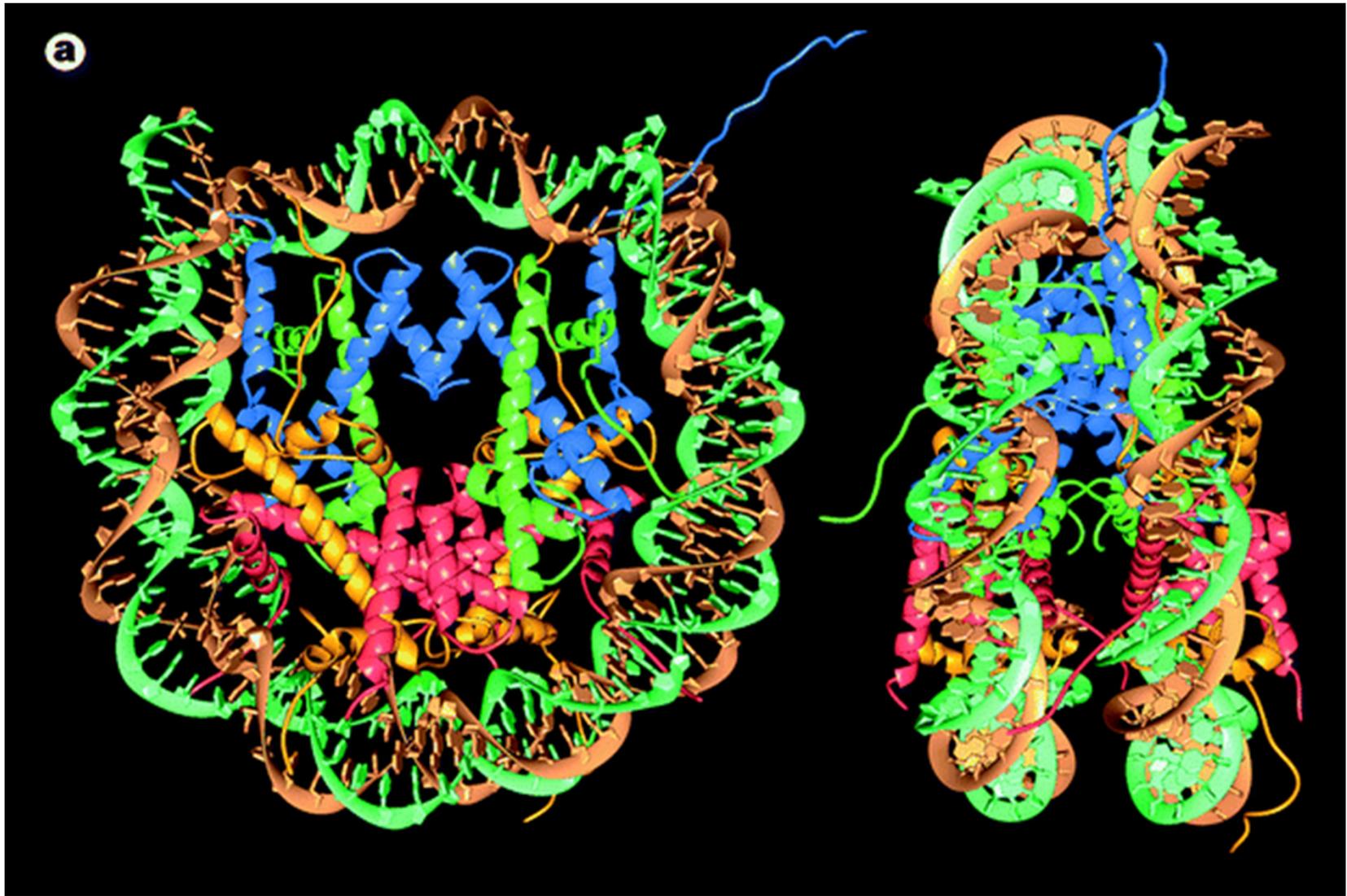
1,400 nm

b

Nucleosome







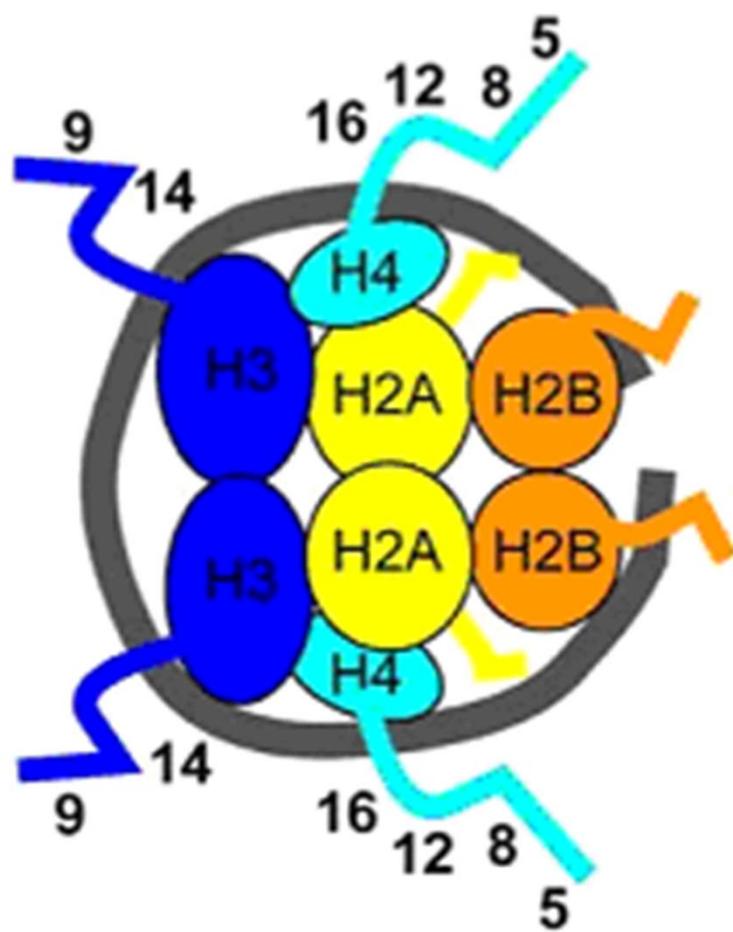
EPIGENETIC MARKS: Histones

1. Nucleosomes have two each of four kinds of histones forming a compact complex:

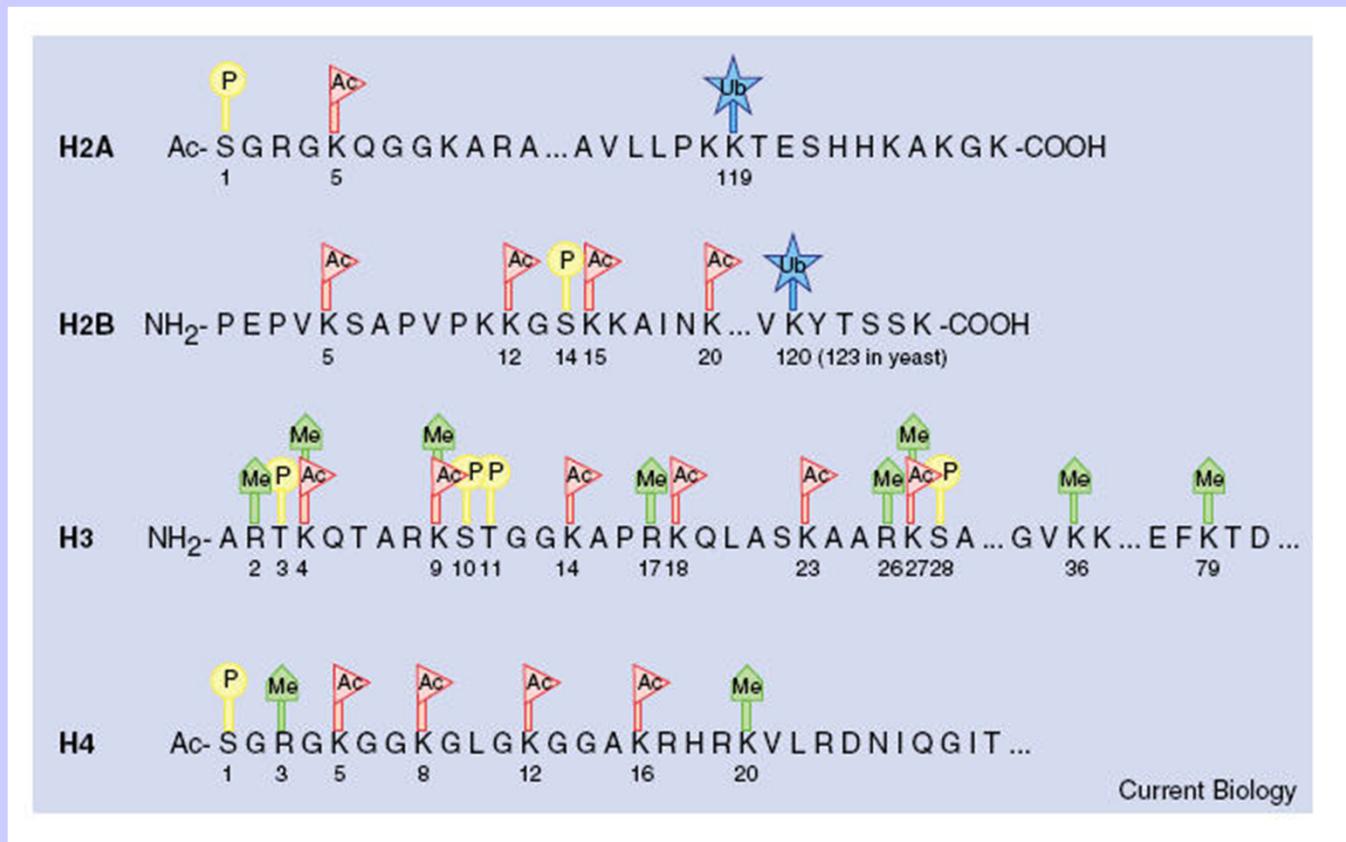
H2A, H2B, H3, and H4

2. Accessible sites on the histones (amino acid side chains mostly on the N and C terminal tails) can be chemically modified within the cell usually after they are incorporated into nucleosomes

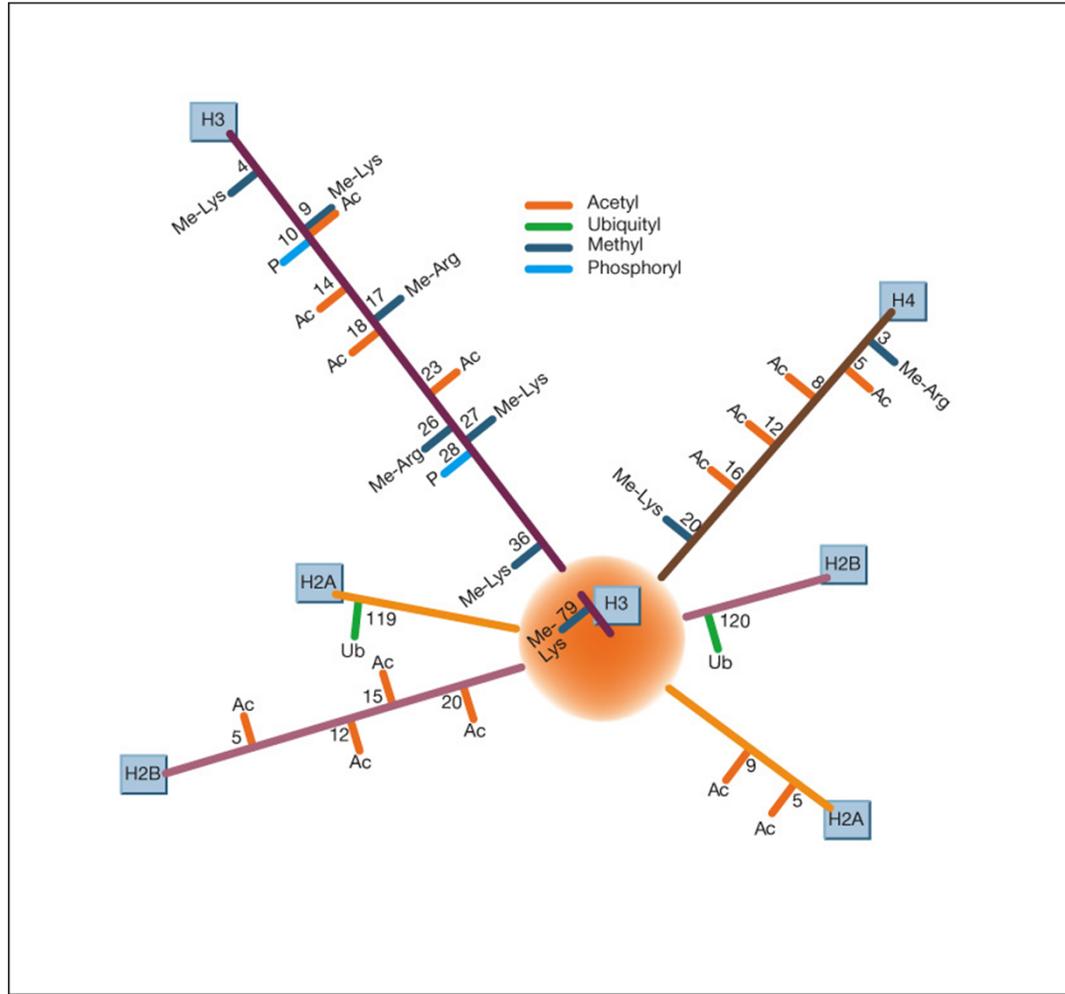
3. In addition, some of the histones exist in variant forms – slightly different proteins coded for by separate genes



AMINO ACIDS WITHIN THE HISTONES CAN BE MODIFIED



Peterson & Lanier Curr. Biol. 2004



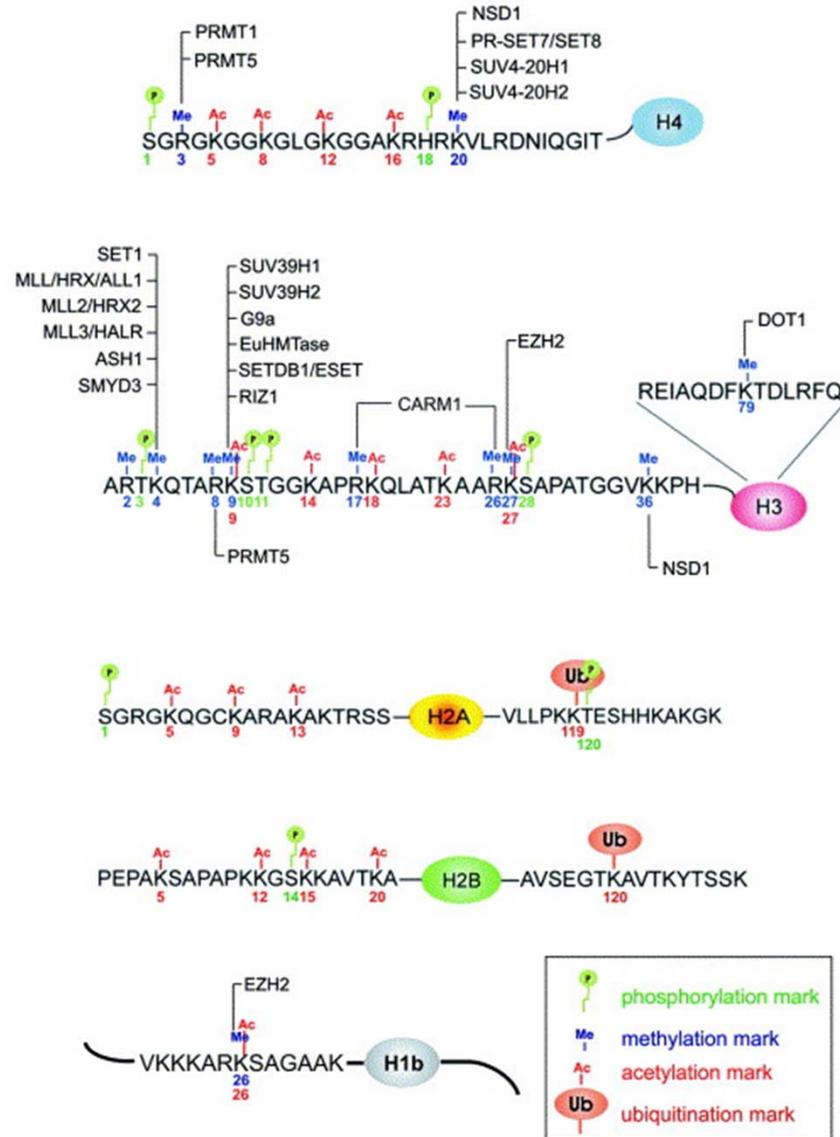
Felsenfeld & Groudine Nature (2003)

ENZYMES ARE REQUIRED

KINDS OF ENZYMES THAT MODIFY HISTONES

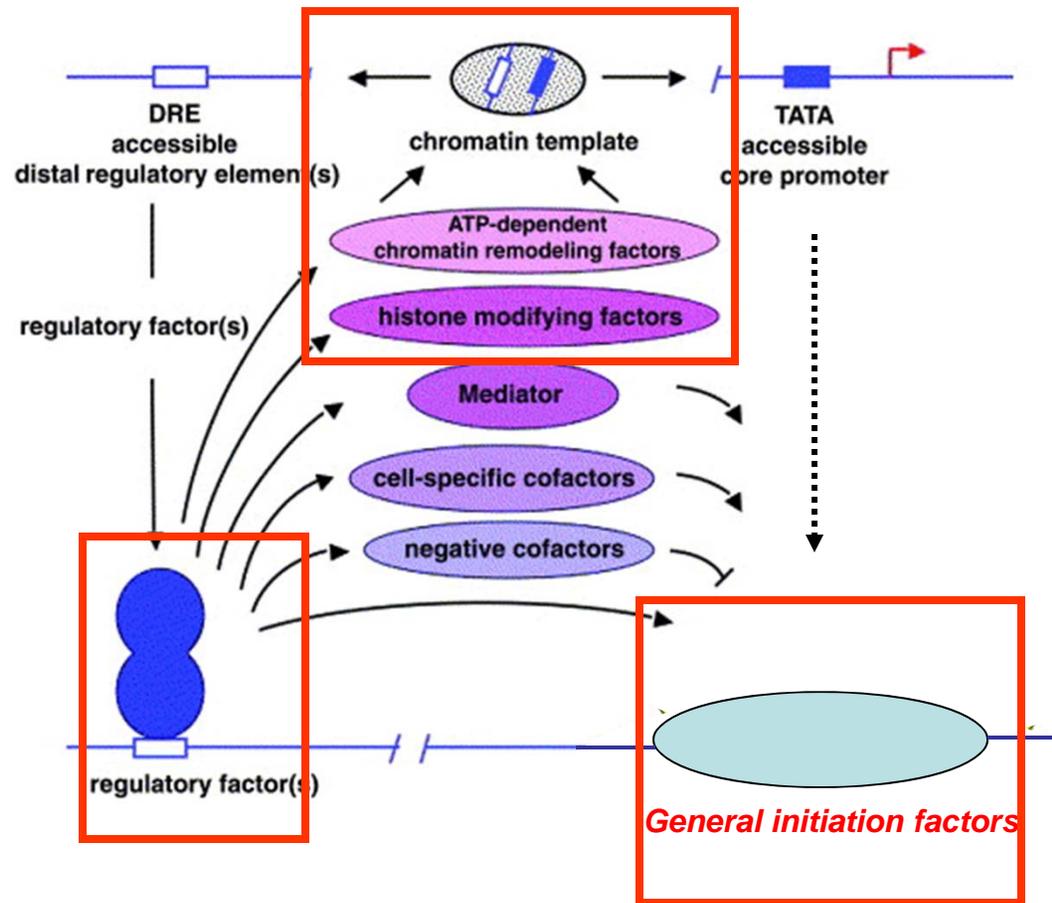
1. Histone Acetylases – Add an acetyl ($\text{H}_3\text{CC}-$ group) to specific lysines
$$\begin{array}{c} \text{H}_3\text{CC}- \\ || \\ \text{O} \end{array}$$
2. Histone Deacetylases – Reverse the acetylation
3. Histone Methylases – Add 1,2 or 3 methyl (CH_3-) groups to lysine or arginine
4. Histone Demethylase – In some cases reverse the methylation
5. Histone Kinases – Add phosphate to serine or threonine
6. Histone Ubiquitinases – Couple a specific small protein to specific lysines

MANY ENZYMES, SPECIFIC FOR INDIVIDUAL SITES, ARE INVOLVED IN HISTONE MODIFICATION



Current Opinion in Genetics & Development

HISTONE MODIFICATIONS AFFECT TRANSCRIPTION

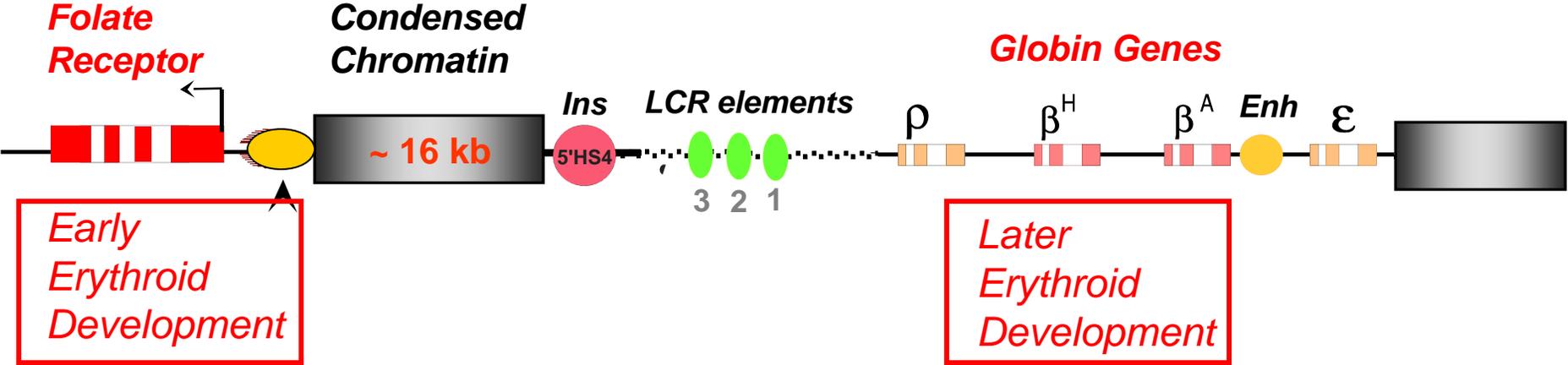


Roeder, FEBS Letters (2004)

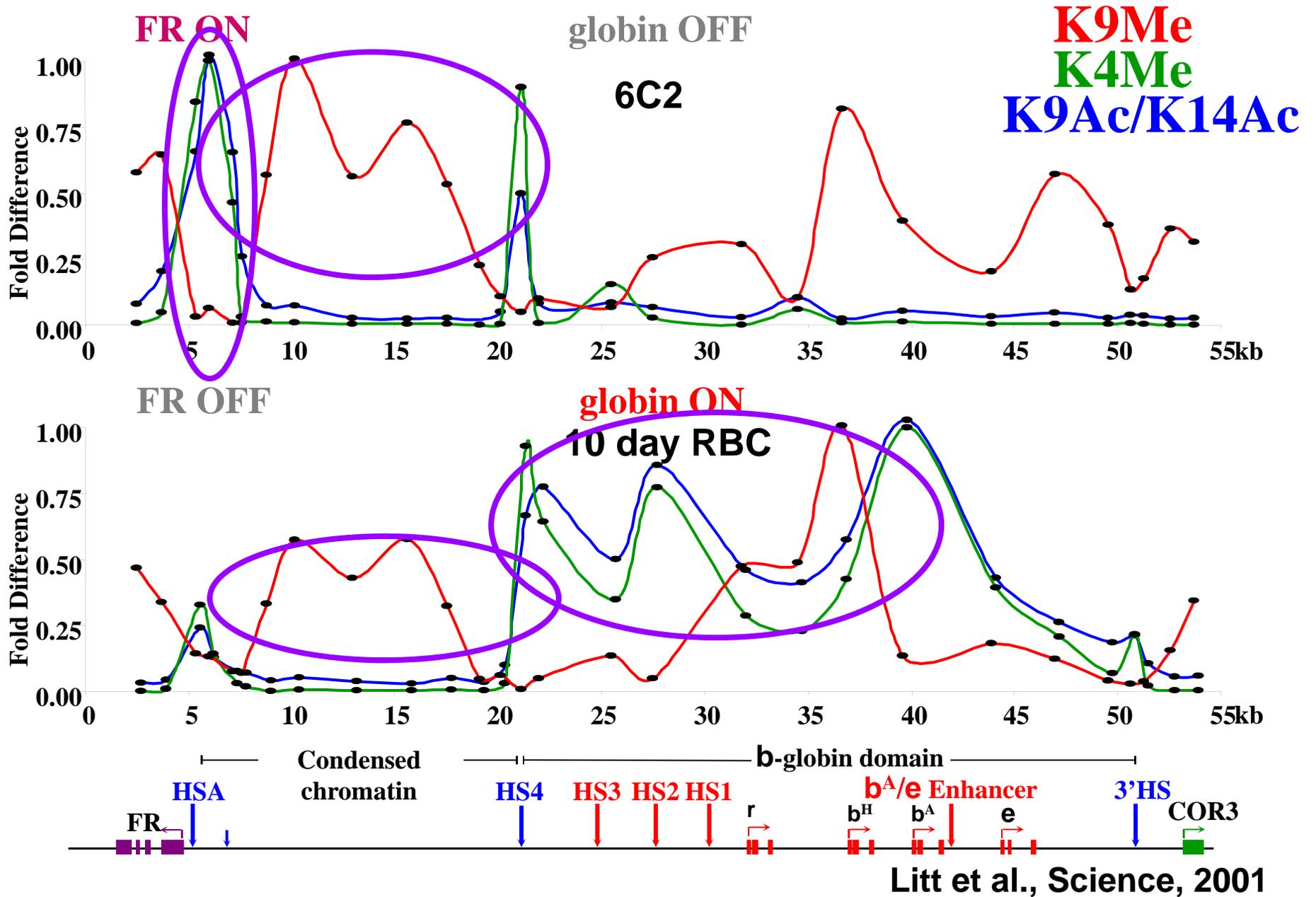
***Some Correlations Between Histone Modifications
and Gene Activity***

<u><i>MODIFICATION</i></u>	<u><i>ACTIVITY</i></u>
H3 Lysine 4 Me	+
H3 Lysine 9 Ac	+
H3 Lysine 9 Me	-
H4 Arg 3 Me	+
H3 Lysine 27	-

Chicken Beta Globin Locus

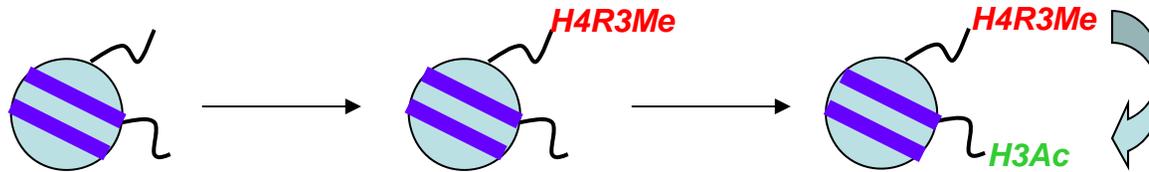


Histone H3 modifications at the chicken b-globin locus

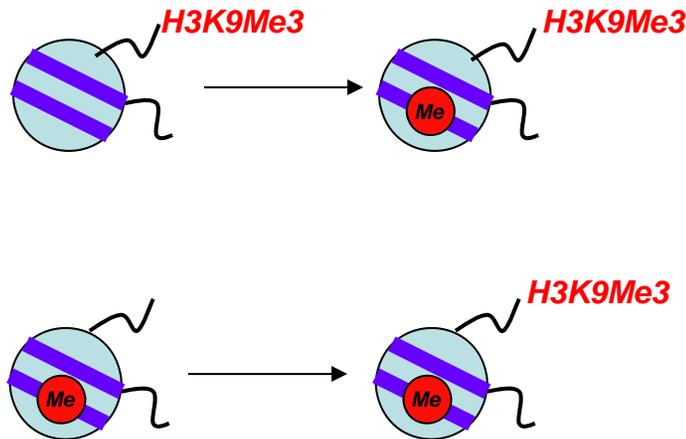


Epigenetic Marks

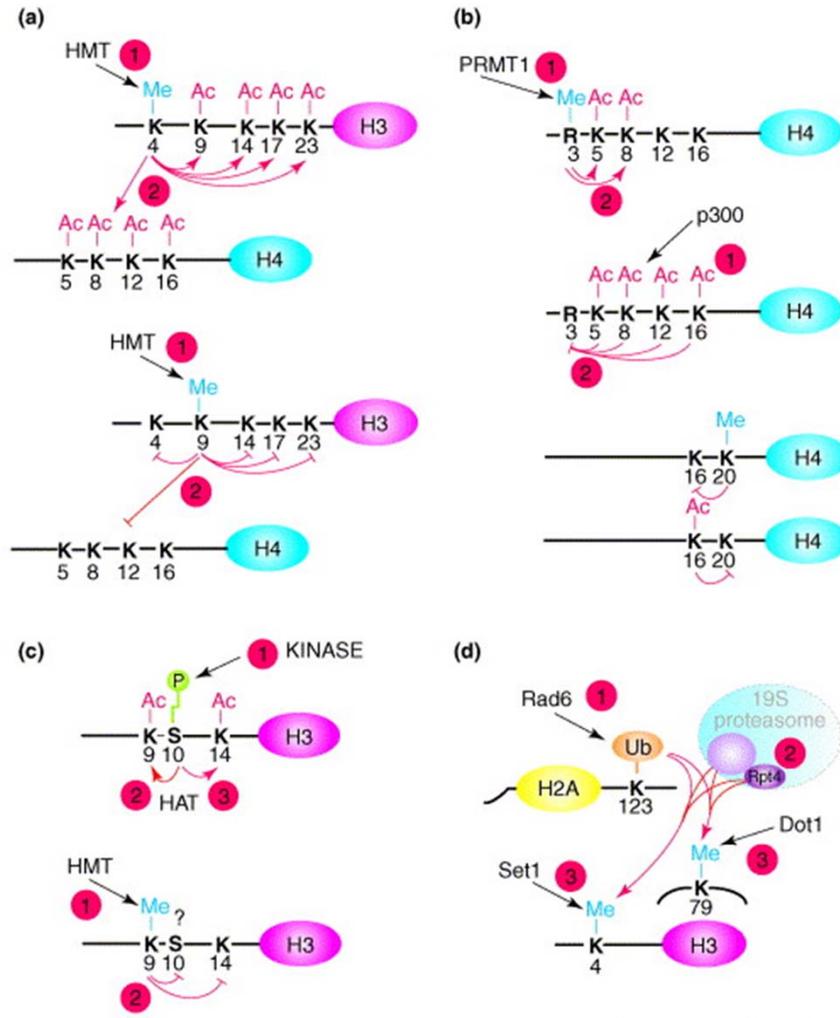
Heirarchical : Me on Histone H4 Arg 3 → Ac on H3



Reciprocal: Histone Methylation → DNA Methylation & vice versa



ONE KIND OF MODIFICATION CAN POTENTIATE OR INHIBIT ANOTHER



Current Opinion in Genetics & Development

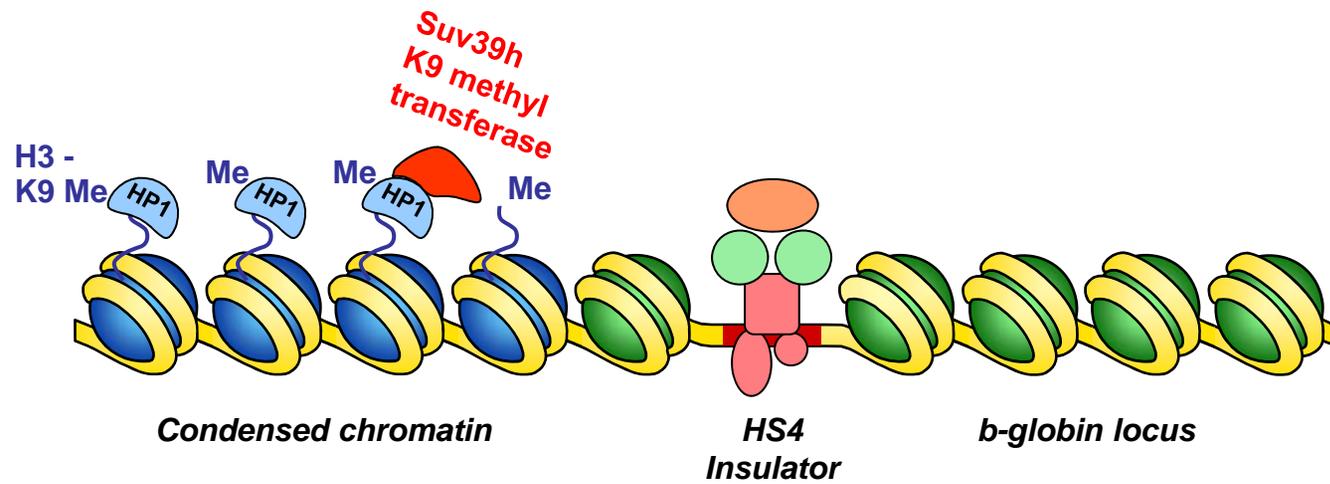
MODIFIED HISTONES RECRUIT OTHER MOLECULES THAT CAN AFFECT CHROMATIN ACTIVITY

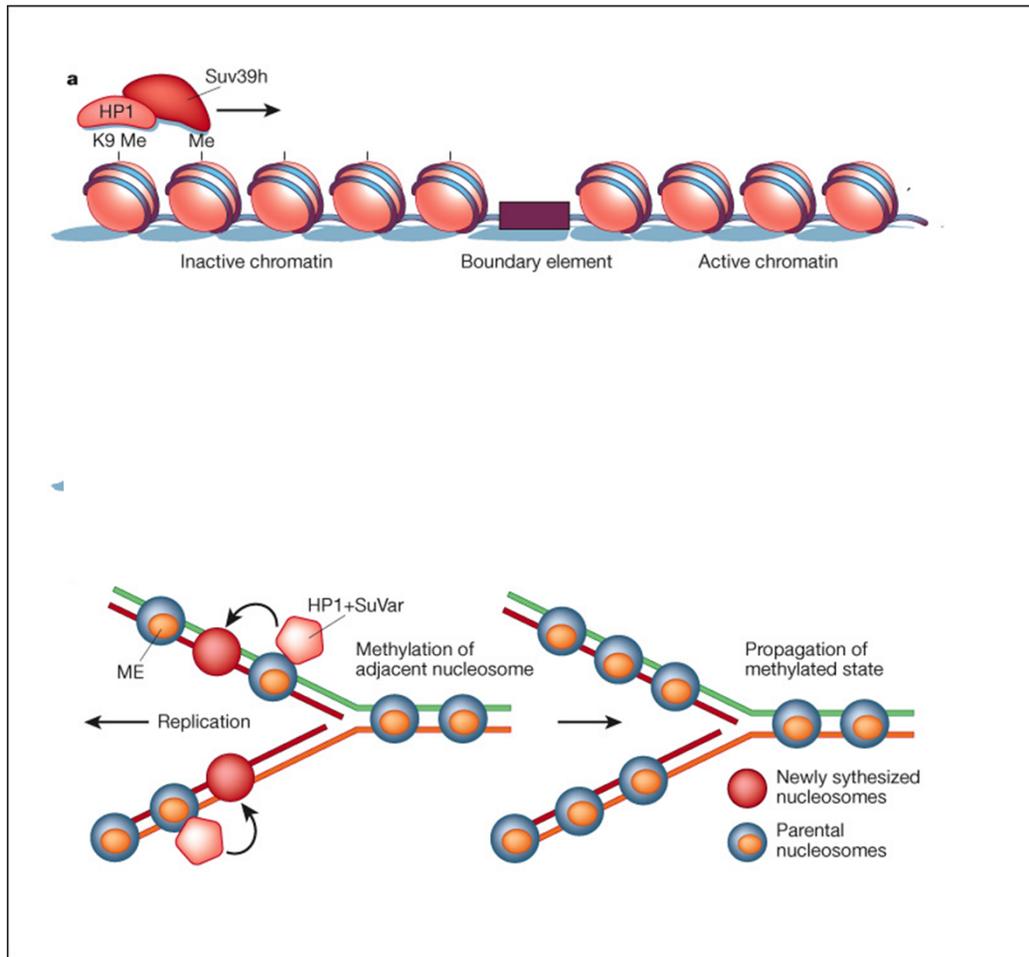


Current Opinion in Genetics & Development

Margueron et al. Curr. Opin. Gen. & Dev. (2005)

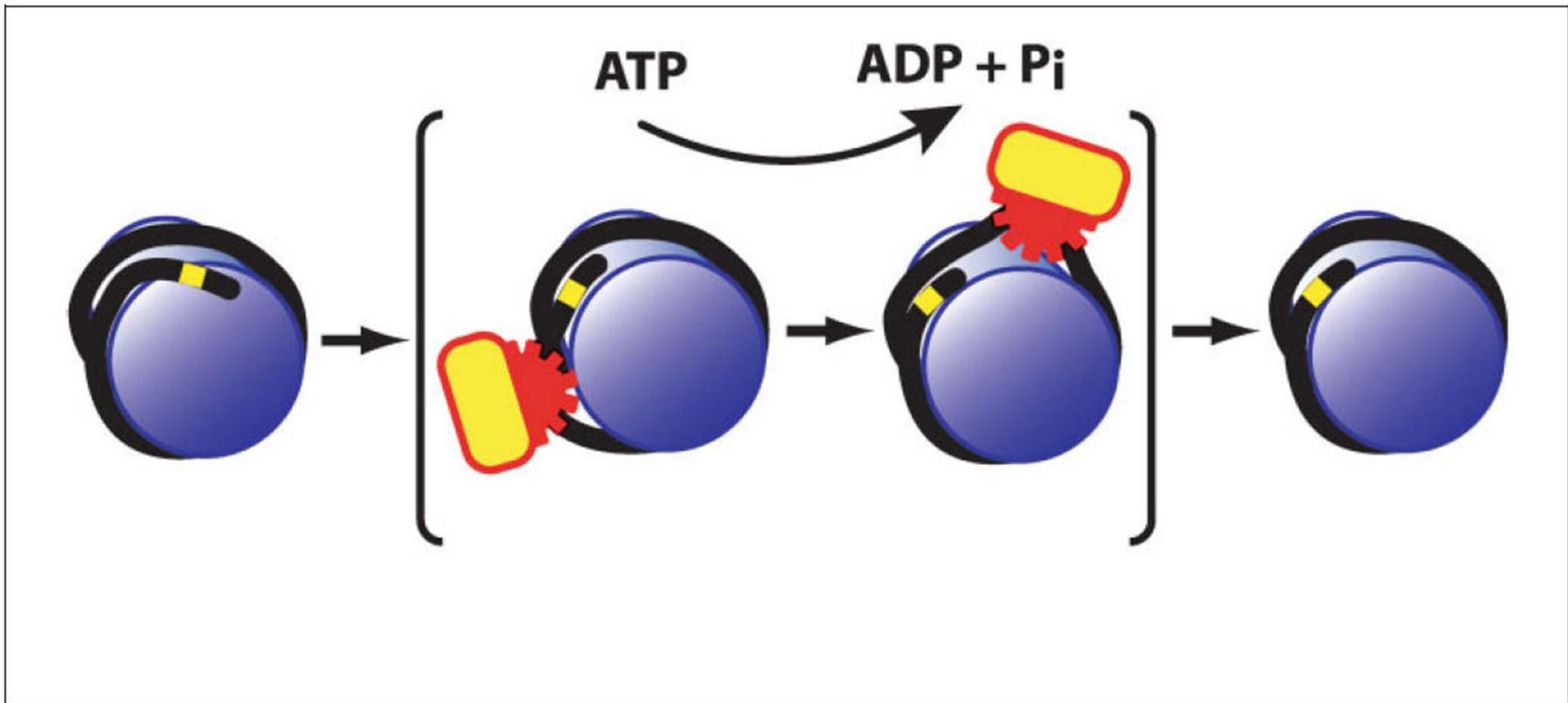
POSSIBLE MECHANISM OF PROPAGATION OF A HISTONE MODIFICATION





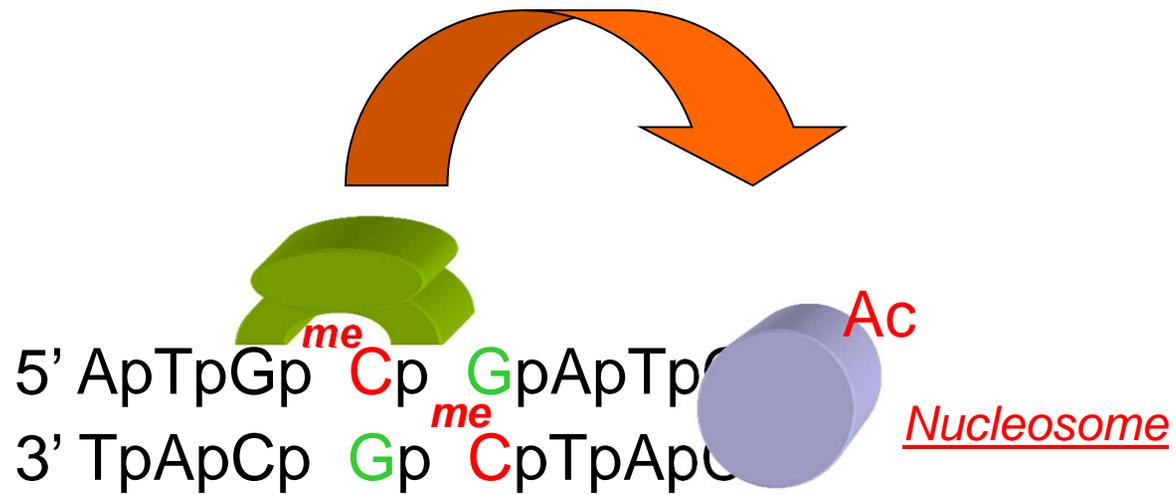
***HISTONE REMODELING FACTORS HELP
TO REPOSITION NUCLEOSOMES AT
PROMOTERS***

- 1. ATP DEPENDENT***
- 2. SOME FACTORS DISRUPT NUCLEOSOME
STRUCTURE (Swi/snf)***
- 3. OTHERS CAUSE NUCLEOSOMES TO 'SLIDE'
(ISWI)***
- 4. CAN BE RECRUITED BY TRANSCRIPTION
FACTORS***
- 5. CAN INTERACT WITH MODIFIED HISTONES***



One model of how nucleosome ATP-dependent remodeling factors could mobilize a nucleosome (Lusser & Kadonaga, Bioessays (2003))

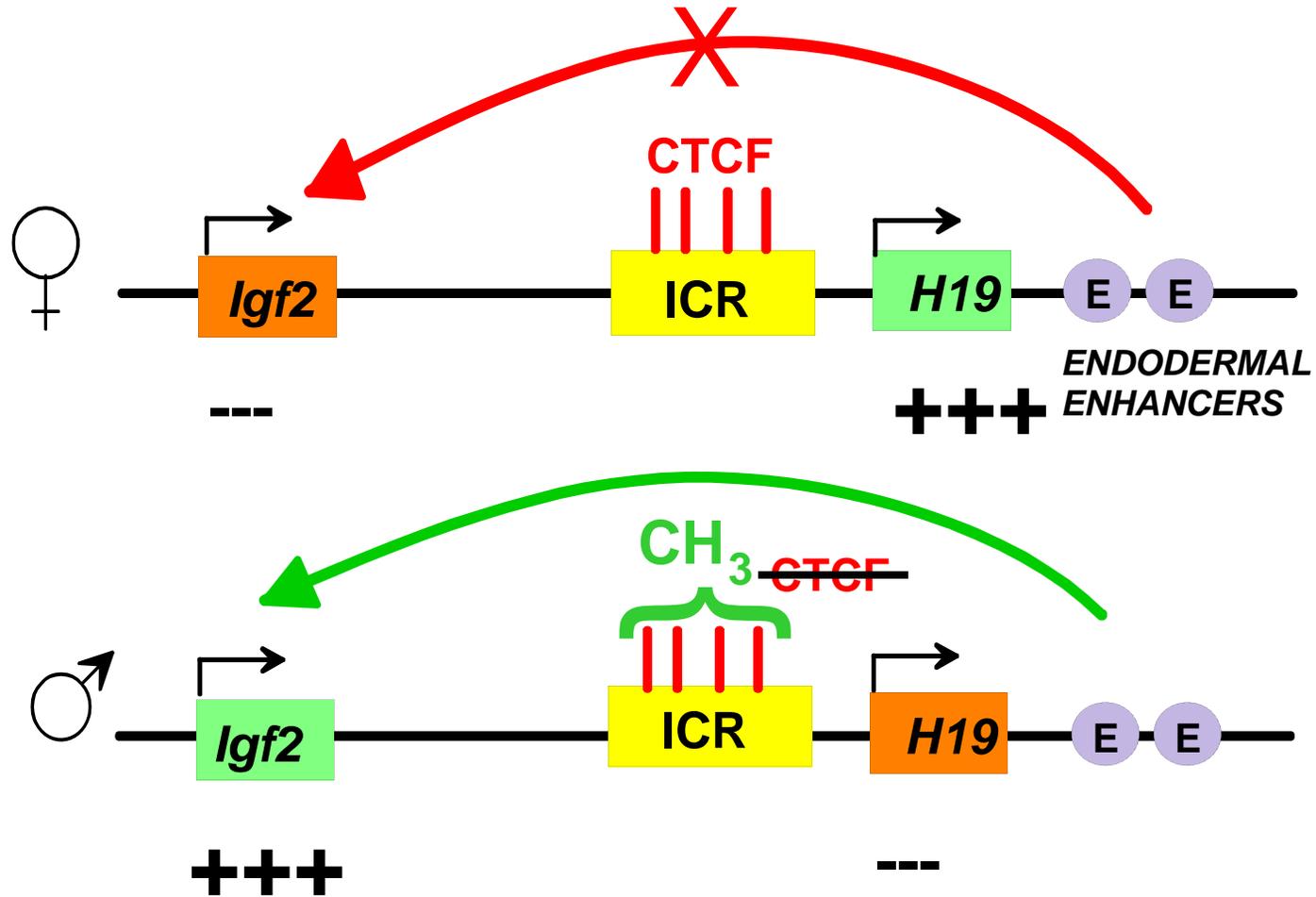
DNA methylation



DNA METHYLATION

1. Methylated sites on DNA recruit proteins that can change histone modifications to create a 'silent' state
2. DNA methylation can directly inhibit the binding of transcription factors
3. Through the above mechanisms, DNA methylation plays a major regulatory role in imprinting and X chromosome inactivation

**IMPRINTING AT THE IGF2/H19 LOCUS:
PRESENCE OF A CTCF-DEPENDENT INSULATOR**



Bell et al. Nature (2001)

Hark et al. Nature (2001)

Ohlsson Curr. Biol. (2001)

HISTONE VARIANTS

1. Unlike modified histones, these differ somewhat in amino acid sequences from the related principal histones

2. Often localized:

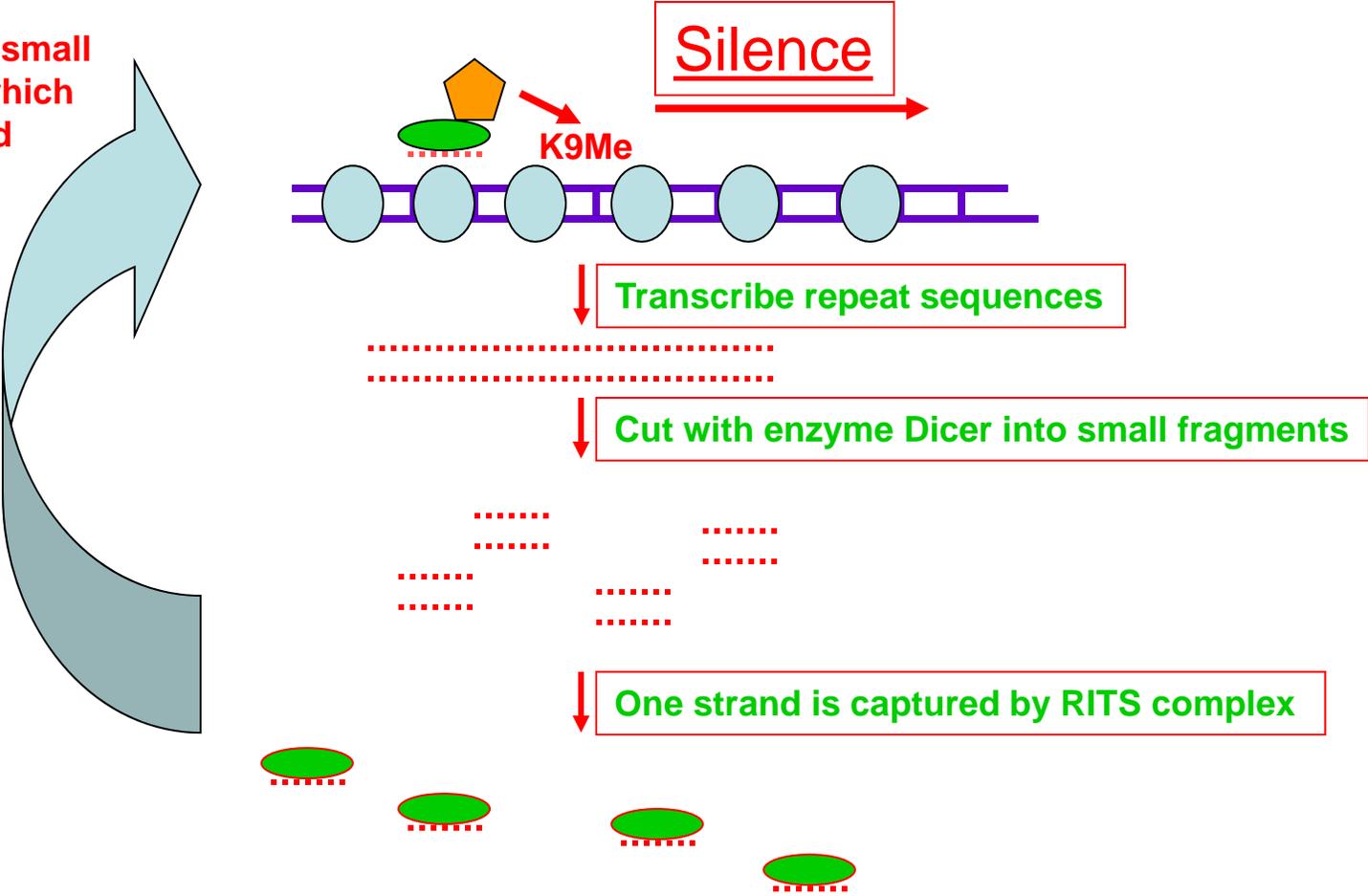
H3.3 tends to be concentrated in transcriptionally active regions

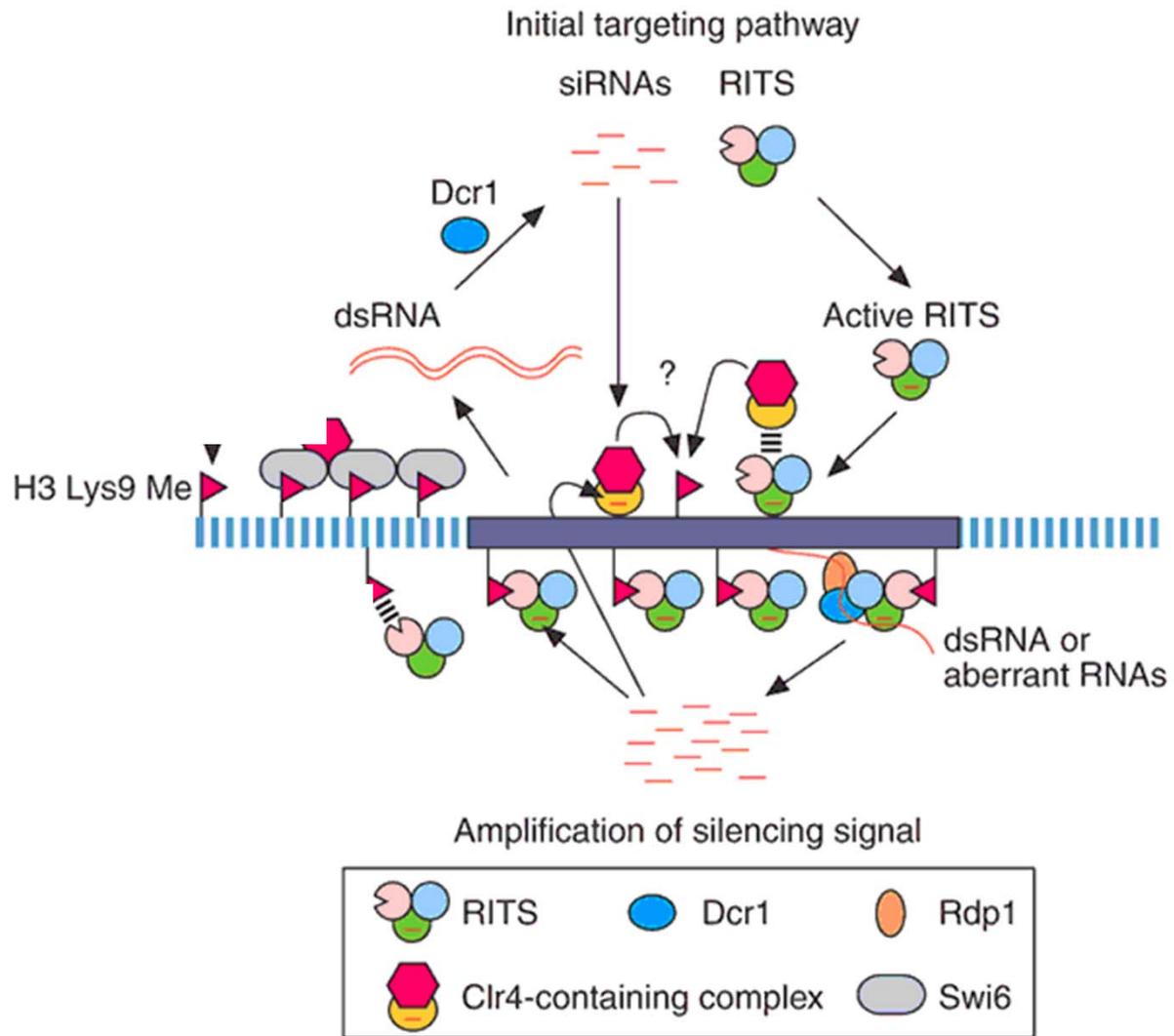
CENP A, another H3 variant, is localized to centromeres

macroH2A concentrated in inactive X chromosome

Production of Small RNAs can Induce Specific Silencing

RITS complex brings small RNA to region from which it was transcribed and recruits a Histone H3 Lysine 9 methylating enzyme





**EPIGENETIC MARKS ARE IMPORTANT NOT ONLY FOR TRANSCRIPTION
BUT FOR:**

**REPLICATION
CHROMOSOME SEGREGATION
DNA STRAND BREAK REPAIR**

ANYTHING ELSE WHICH INVOLVES DNA METABOLISM

Z

