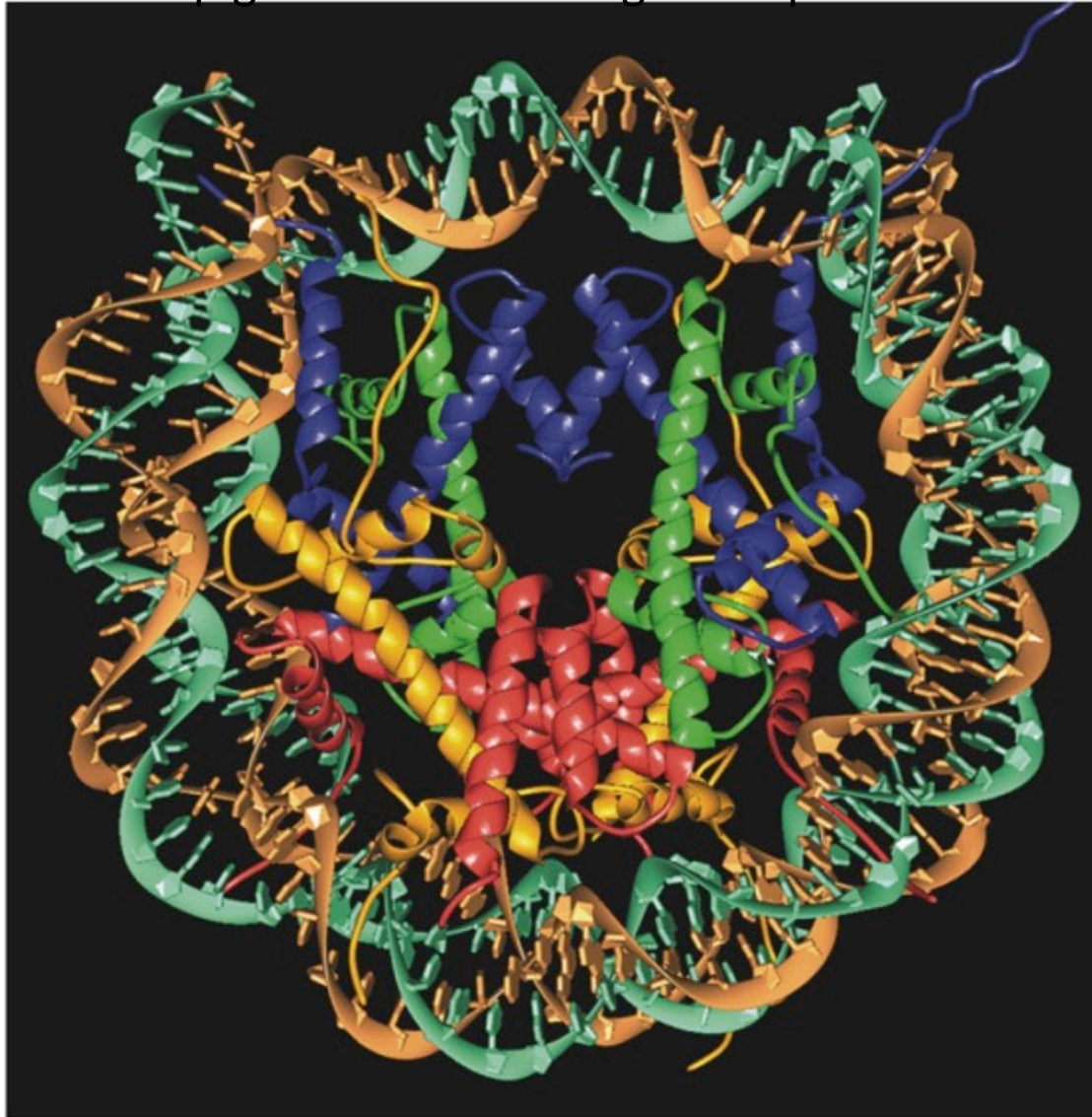


Epigenetic Control of Gene Expression

- Readings from Gilbert
- 11 edition : 50-52, 68-73
- (10 edition): pp 34-35, 45- 53
- (9th ed 35-36, 46-50

(A) Epigenetic control of gene expression



Transcriptional programs drive cell identity during development of multicellular organisms

- Interplay between a) **signal transduction pathways**, b) **transcription factors** and c) **chromosome packaging of the genome** sets the gene expression pattern of a cell

What is epigenetics?

- Heritable traits that are not linked to changes in DNA sequence!
- BUT, in broader sense: refers to mechanisms by which chromatin associated proteins and post translational modifications (PTMs) of a) histones and b) DNA regulate transcription

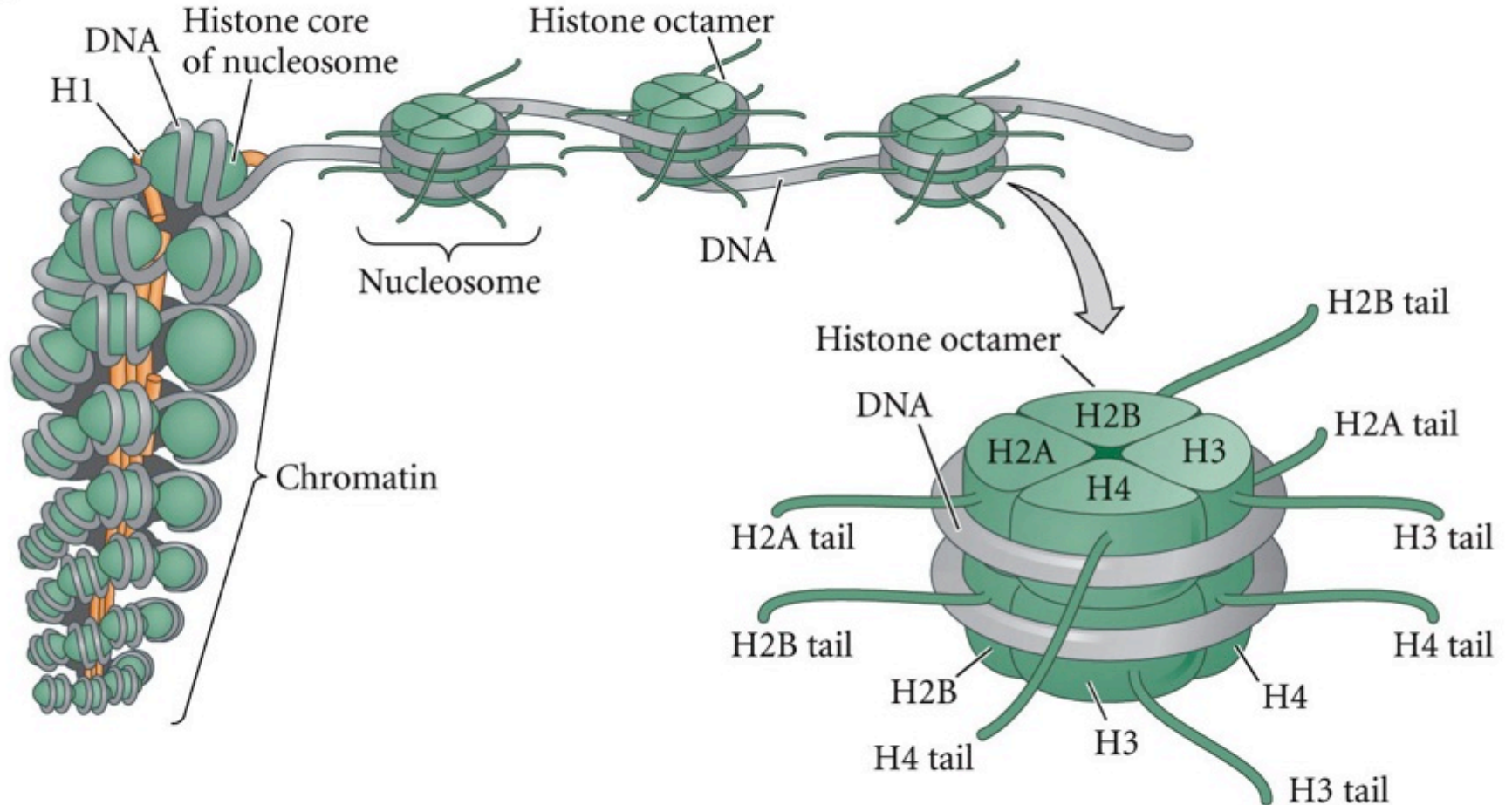
Adrian Bird

- Defined epigenetics as:

The structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states

Bird A. "Perceptions of epigenetics" Nature 447 (7143):396-8, 2007

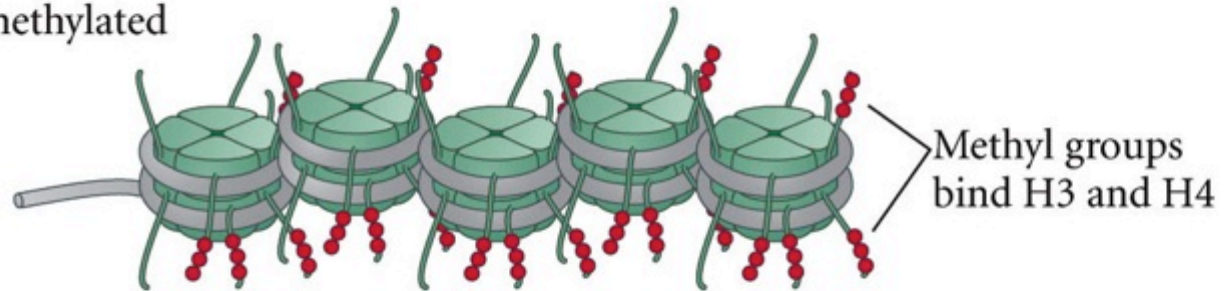
(C)



(D)

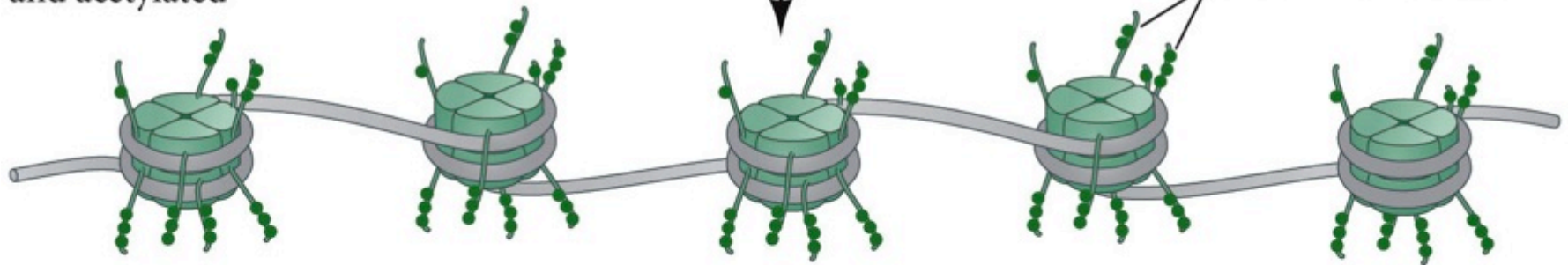
Condensed nucleosomes:

Histone tails largely methylated

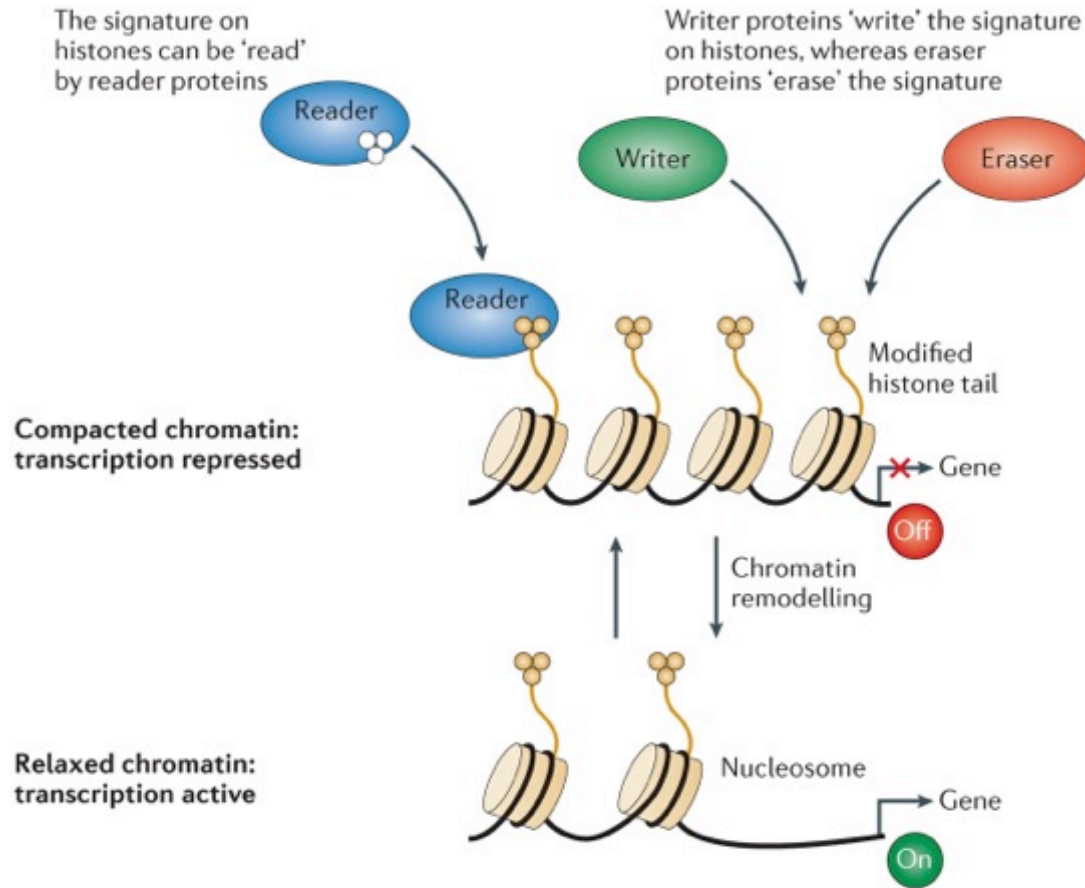


Uncondensed nucleosomes:

Histone tails largely unmethylated and acetylated



Histone code hypothesis



Reader's

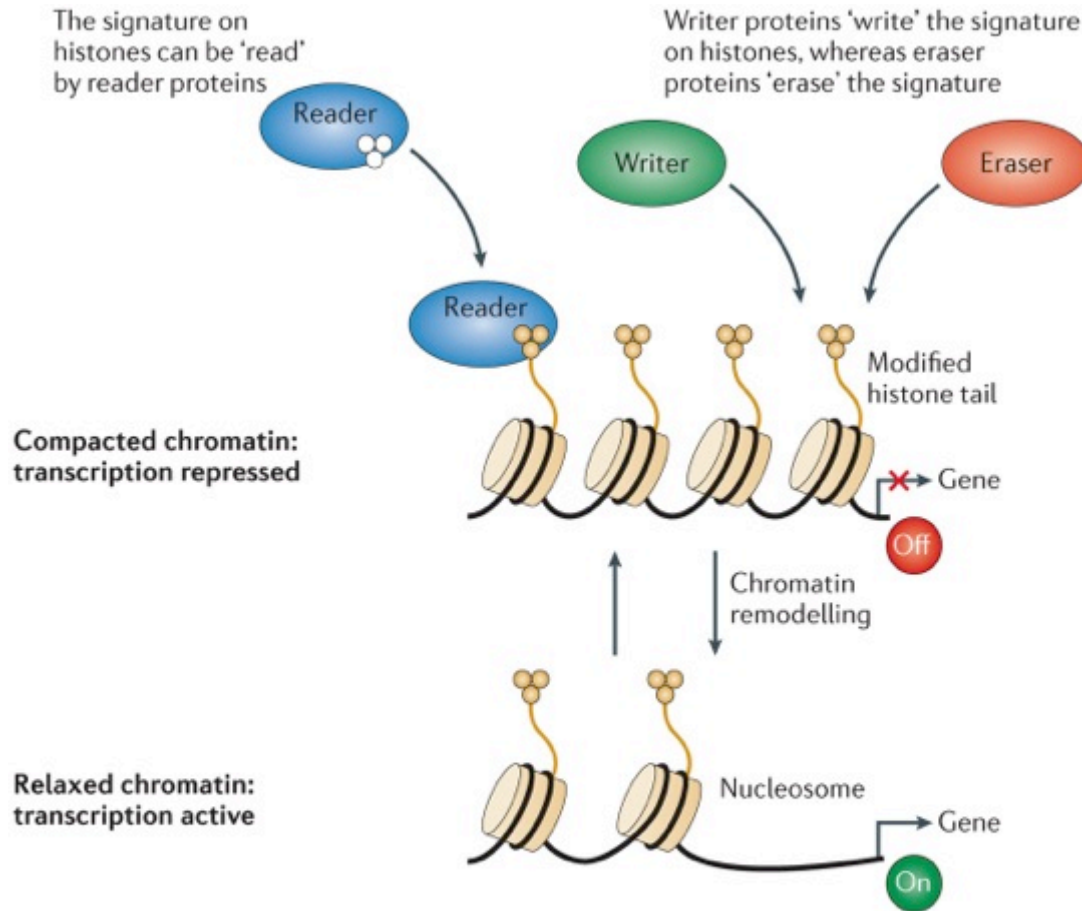
Proteins with domains:
Bromo,chromo,tudor

Writer's

Methyltransferases,
acetyltransferases,
Kinases and Ubiquitin ligases

Eraser's

Demethylases,deacetylases,
phosphatases



Writer's: Methyltransferases, Acetyltransferases, Kinases and Ubiquitin ligases

- Histone methyltransferases (HMT):
eg EZH2 (enzymatic part of Polycomb protein complex (PRC2) target H3K27me3
- Histone acetyltransferases (HATs)
eg CBP, p300

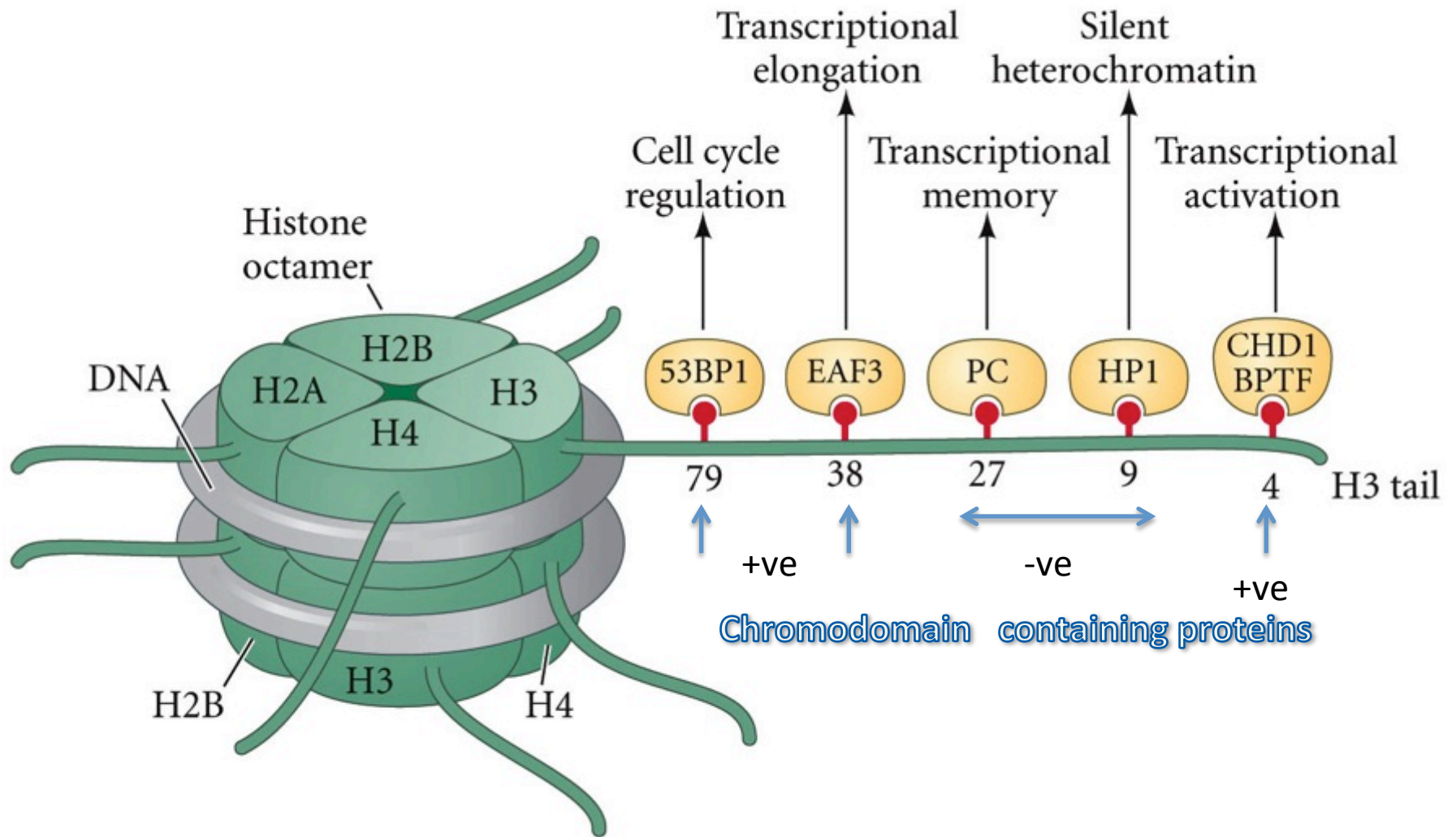
Reader's

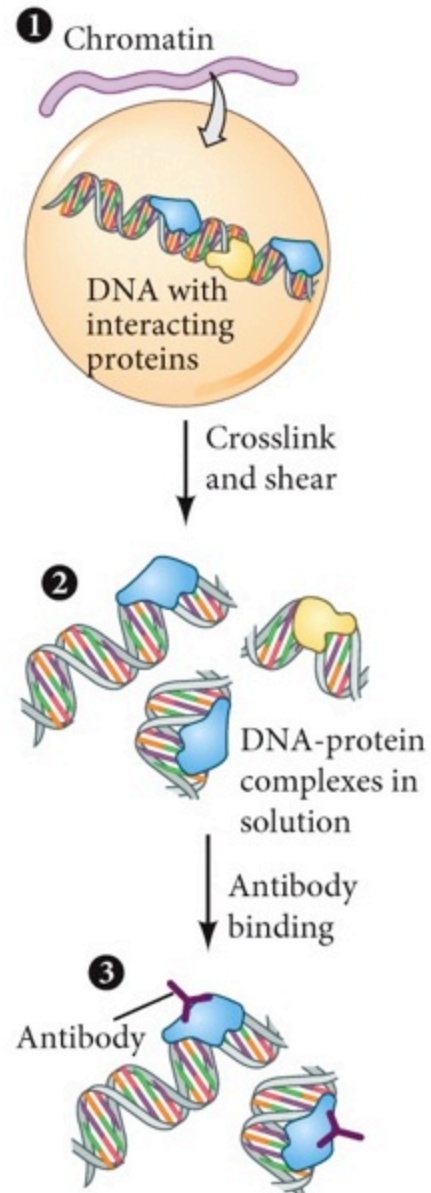
- Proteins with bromo/chromo/tudor domains
- Eg bromodomain binds acetylated lysines
- Chromodomain and Tudor domain containing proteins bind methylated lysines

Eraser's

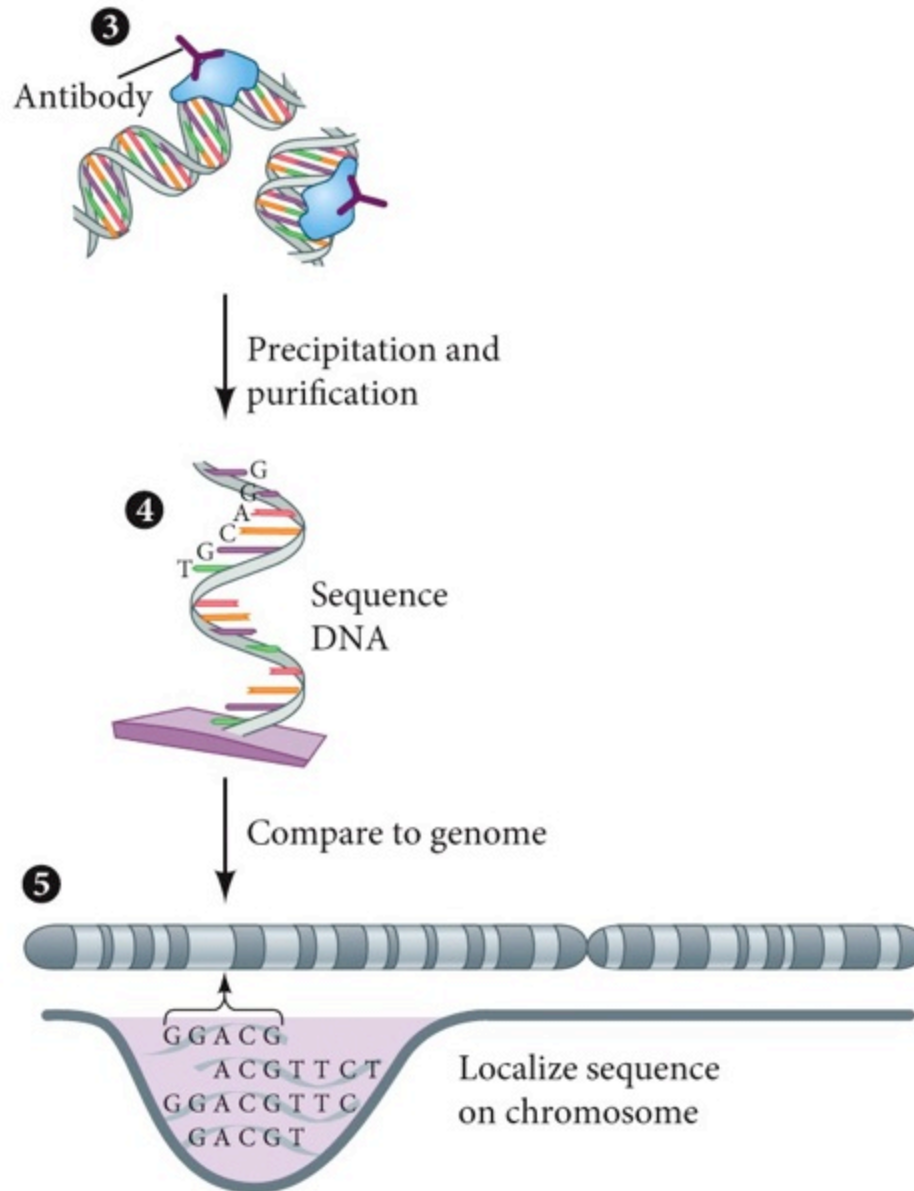
- Histone demethylases eg JmjC-domain lysine demethylase family target trimethylated lysines; Jarid2- H3K4me3
- Histone deacetylases (HDACs)

HDAC4



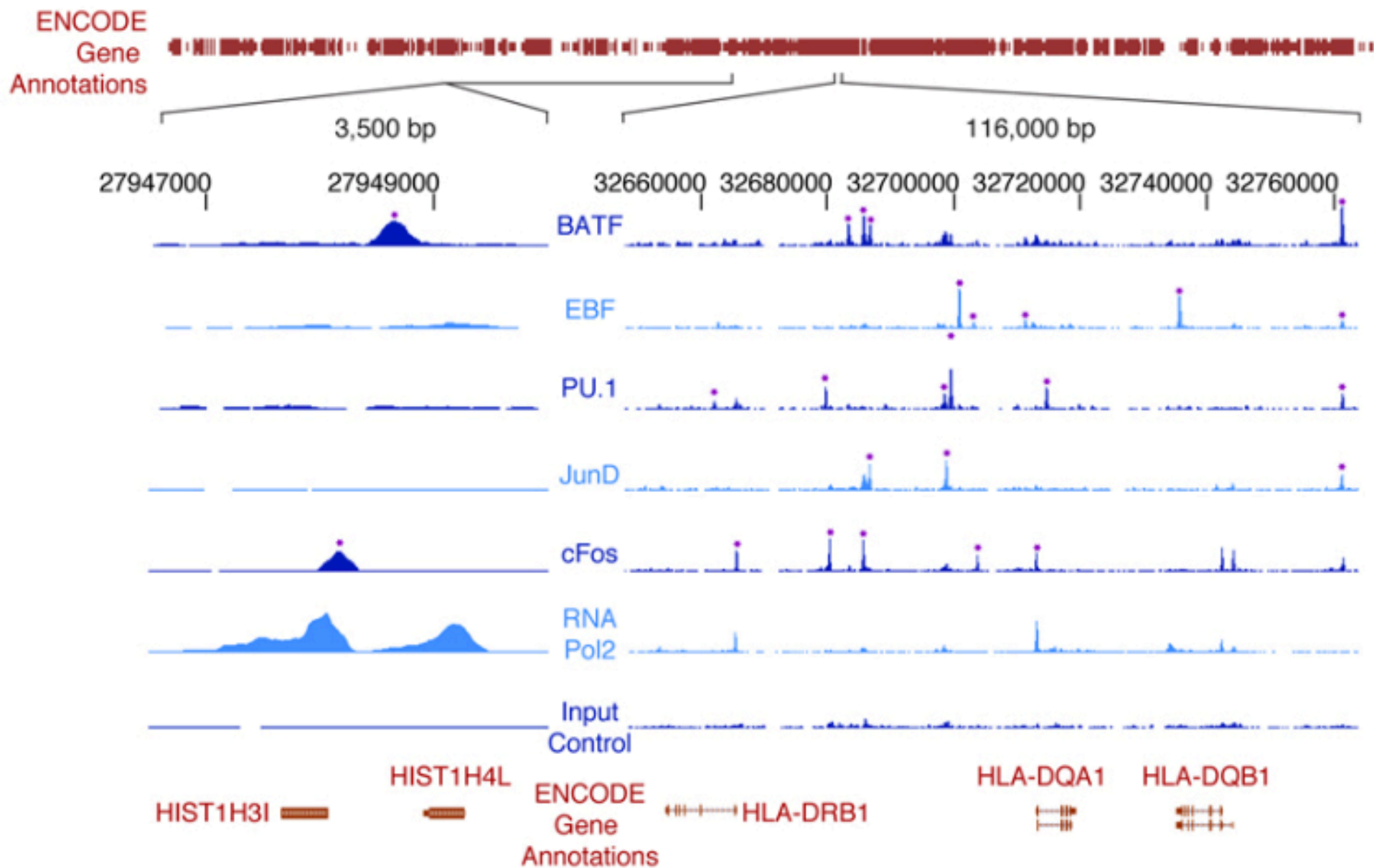


DEVELOPMENTAL BIOLOGY 10e, Figure 2.14 (Part 1)

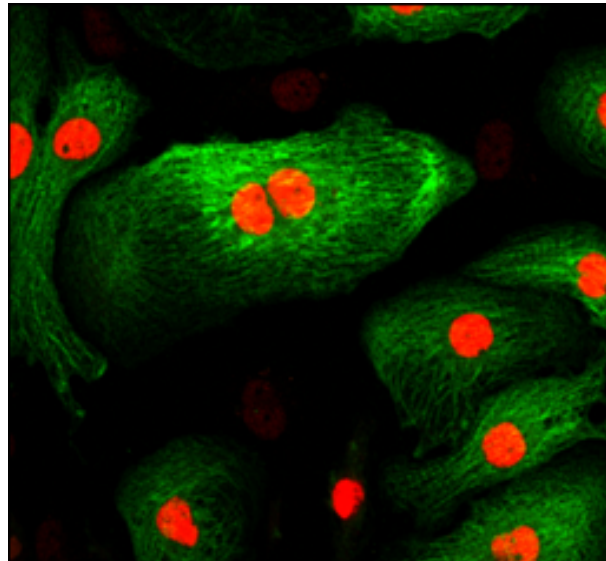
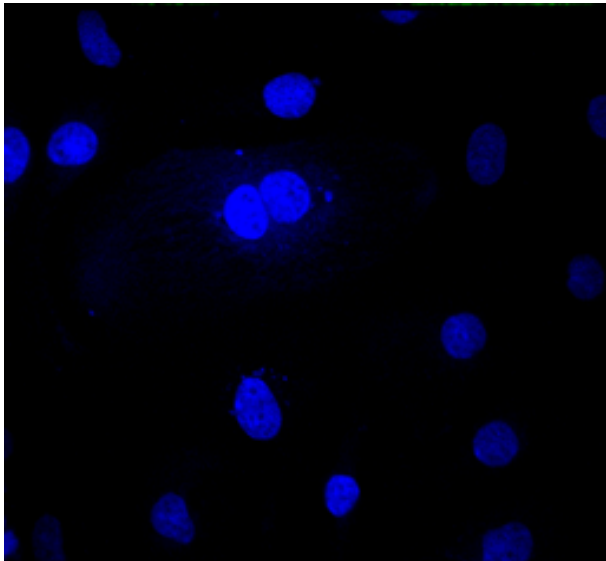
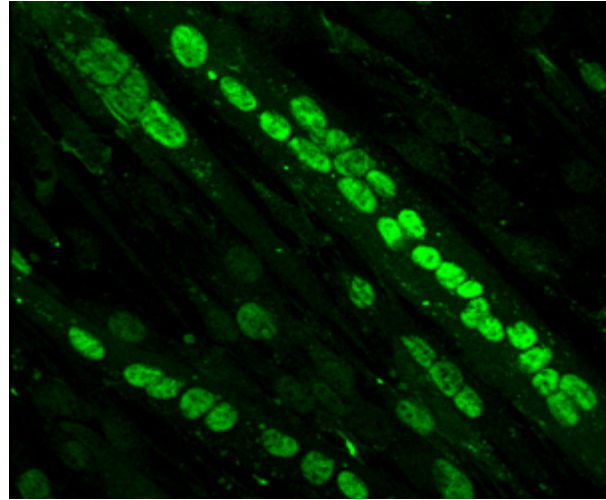
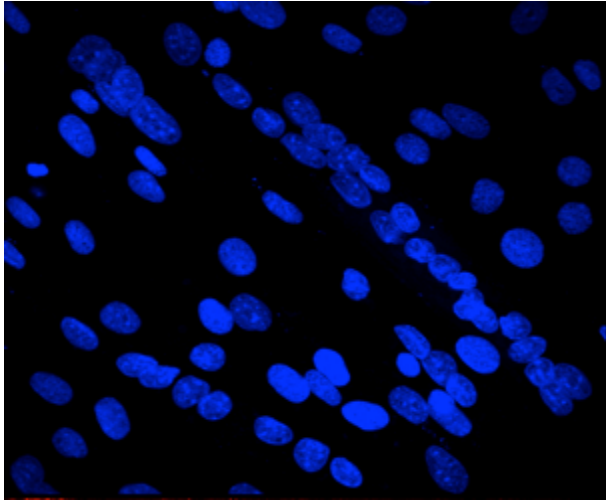


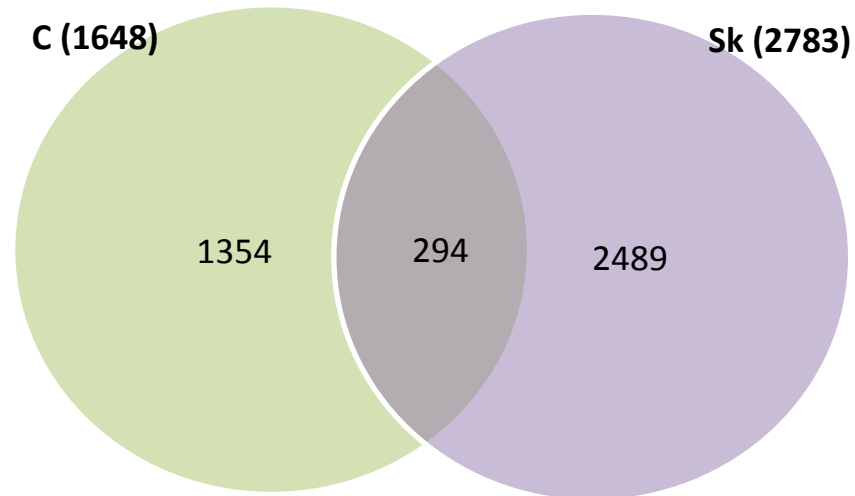
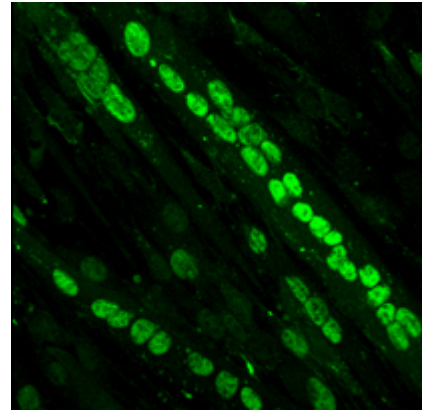
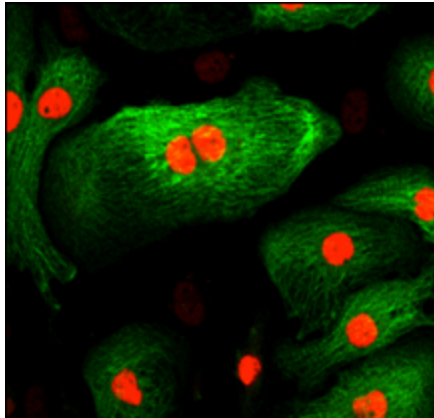
DEVELOPMENTAL BIOLOGY 10e, Figure 2.14 (Part 2)

ENCODE ChIP-seq



MEF2A targets in striated muscle ?





Nucleic Acids Res. 2014 Oct;42(18):11349-62. doi: 10.1093/nar/gku813. Epub 2014 Sep 12.
Global MEF2 target gene analysis in cardiac and skeletal muscle reveals novel regulation of DUSP6 by p38MAPK-MEF2 signaling.
[Wales S, Hashemi S1, Blais A, McDermott JC.](#)

ChIP-Exo
αMEF2A

Primary
Cardiomyocyte

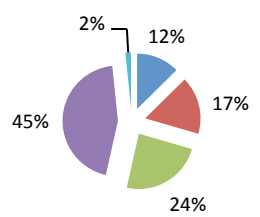
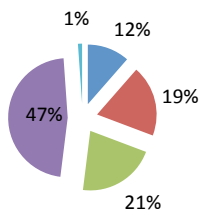
C2C12
Skeletal Myoblast

Compare MEF2 binding locations

C

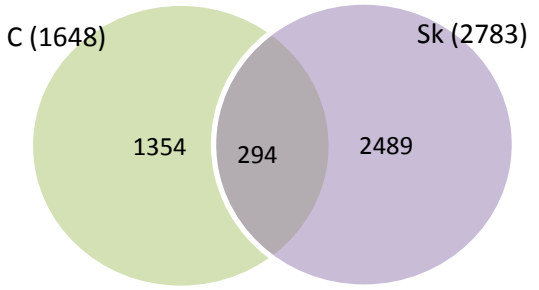
Skeletal Muscle

Cardiac Muscle



■ Proximal Promoter
■ Upstream
■ Downstream
■ Intergenic
■ No Gene Associations

B



D

Rank	Family	Logo	p-value
1	MEF2		0
2	AP1		0
3	BACH		0
4	CREB		0
5	NRF		0

Rank	Family	Logo	p-value
1	MEF2		0
2	AP1		0
3	CREB		0
4	BACH		0
5	ERE		2.47E-9

In collaboration with Dr Alex Blais, U of Ottawa

E

Skeletal Myoblasts

Cardiomyocytes

GO Biological Processes

Term Name	Binom Raw P-Value
actin cytoskeleton organization	2.04113e-18
actin filament-based process	2.60016e-18
regulation of MAP kinase activity	7.93509e-17
regulation of protein serine/threonine kinase activity	9.60009e-17
wound healing	3.50272e-12

Term Name	Binom Raw P-Value
induction of apoptosis	1.45821e-6
induction of programmed cell death	1.57943e-6
actin filament-based process	2.32590e-6
actin cytoskeleton organization	2.32691e-6
fat cell differentiation	2.52762e-6

GO Cellular Component

Term Name	Binom Raw P-Value
actin cytoskeleton	8.16180e-21
contractile fiber	3.91908e-14
contractile fiber part	1.01278e-13
myofibril	2.48759e-13
sarcomere	8.10082e-11

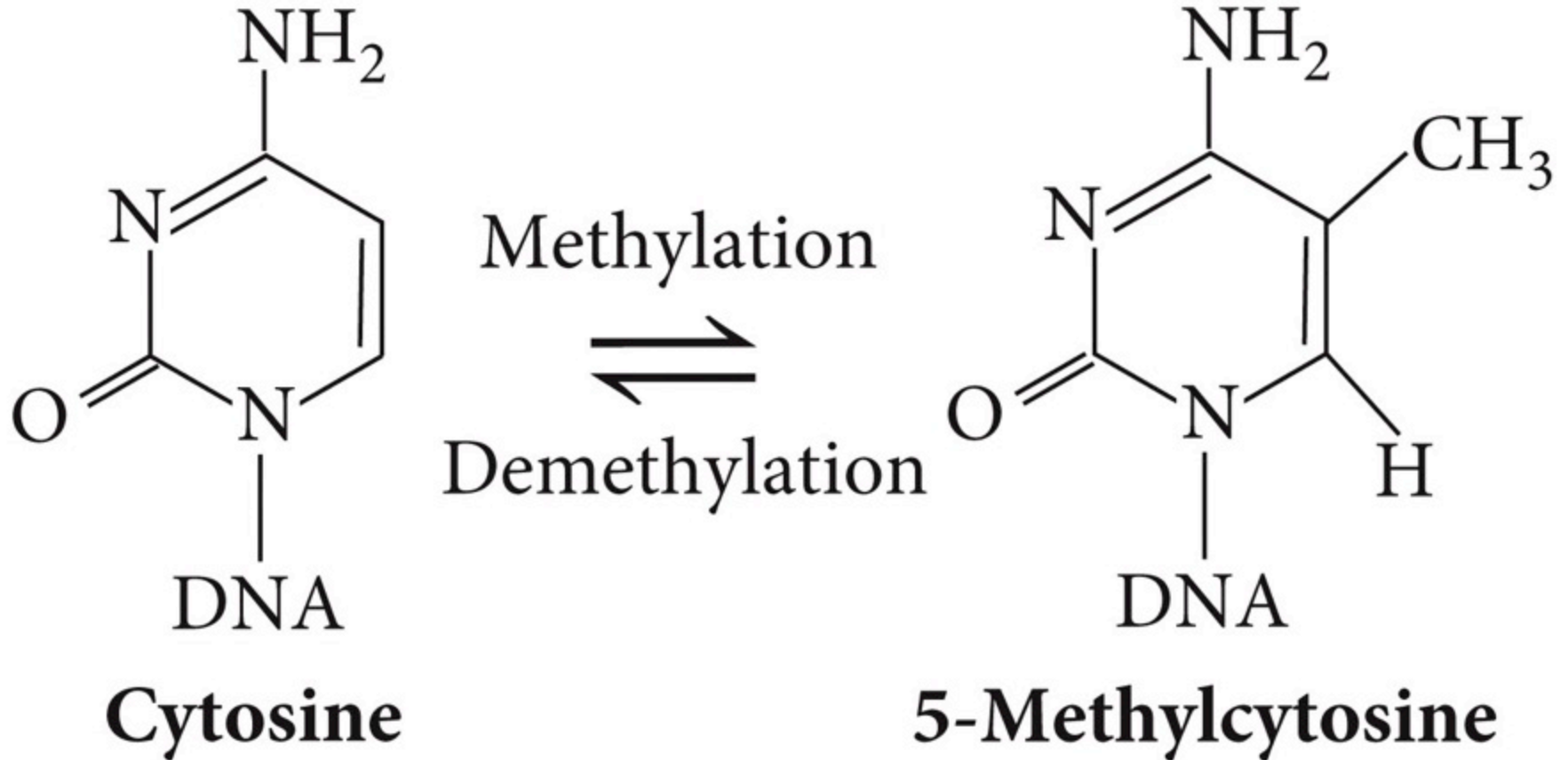
Term Name	Binom Raw P-Value
contractile fiber	1.41625e-16
contractile fiber part	9.09139e-16
myofibril	1.82259e-15
sarcomere	3.19807e-14
focal adhesion	6.45979e-10

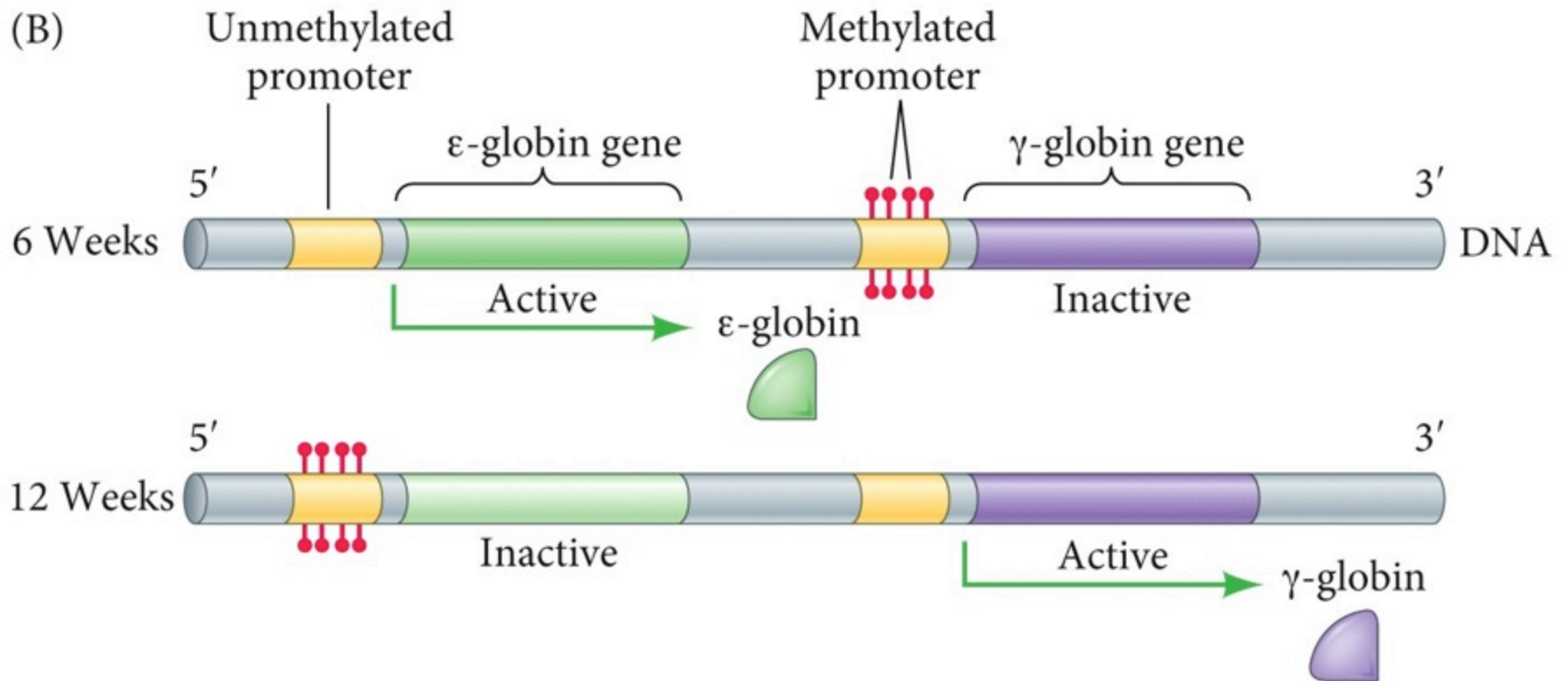
[Nucleic Acids Res. 2014 Oct;42\(18\):11349-62. doi: 10.1093/nar/gku813. Epub 2014 Sep 12.](#)

Global MEF2 target gene analysis in cardiac and skeletal muscle reveals novel regulation of DUSP6 by p38MAPK-MEF2 signaling.

[Wales S, Hashemi S1, Blais A, McDermott JC.](#)

(A)

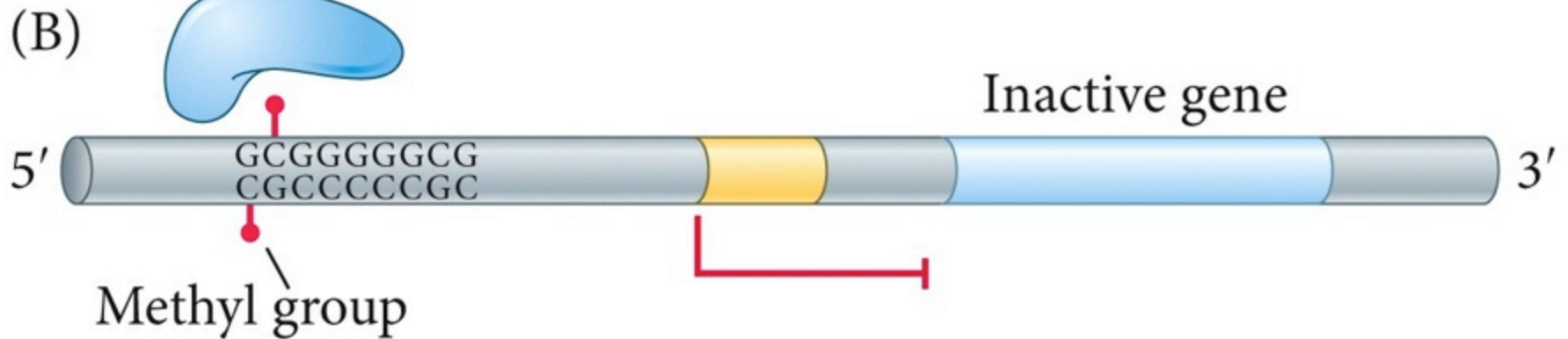
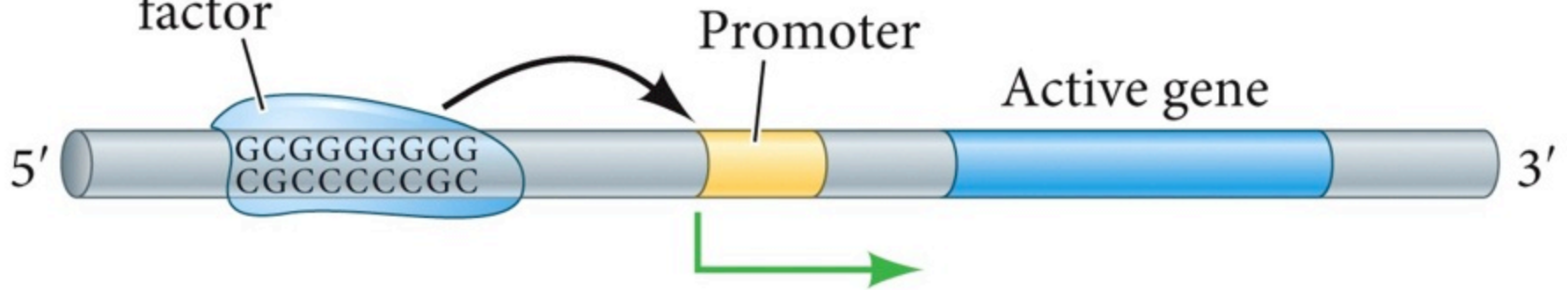


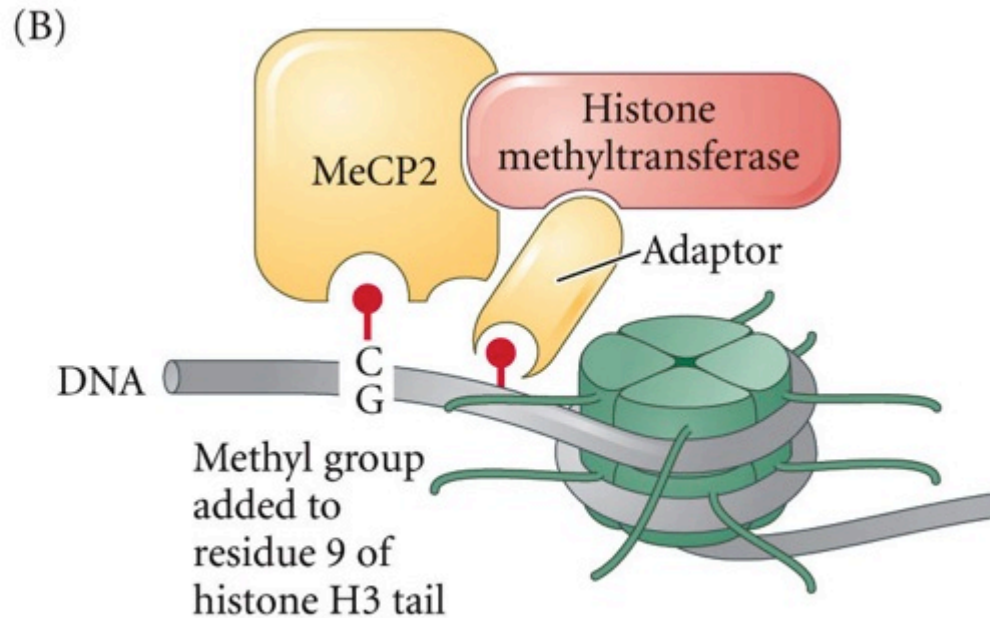
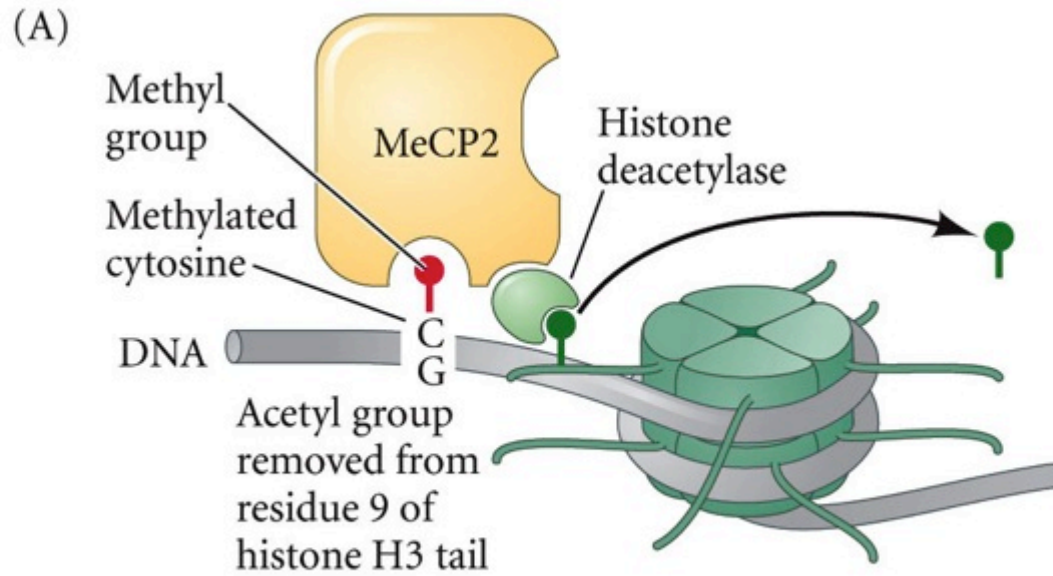


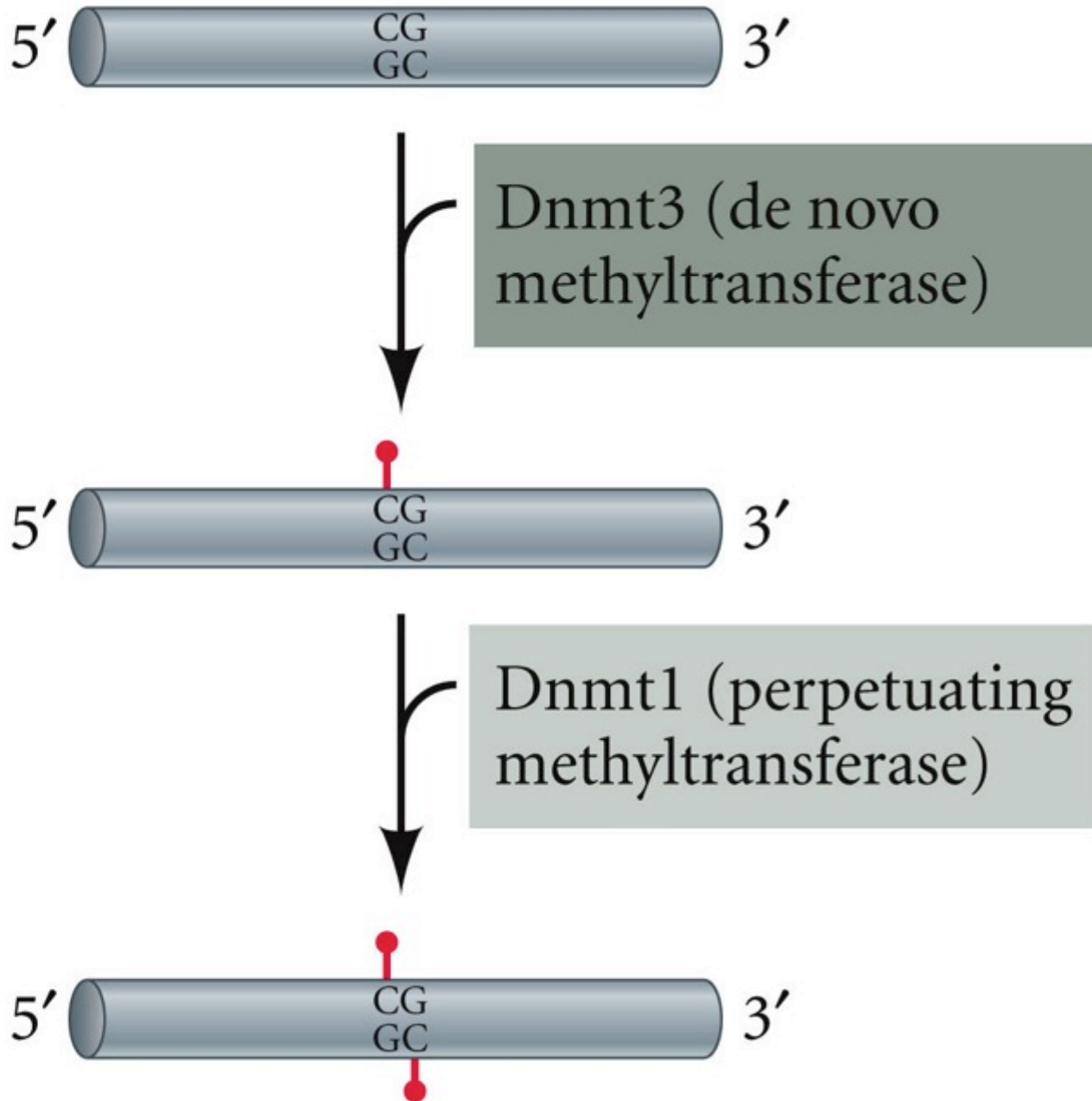
DEVELOPMENTAL BIOLOGY 10e, Figure 2.16 (Part 2)

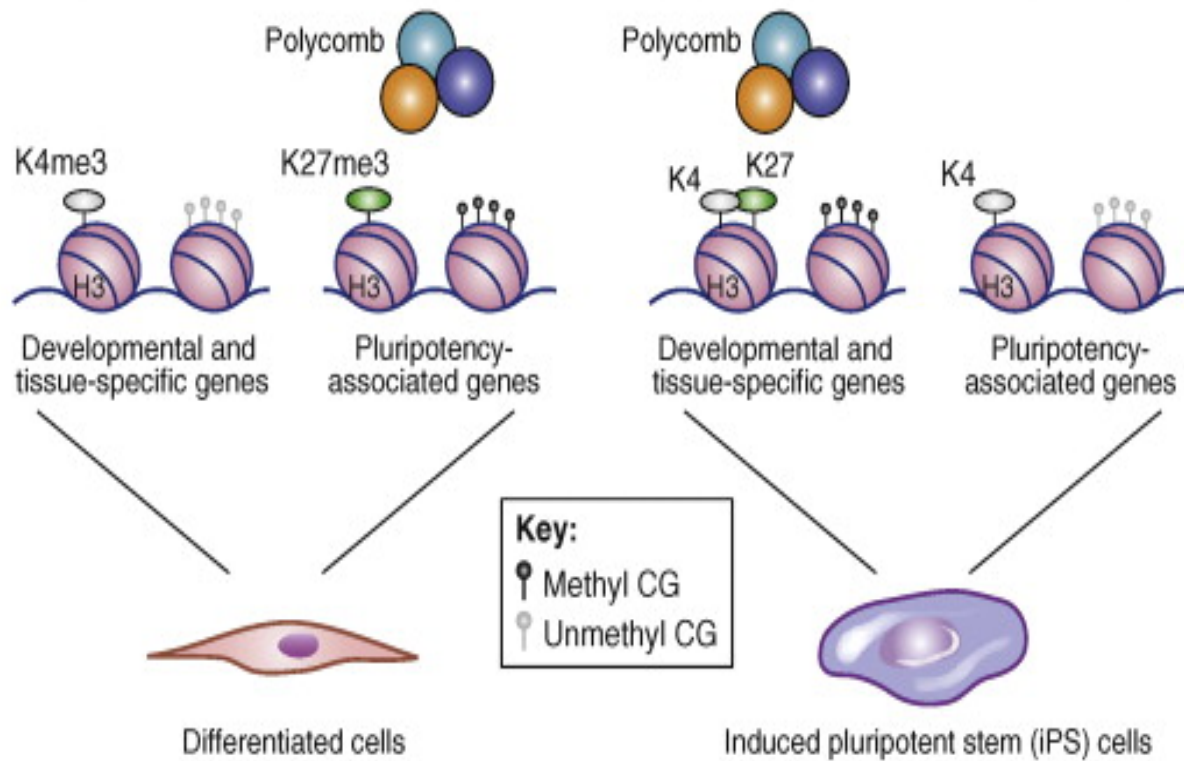
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(A) Egr1 transcription factor









TRENDS in Molecular Medicine

Adapted from Amabile, G and Meissner A 2009
 Trends Mol Med 15, 59