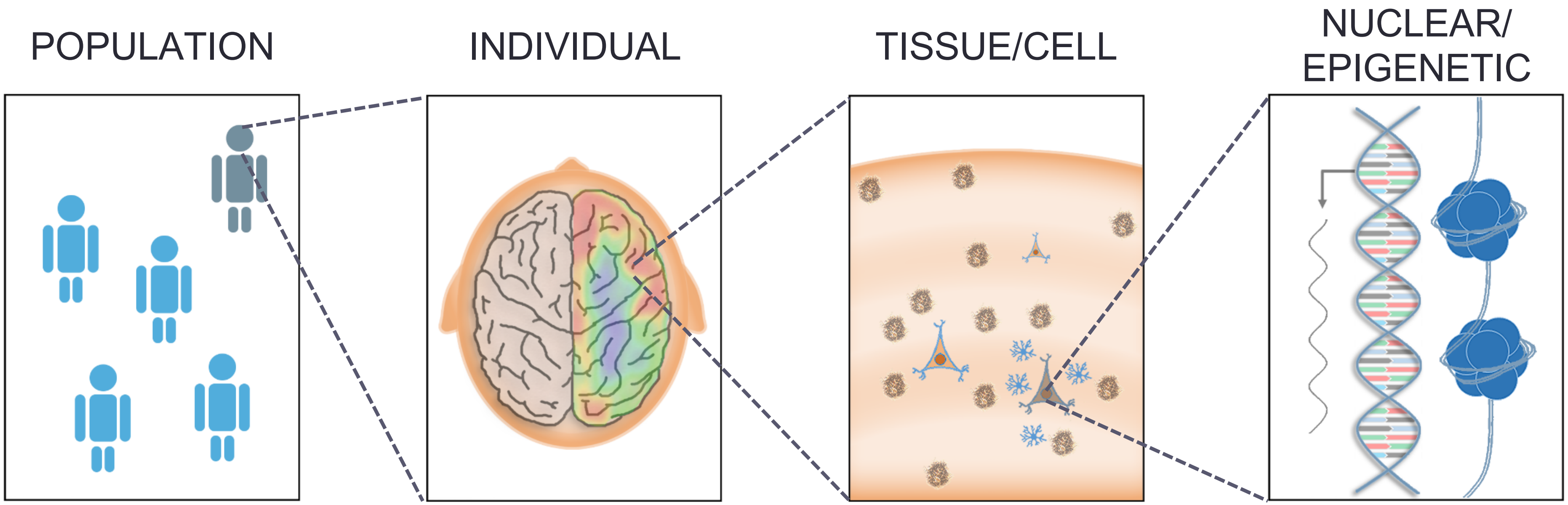
WEEK 11

NEUROEPIGENETICS

Levels of investigation in neurodegenerative disorders



Sanchez-Mut and Gräff, 2015, Front Behav Neurosci

- Cognitive decline
- Genetics

- Abnormal activity
  - fMRI
  - PET scans

- Abnormalities
  - proteinopathies
  - neuronal death

- Dysregulation in
  - transcription
  - **epigenetics**

Neuroepigenetics

1) **The chromatin – Epigenetic basics (Lecture 1)**

- Chromatin condensation
- Regulation of chromatin structure
- Environmental influences on epigenetics
- Epigenetic inheritance

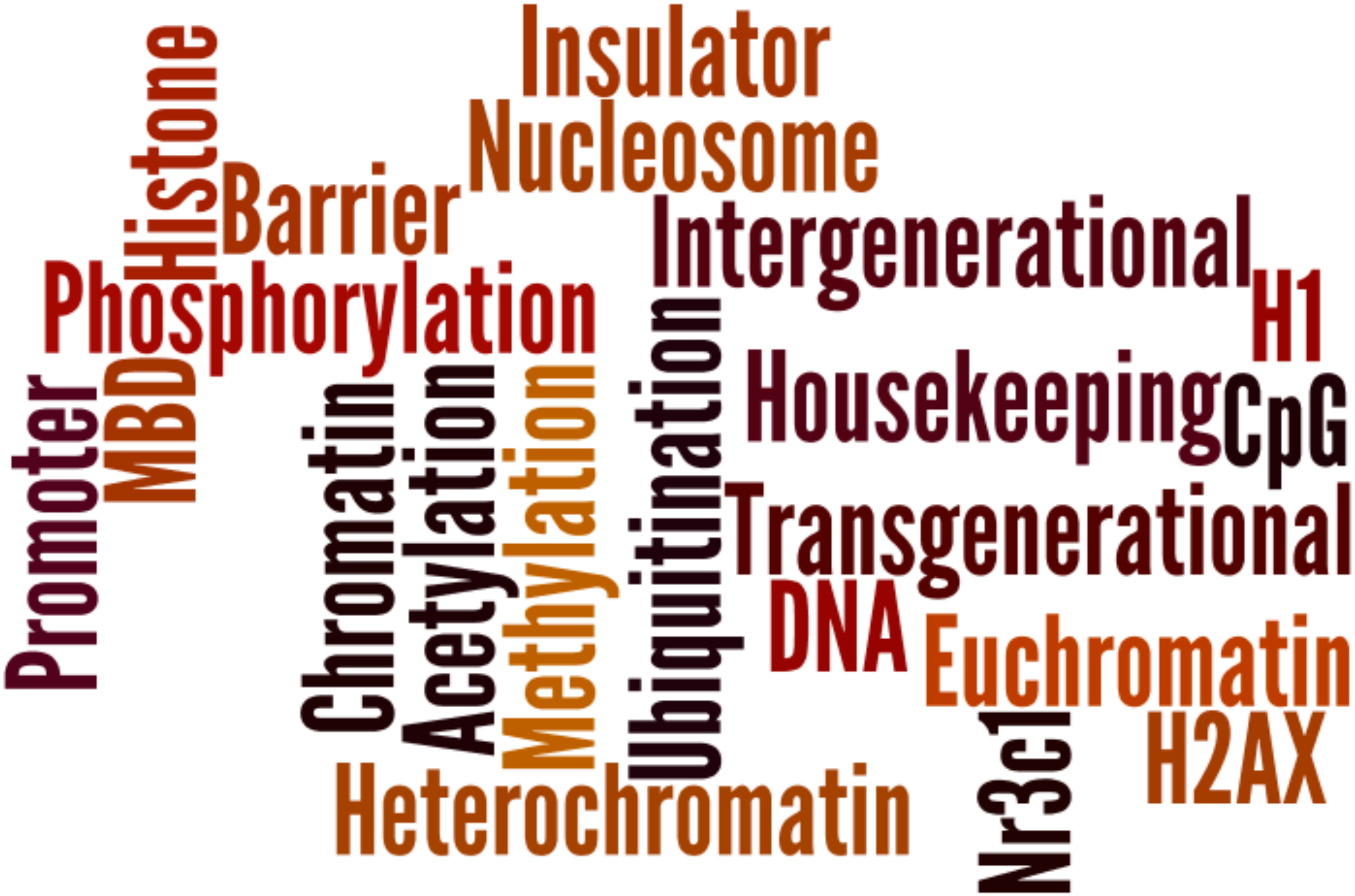
2) **Epigenetic dysregulation (Lecture 2)**

- in AD

Learning objectives

At the end of this week you will be able to

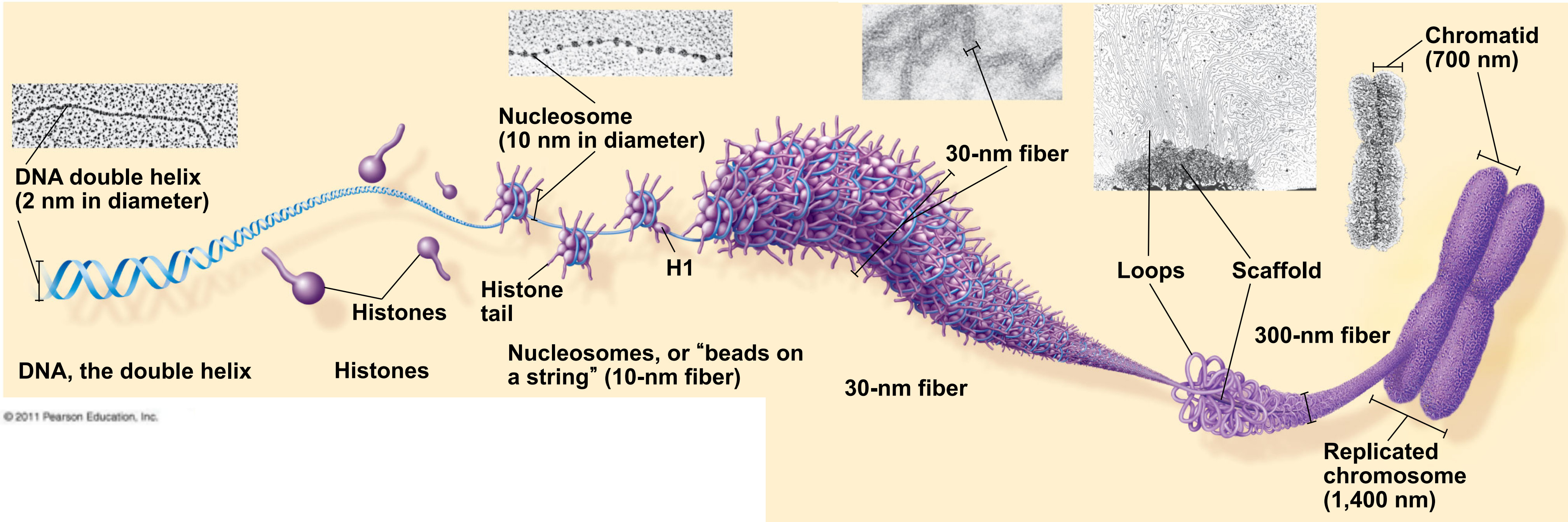
- Know about the core components of chromatin
- Define core epigenetic mechanisms of gene expression
- Know examples of how epigenetics can be influenced by the environment
- Differentiate between genetic and epigenetic modes of inheritance
- Explain how early life stress can alter adult behavior via epigenetic modifications


Insulator
Nucleosome
Histone
Barrier
Intergenerational
Phosphorylation
H1
Promoter
MBD
Housekeeping
CpG
Chromatin
Acetylation
Methylation
Ubiquitination
Transgenerational
DNA
Euchromatin
H2AX
Nr3c1
Heterochromatin

Some definitions:

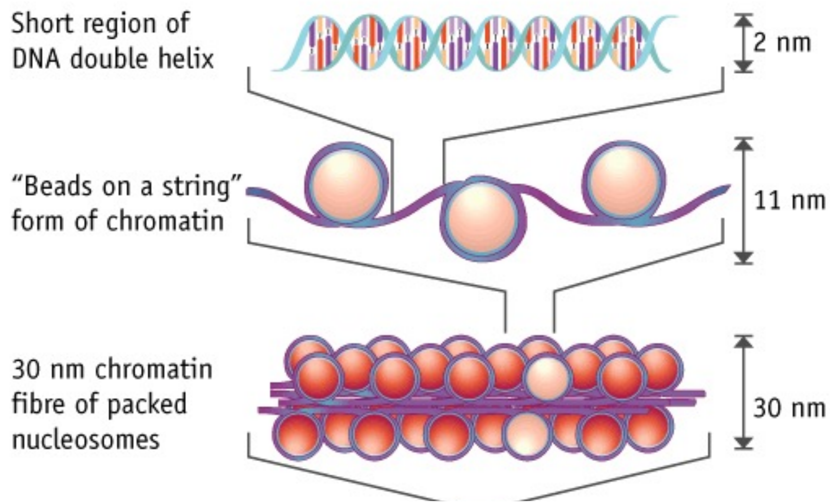
- **Chromatin** = DNA + histones and nonhistone chromatin binding proteins
- **Epi-genetic** = “On” or “above” the genes
  - “The structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states” Adrian Bird
- **3 main types of structural adaptations:**
  - Posttranslational modifications of histone proteins
  - DNA methylation
  - Non-coding RNAs

Chromatin condensation:

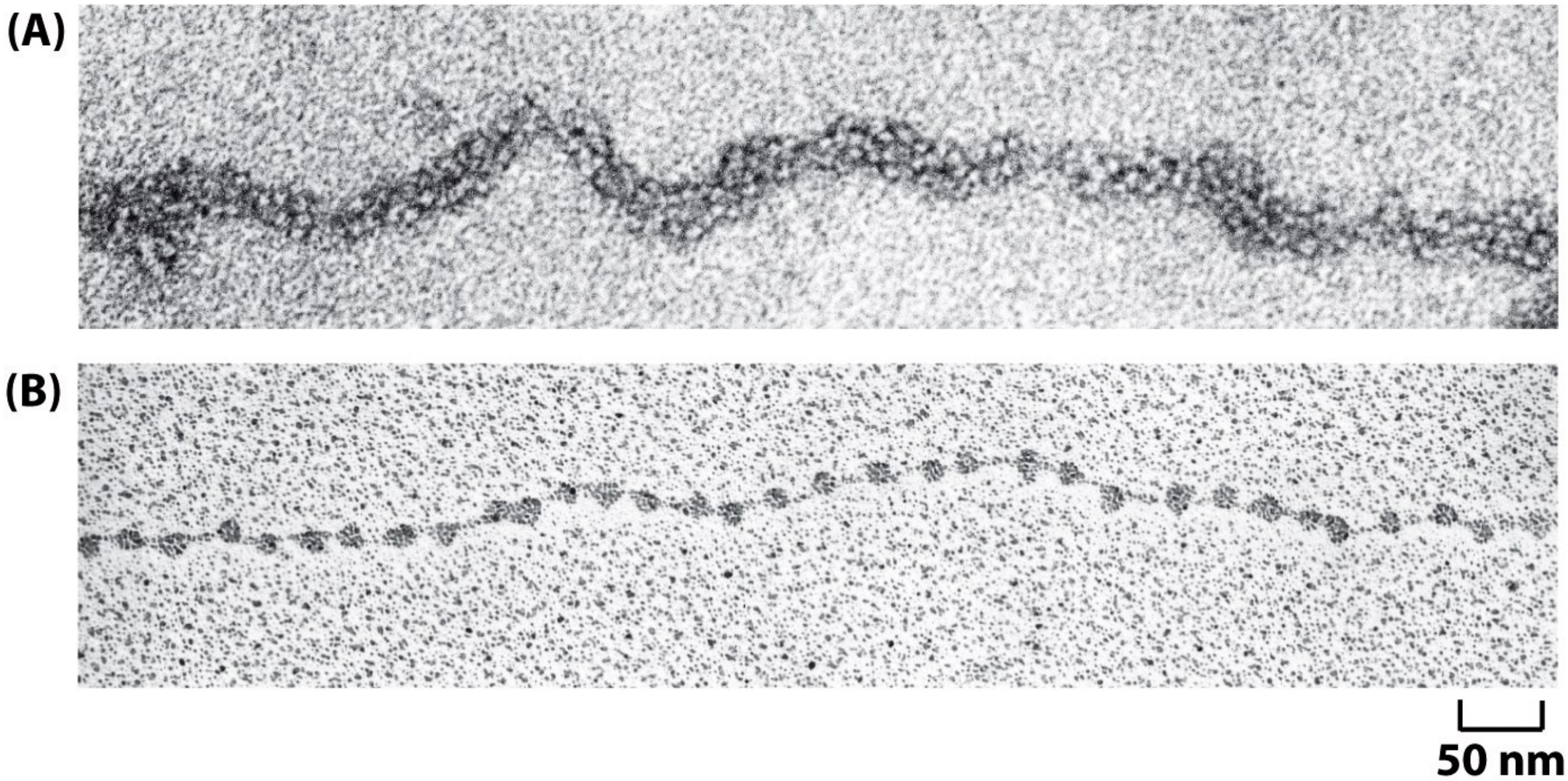


Chromatin condensation:

- 2nm: double helix
- 11nm: beads on a string ("collier en perles")
- 30nm: fibre of condensed nucleosomes



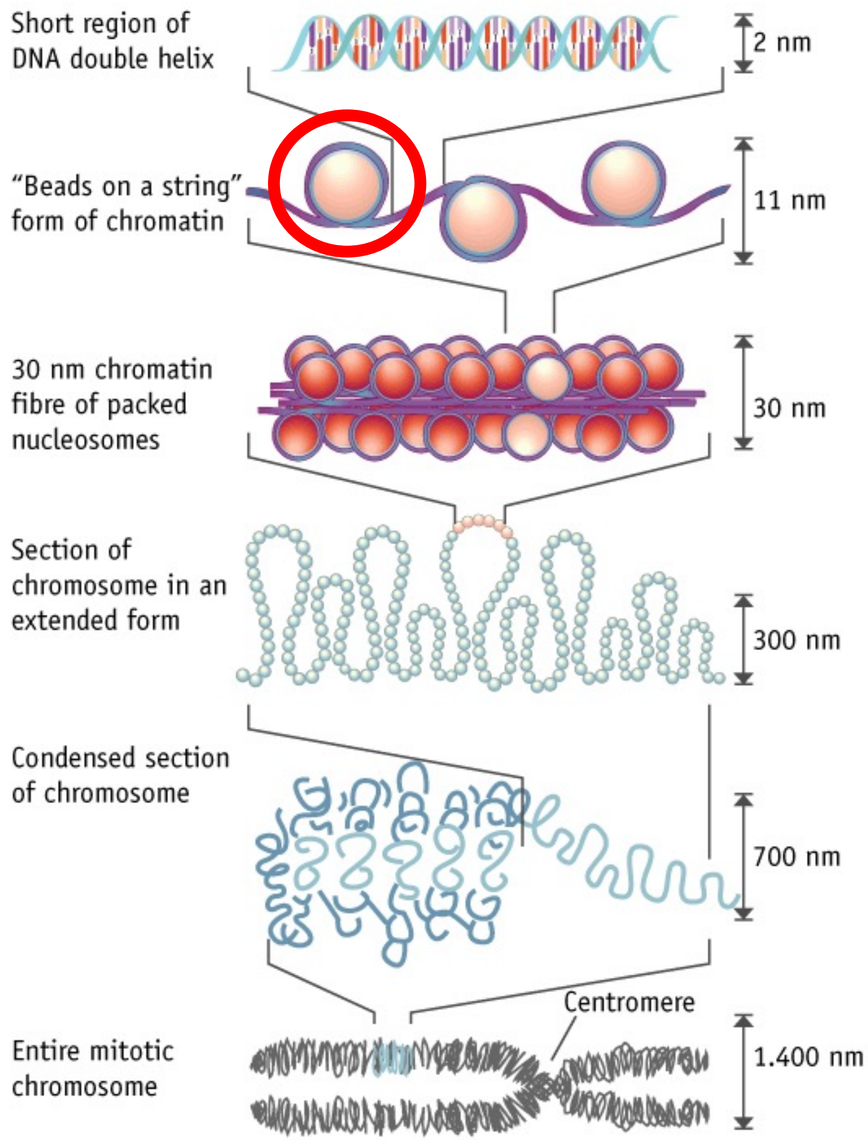
Chromatin condensation:



(A): 30nm fibre (B): 11nm beads on a string

Chromatin condensation:

- 2nm: double helix
- 11nm: beads on a string (“collier en perles”)
- 30nm: fibre of condensed nucleosomes
- 300nm: chromatin loops



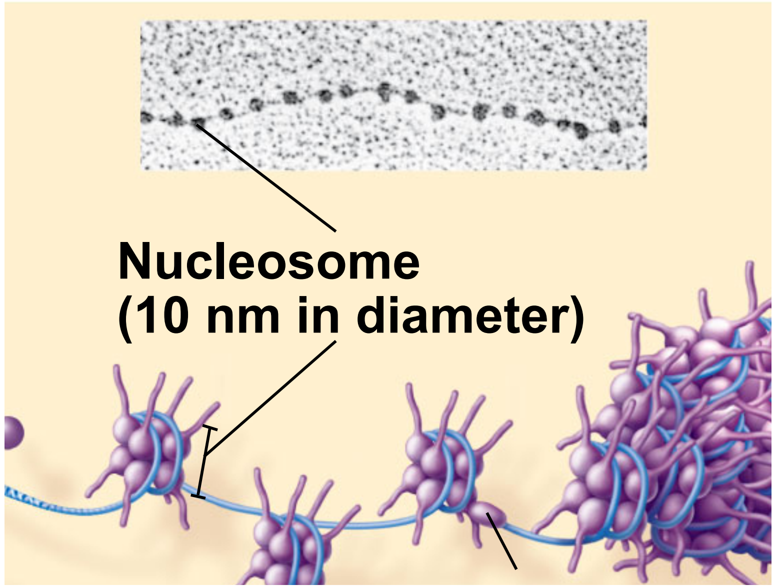
Net result: 10’000x condensation in length

The nucleosome

- Contains about 200bp of DNA

- Nucleosome core particle:
  - 147bp DNA
  - 8 core histone proteins (histone octamer)
    - H2A (2)
    - H2B (2)
    - H3 (2)
    - H4 (2)

- Linker DNA and linker histone



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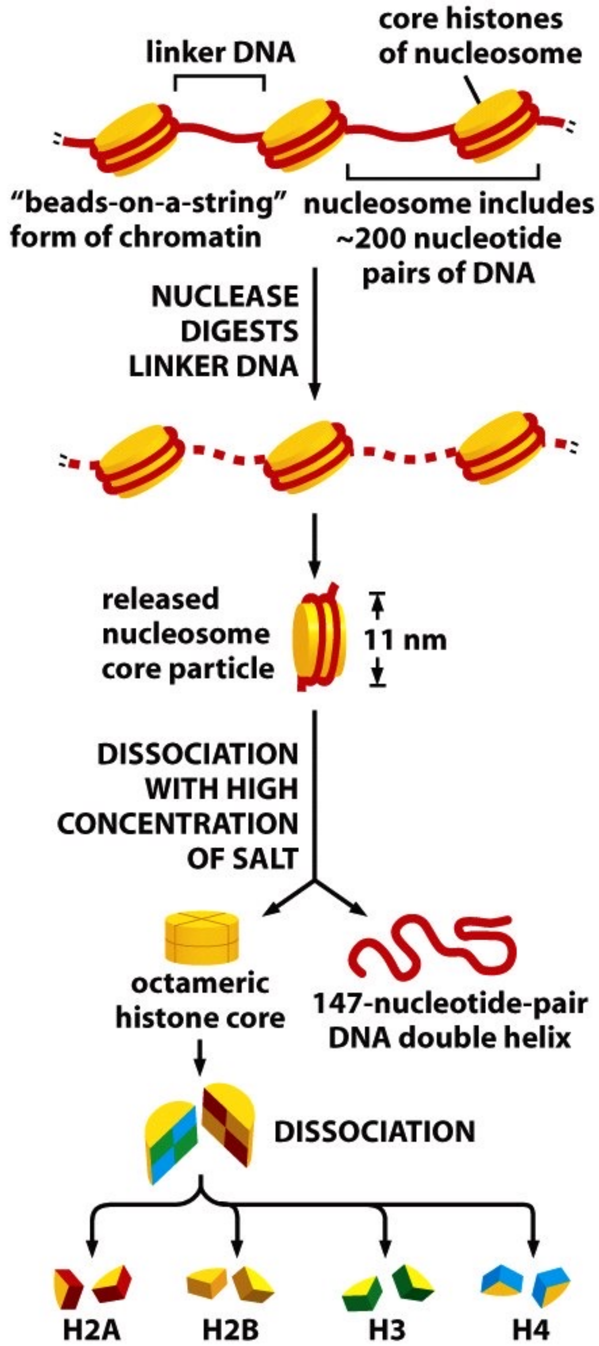
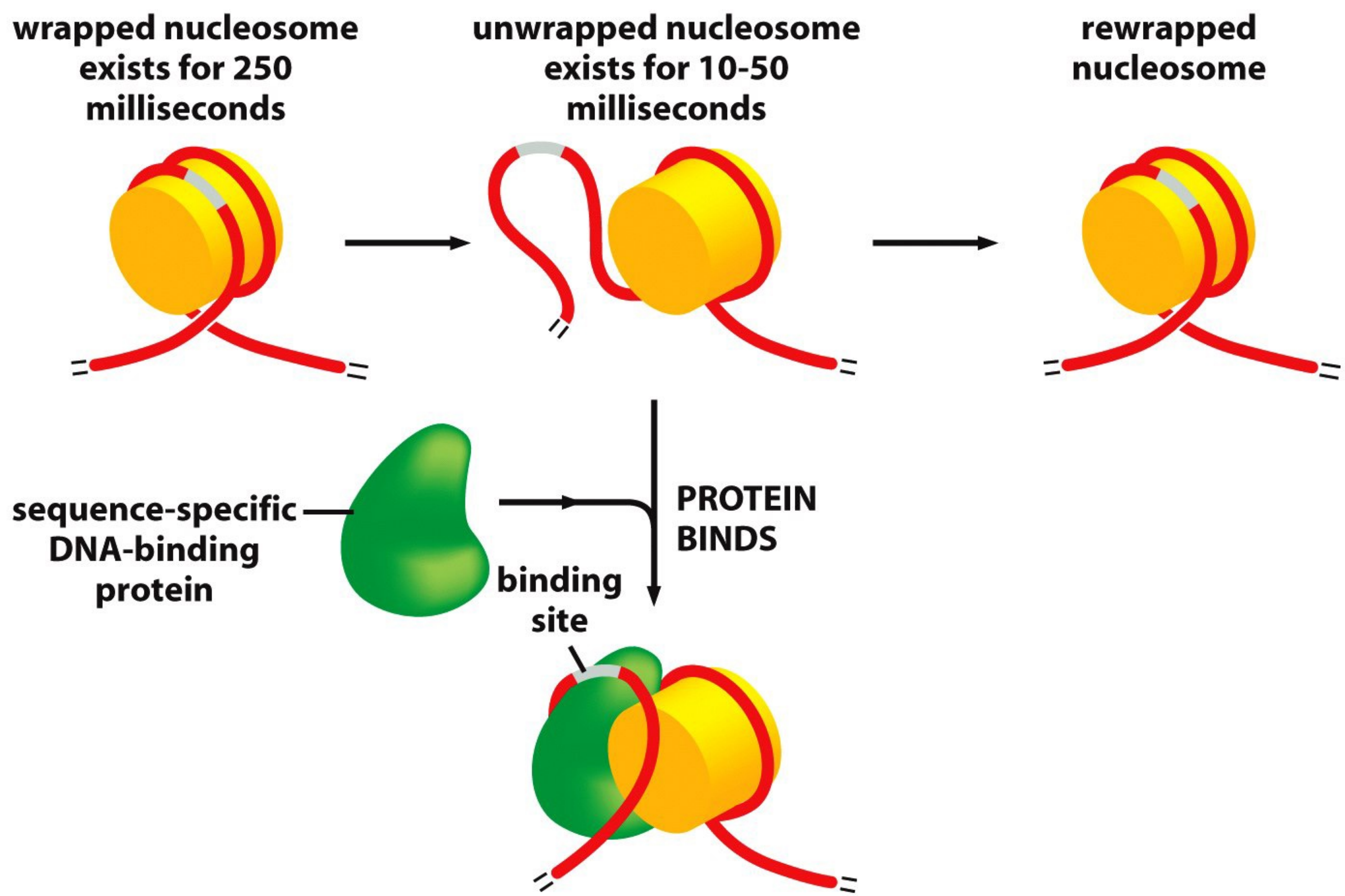


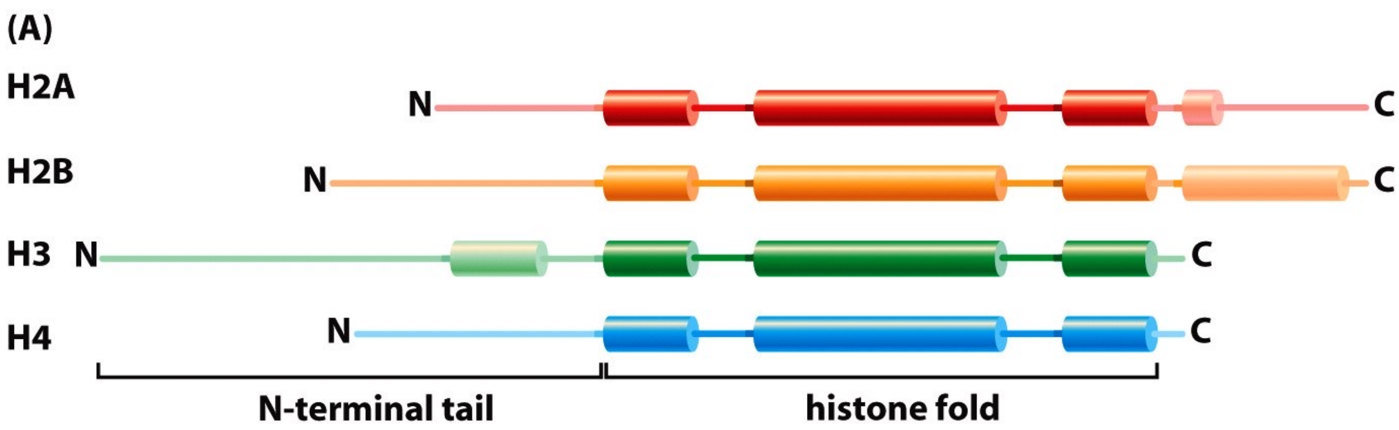
Dynamic nature of the nucleosome



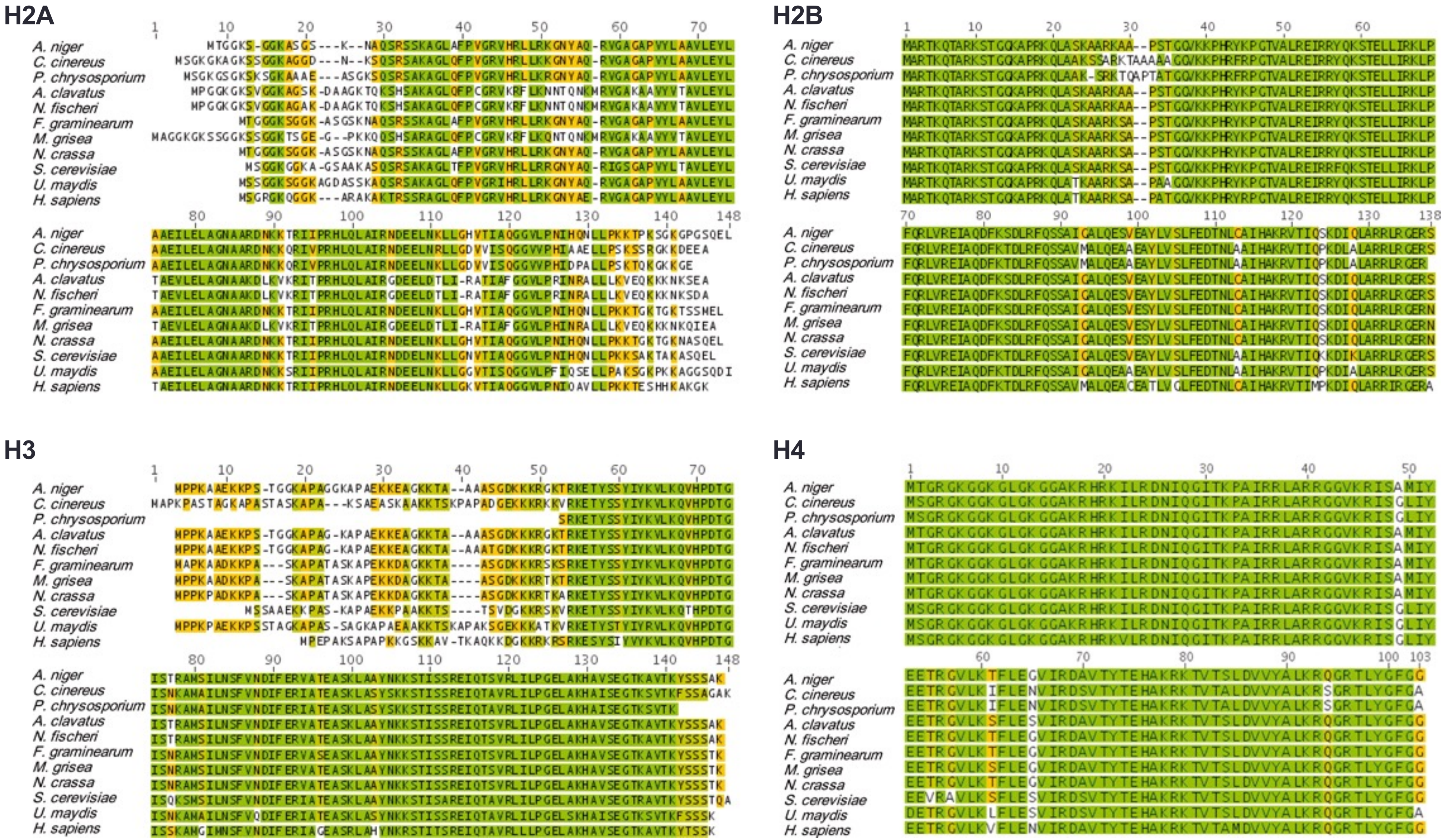
The core histones

- Histone fold: Important for dimerization

- N-terminal domain: Important for posttranslational modifications



Evolutionary conservation of the core histones



Neuroepigenetics

1) **The chromatin – Epigenetic basics (Lecture 1)**

- Chromatin condensation
- **Regulation of chromatin structure**
- Epigenetic inheritance
- Environmental influence on epigenetics

2) **Epigenetic dysregulation (Lecture 2)**

- in AD

Regulation of chromatin structure:

1) Posttranslational histone modifications

2) Histone variants

3) DNA Methylation

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What is contained within a nucleosome?

A. 4 core histones + ~200bp DNA
B. 8 core histones + ~200bp DNA
C. 8 core histones + 147bp DNA
D. 4 core histones + 147bp DNA

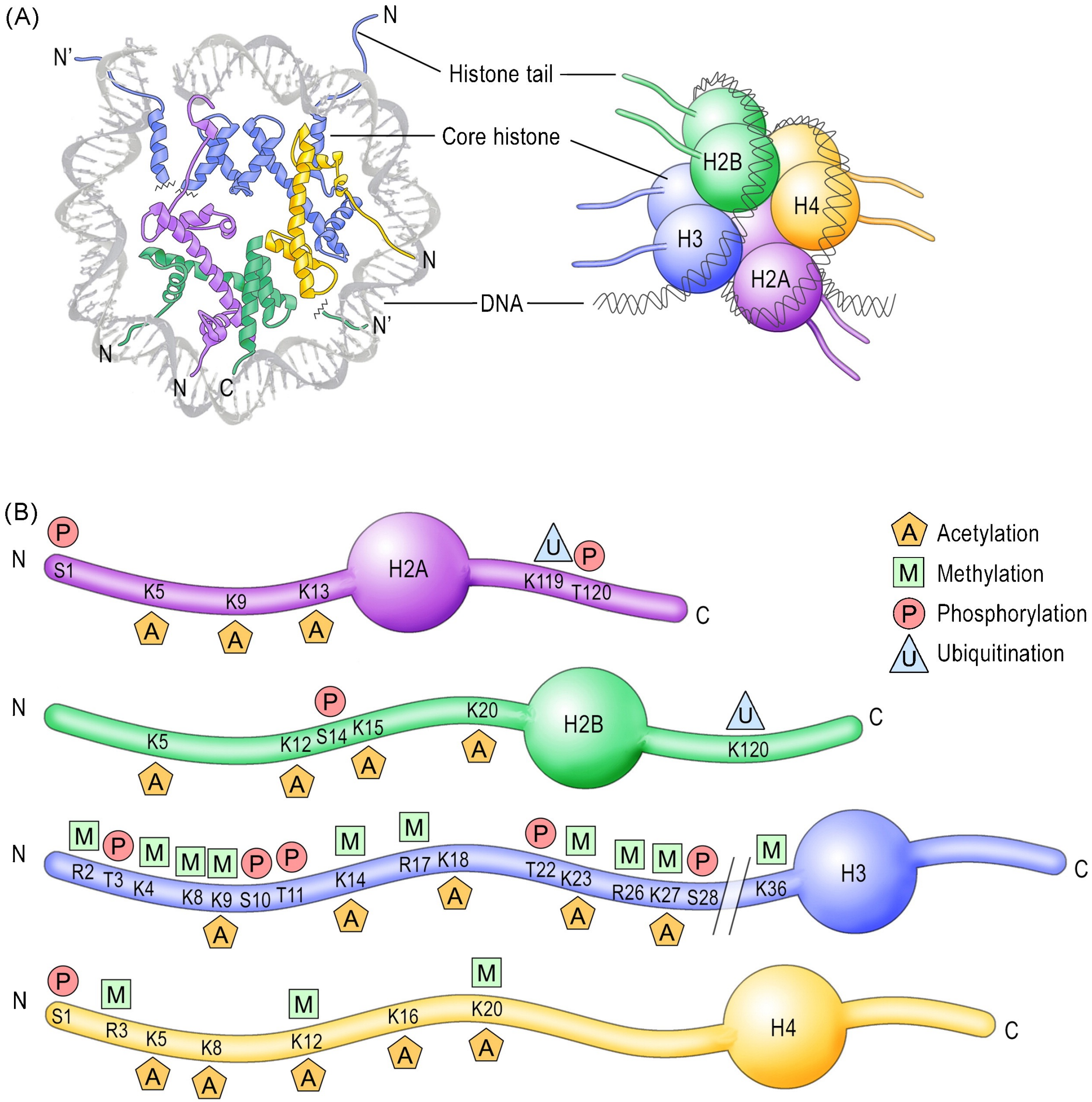
Regulation of chromatin structure:

1) **Posttranslational histone modifications**

2) Histone variants

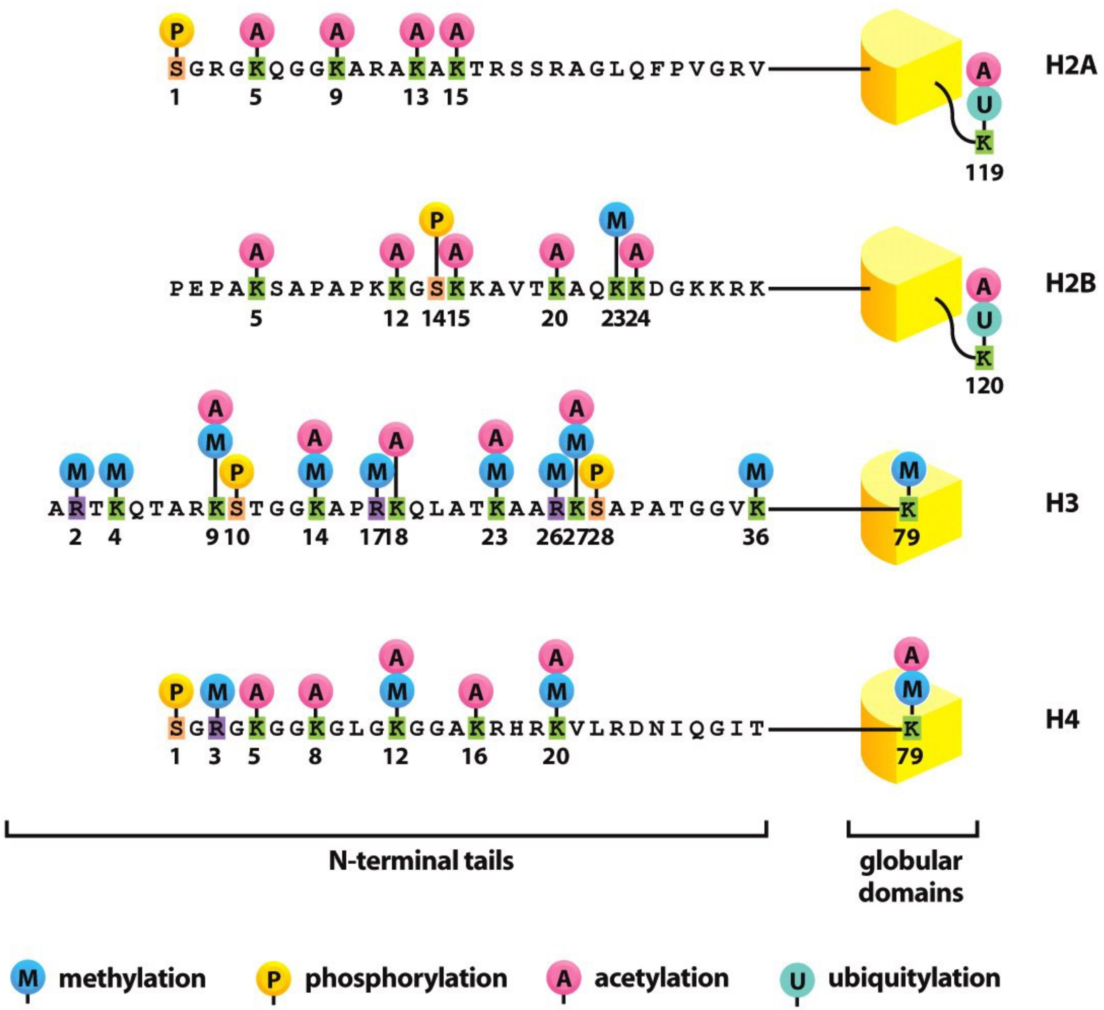
3) DNA Methylation

2) Posttranslational modifications (PTMs) of histones

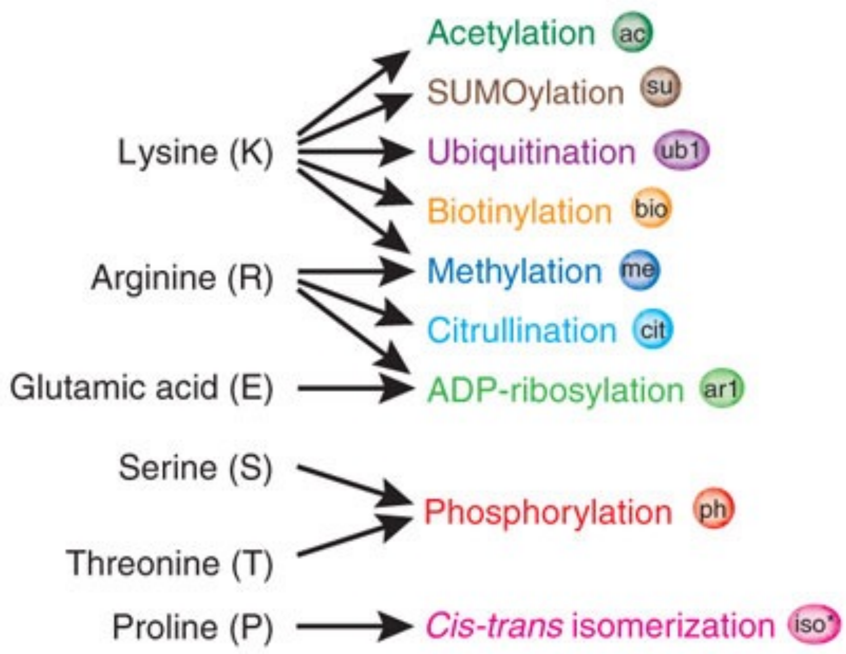


Chromatin structure – Regulation – Histone PTMs

- **Histone PTMs predominantly occur on the N-terminal tail**



- **Amino acids in histones that can be modified:**



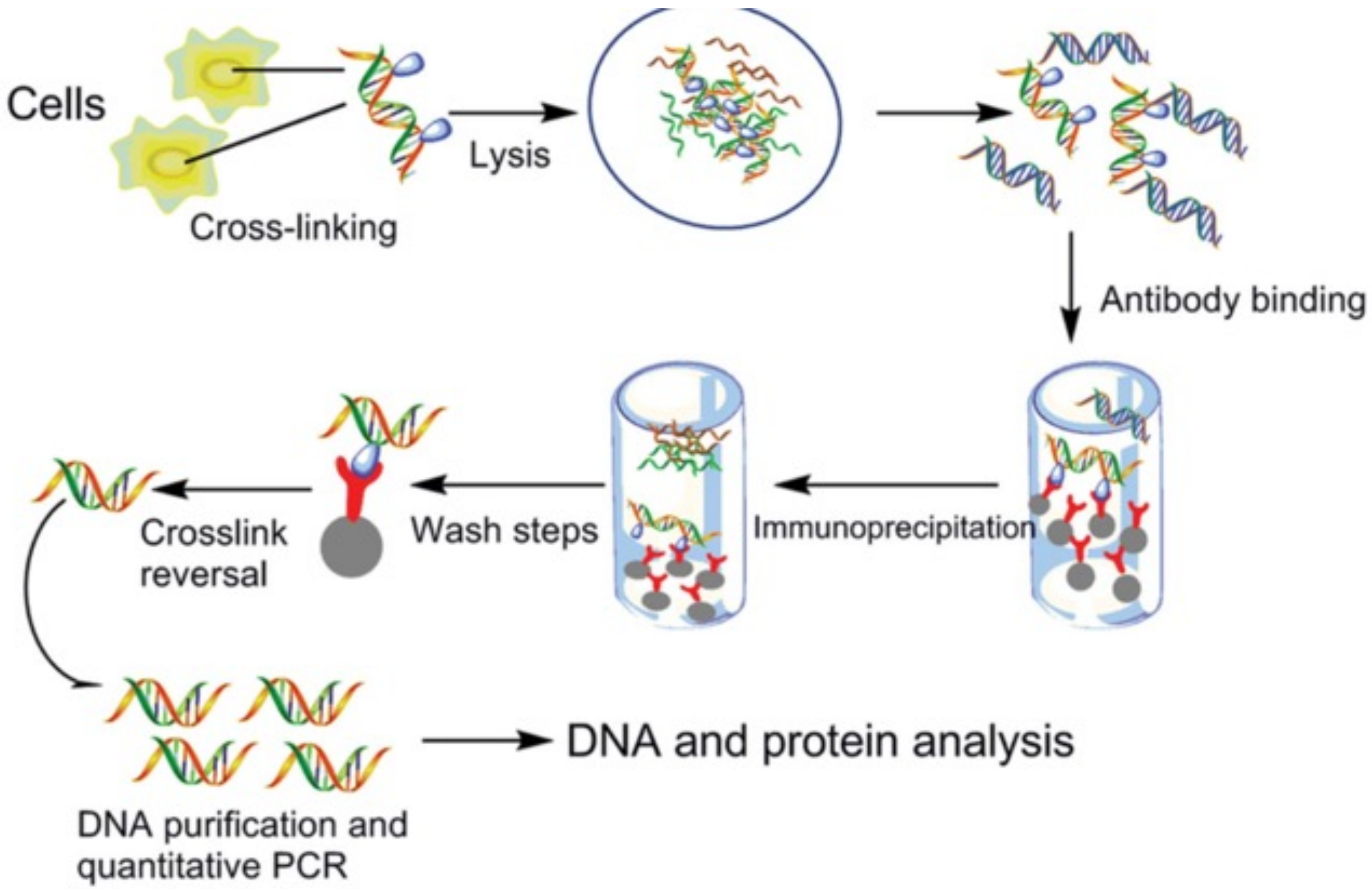
Chromatin structure – Regulation – Histone PTMs

- **2 groups of histone PTMs**
  - Group 1: Small chemical groups
  - Group 2: Large chemical groups

	Role in transcription	Histone-modified sites
GROUP 1		
Acetylation	activation	H3 (K9,K14,K18,K56) H4 (K5,K8K12,K16) H2A H2B (K6,K7,K16,K17)
Phosphorylation	activation	H3 (S10)
Methylation	activation	H3 (K4,K36,K79)
	repression	H3 (K9,K27) H4 (K20)
GROUP 2		
Ubiquitylation	activation	H2B (K123)
	repression	H2A (K119)
Sumoylation	repression	H3 (?) H4 (K5,K8,K12,K16) H2A (K126) H2B (K6,K7,K16,K17)

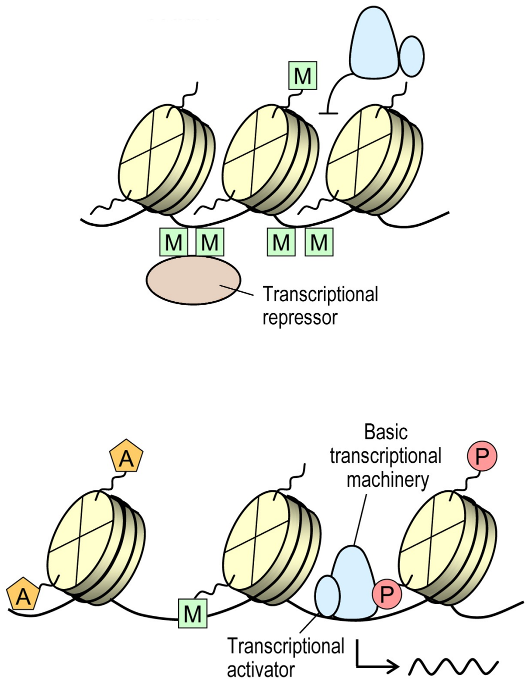
- **How to experimentally measure histone PTMs:**

Chromatin Immunoprecipitation (ChIP)



Chromatin structure – Regulation – Histone PTMs

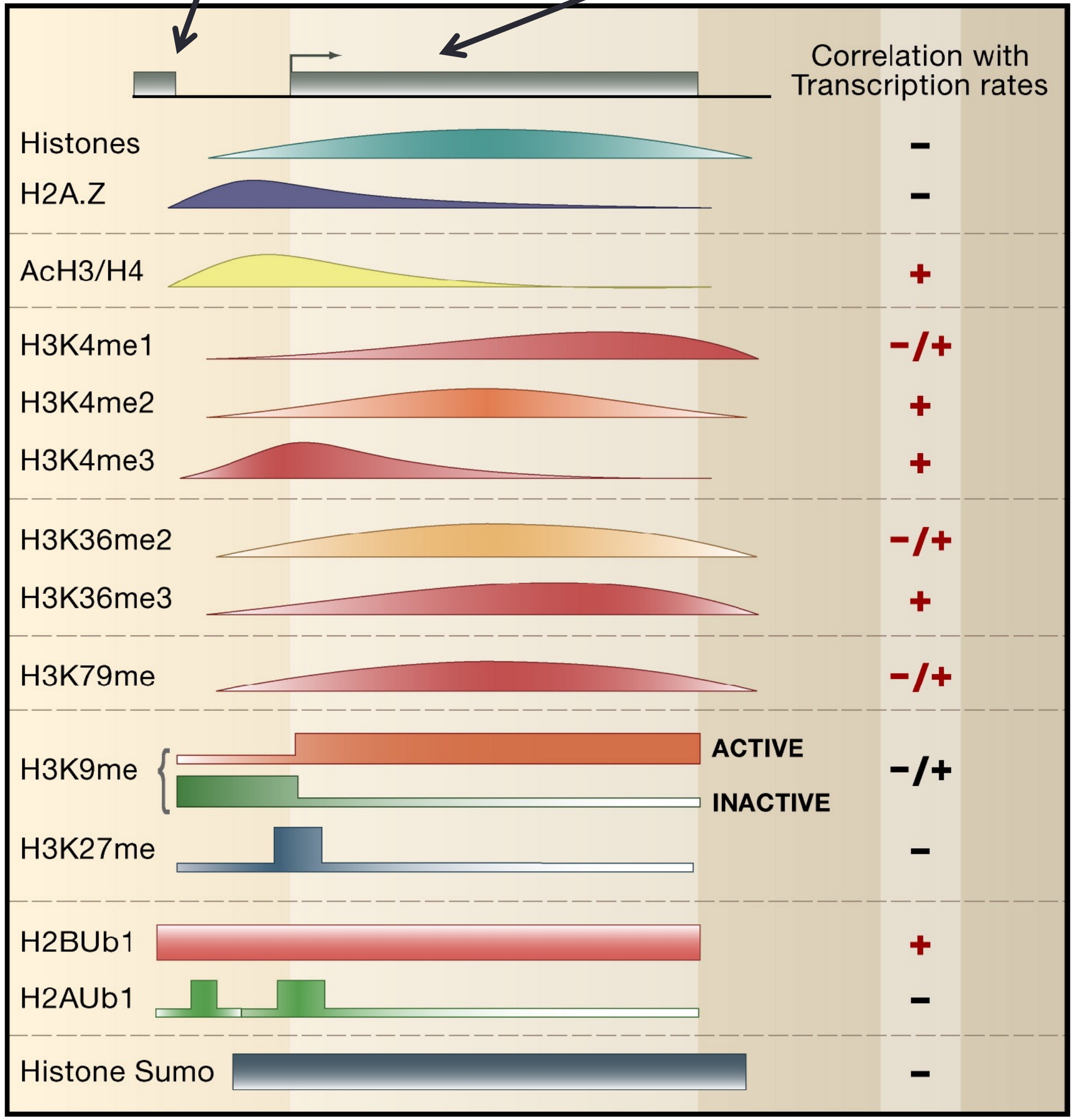
- **Epigenetic mechanisms and their effect on transcription**
  - Mechanisms regulating the compaction of the chromatin
  - Regulate **gene transcription** by regulating chromatin compaction
  - **Types**
    - DNA methylation
    - Histone modifications
      - Phosphorylation
      - Methylation
      - Acetylation



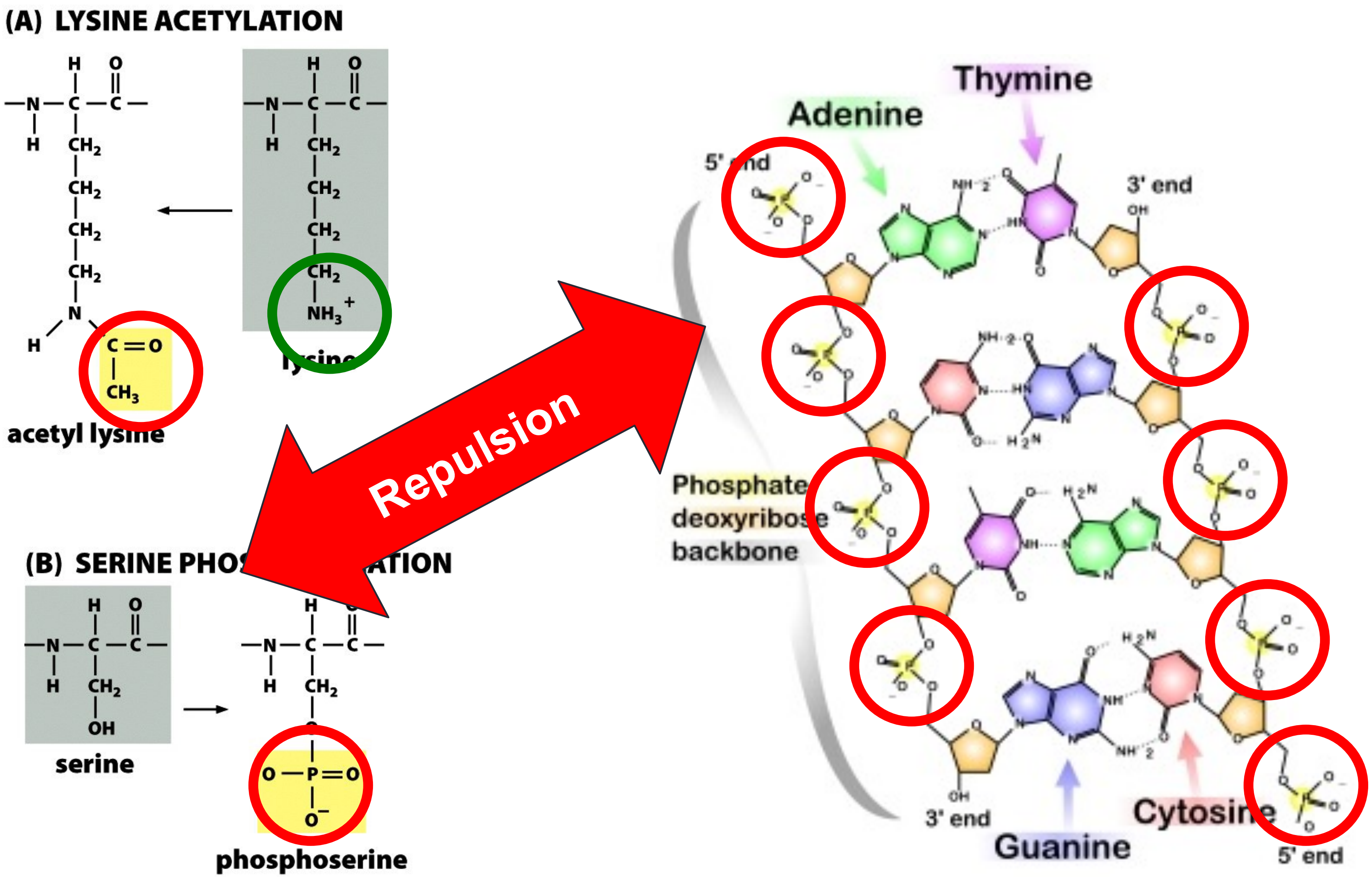
from Gräff and Mansuy, BehavBrainRes, 2008

Histone PTMs can occur in a gene's promoter region or in the coding region!

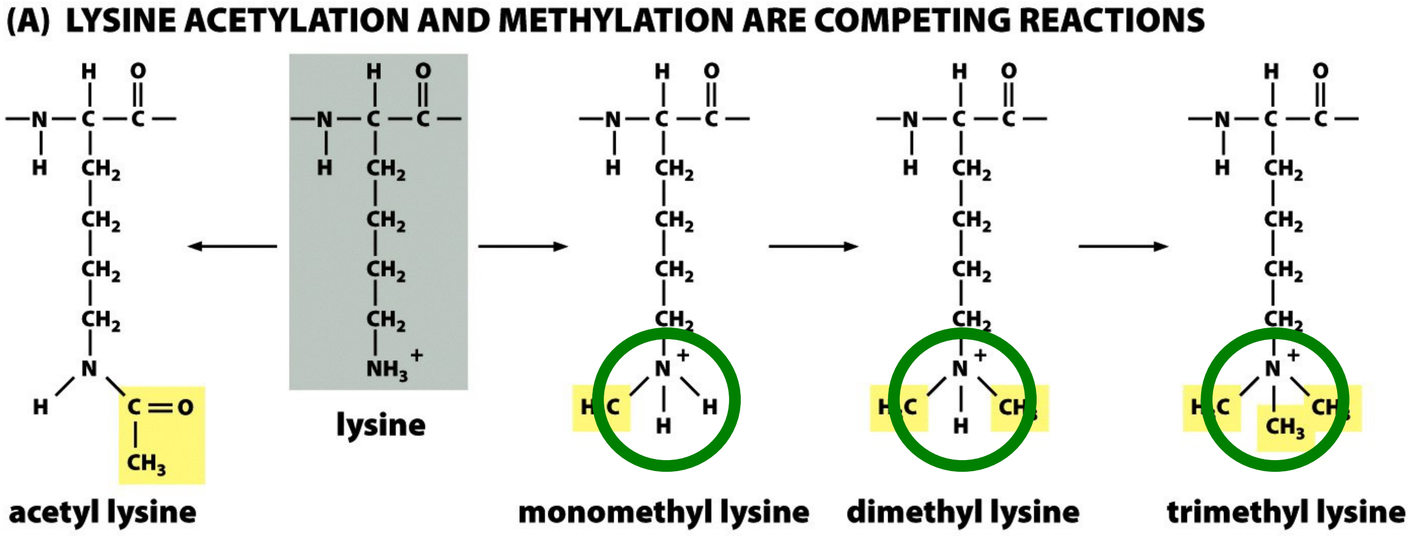
- **Effect on transcription**
  - Transcription ↗
    - Acetylation
    - Phosphorylation
    - H2B ubiquitination
  - Transcription ↘
    - H2A ubiquitination
    - Sumoylation



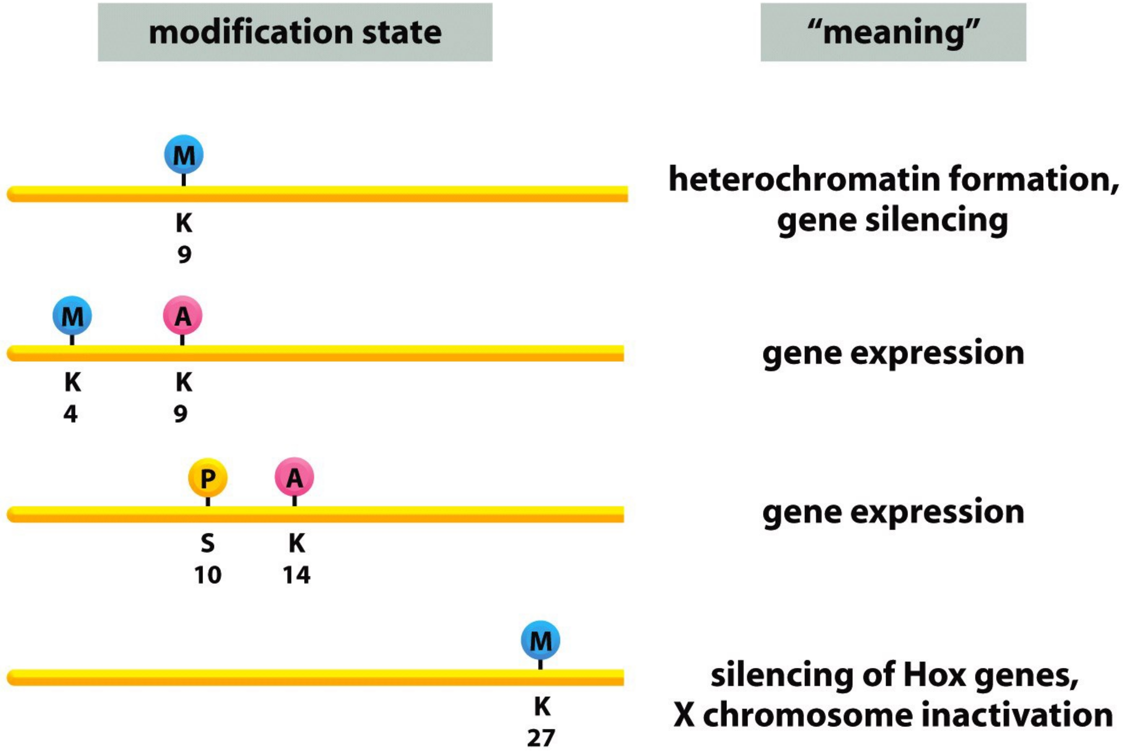
- **Effect on transcription – acetylation and phosphorylation**



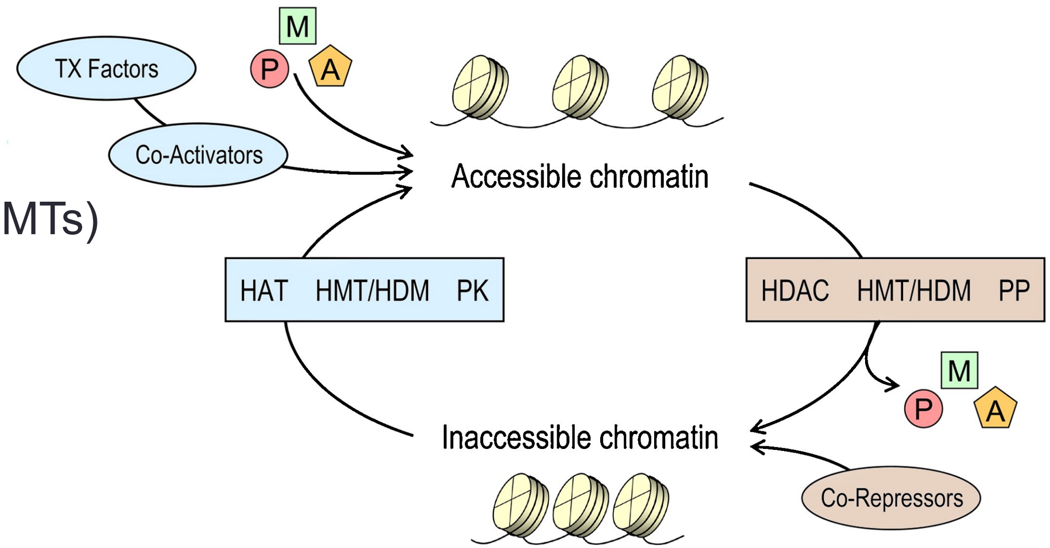
- **Effect on transcription – acetylation and methylation**



- **Co-occurrence of histone PTMs can influence the rate of gene transcription**



- **Enzymes regulating histone PTMs:**
  - Acetylation
    - Histone acetyl transferases (HATs)
    - Histone deacetylases (HDACs)
  - Methylation
    - Histone methyl transferases (HMTs)
    - Histone demethylases (HDMs)
  - Phosphorylation
    - Protein kinases (PKs)
    - Protein phosphatases (PPs)



- **New histone PTMs keep being discovered**

LETTER

https://doi.org/10.1038/s41586-019-1024-7

Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3

Lorna A. Farrelly[1], Robert E. Thompson[2], Shuai Zhao[3,4], Ashley E. Lepack[1], Yang Lyu[1], Natarajan V. Bhanu[5], Baichao Zhang[3,4], Yong-Hwee E. Loh[1], Aarthi Ramakrishnan[1], Krishna C. Vadodaria[6], Kelly J. Heard[6], Galina Erikson[6], Tomoyoshi Nakadai[7], Ryan M. Bastle[1], Bradley J. Lukasak[2], Henry Zebroski III[8], Natalia Alenina[9], Michael Bader[9], Olivier Berton[1], Robert G. Roeder[7], Henrik Molina[8], Fred H. Gage[6], Li Shen[1], Benjamin A. Garcia[5], Haitao Li[3,4], Tom W. Muir[2] & Ian Maze[1,10]*

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Article

Metabolic regulation of gene expression by histone lactylation

https://doi.org/10.1038/s41586-019-1678-1

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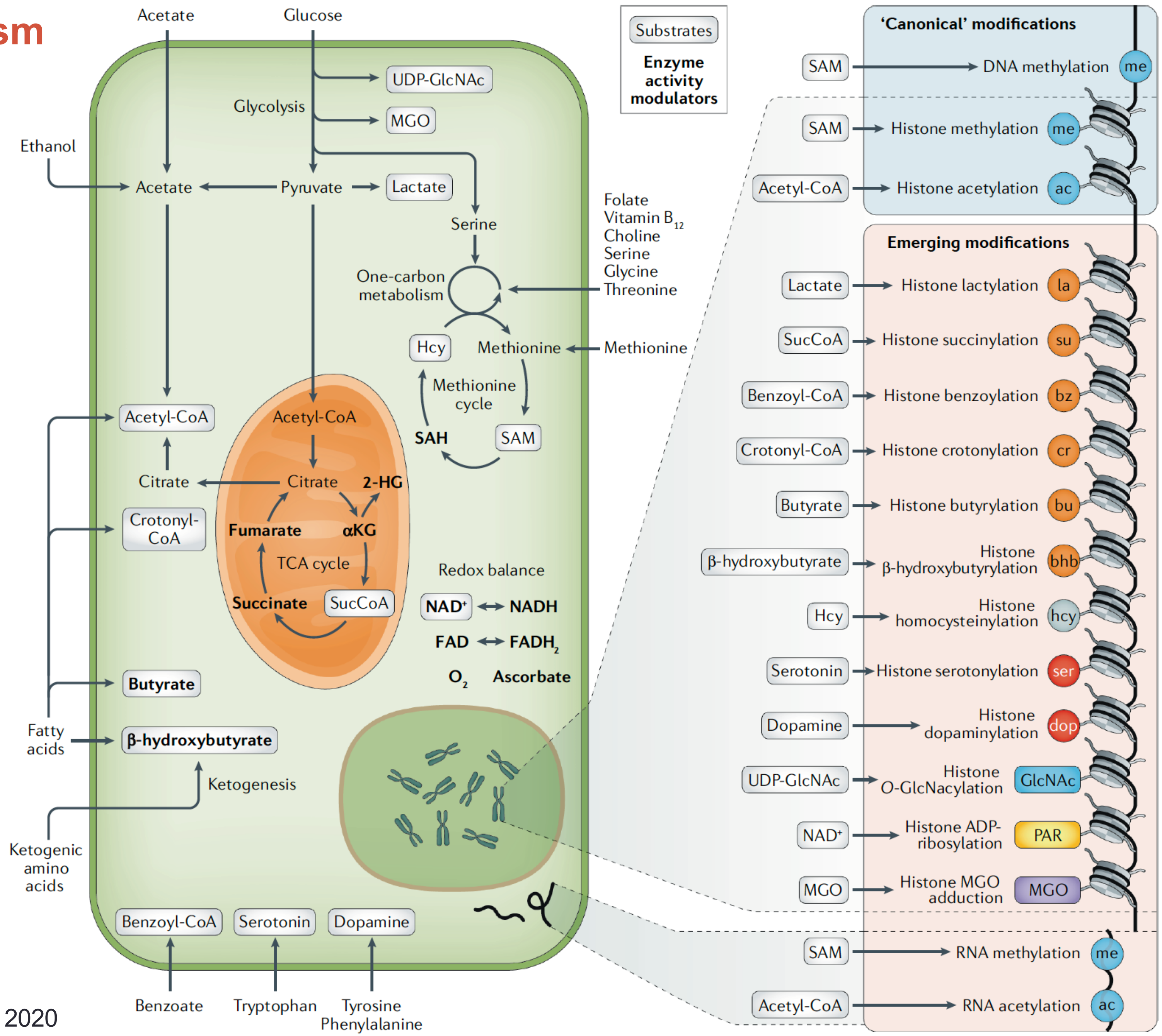
Di Zhang[1,12], Zhanyun Tang[2,12], He Huang[1,9], Guolin Zhou[1], Chang Cui[1], Yejing Weng[1], Wenchao Liu[1], Sunjoo Kim[3], Sangkyu Lee[3], Mathew Perez-Neut[1], Jun Ding[1], Daniel Czyz[4], Rong Hu[5,6], Zhen Ye[5,6], Maomao He[7], Y. George Zheng[7], Howard A. Shuman[4], Lunzhi Dai[1,10], Bing Ren[5,6], Robert G. Roeder[2], Lev Becker[1,8,11]* & Yingming Zhao[1,8]*

Metabolism

Histone PTMs



Regulation of chromatin structure:

1) Posttranslational histone modifications

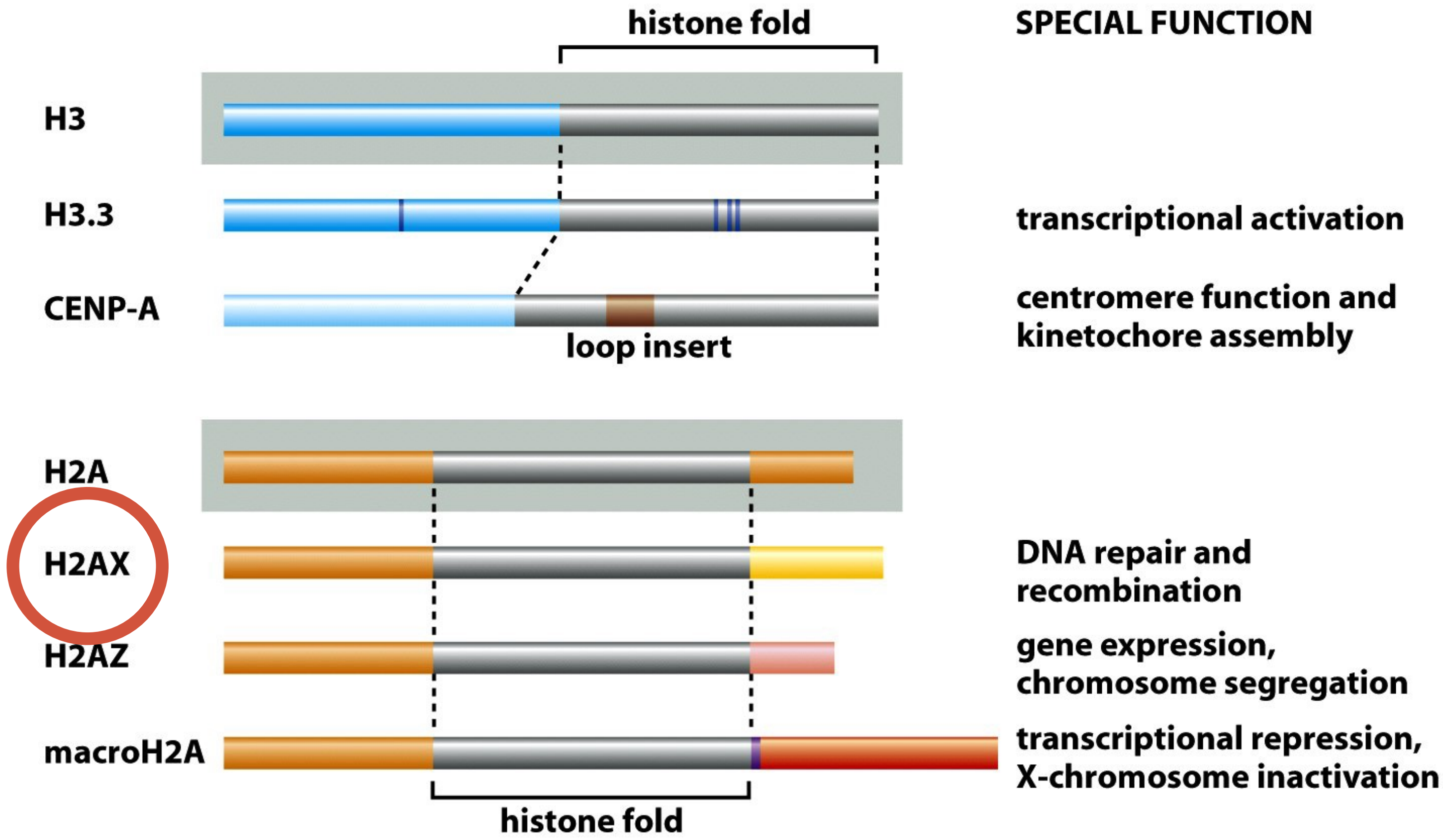
2) **Histone variants**

3) DNA Methylation

Histone variants:

- Structural variants of the core histones
- Specialized function
- Inserted by histone-exchange process

- **Histone variants – structure and function**

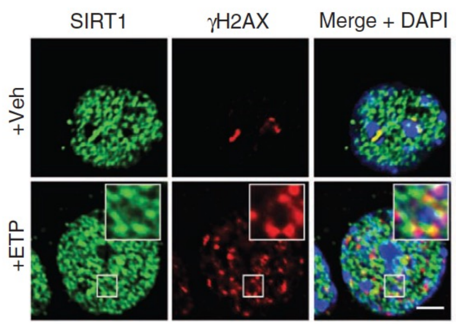


Chromatin structure – Histone variants

↖ Lecture
Aging

- **Histone variants – structure and function**

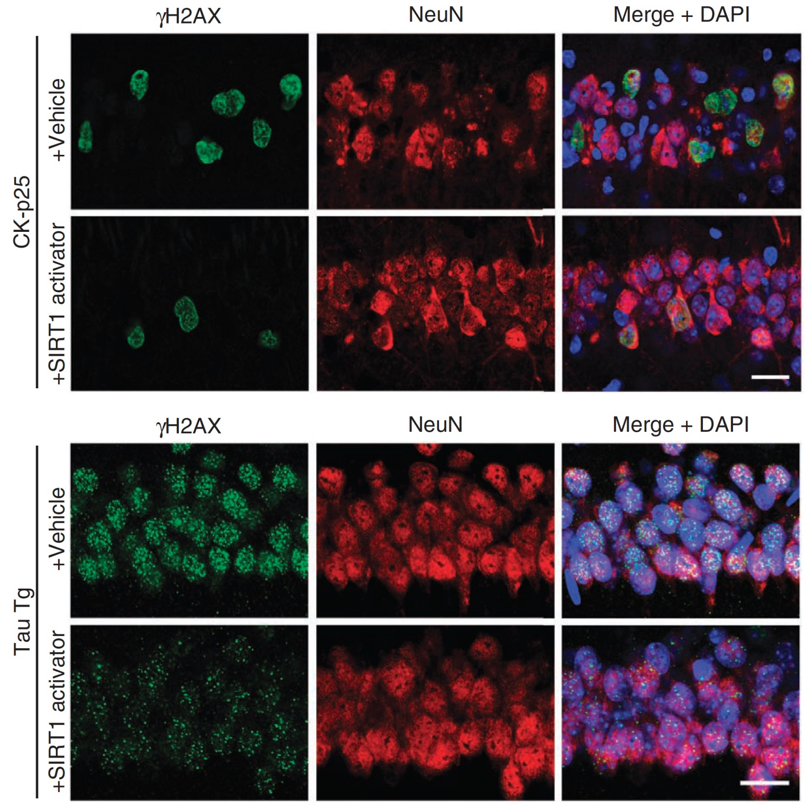
- H2AX (aka γH2AX), a marker of DNA damage and repair



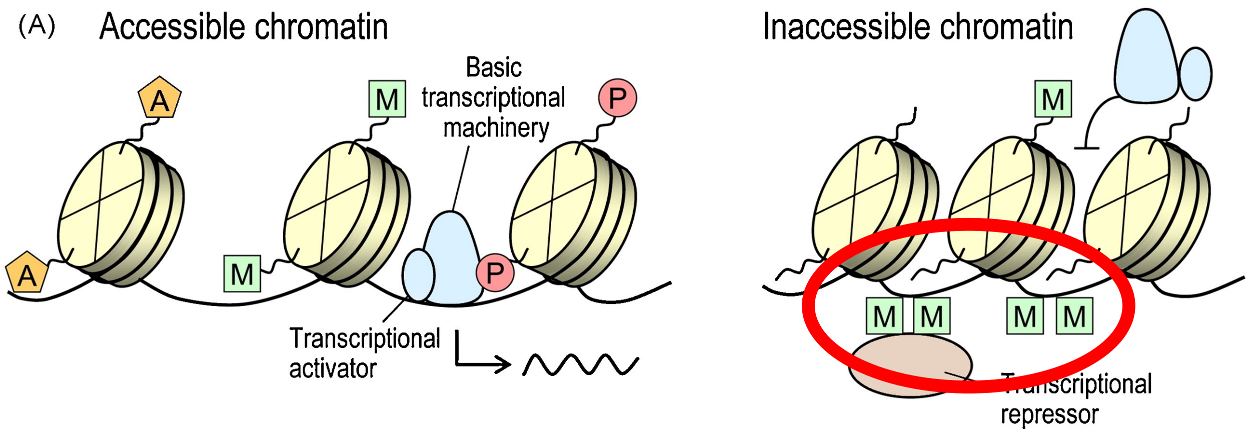
ETP, etoposide, induces DNA double strand breaks

A mouse model of AD (amyloid)

A mouse model of AD (tau)



- **A histone code regulating the accessibility of the chromatin for transcription:**



➢ **Together with DNA methylation, this forms an <u>epigenetic code</u> regulating the accessibility of the chromatin for transcription**

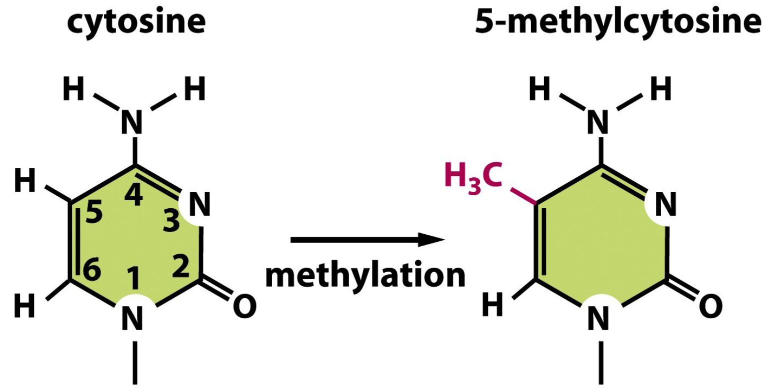
Regulation of chromatin structure:

1) Posttranslational histone modifications

2) Histone variants

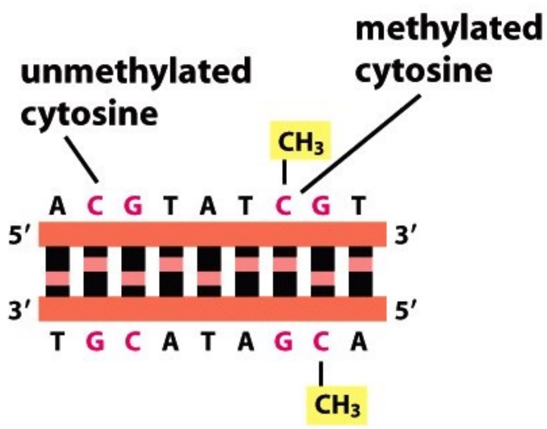
3) **DNA Methylation**

DNA methylation

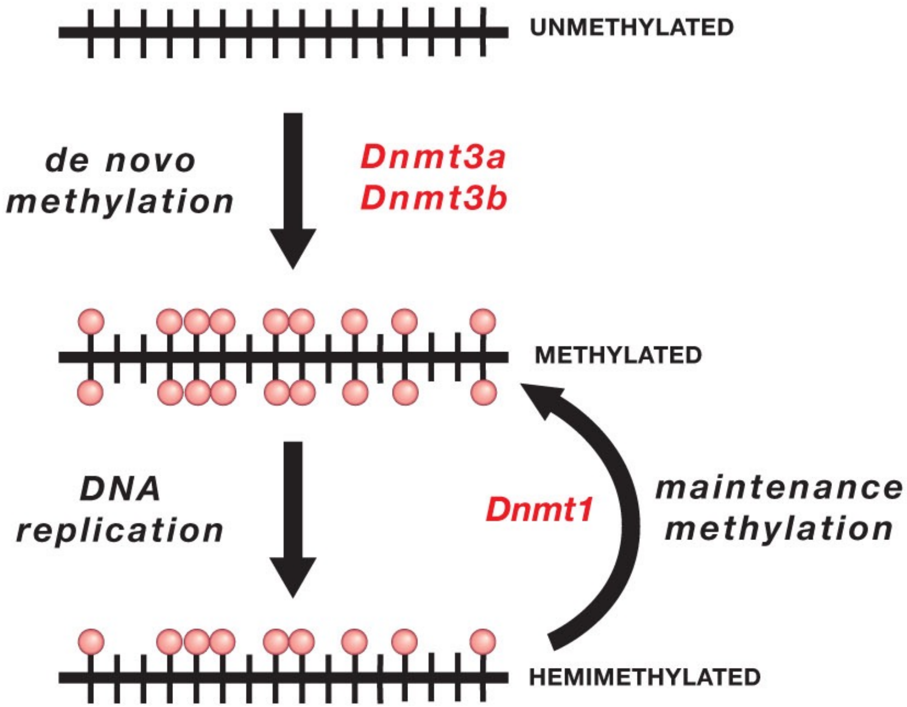


- On cytosines

- … followed by guanine
  - “CG island”
  - “CpG island”



- **2 types of DNA methylation-inducing enzymes**
  - De novo DNA methyltransferases
  - Maintenance DNA methyltransferases

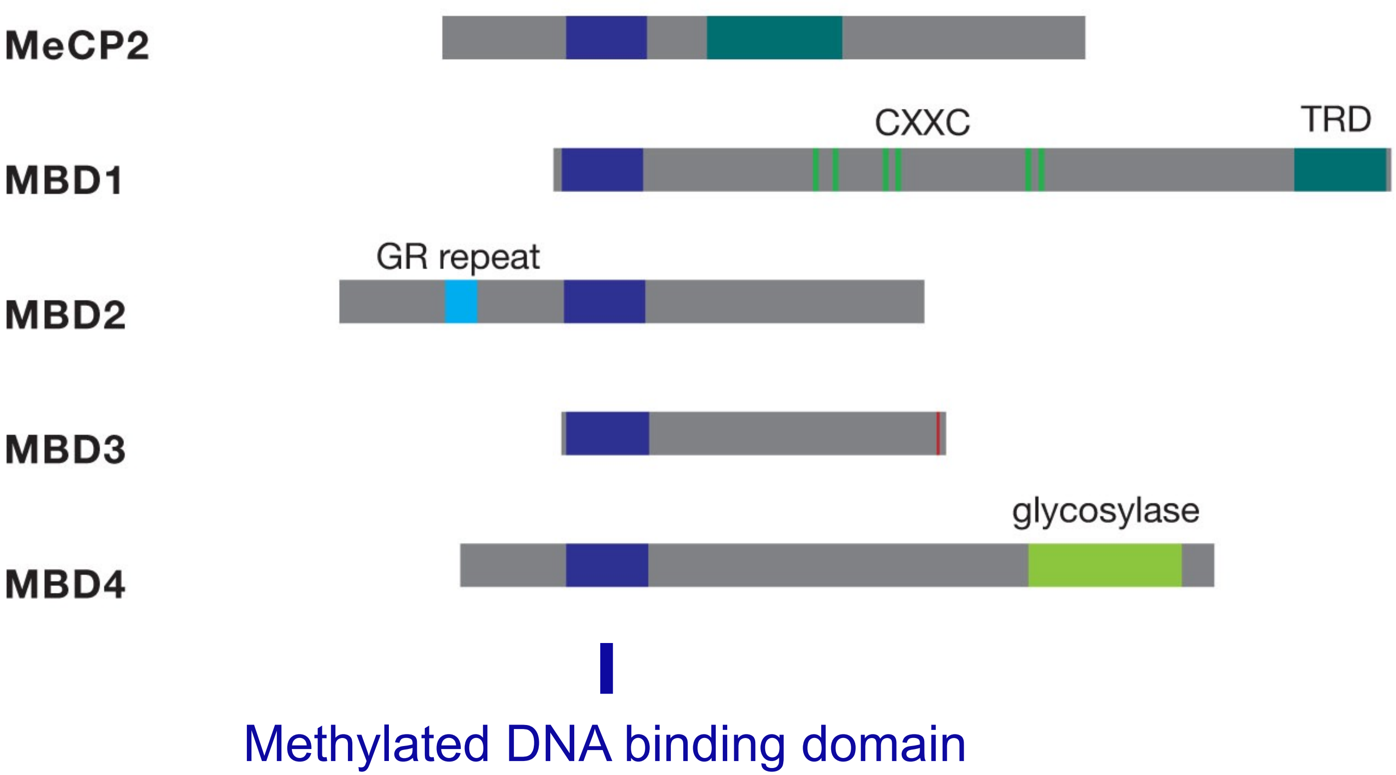


- **2 types of DNA methylation-inducing enzymes**

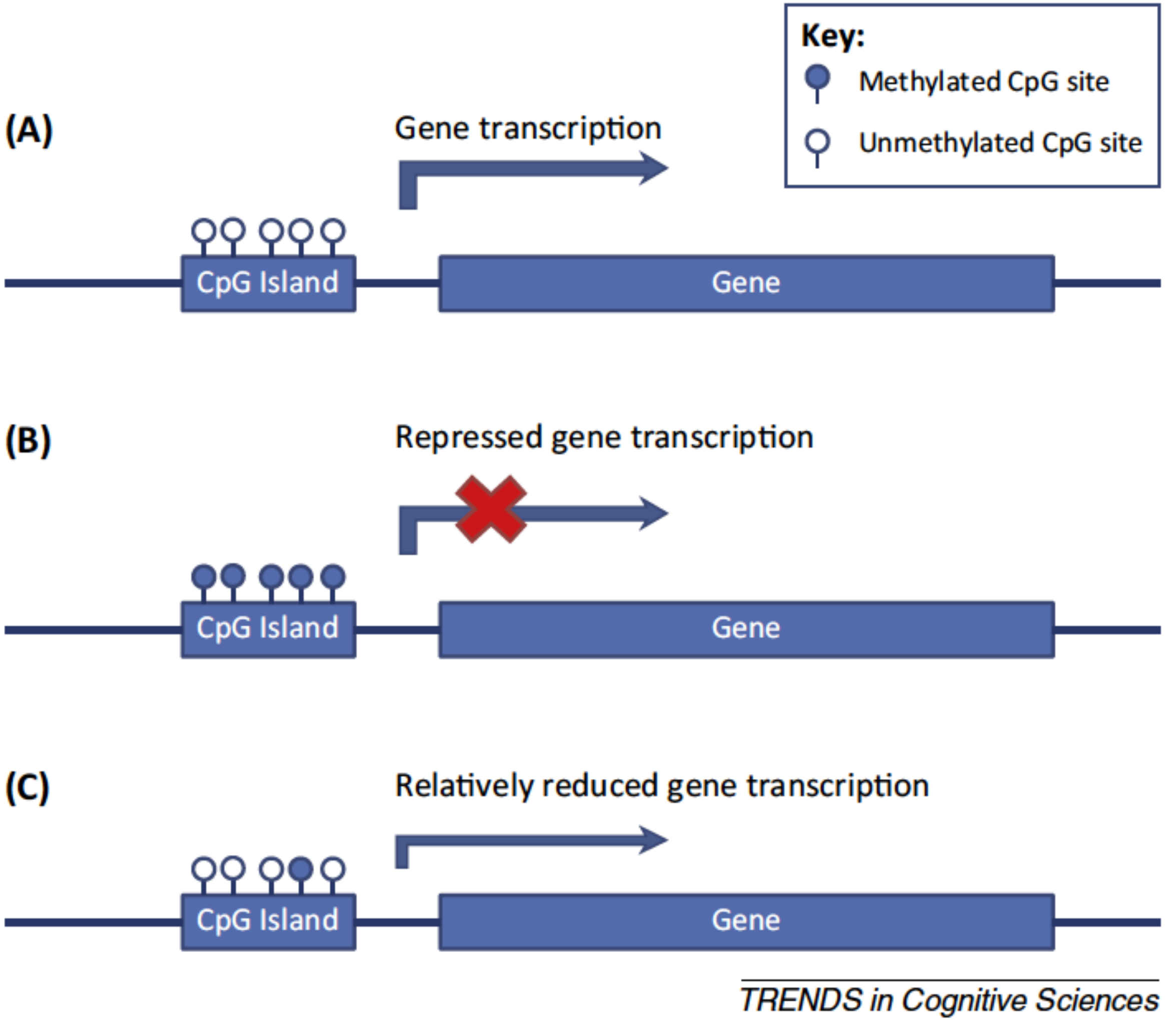
Table 1. Functions of mammalian DNA methyltransferases

DNA methyltransferase	Species	Major activity	Major phenotypes of loss-of-function mutations
Dnmt1	mouse	maintenance methylation of CpG	genome-wide loss of DNA methylation, embryonic lethality at embryonic day 9.5 (E9.5), abnormal expression of imprinted genes, ectopic X-chromosome inactivation, activation of silent retrotransposon
Dnmt2	mouse	weak activity	no change in CpG methylation, no obvious developmental phenotypes
Dnmt3a	mouse	de novo methylation of CpG	postnatal lethality at 4–8 weeks, male sterility, and failure to establish methylation imprints in both male and female germ cells
Dnmt3b	mouse	de novo methylation of CpG	demethylation of minor satellite DNA, embryonic lethality around E14.5 days with vascular and liver defects (embryos lacking both Dnmt3a and Dnmt3b fail to initiate de novo methylation after implantation and die at E9.5)
DNMT3B	human	de novo methylation of CpG	ICF syndrome: immunodeficiency, centromeric instability, and facial anomalies; loss of methylation in repetitive elements and pericentromeric heterochromatin

- Methylated portions of the DNA attract **Methyl-Binding-Domain** containing Proteins (MBD), which act as co-activators or co-repressors

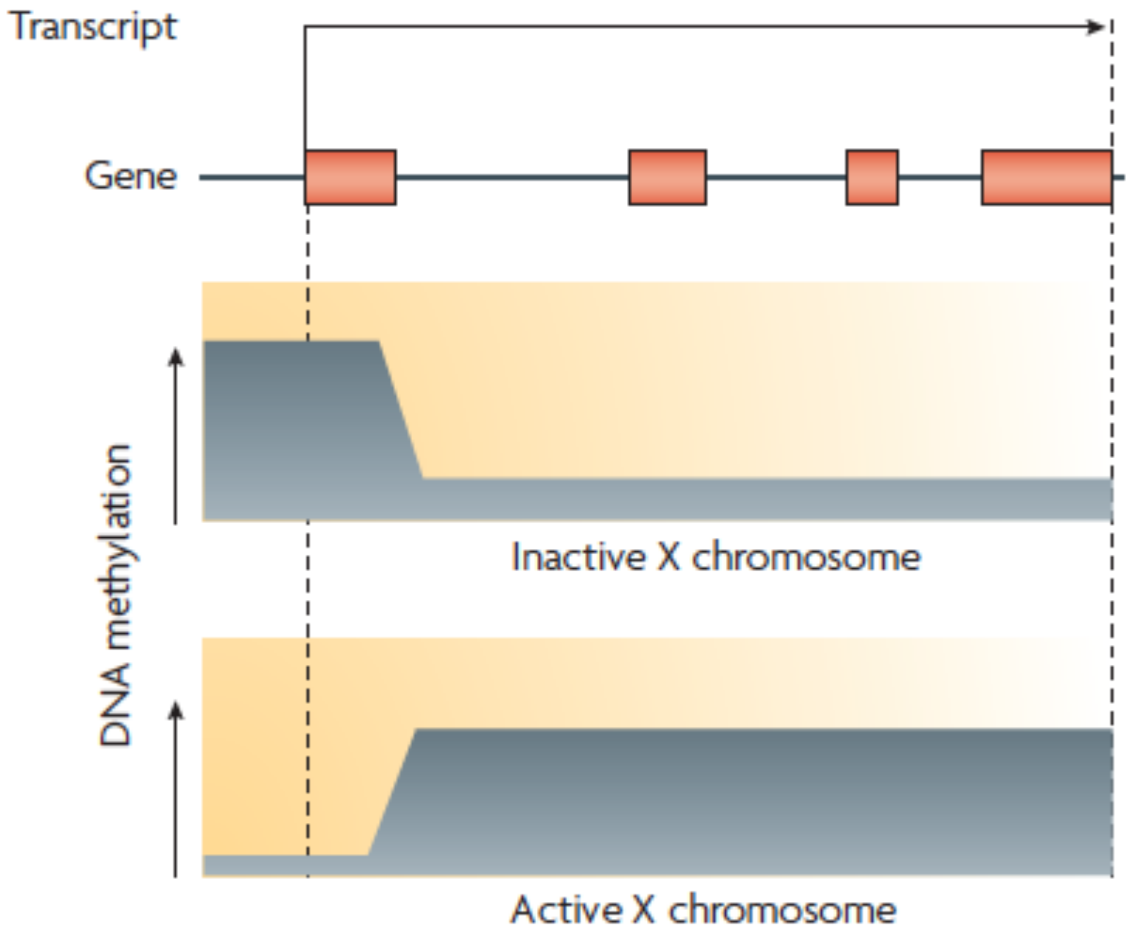


- **Function of DNA methylation: Repression (in general)**



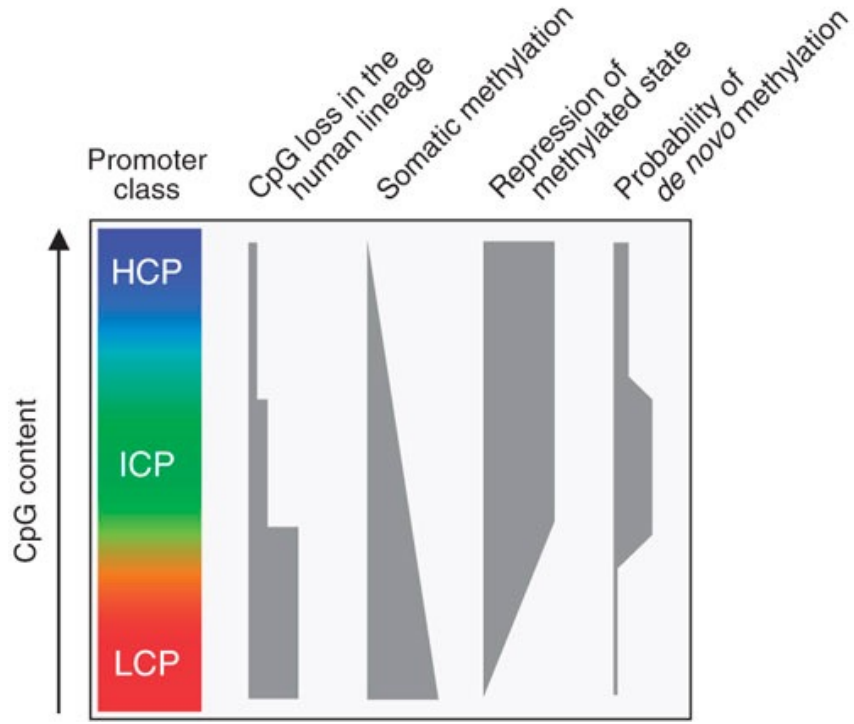
- **Function of DNA methylation: Repression or Activation**

  - Depends on the genetic context



- **Function of DNA methylation: Repression or Activation**

  - Depends on the CpG content



H=High CpG Promoter
I=Intermediate CpG promoter
L=Low CpG promoter

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What is the effect of histone phosphorylation on gene transcription?

The transcriptional effect of DNA methylation depends on which factors?

Neuroepigenetics

1) **The chromatin – Epigenetic basics (Lecture 1)**

   - Chromatin condensation
   - Regulation of chromatin structure
   - **Epigenetic inheritance**
   - Environmental influence on epigenetics

2) **Epigenetic dysregulation (Lecture 2)**

   - in AD

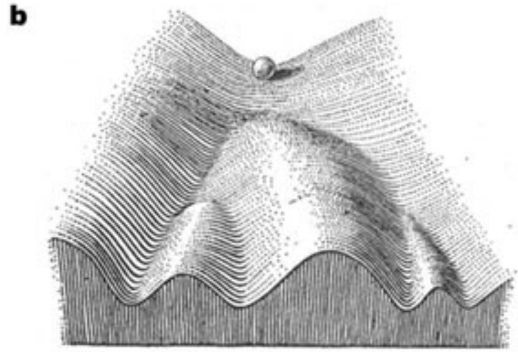
Epigenetic modifications can be...

- **inherited** through mitosis
  - development/differentiation
- **inherited** through meiosis
  - transgenerational epigenetic inheritance

➢ In both cases, they can be influenced/installed by the environment

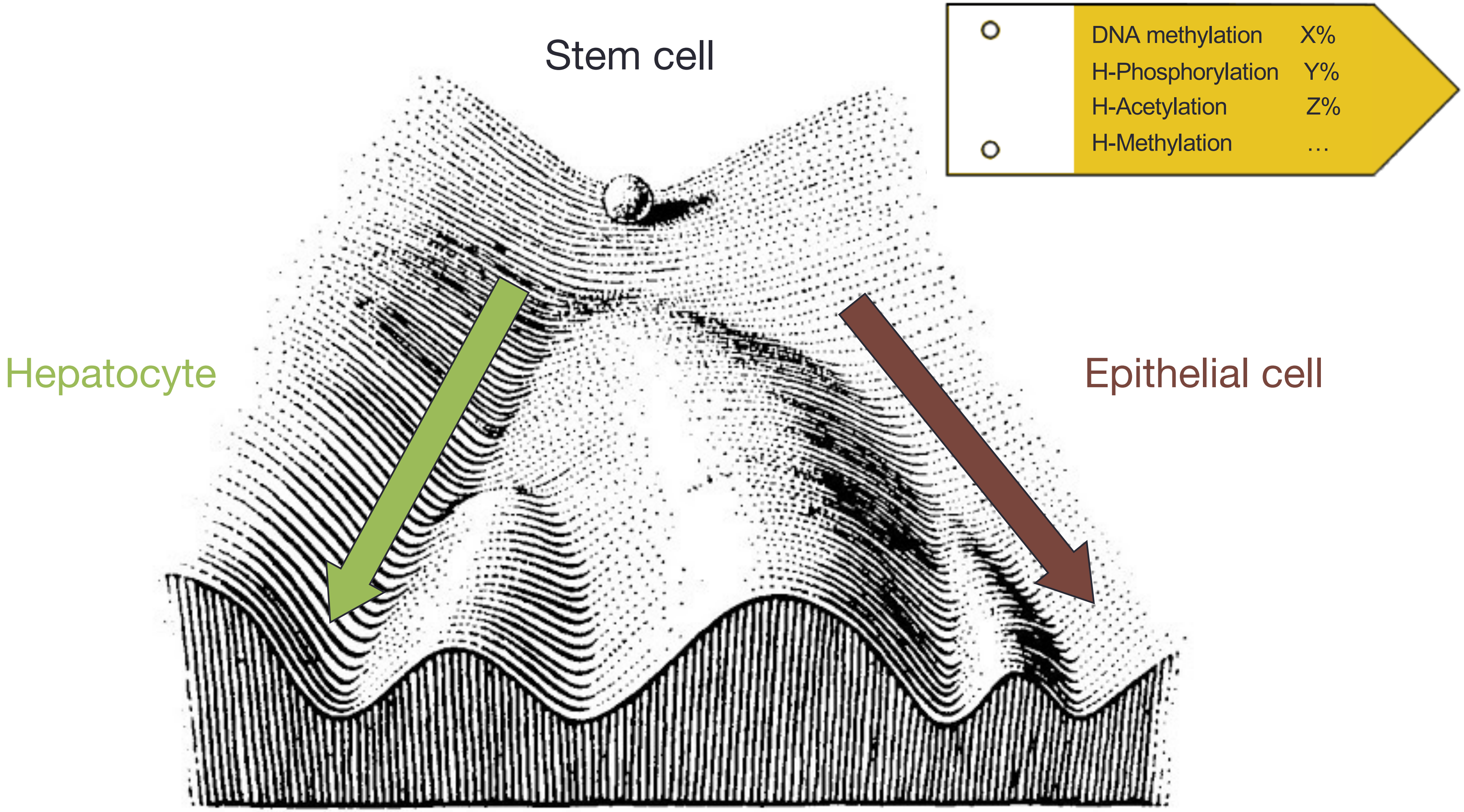
1) Epigenetic inheritance during development

- The developmental epigenetic landscape *sensu* Waddington (1905-1975)



Nature Reviews | Genetics

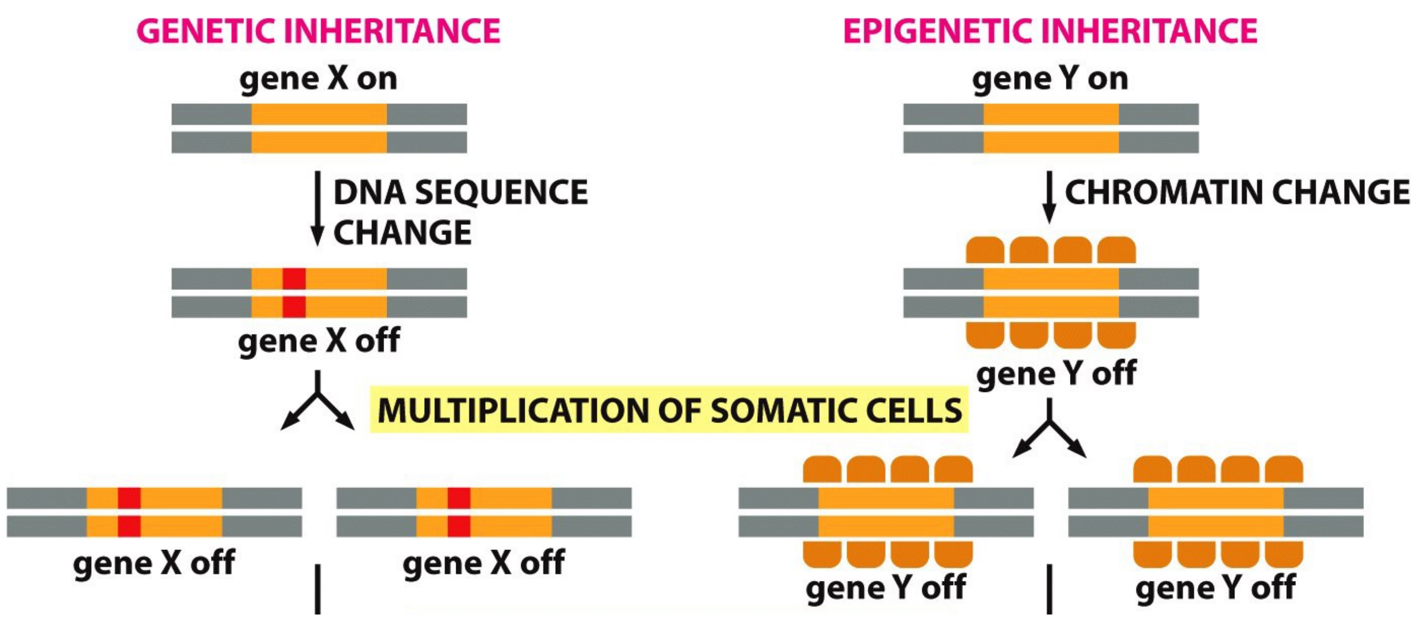
1) Epigenetic inheritance during development



Waddington’s epigenetic landscape (1957):
The trajectory paths (the valleys) a cell can take
are defined by epigenetic boarders (the hills)

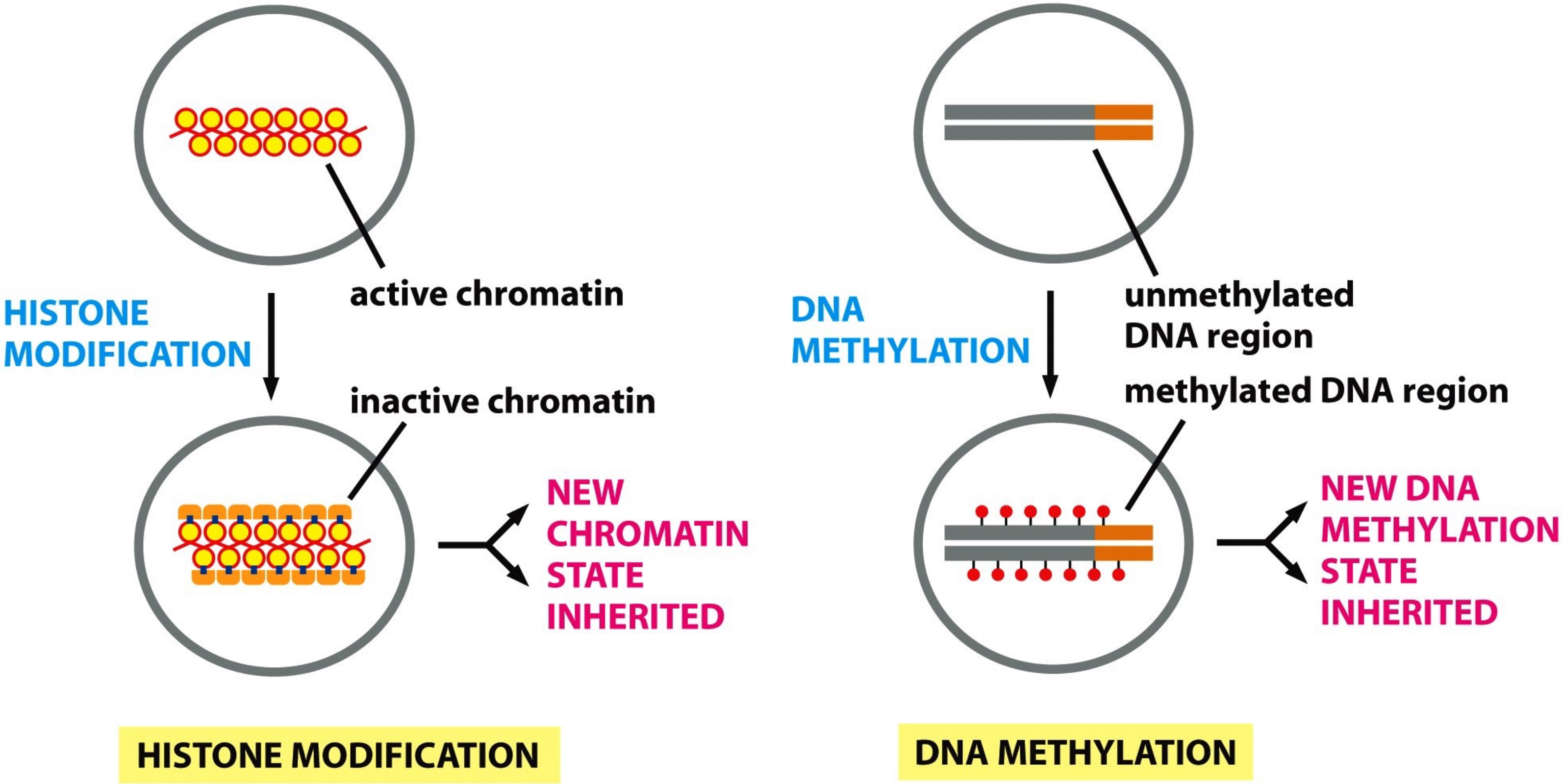
1) Epigenetic inheritance during development

- Epigenetic vs genetic inheritance



On a locus-specific level

- Both histone modifications and DNA methylation changes can be inherited

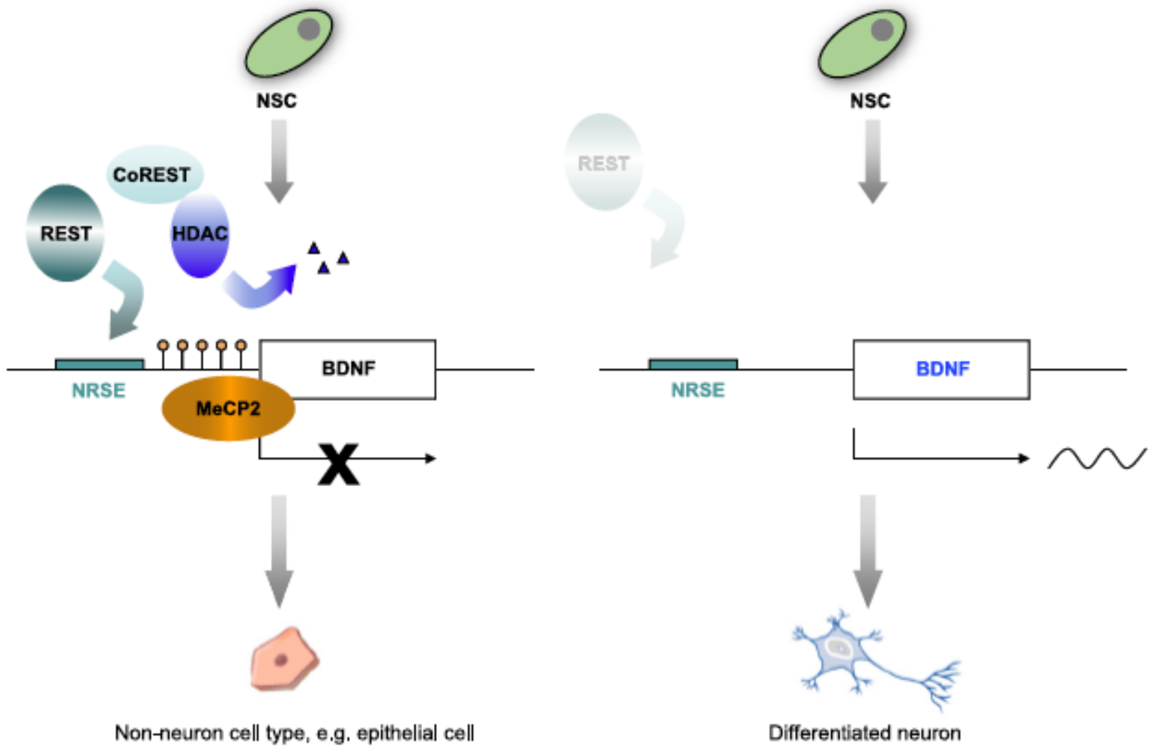


On a locus-specific level

- Differentiation of neurons during development

NSC=Neural stem cell; NRSE=Neuron restrictive silencer element; REST=Repressor; BDNF=brain derived neurotrophic factor

REST is a neuron-specific repressor

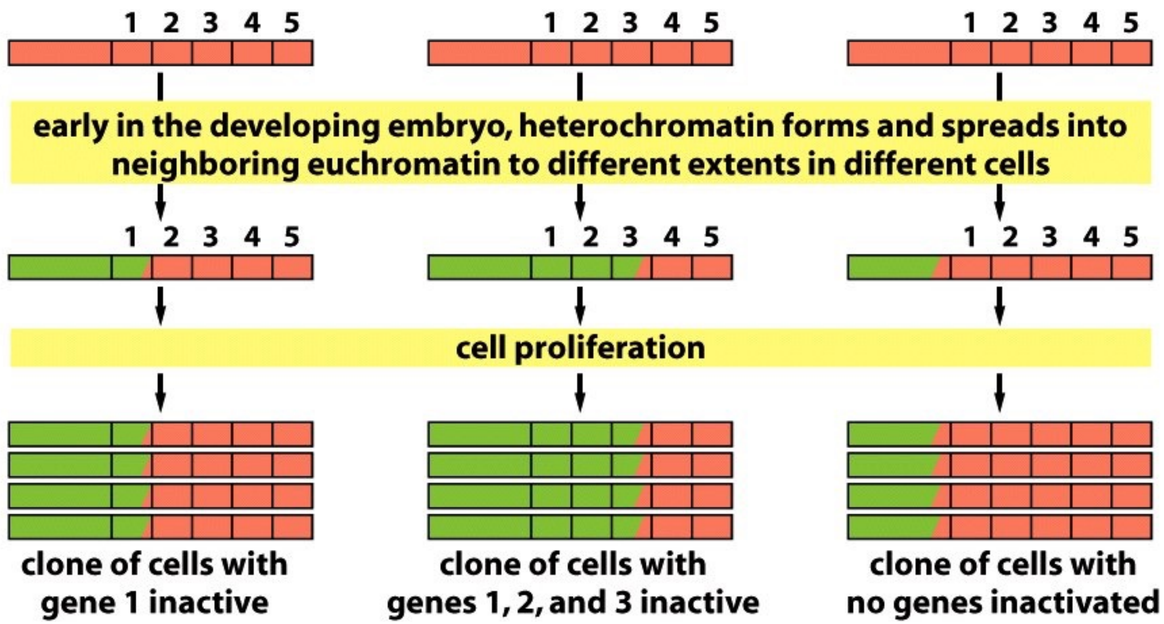


On a “regional” level:

transcriptionally silent

transcriptionally active

- Distinction between hetero- and euchromatin is inherited through development



Which of the following is correct?

A. Epigenetic modifications can be inherited through mitosis, but not meiosis
B. Only DNA methylation, but not post-translational histone modifications can be inherited through mitosis
C. Euchromatin and heterochromatin regions cannot be changed during development
D. All A-C are correct
E. None of the above is correct

Neuroepigenetics

1) **The chromatin – Epigenetic basics (Lecture 1)**

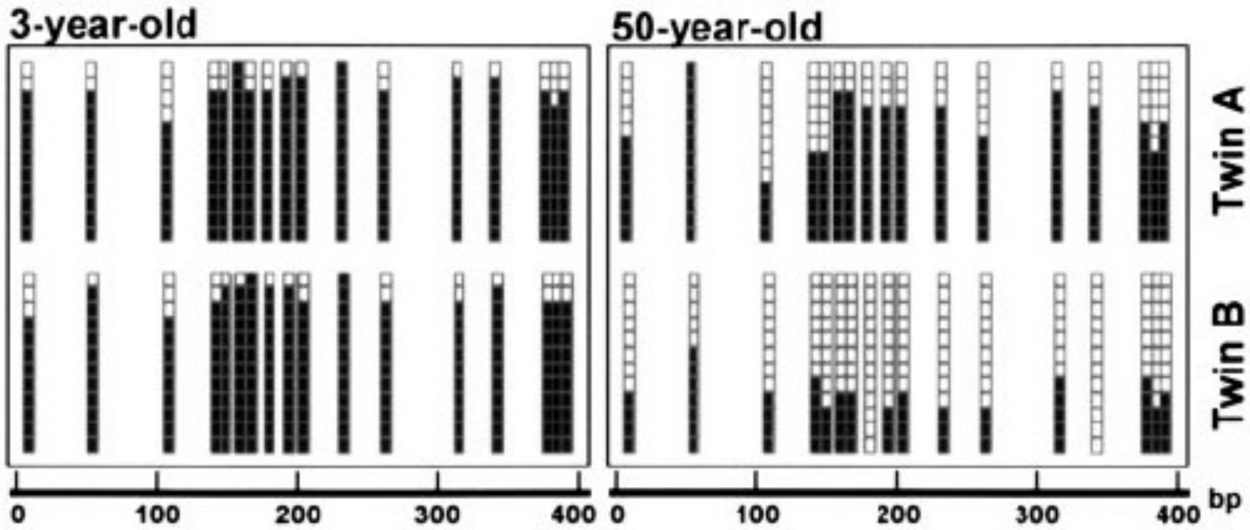
- Chromatin condensation
- Regulation of chromatin structure
- Epigenetic inheritance
- **Environmental influence on epigenetics**

2) **Epigenetic dysregulation (Lecture 2)**

- in AD

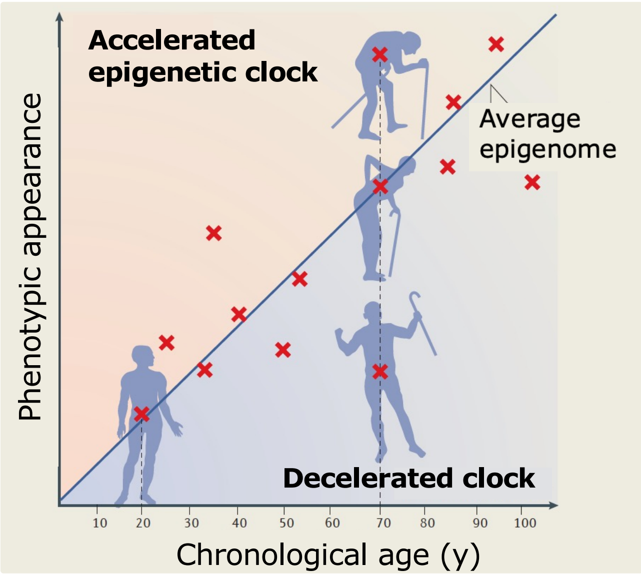
1) Epigenetic inheritance during development

- Influence of the environment I/II – the case of monozygotic twins



1) Epigenetic inheritance during development

- Influence on epigenetic clocks



Benayoun et al., 2015,
Nat Rev Mol Cell Biol

↖ Lecture
Aging

1) Epigenetic dysregulation following stress

- Influence of the environment II/II – The case of early-life stress

2) Epigenetic inheritance during development can be influenced by the environment

- Maternal care

"Good mothers"

stress resistant

low levels of anxiety

normal behavior

"Bad mothers"

stress susceptible

high levels of anxiety

depressive-like behavior

2) Epigenetic inheritance during development can be influenced by the environment

- Maternal care

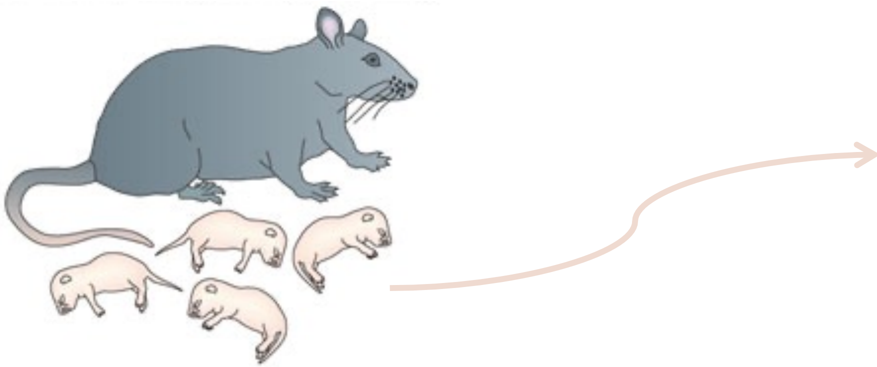
"Good mothers"

Reduced DNA methylation

Nr3c1 (coding for GR) can be expressed

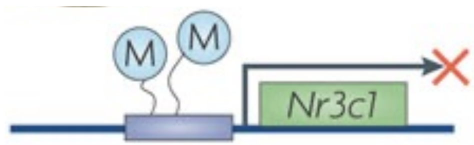
Normal stress response

"Bad mothers"



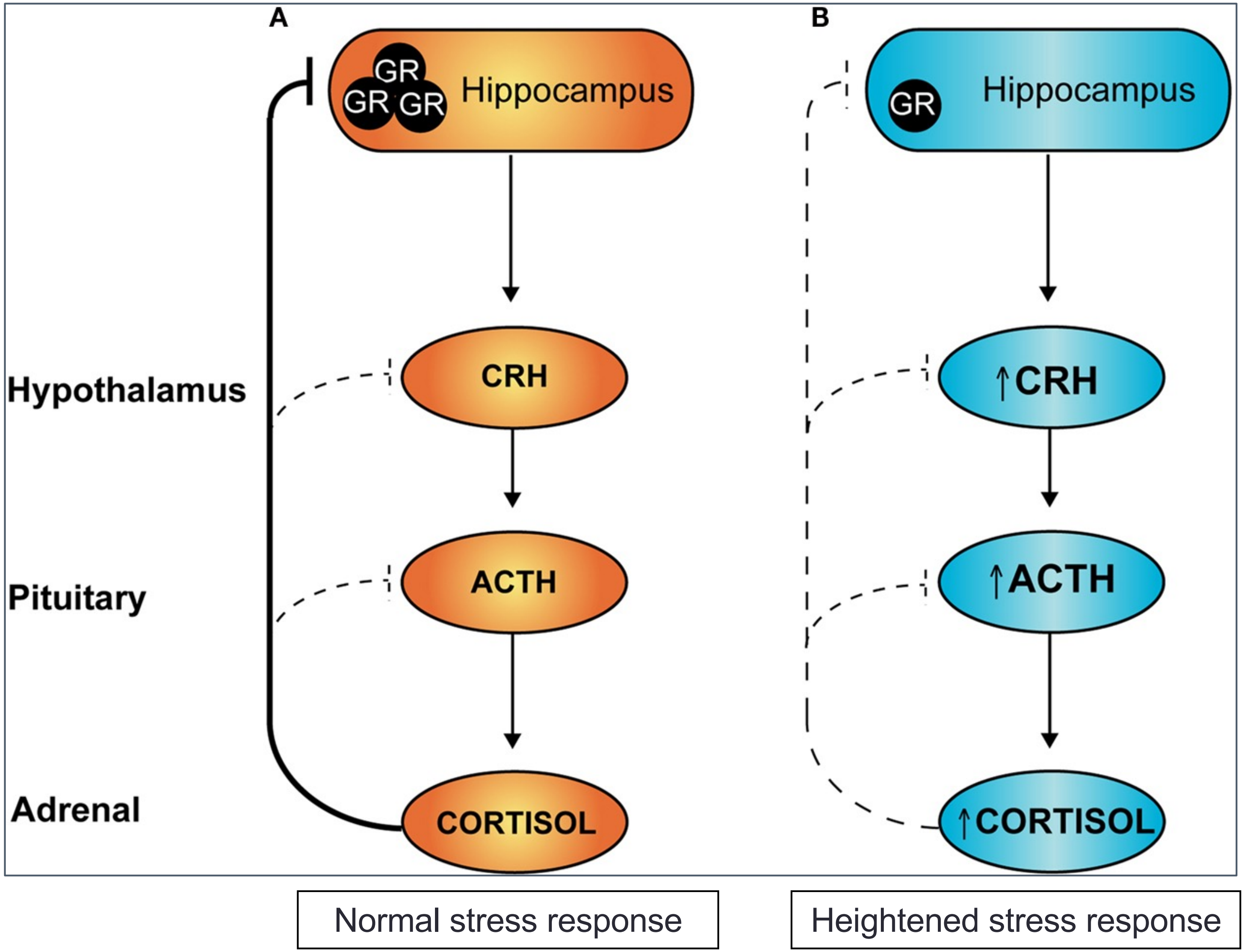
Increased DNA methylation

Nr3c1 is not expressed

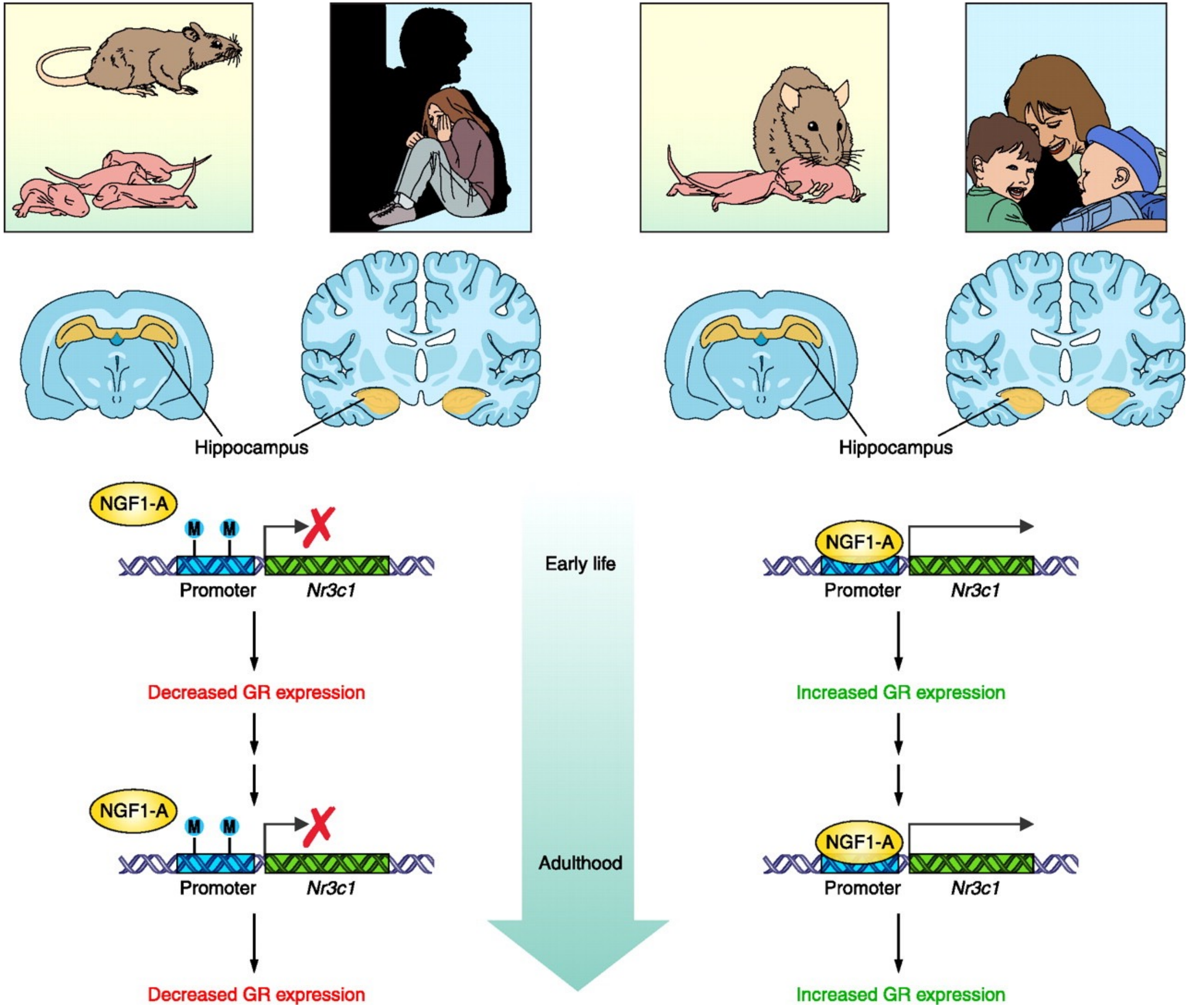


Elevated stress response

Glucocorticoids, **glucocorticoid receptors** and the stress response



Epigenetic Inheritance



Nr3c1, the gene coding for glucocorticoid receptor 1 (GR); NGF1-A, a transcription factor

Which of the following is correct?

Offspring with reduced maternal care are...

A. more susceptible to stress
B. less susceptible to stress
C. genetically different than offspring with enhanced maternal care
D. epigenetically identical to offspring with enhanced maternal care