UPPSALA
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NEUROEPIGENETICS: TIME FOR A GOLD RUSH

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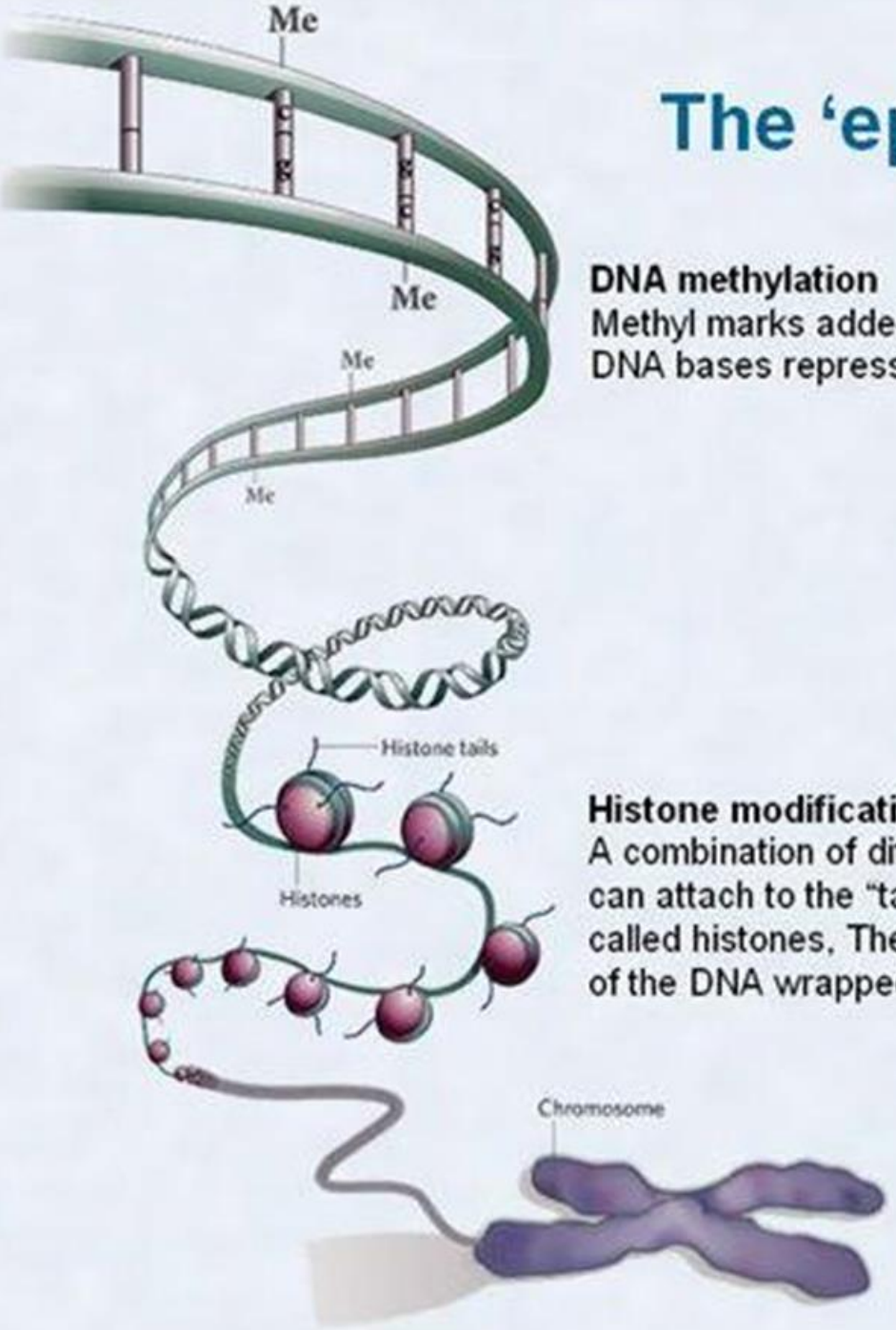
Dogma in Neuroscience

Epigenetics refers to:

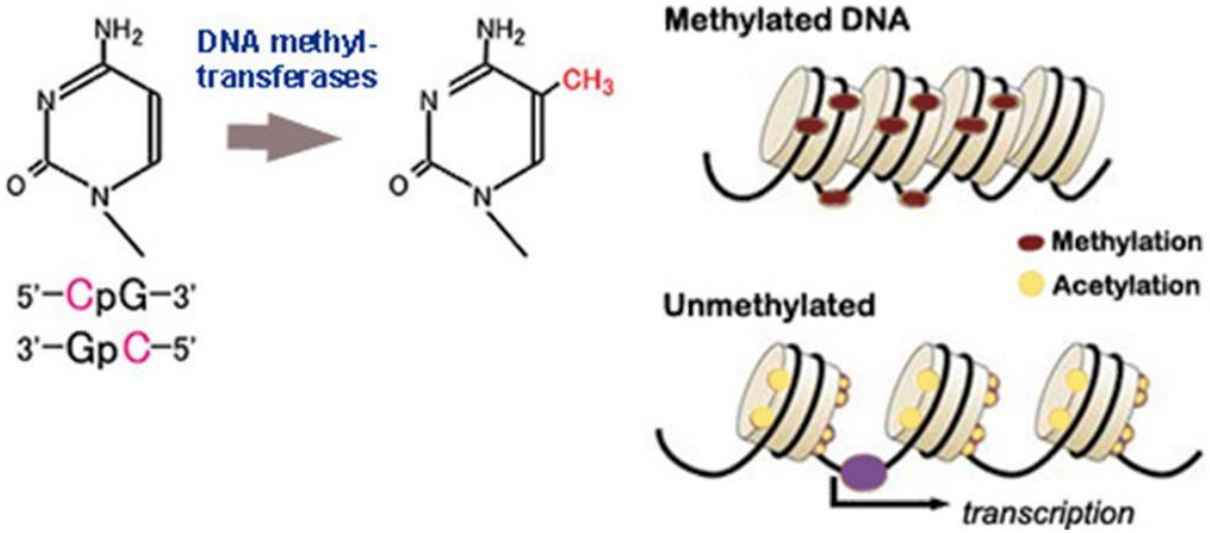
- heritable alterations in gene expression that do NOT arise from altered DNA sequence
  - ➡ changes in DNA methylation, histone modification and nucleosome positioning

The ‘epigenetic’ code



DNA methylation
Methyl marks added to certain DNA bases repress gene activity

Histone modification
A combination of different molecules can attach to the “tails” of proteins called histones. These alter the activity of the DNA wrapped around them



Cytosine methylation

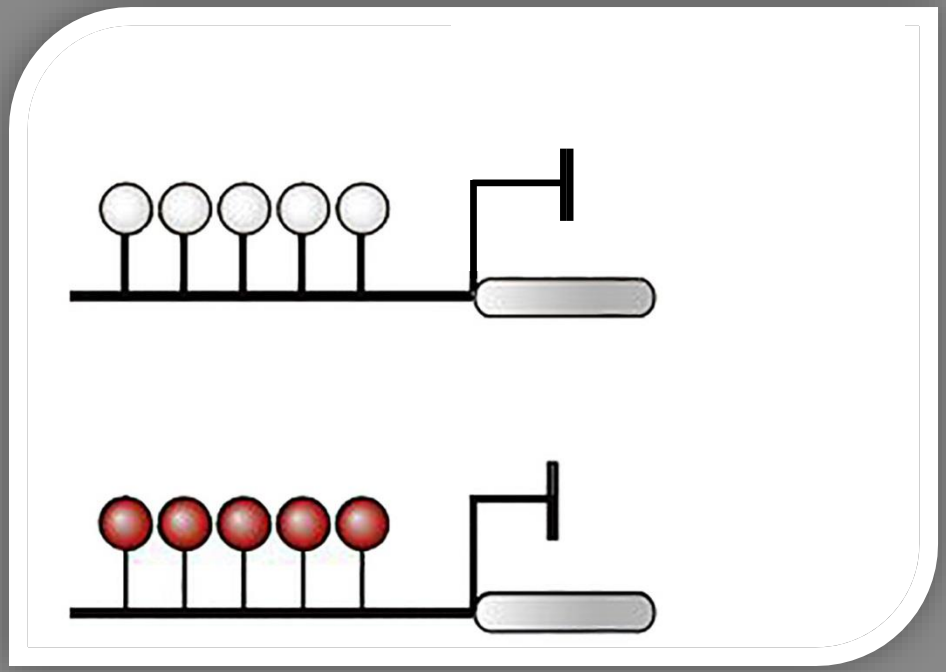
- Cell differentiation
- Imprinting
- Aging

- Gene expression

Epigenetic regulation of gene expression

Non-methylated

Methylated



DMR

(Differentially Methylated Region)

www.aging-us.com AGING 2018, Vol. 10, No. 4

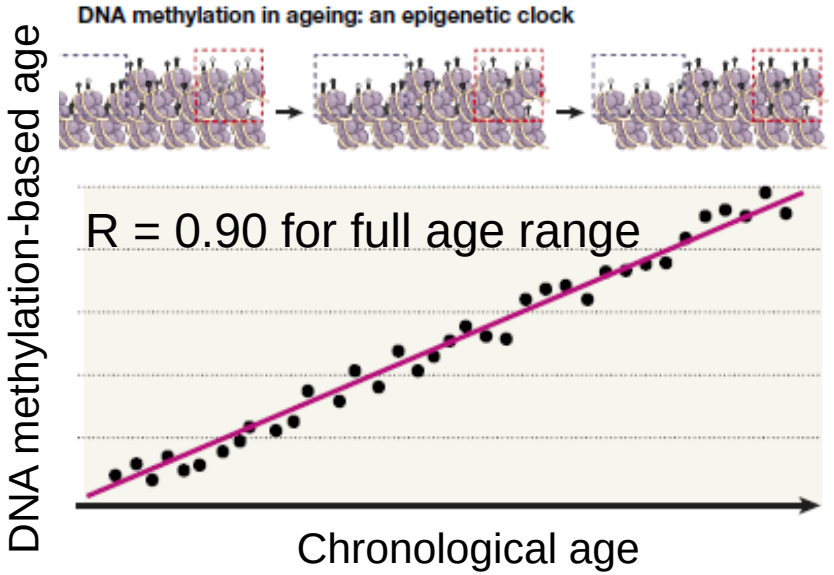
Research Paper

An epigenetic biomarker of aging for lifespan and healthspan

Morgan E. Levine[1], Ake T. Lu[1], Austin Quach[1], Brian H. Chen[2], Themistocles L. Assimes[3], Stefania Bandinelli[4], Lifang Hou[5], Andrea A. Baccarelli[6], James D. Stewart[7], Yun Li[8], Eric A. Whitsel[7,9], James G Wilson[10], Alex P Reiner[11], Abraham Aviv[12], Kurt Lohman[13], Yongmei Liu[14], Luigi Ferrucci[2,*], Steve Horvath[1,15,*]

The epigenetics of ageing

- CpG methylation highly correlates with age
- The epigenetic clock is the best biological age predictor



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- **DNAm PhenoAge**
  - adversely accelerated by a high body mass index
  - reduced by high levels of education or physical activity,
    a low body mass index
    consumption of fish, poultry, fruits and vegetables
  - is associated with activation of pro-inflammatory and interferon pathways, decreased activation of transcriptional/translational machinery, DNA damage response and mitochondria
- Many “aging” CpGs are located close to poised promoters of bivalent genes (marked by H3K4me3 and H3K27me3)
  ageing may correlate with reduced gene plasticity

BBC

Ученые впервые омолодили людей на уровне ДНК при помощи лекарств

Участники медицинского эксперимента "помолодели" в результате приема прописанных им препаратов - снизили свой биологический возраст, определяемый маркерами ДНК

nature
International journal of science

NEWS 05 SEPTEMBER 2019

A person's biological age, measured by the epigenetic clock, can lag behind or exceed chronological age.

EPIGENETICS

Trial hints at age–clock reversal

In a small trial, a drug cocktail seemingly rolled back the epigenetic clock, which tracks a person's biological age.

Received: 11 May 2019 | Revised: 16 July 2019 | Accepted: 4 August 2019

DOI: 10.1111/acel.13028

ORIGINAL ARTICLE

Aging Cell WILEY

Reversal of epigenetic aging and immunosenescent trends in humans

Gregory M. Fahy[1] | Robert T. Brooke[1] | James P. Watson[2] | Zinaida Good[3] | Shreyas S. Vasanawala[4] | Holden Maecker[5] | Michael D. Leipold[5] | David T. S. Lin[6] | Michael S. Kobor[6] | Steve Horvath[7]

- Ten nominally healthy adult men from 51–65 years of age were
- Growth hormone (GH) has thymotrophic and immune¨reconstituting effects in animals and human HIV patients
- GH-induced hyperinsulinemia might affect thymic regeneration and immunological reconstitution
  GH was combined with
  - dehydroepiandrosterone which has many effects oppose deleterious effects of aging
  - metformin is a powerful calorie restriction mimetic in aging mice and a candidate for slowing aging in humans

- A gain of approximately 2.1 years at 12 months
- The rate of aging regression appeared to accelerate with increasing treatment time of −1.56 / year in the first 9 months to −6.48 years / year in the last 3 months of treatment

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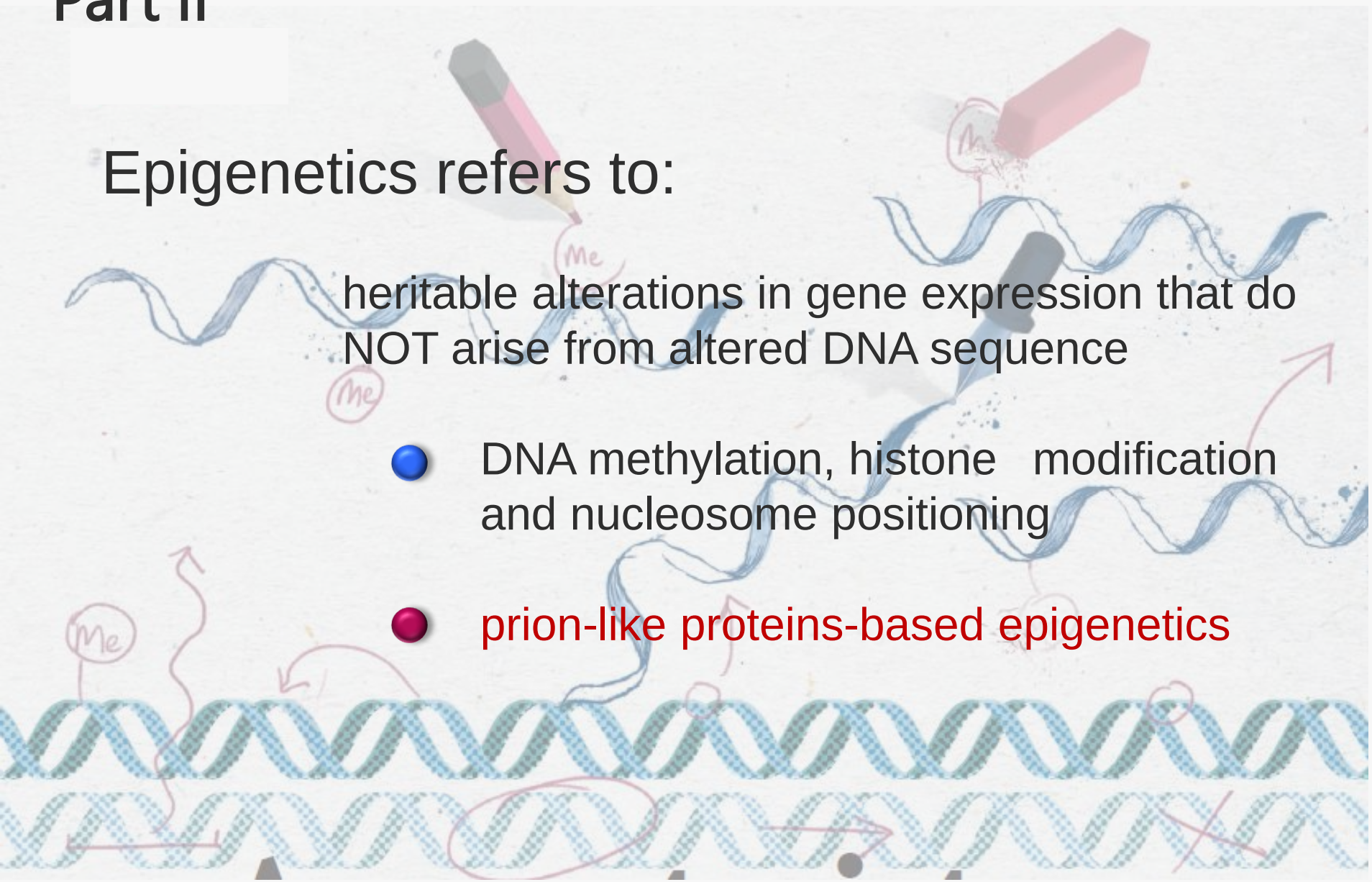
- A single epigenetic marker captures risks for diverse outcomes across multiple tissues and cells, and provide insight into important pathways in aging

Part II

Epigenetics refers to:

heritable alterations in gene expression that do NOT arise from altered DNA sequence

- DNA methylation, histone modification and nucleosome positioning
- prion-like proteins-based epigenetics



Molecular Cell
Review

Protein-Based Inheritance: Epigenetics beyond the Chromosome

Zachary H. Harvey,[1,3] Yiwen Chen,[1,3] and Daniel F. Jarosz[1,2,*]
[1]Department of Chemical and Systems Biology
[2]Department of Developmental Biology
Stanford University School of Medicine, 269 Campus Drive, Stanford, CA 94305, USA
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https://doi.org/10.1016/j.molcel.2017.10.030

Many epigenetic traits are linked to self-perpetuating changes in the activity of proteins – prions

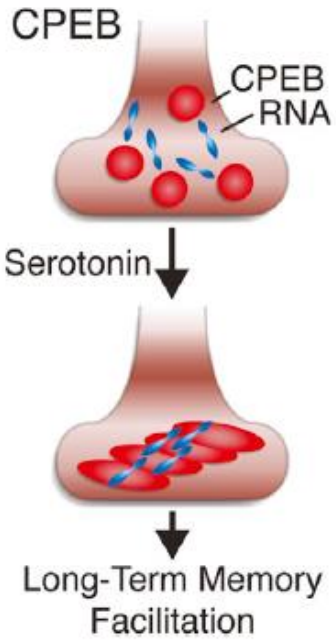
- they may adopt conformation that self-templates over long biological timescales
- self-templating can produce multiple activity states

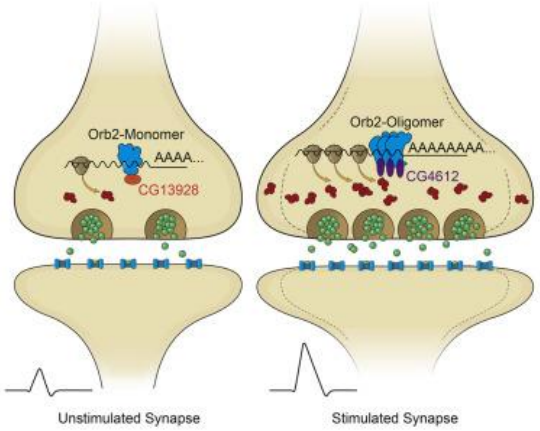
Cell, Vol. 115, 879–891, December 26, 2003, Copyright ©2003 by Cell Press

A Neuronal Isoform of the *Aplysia* CPEB Has Prion-Like Properties

Kausik Si,[2,*] Susan Lindquist,[3] and Eric R. Kandel[1,2,*]

Rather, they produce cha
conventional loss-of-func





CPEB, the cytoplasmic polyadenylation element-binding protein: upon serotonin signaling, CPEB oligomerizes with RNA in a self-templating complex, leading to long-term memory facilitation

Model

- persistence of long-term memory results from CPEB assembly into aggregates
- these aggregates serve as functional prions and regulate protein synthesis necessary for the maintenance of long-term memory

Cellular/Molecular

Identification of Flap Structure-Specific Endonuclease 1 as a Factor Involved in Long-Term Memory Formation of Aversive Learning

Lorena Saavedra-Rodríguez,[1,2] Adrinel Vázquez,[1,2] Humberto G. Ortiz-Zuazaga,[4] Nataliya E. Chorna,[3] Fernando A. González,[3] Lissette Andrés,[1] Karen Rodríguez,[1] Fernando Ramírez,[1] Alan Rodríguez,[1] and Sandra Peña de Ortiz[1,2]

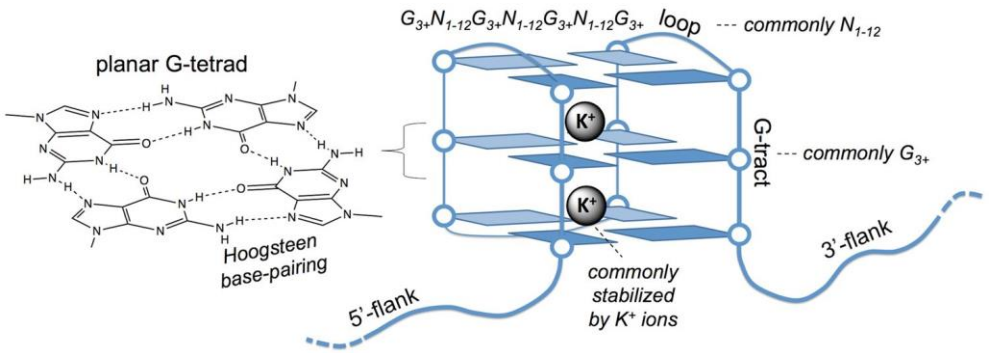
REVIEW ARTICLE
https://doi.org/10.1038/s41593-018-0257-3
nature neuroscience

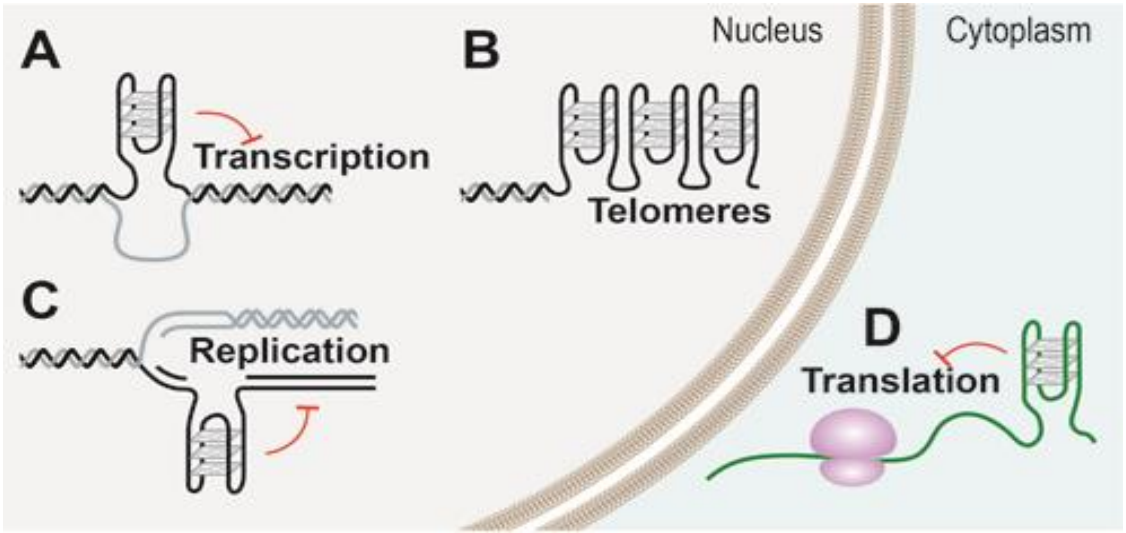
Somatic mosaicism and neurodevelopmental disease

Alissa M. D'Gama[1,2,3] and Christopher A. Walsh[1,2,3*]

Traditionally, we have considered genetic mutations that cause neurodevelopmental diseases to be inherited or de novo germline mutations. Recently, we have come to appreciate the importance of de novo somatic mutations, which occur postzygotically and are thus present in only a subset of the cells of an affected individual. The advent of next-generation sequencing and single-cell sequencing technologies has shown that somatic mutations contribute to normal and abnormal human brain development. Somatic mutations are one important cause of neuronal migration and brain overgrowth disorders, as suggested by visible focal lesions. In addition, somatic mutations contribute to neurodevelopmental diseases without visible lesions, including epileptic encephalopathies, intellectual disability, and autism spectrum disorder, and may contribute to a broad range of neuropsychiatric diseases. Studying somatic mutations provides insight into the mechanisms underlying human brain development and neurodevelopmental diseases and has important implications for diagnosis and treatment.

Structure of G-quadruplexes formed in DNA or RNA sequences

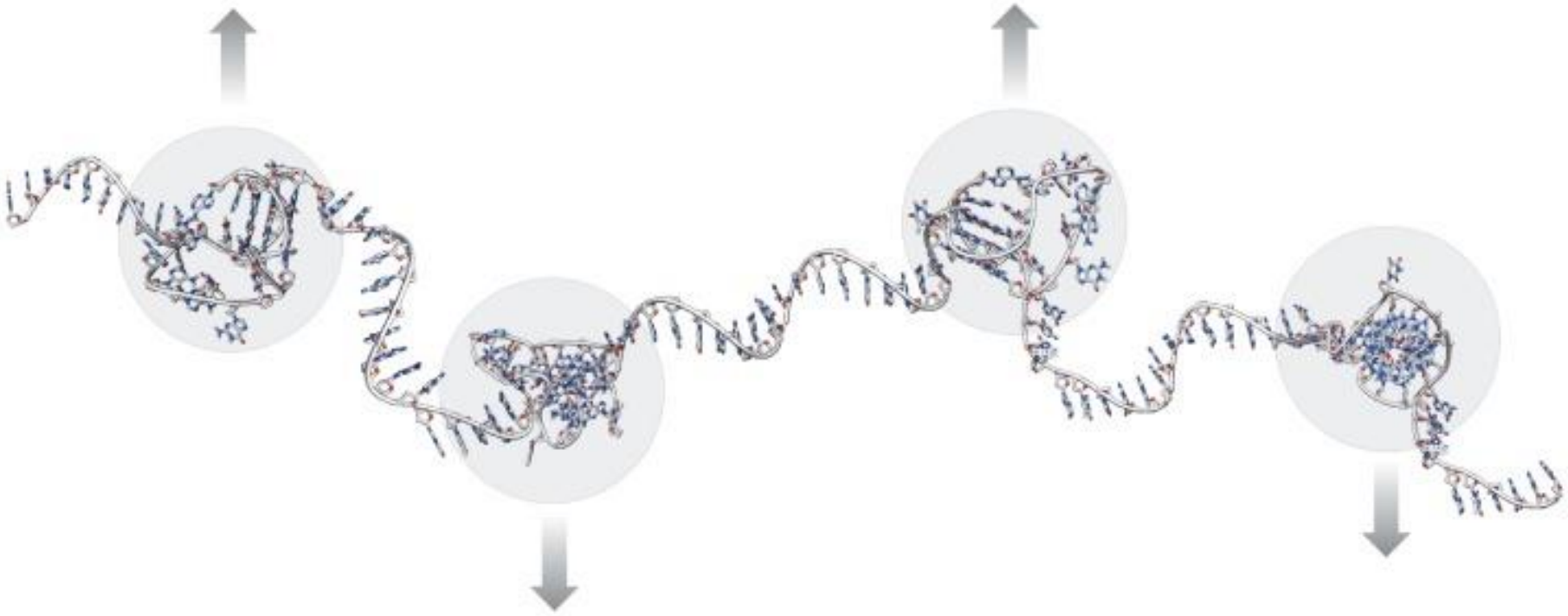





I'm stressed!
My genome is being methylated!
mom
I'm anxious!
Now my genes are being methylated!
daughter
where does it end?
granddaughter
Could CPEB expression help?

- Visualization of G4-DNA in ciliates and human cells
- Located at telomeric and non-telomeric regions
- Replication dependent formation

- Over-represented in regulatory regions
- Detectable in human genomic DNA
- Co-localize with *in vitro* identified G4-binding proteins



- Associated with genomic and epigenetic instability
- Processed by helicases conserved from bacteria to humans
- Promote recombination and rearrangement

- Associated with diseases and cancer phenotypes
- Relevant target for new therapies
- Potential for chemical synthetic lethality approaches

Current Opinion in Genetics & Development

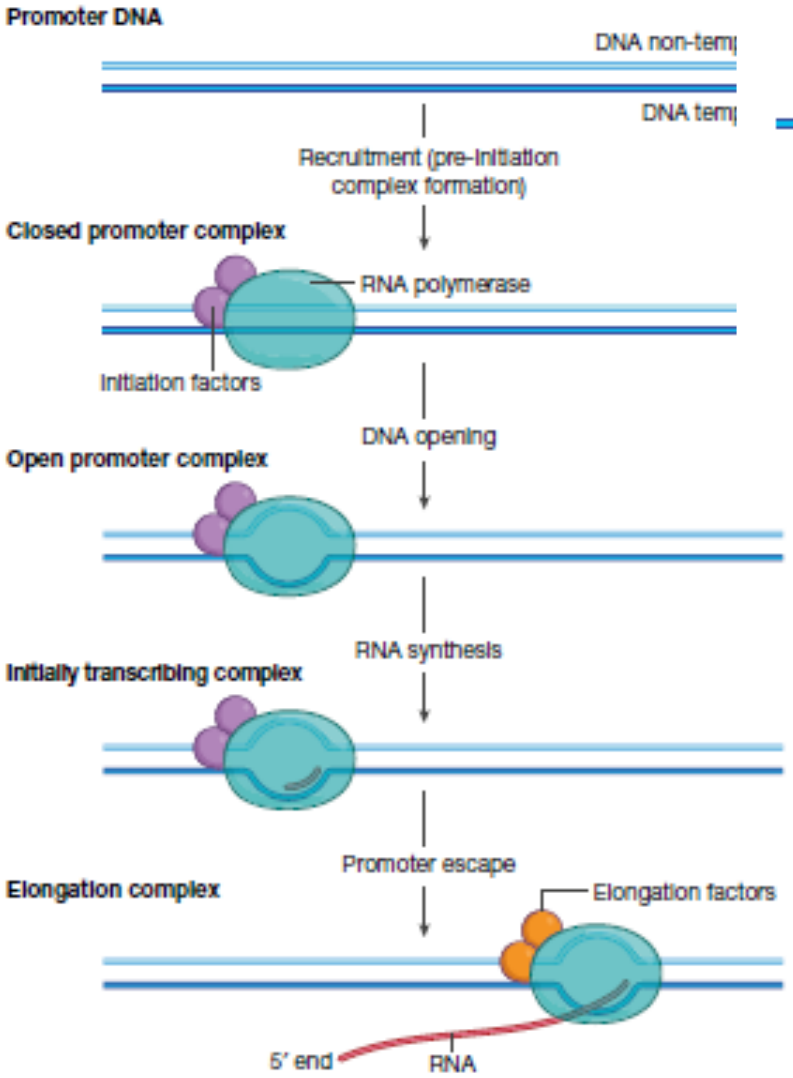
Major carriers of epigenetic information

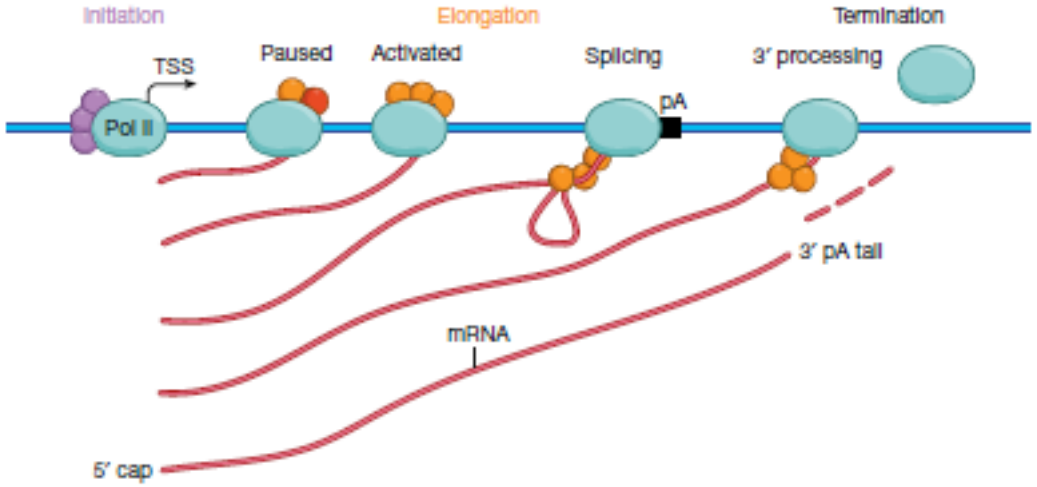
Heterochromatin components
Pericentric heterochromatin: its distinctive feature is the presence of megabase sized repetitive DNA domains coated in a specific histone H3K9 trimethylation mark

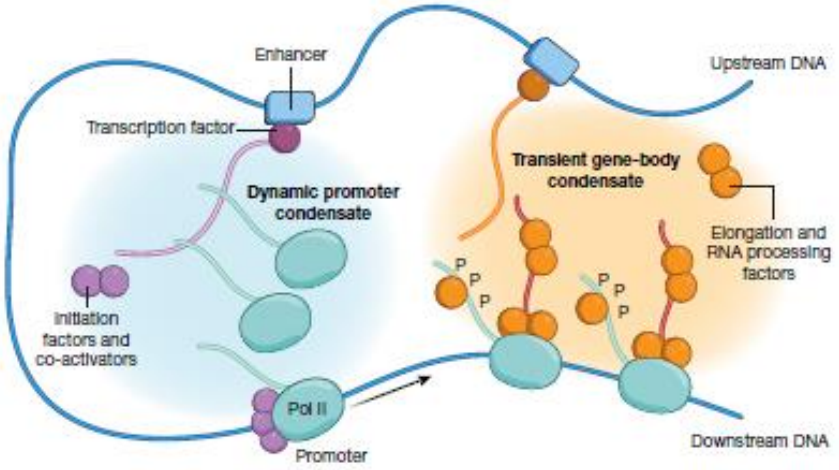
Polycomb proteins
Polycomb (PcG) and Trithorax maintain the memory of spatial patterns of gene expression throughout development
have key roles in the maintenance of developmentally or environmentally programmed expression states
PcG proteins are responsible for deposition of the H3K27me3 and H2AK119Ub marks
can be recruited to specific regions of the genome by DNA-binding proteins or noncoding RNAs3.

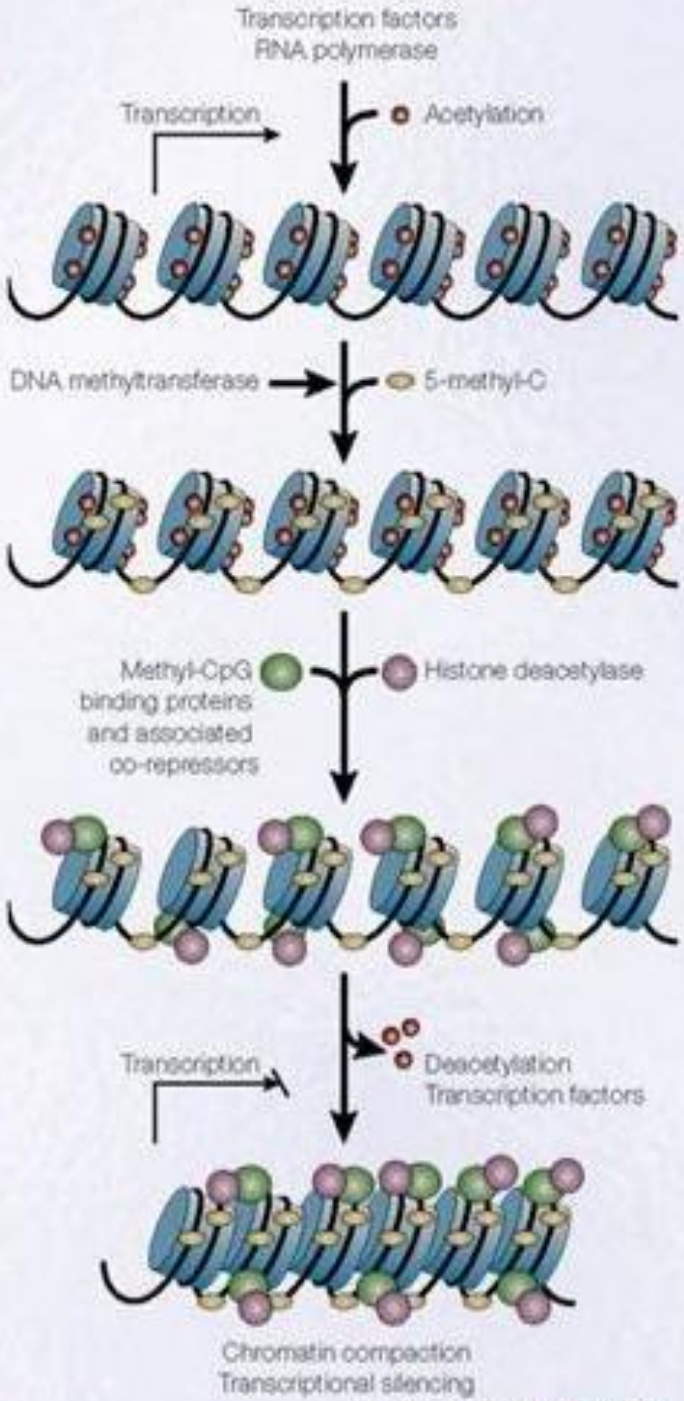
Noncoding RNAs

DNA methylation
The mechanisms that allow DNA methylation to be copied during DNA replication DNA methylation is maintained by the DNA methyltransferase DNMT1


Promoter DNA
DNA non-temp
DNA temp
Recruitment (pre-initiation complex formation)
Closed promoter complex
RNA polymerase
Initiation factors
DNA opening
Open promoter complex
RNA synthesis
Initially transcribing complex
Promoter escape
Elongation complex
Elongation factors
5′ end
RNA

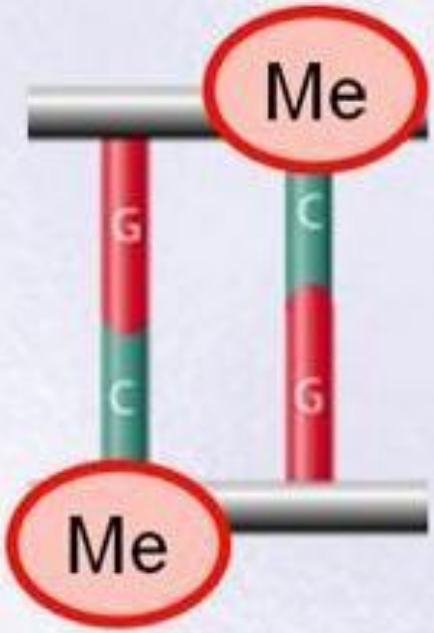

Initiation
Elongation
Termination
TSS
Paused
Activated
Splicing
3′ processing
Pol II
pA
3′ pA tail
mRNA
5′ cap


Enhancer
Upstream DNA
Transcription factor
Transient gene-body condensate
Dynamic promoter condensate
Elongation and RNA processing factors
P
Initiation factors and co-activators
Pol II
Promoter
Downstream DNA



Nature Reviews | Genetics

Cytosine methylation

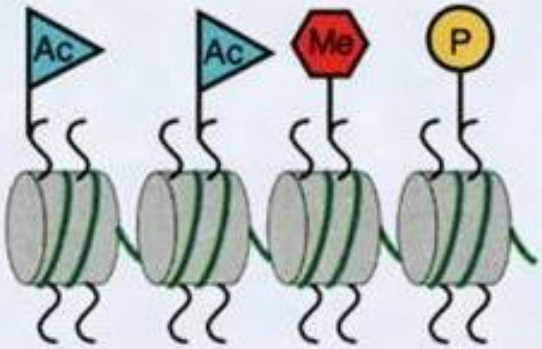


^{m}CpG

Structure & Epigenetics of Euchromatin versus

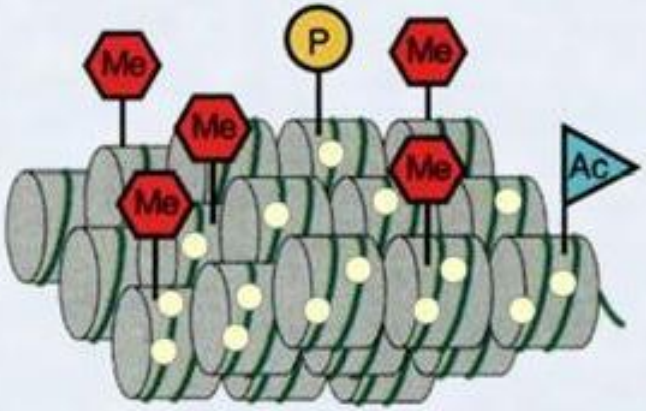
DNA methylation and histone modifications help to compartmentalize the genome into domains of different transcriptional potentials

Euchromatin



- High histone acetylation
- Low DNA methylation
- H3-K4 methylation

Heterochromatin



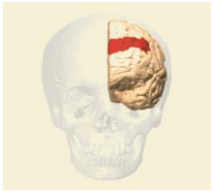
- Low histone acetylation
- Dense DNA methylation
- H3-K9 methylation

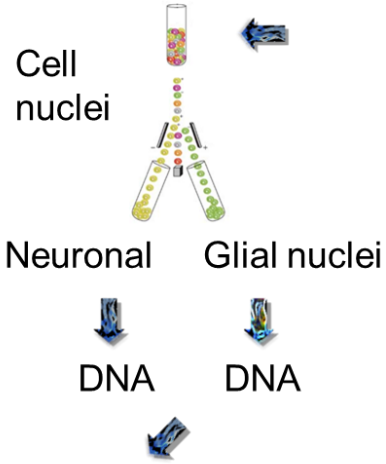
Fluorescence Activated cellular sorting (FACS):

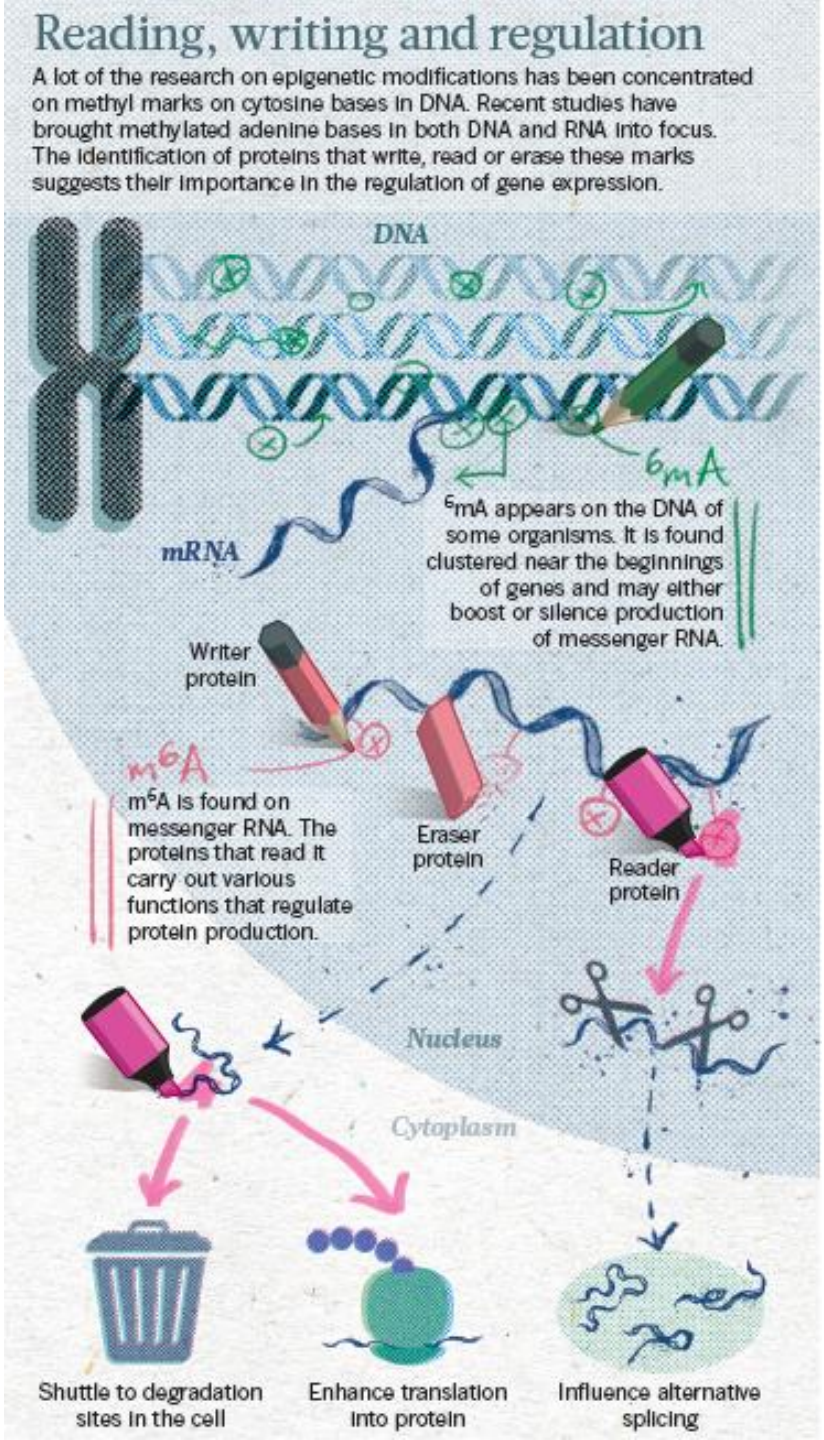
- isolation of neuronal / glial nuclei from frozen human brain samples

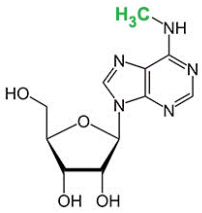
Epigenome wide analysis of DNA methylation:

- identification of neuron and glia specific DNA methylation patterns (10,000 CpGs)









RNA methylation is a reversible post-translational modification to RNA including tRNA, rRNA, mRNA, tmRNA, snRNA, snoRNA, miRNA, and viral RNA

N6-methyladenosine (m^6A) is the most common and abundant methylation modification
is thought to be important for mRNA regulation due to enrichment of m^6A at 3'UTRs

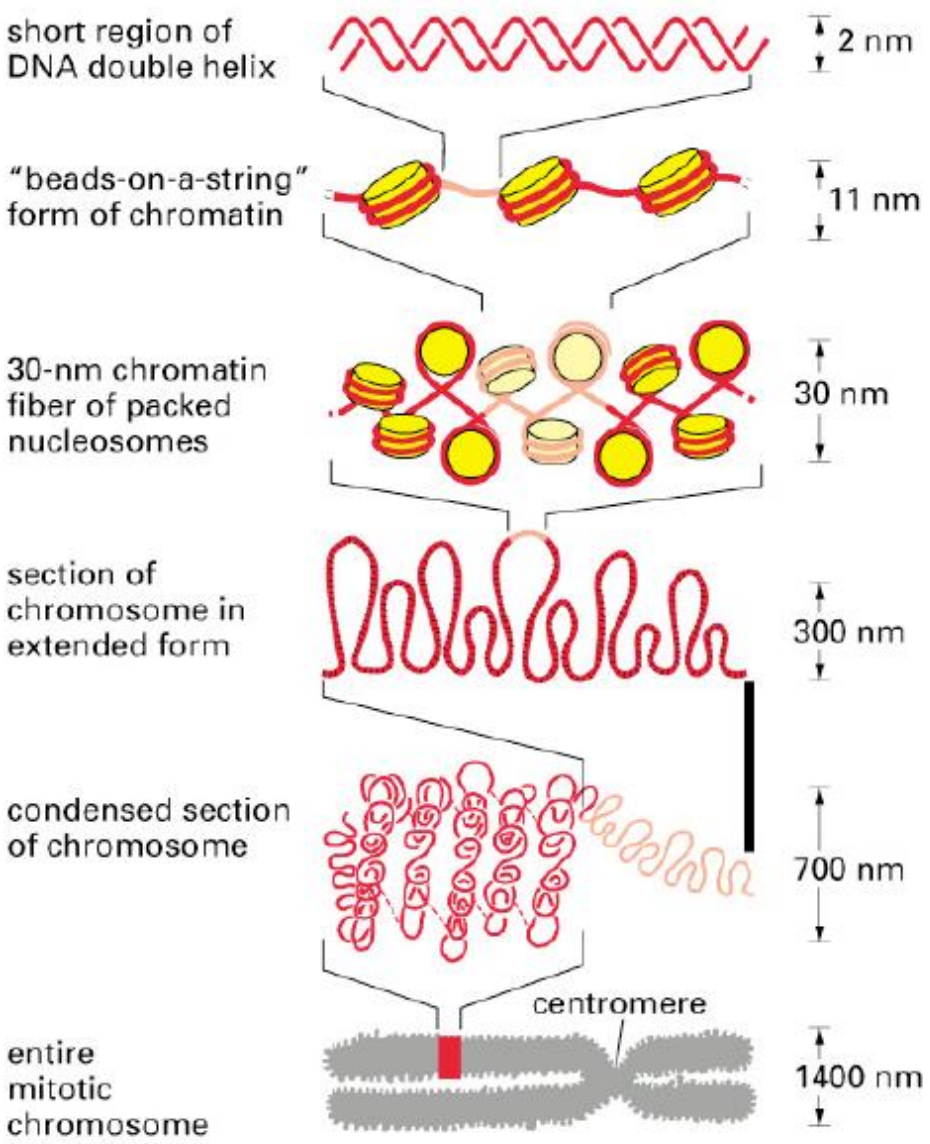
5-methylcytosine (5-mC)

m^6A and 5-mC RNA methylation affects the regulation of various biological processes such as RNA stability and mRNA translation,

loss of 5-mC in vault RNAs causes aberrant processing into Argonaute-associated small RNA fragments that can function as microRNAs

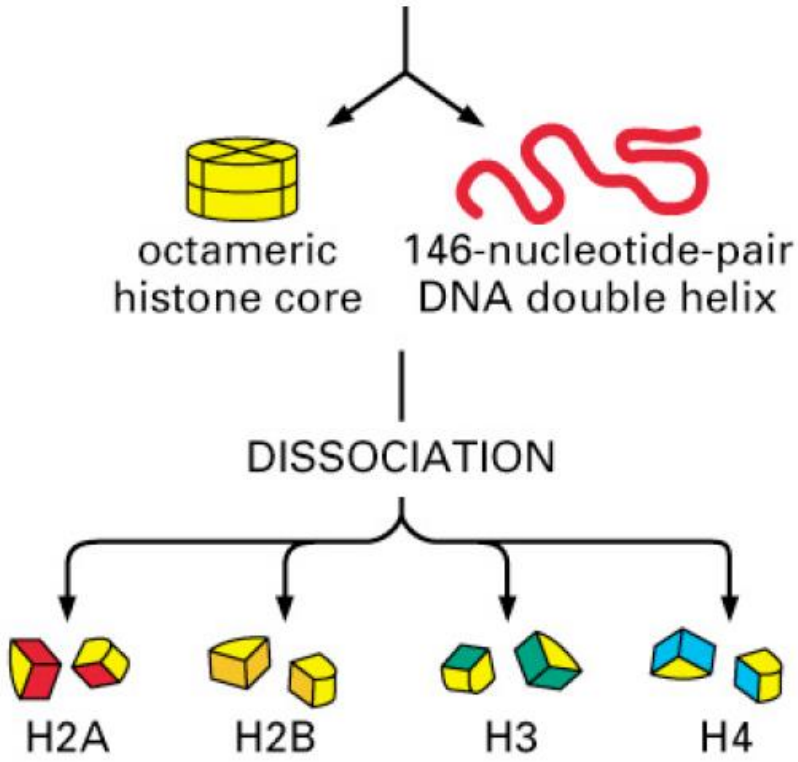
Chromatin Organization

Multiple Levels of packing are required to fit the DNA into the cell nucleus

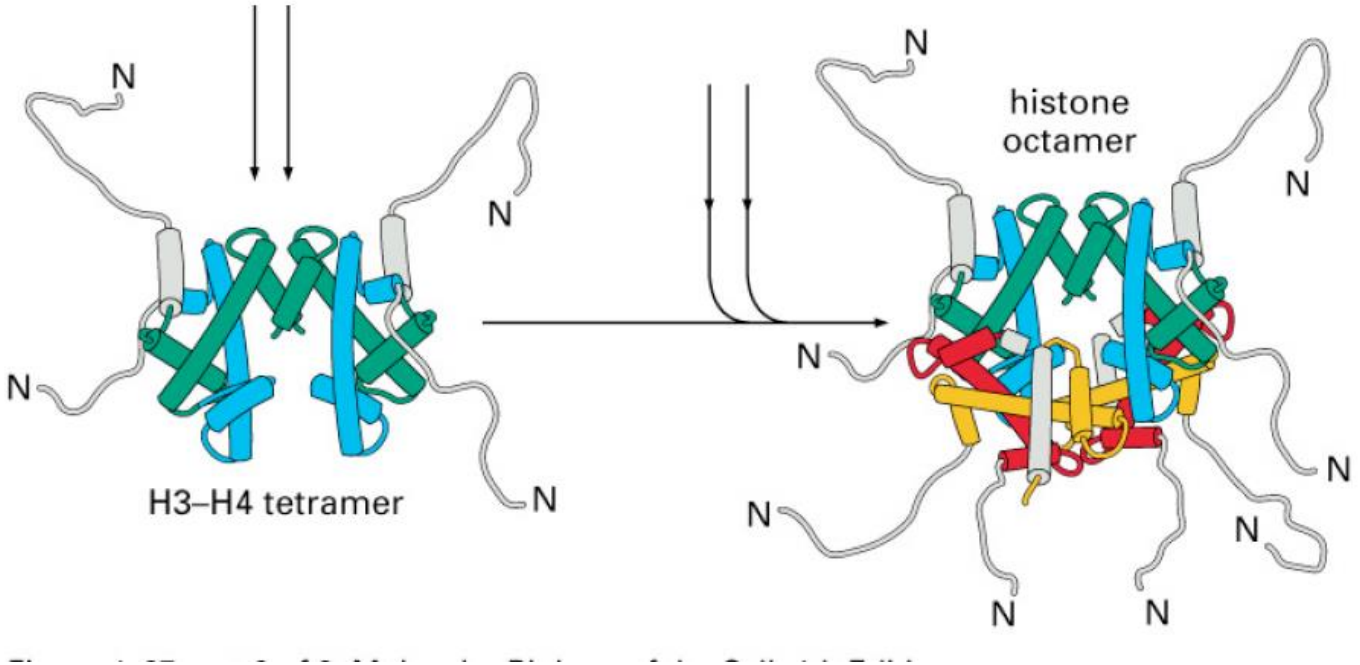


NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 10,000-FOLD SHORTER THAN ITS EXTENDED LENGTH

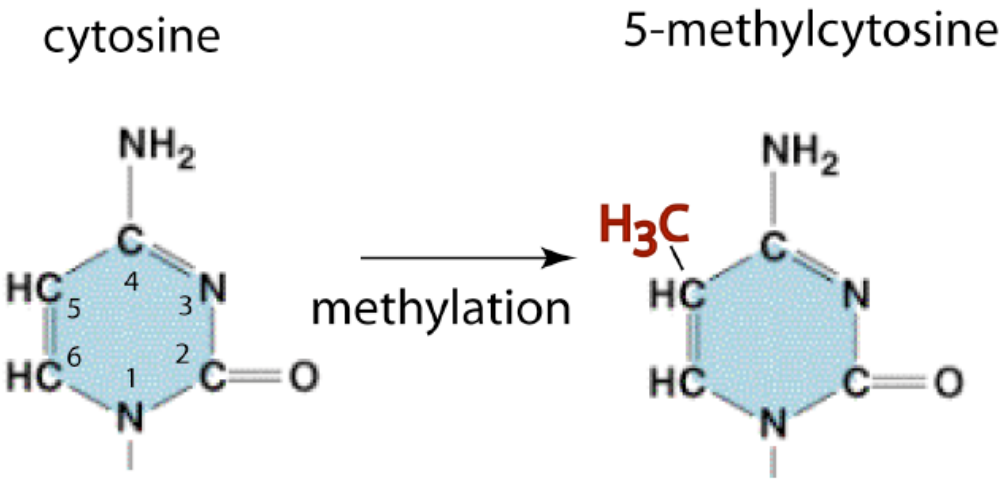
The **nucleosome** consists of 146bp of DNA wrapped around a protein core of 8 histones



Histone octamers assemble from pairs of dimers

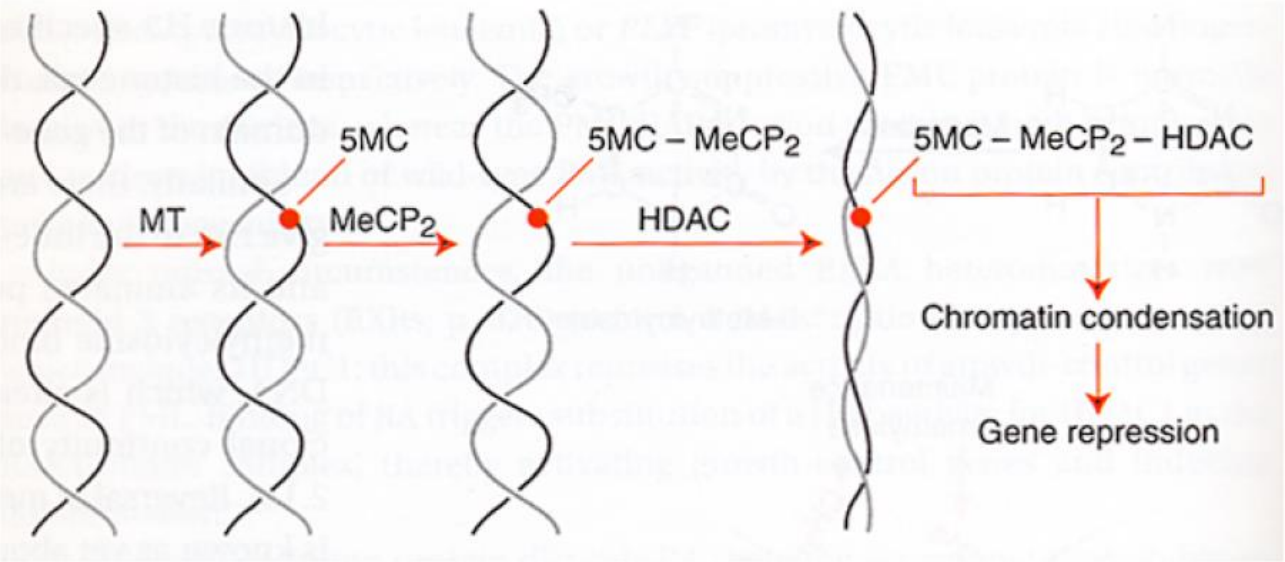


DNA Methylation



DNA methylation occurs at 5MC within CpG dinucleotides.
5MC constitutes <1% of nucleotides

The presence of 5-methylcytosine leads to the silencing of genes in that local area of the chromosome

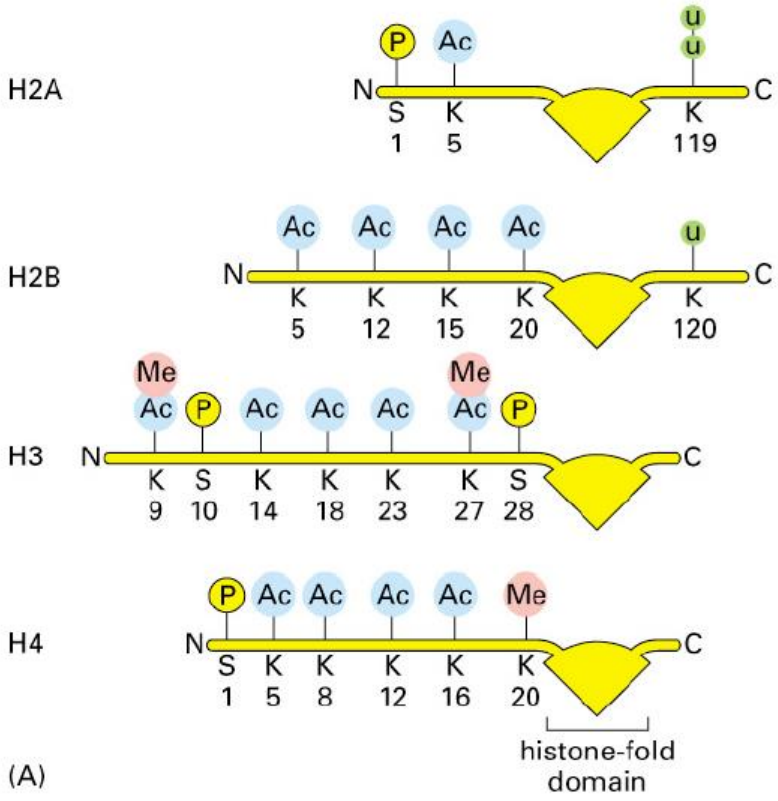


MT = DNA methyltransferase
MeCP2 = Methyl-CpG-binding protein

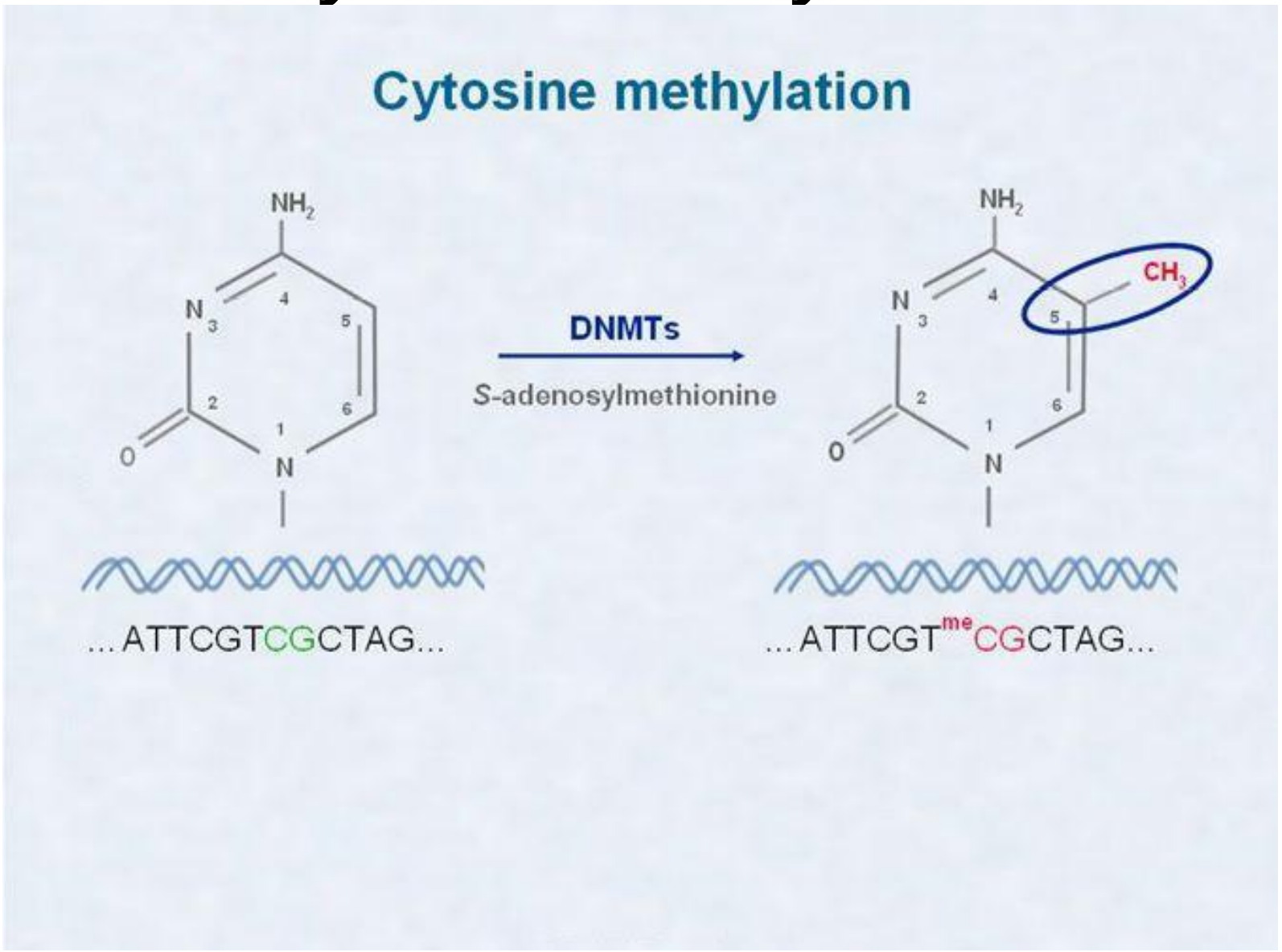
HDAC = Histone Deacetylase

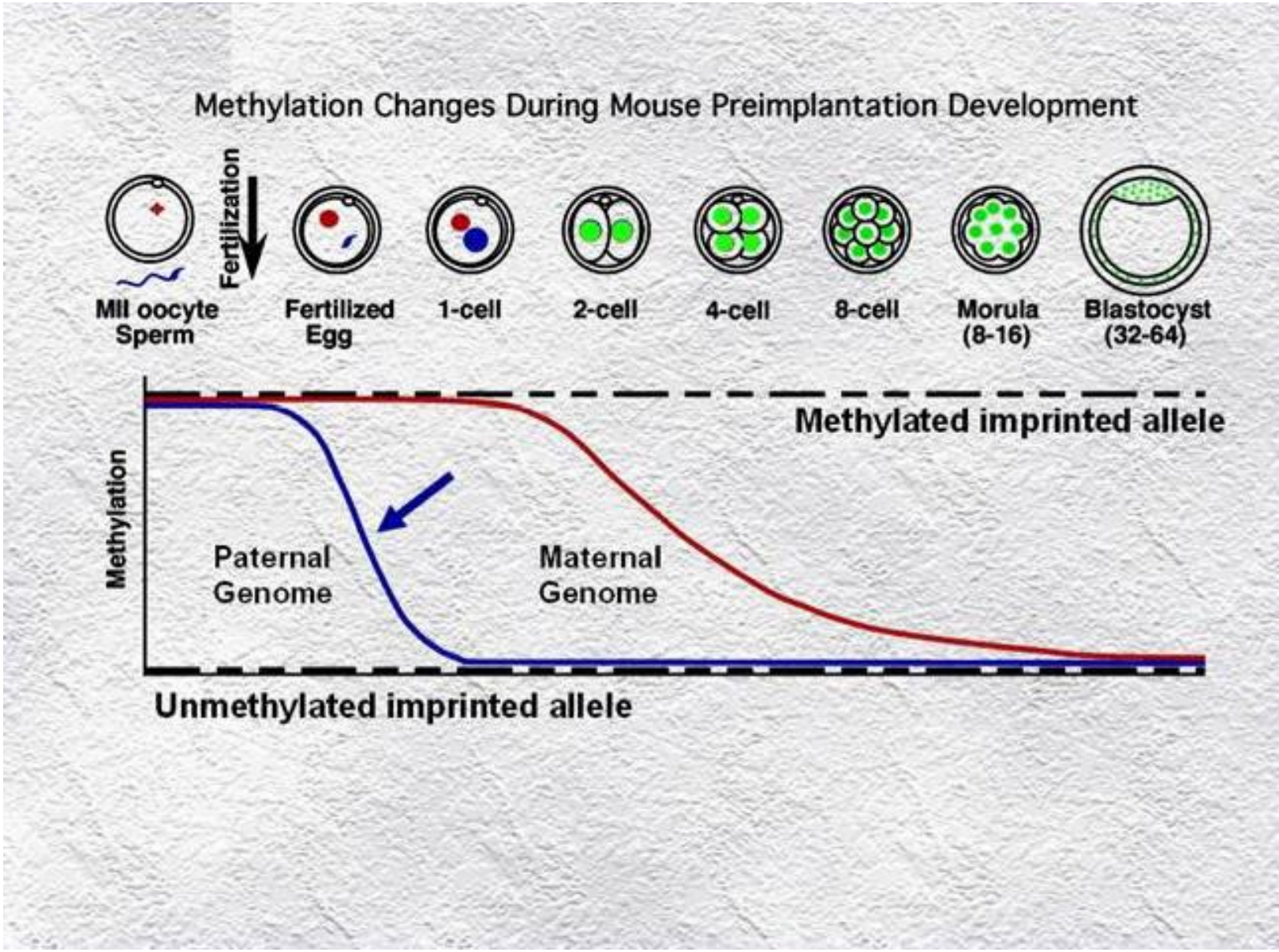
Histone code hypothesis

Histone Tails are subject to a variety of covalent modifications



Methylation of Cytosine in




Methylation Changes During Mouse Preimplantation Development
Fertilization
MII oocyte
Sperm
Fertilized
Egg
1-cell
2-cell
4-cell
8-cell
Morula
(8-16)
Blastocyst
(32-64)
Methylated imprinted allele
Methylation
Paternal
Genome
Maternal
Genome
Unmethylated imprinted allele