REP-EAT

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Epigenetic control of gene expression: focus on Alzheimer's Disease

Andrea Fuso

Sapienza University of Rome, Italy

SAPIENZA
UNIVERSITÀ DI ROMA

System Biology Group Lab
http://www.sbglab.org/sbglab/

andrea.fuso@uniroma1.it

OUTLINE:

EPIGENETICS

ENVIRONMENT (NUTRITION) AND EPIGENETICS

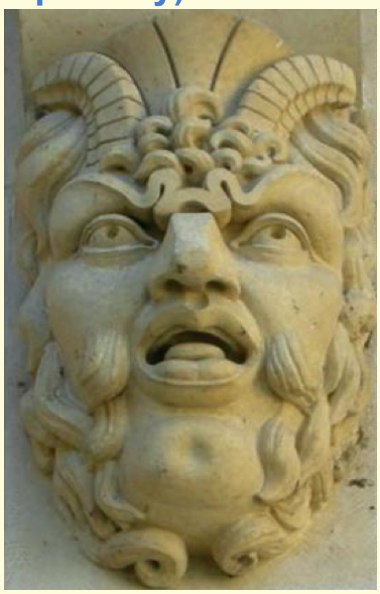
EPIGENETICS AND NEURODEGENERATION

NUTRITION, EPIGENETICS AND NEURODEGENERATION

… AND THE GUT MICROBIOME

NON CpG METHYLATION

ART (philosophically)



manifesting different "complex expressions" starting form the same raw material

Epigenetics (historically)

"..the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being."

Conrad Hal Waddington, 1942

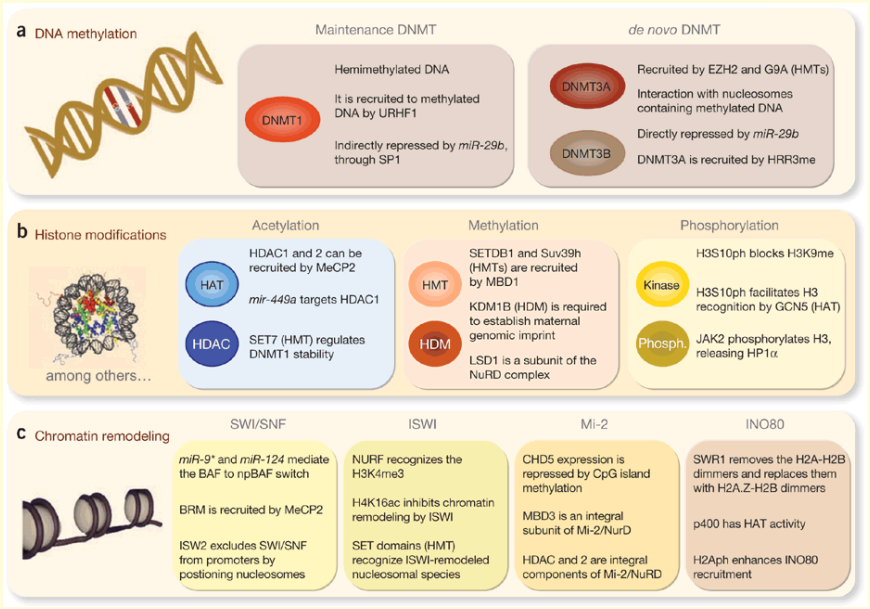
- biochemical nature of genes: unknown

- role as repositories and transmitters of the genetic information: unknown.

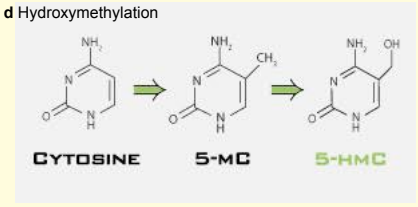
"The study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms"

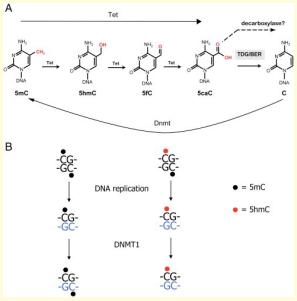
Holliday R., 1990.

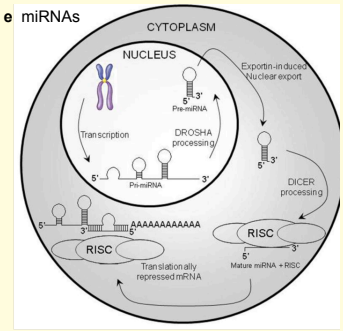
Epigenetics (biologically)

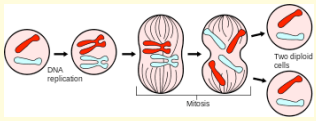


Epigenetics (biologically) ... with some caveats

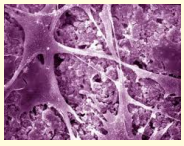


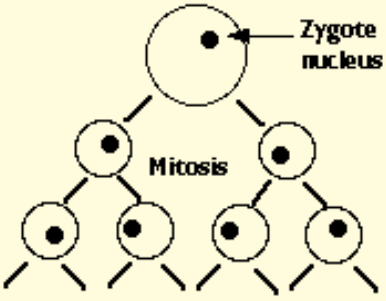


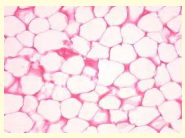


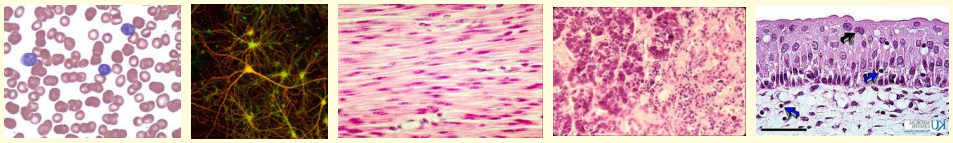


DIFFERENTIATION

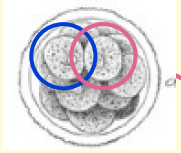


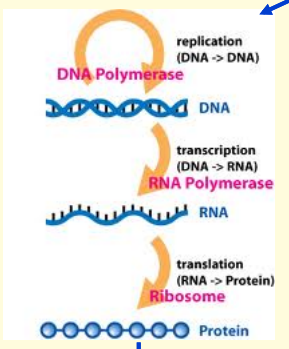






THE CENTRAL DOGMA



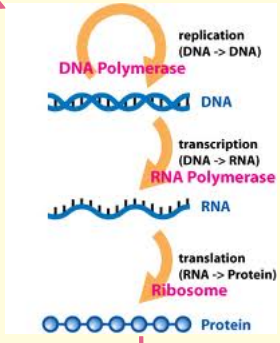


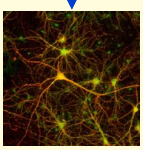
Neurogenin

Myogenin

Neurogenin

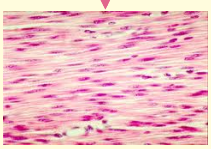
Myogenin





Neuron

Myotube



Genetics vs. Epigenetics

Genetic mutation:

…ATAGCTACCGT… → …ATAGTTACCGT…

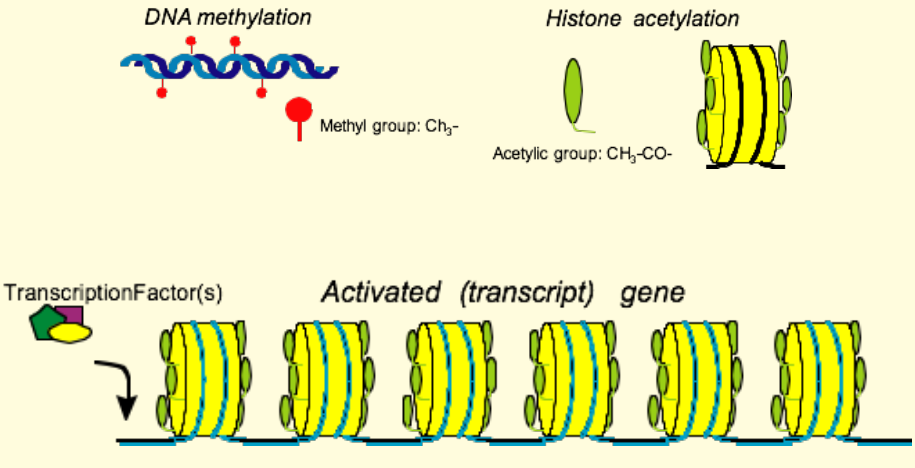
•Protein function loss or alteration
•Gene expression alteration } IRREVERSIBLE

Epigenetic modification

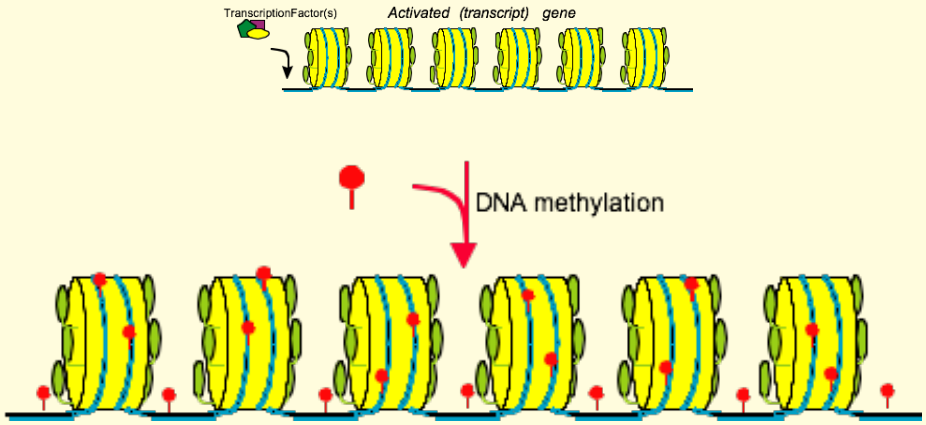
…ATAGCTACCGT… → …ATAGCTACCGT…

•Gene expression alteration } REVERSIBLE

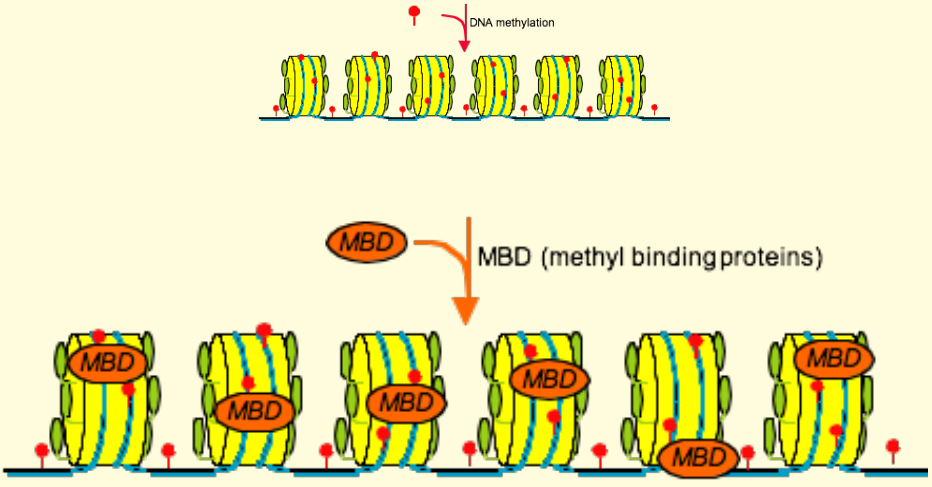
Epigenetics and gene expression (1)



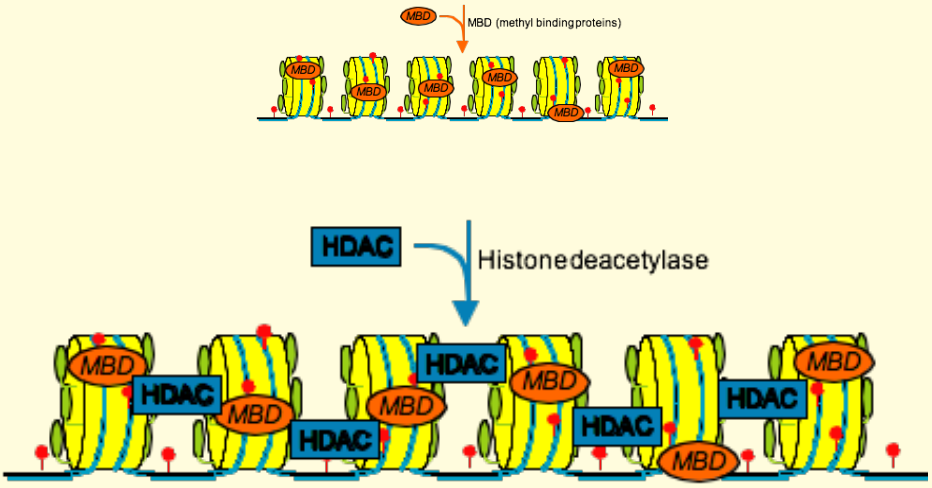
Epigenetics and gene expression (2)



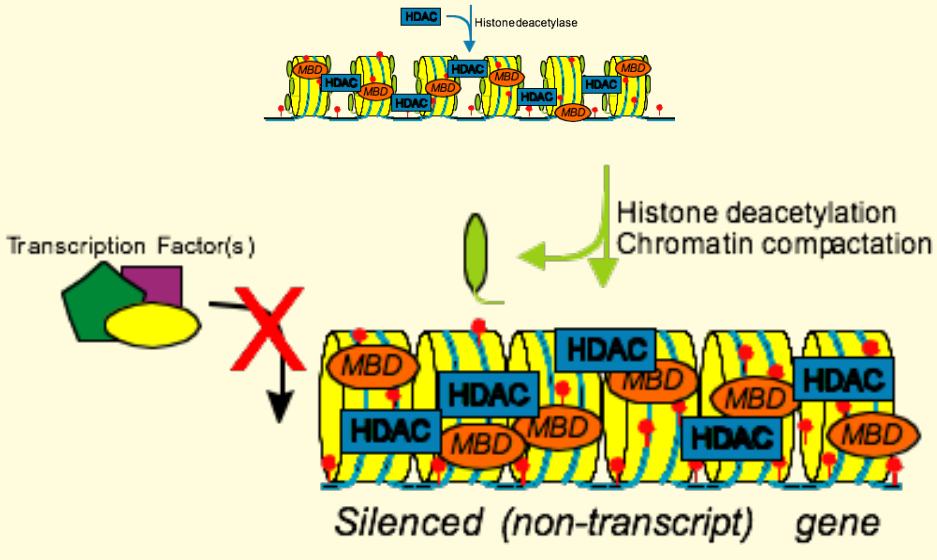
Epigenetics and gene expression (3)



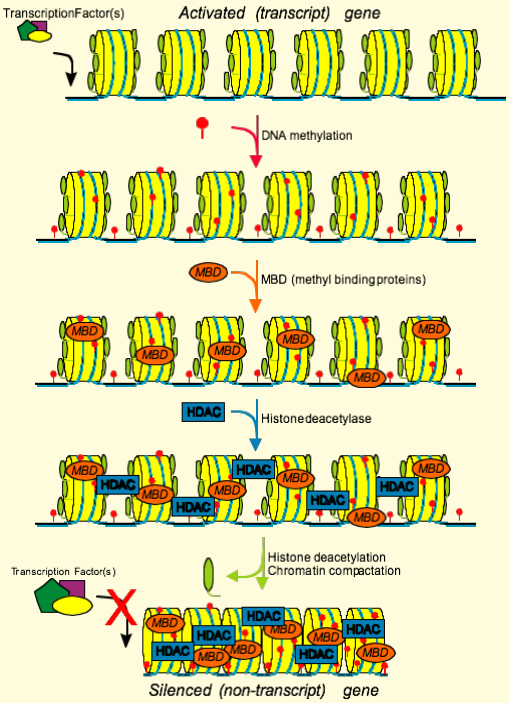
Epigenetics and gene expression (4)



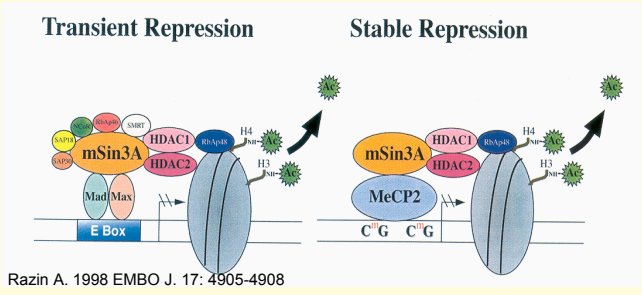
Epigenetics and gene expression (5)



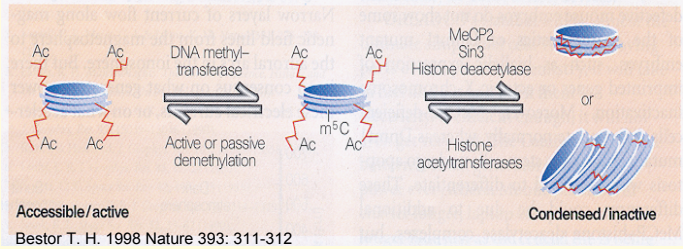
Epigenetics and gene expression



DNA methylation and histone acethylation

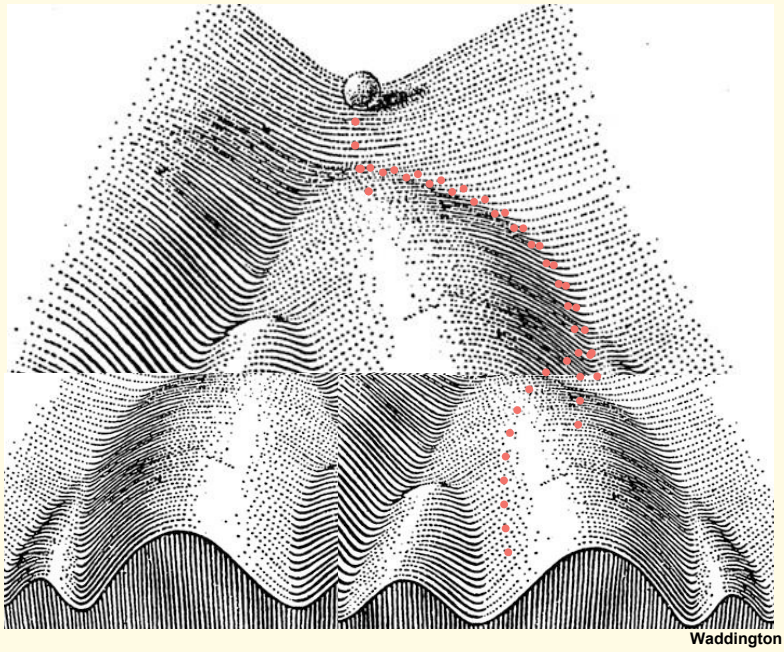


Razin A. 1998 EMBO J. 17: 4905-4908



Bestor T. H. 1998 Nature 393: 311-312

The "epigenetic landscape" applied to Aging



Waddington CH, 1942

A CAUSAL CONNECTION

ENVIRONMENT → **EPIGENETICS** → **AGING**

1) *epigenetic* modifications appear to be *causative of*, or at least *involved in*, an increasing number of multifactorial, *aging-dependent human diseases*

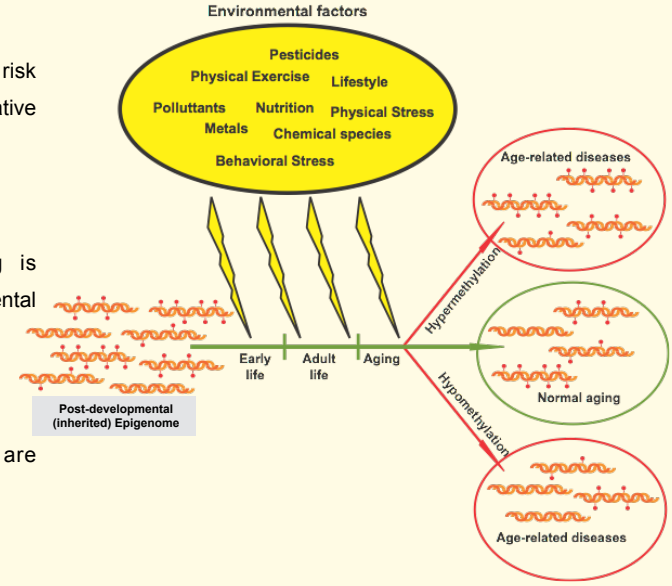
2) epigenetic mechanisms could be triggered by environmental factors or, in a slightly different point of view, *epigenetics exerts the role of mediator* of environmental stimuli

Environment- and aging-dependent diseases

•Aging is the greatest risk factor for neurodegenerative diseases.

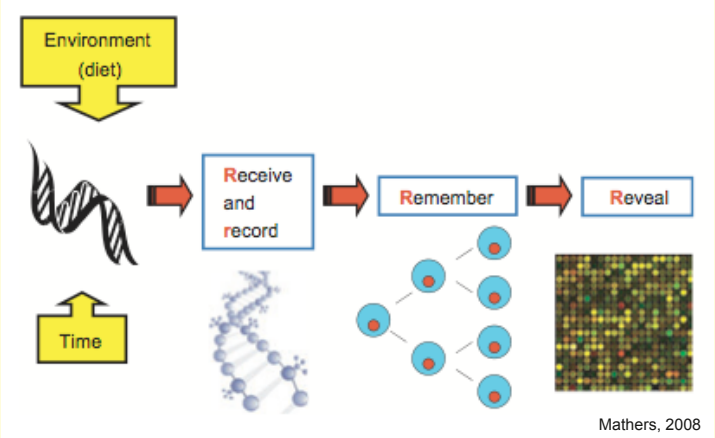
•Normal/diseased aging is influenced by environmental stimuli.

•Environmental stimuli are mediated by epigenetics.



Fuso A., Aging and Disease: the Epigenetic Bridge
In: Epigenetics and Human Disease; Ed. Tollefsbol T., 2012, Elsevier

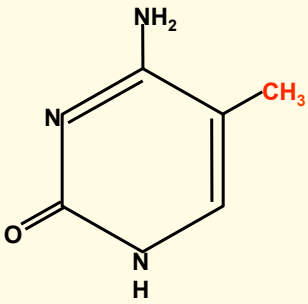
LEARn: Latent Early-life Associated Regulation



Mathers, 2008

The 4 Rs of the nutritional epigenomics.
It is a conceptual model describing the key processes responsible for Receiving, Recording, Remembering and Revealing of the epigenetic patterns alteration as a consequence of the exposition to nutritional (or environmental) factors.

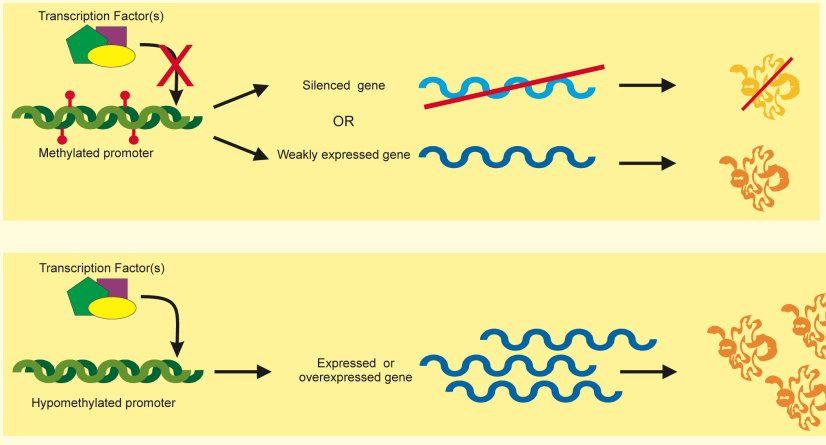
DNA METHYLATION



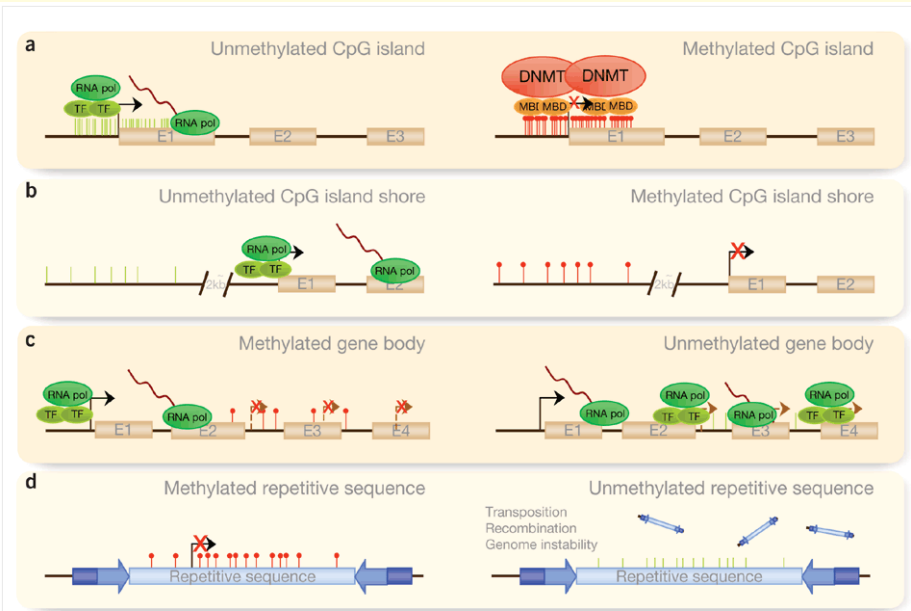
5-methylcitosine
(*mainly in CpG moieties*)

- X chromosome inactivation
- Genomic imprinting
- Mutagenesis and carcinogenesis
- Cellular senescence
- Viral latency
- **Transcriptional Control**

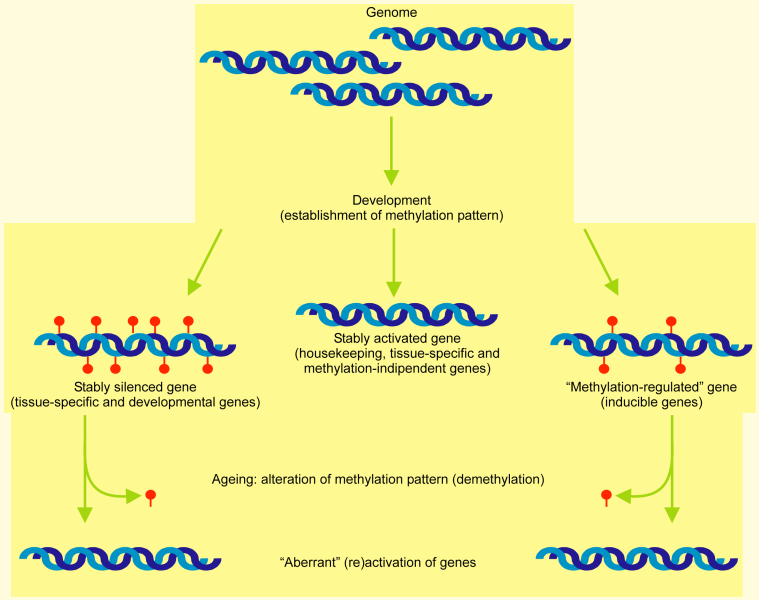
DNA methylation and gene silencing



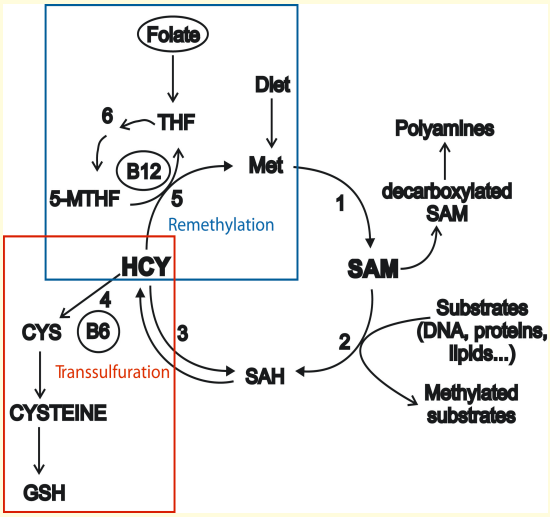
Effects of DNA methylation on different gene regions



DNA METHYLATION: DEVELOPMENT AND AGING



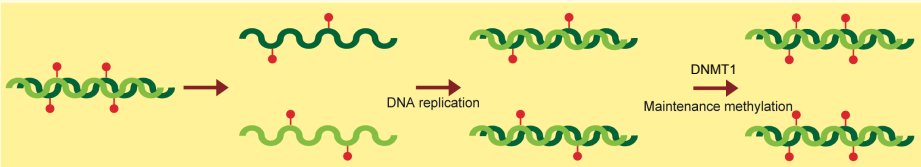
One-carbon metabolism

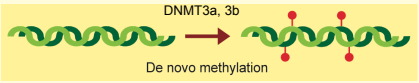


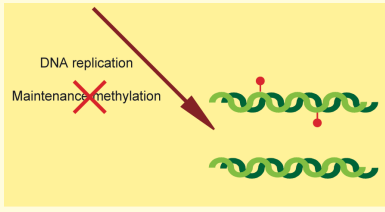
Met, Methionine
SAM, S-adenosylmethionine
SAH, S-adenosylhomocysteine
HCY, Homocysteine
CYS, Cystathionine
GSH, Glutathione
THF, Tetrahydrofolate
MTHF, methyltetrahydrofolate
B12, Vitamin B12
B6, Vitamin B6

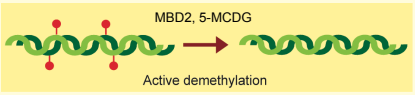
1,Methionine adenosyltransferase (MAT)
2, Methyltransferase(s)
3, SAH hydrolase
4, Cystathionine-β-synthase (CBS)
5, Methionine synthase
6, Methylenetetrahydrofolate reductase (MTHFR)

Methylation mechanisms

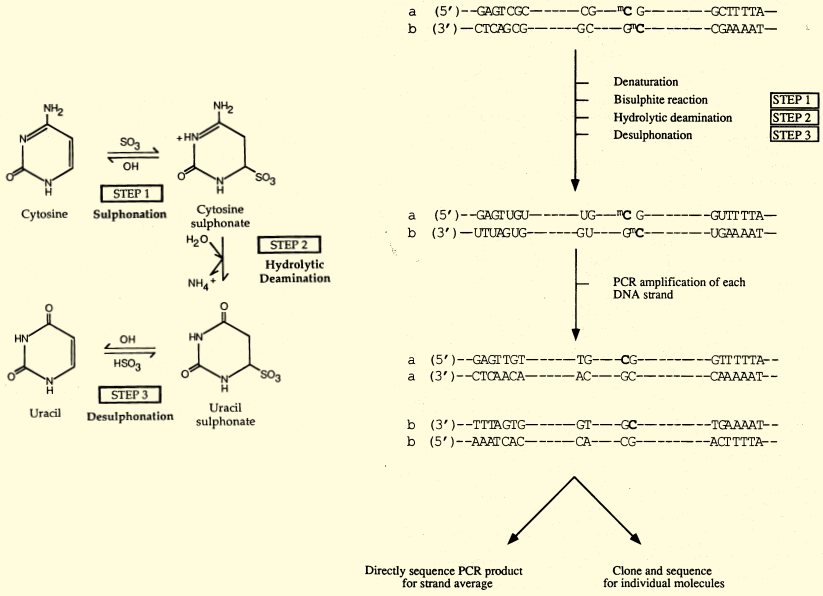






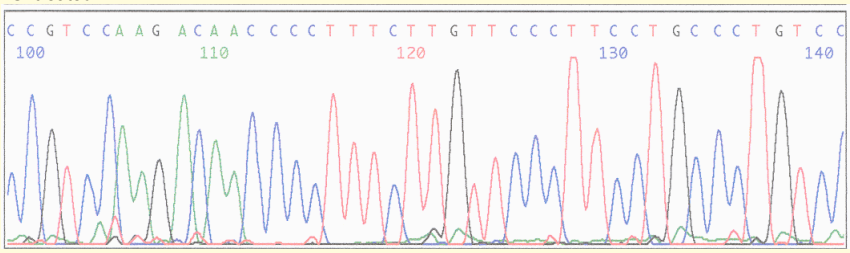


Methylation analysis by Sodium Bisulfite assay

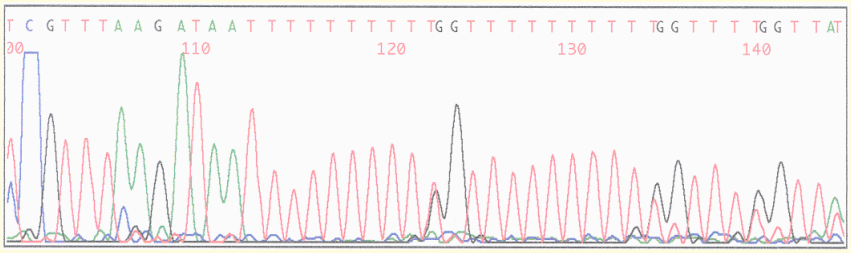


Bisulfite assay and sequencing (controls)

Untreated

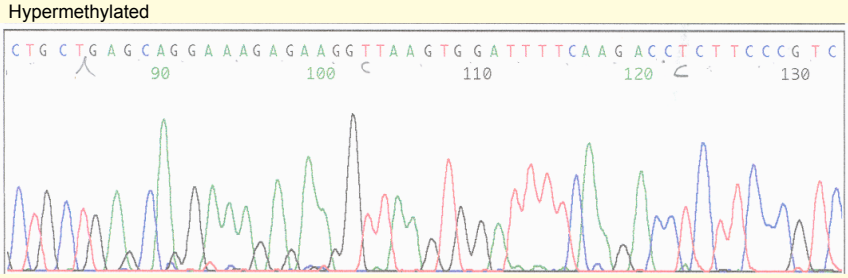


Bisulphite treated (SssI methylated)

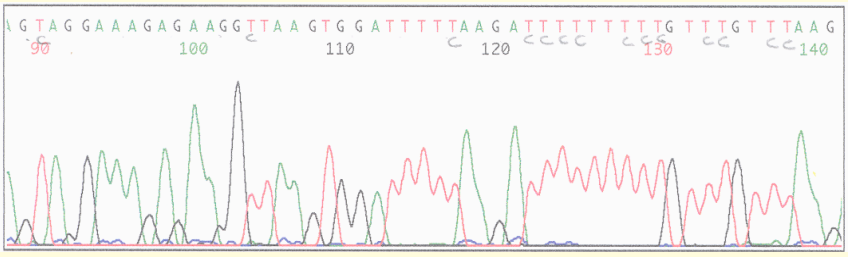


Bisulfite assay and sequencing (experimental)

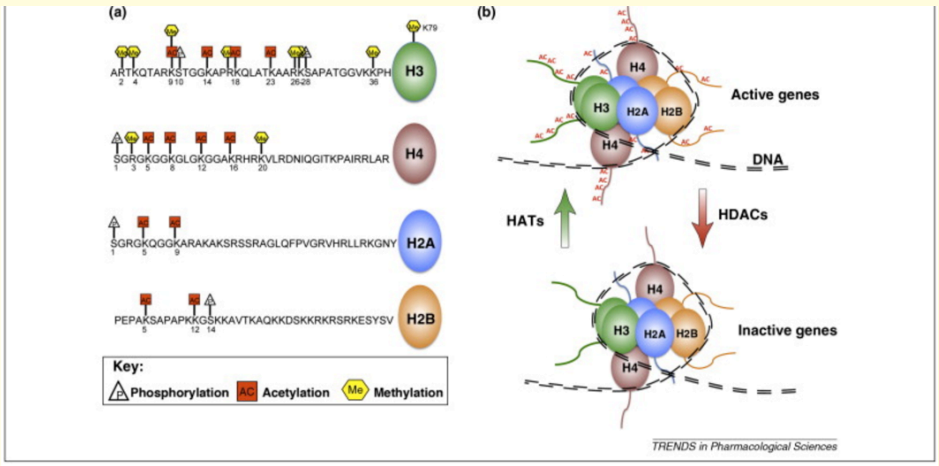
Hypermethylated



Hypomethylated



The histone “code”



Histone modifications are studied by immunochemistry: western blotting, ELISA, IP....