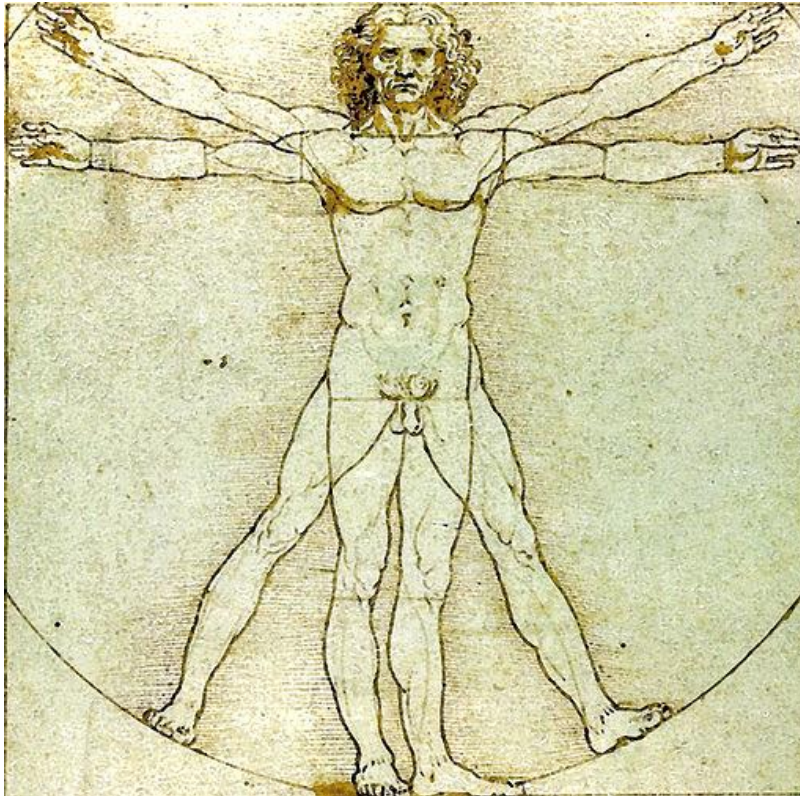


Introduction to Epigenetics for Radiation Protectionists

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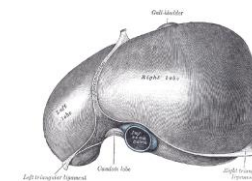


Source: Leonardo da Vinci, public domain

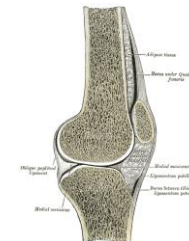
- about 4×10^{13} cells.
- more than 200 cell types
- all have +/- the same genetic information
- about 20 000 protein coding genes



Source: Woutergroen, public domain



Source: HC Carter, public domain

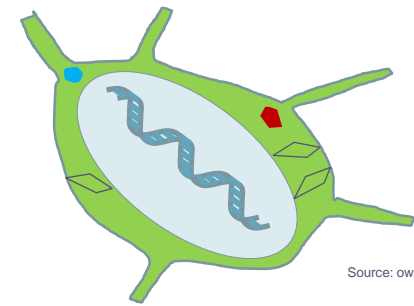
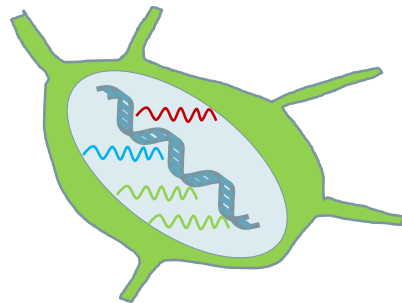
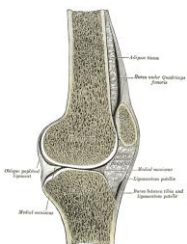
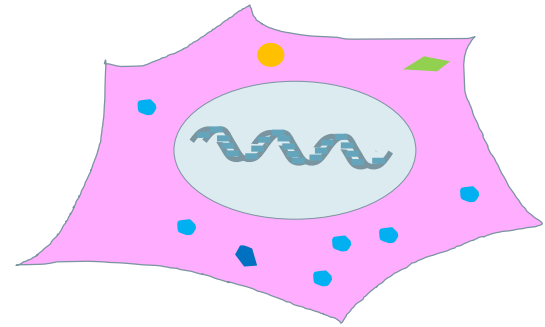
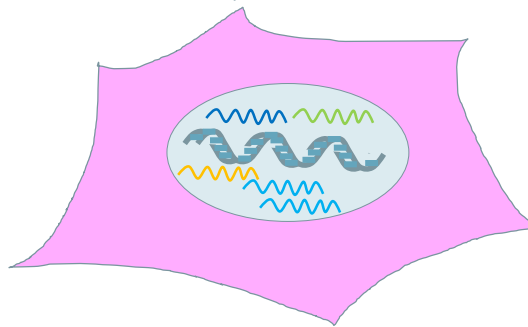
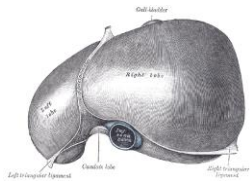
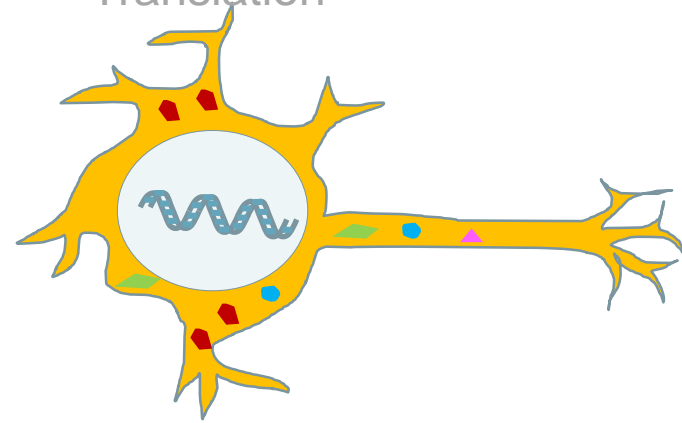
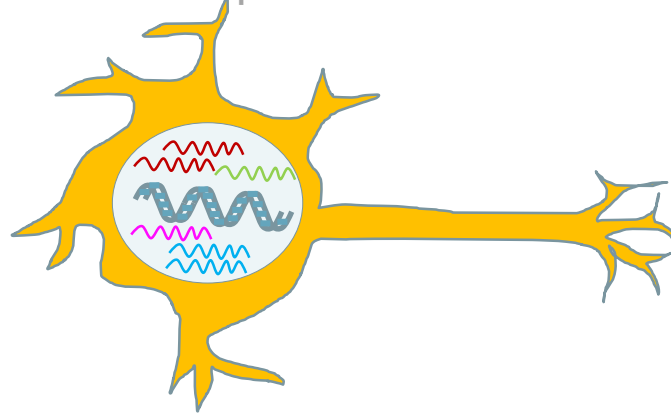
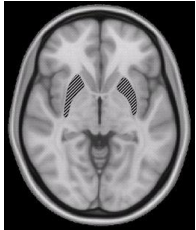


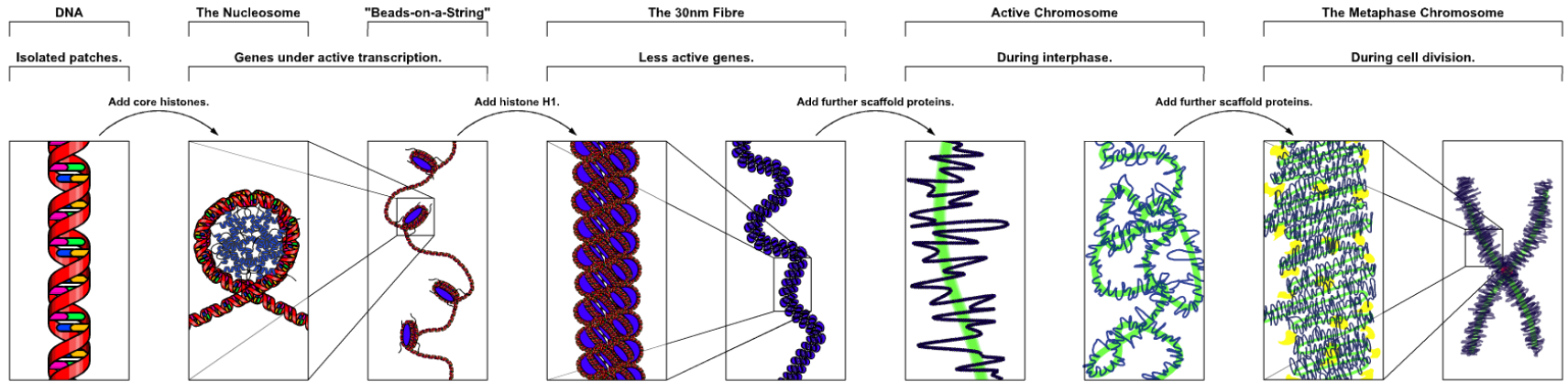
Source: HC Carter, public domain



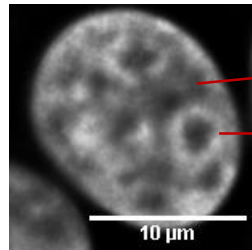
Transcription

Translation





Source: R Wheeler, GNU Free Documentation License



Source: own art-work

Euchromatin: Transcription ON

Heterochromatin: Transcription OFF

Human breast cancer cell,
stained with DAPI



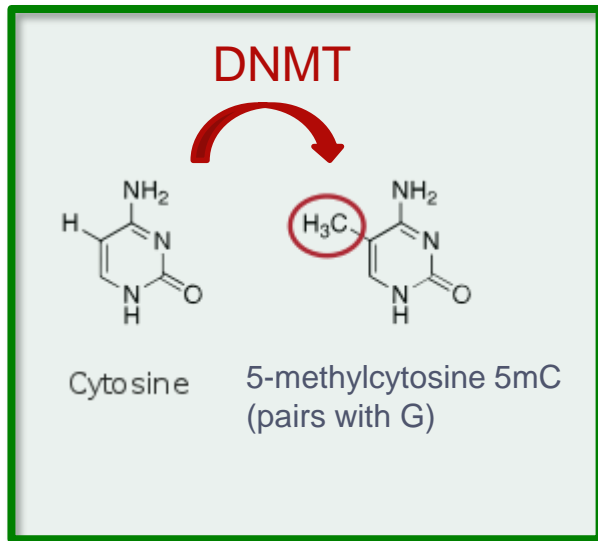
Def. 1942: „changes in phenotype without changes in genotype“

Def. 2001: “the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail change in DNA sequence.”

Epigenetics

- determination of cell type
- transmitted to daughter cells
- apparently quite stable
- alterations affect cell function and can result in disease (e.g. cancer)

- ensuring cell plasticity
- responds to alterations in cell environment
- reversible: writers and erasers
- but also transmittable to daughter cells



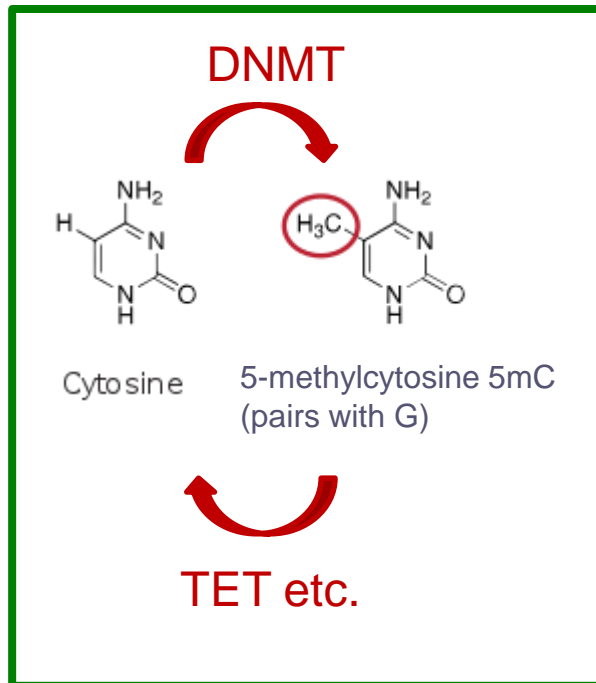
DNA methyltransferases (DNMTs)

- **de novo** methylation of unmethylated sequence
- or **maintenance** methylation at hemimethylated sequence (after replication)
- predominantly at **CpG** dinucleotides



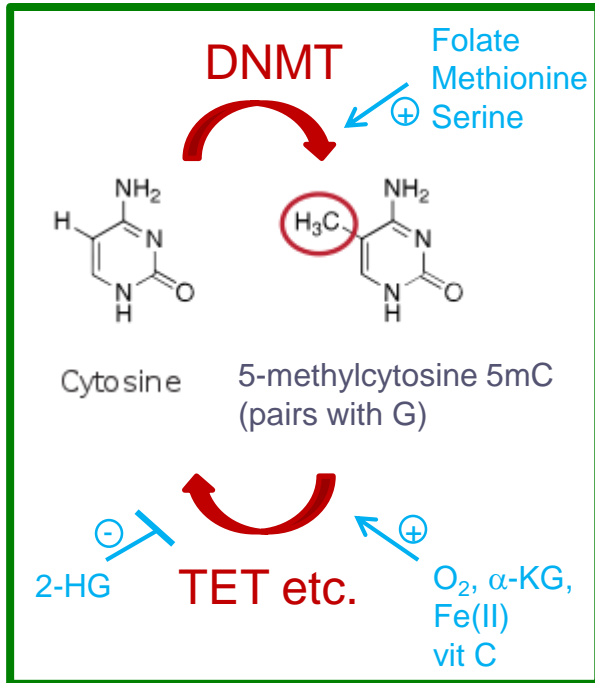
DNA methylation is mostly associated with repression of transcription / silencing of genes.

Inappropriate silencing of genes can cause diseases:
e.g.: silencing of tumor suppressor genes may lead to cancer

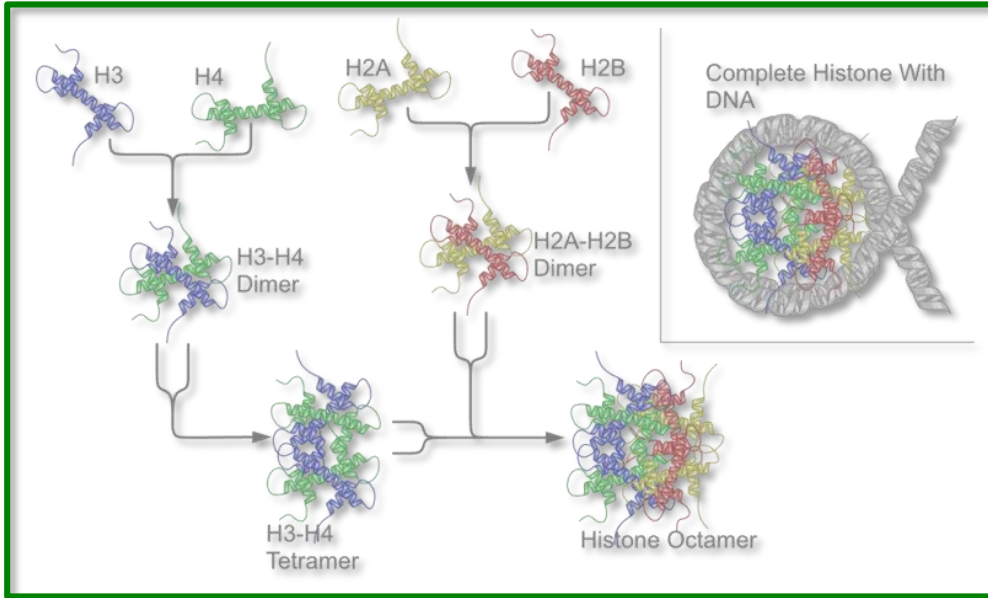


TET enzymes

- oxidize 5mC to form 5hmC, 5fC, 5caC
- these are not recognized by maintenance DNMT (dilution of methylation mark after replication)
- 5fC, 5caC are actively removed by „repair process“

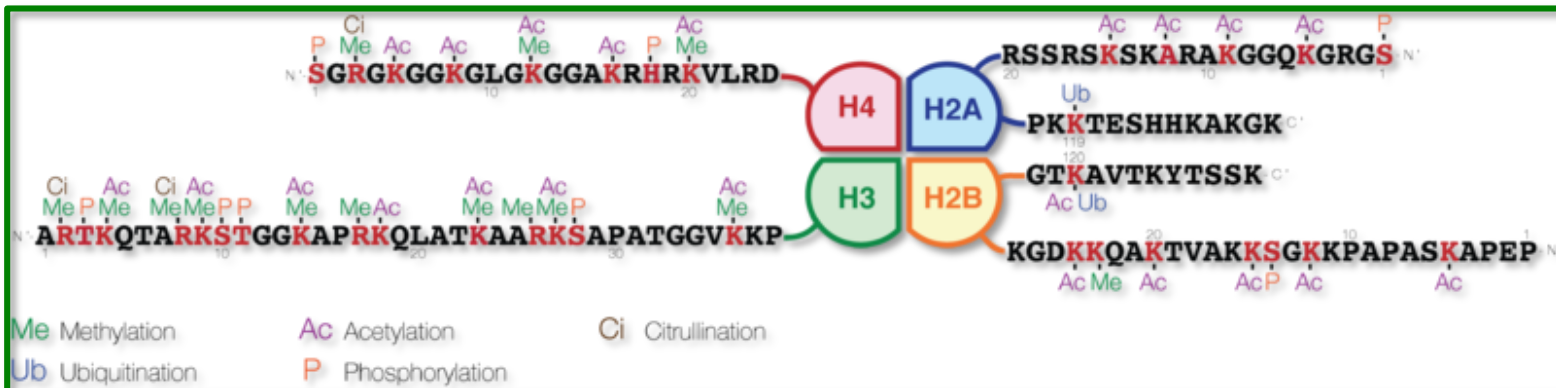


DNA Methylation and Demethylation
respond to metabolic alterations

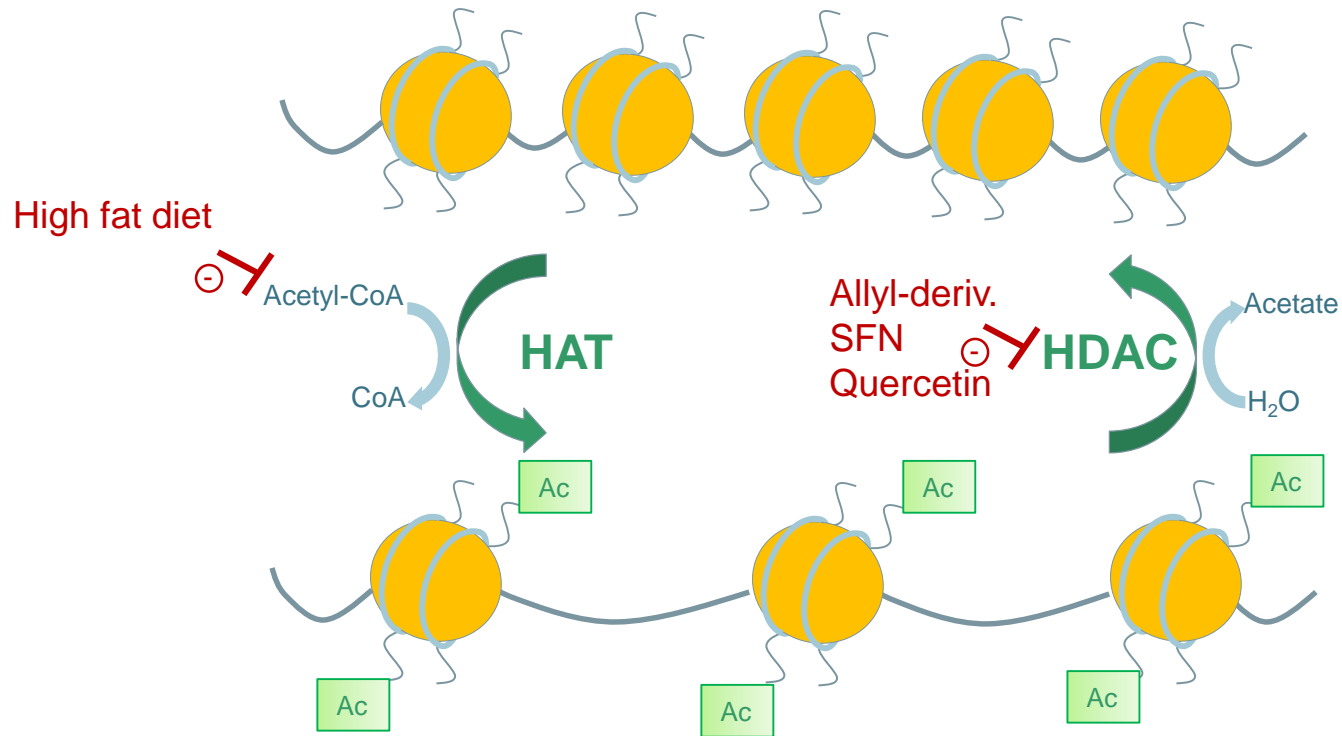


= nucleosome

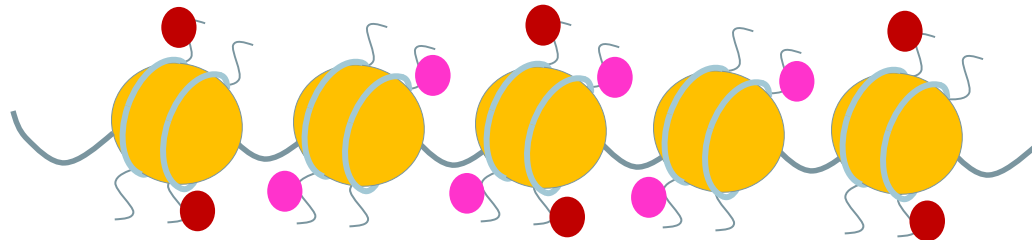
Source: R Wheeler, GNU Free Documentation License



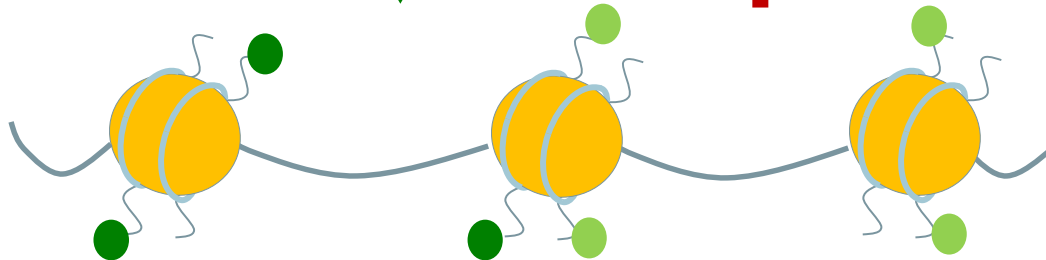
Source: Creative Commons, Based on Rodriguez-Paredes and Esteller, Nature, 2011



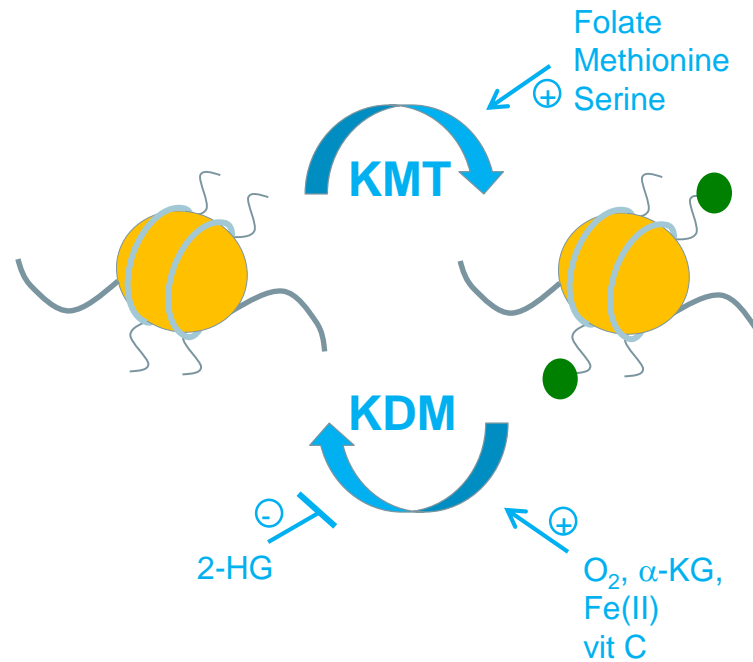
HAT = Histone Acetyl Transferase
HDAC = Histone Deacetylase



Repressive marks
e.g. H3K9me3, H3K27me3



Active marks
e.g. H3K4me3, H3K36me3



KMT = Lysine Methyl Transferase
KDM = Lysine Demethylase



The differentiation of epigenetic processes from other processes affecting gene expression is sometimes difficult (depending on the definition...). The following mechanisms have been addressed as „epigenetic“:

- Histone variants, chromatin remodeling, chromatin folding
- non-coding RNAs or long non-coding RNAs

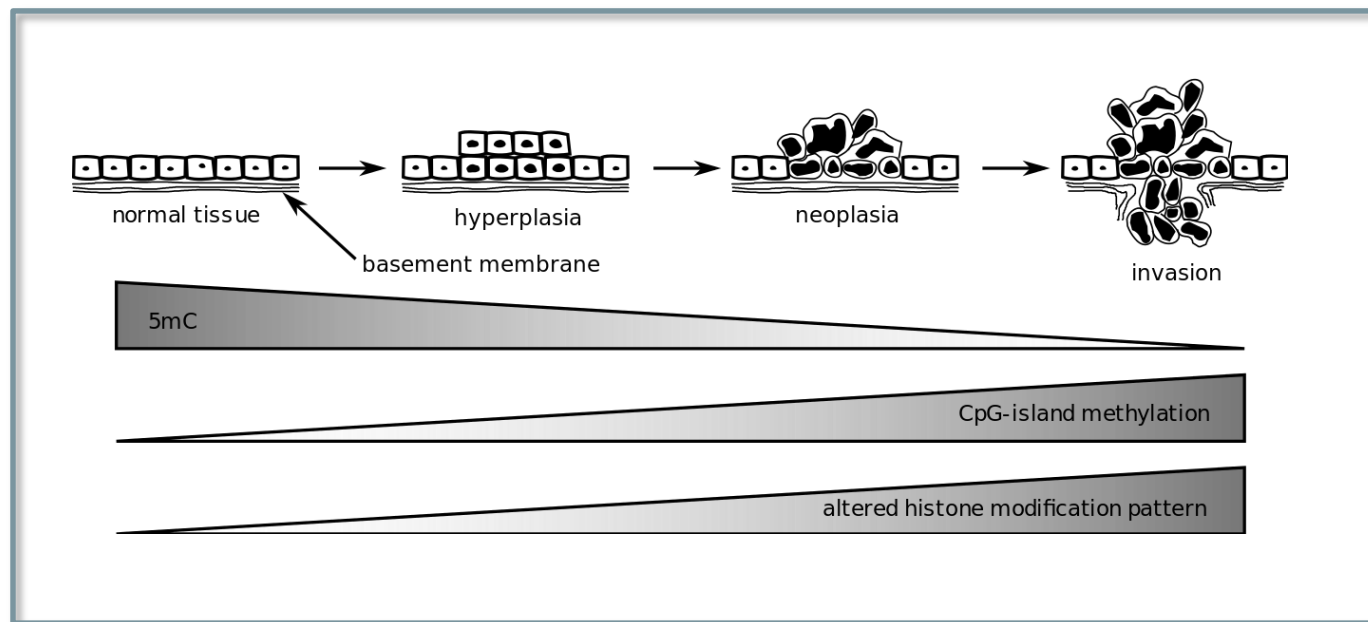


Epigenetic pattern



Disease

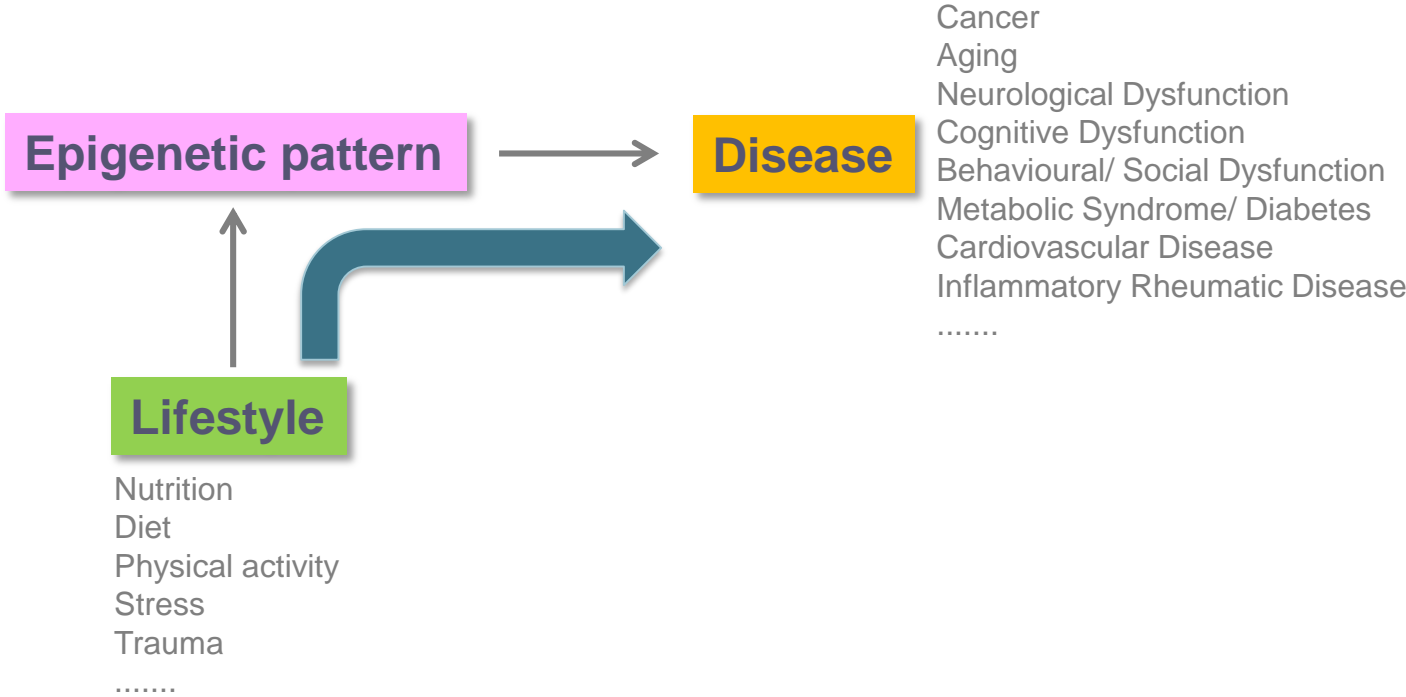
- Cancer
- Aging
- Neurological Dysfunction
- Cognitive Dysfunction
- Behavioural/ Social Dysfunction
- Metabolic Syndrome/ Diabetes
- Cardiovascular Disease
- Inflammatory Rheumatic Disease
-

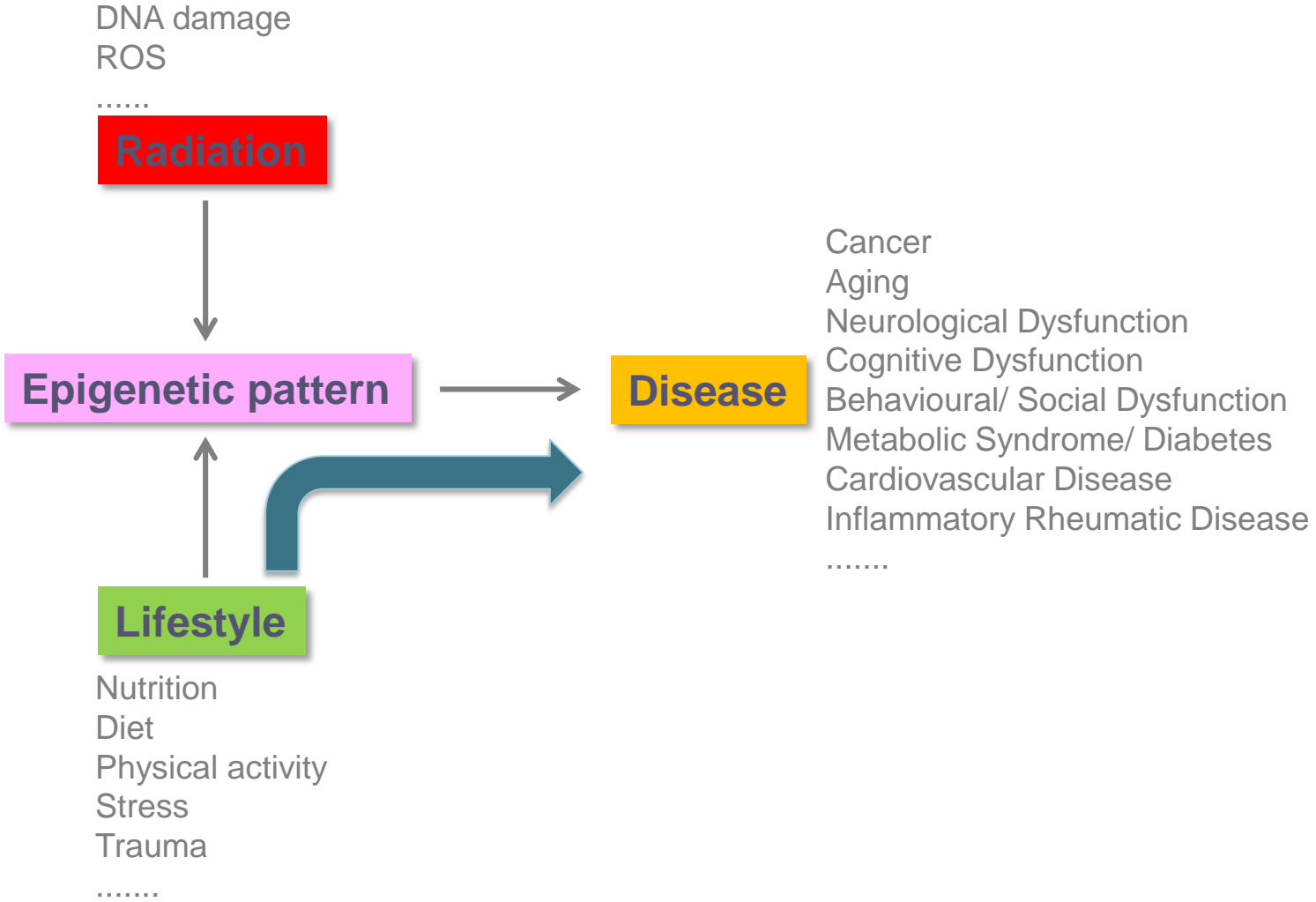


Source: Creative Commons, based on Barillot et al 2012

EMA- and/or FDA-approved epigenetic drugs:

- DNA methylation inhibitors for AML and MDS
- Histone Deacetylase Inhibitors for Lymphomas and Multiple Myeloma

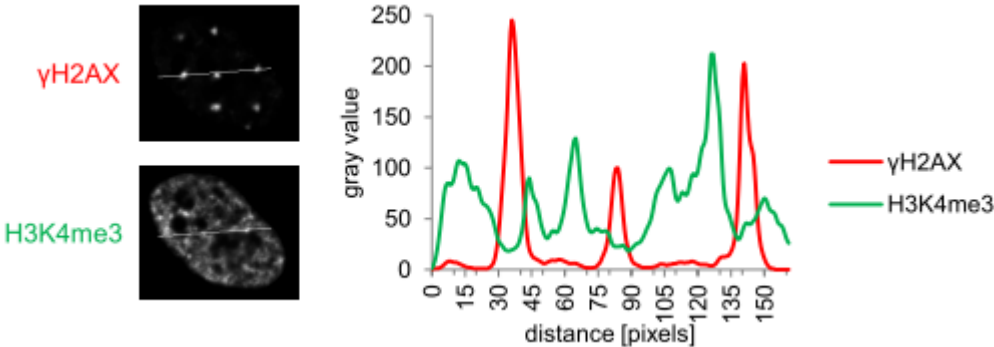
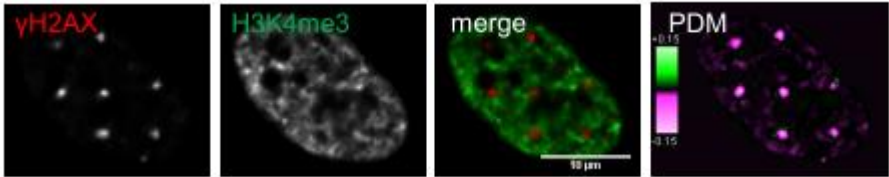




Radiation-induced long-term alterations of epigenetic patterns:

1. Left-over from repair (infrequent, at former damage site, random distribution)

e.g. exclusion of H3K4me3 at γ -H2AX foci (Seiler et al. 2011, Penterling et al. 2016)

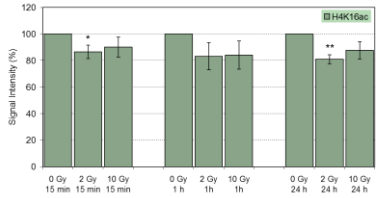
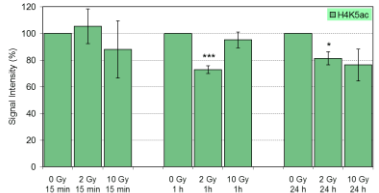
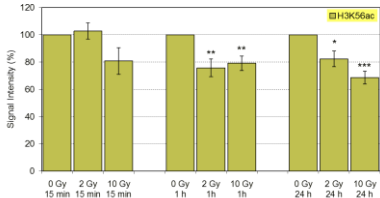
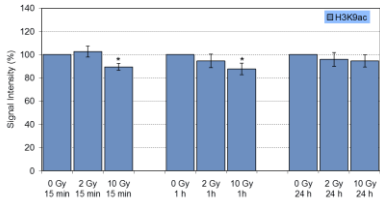
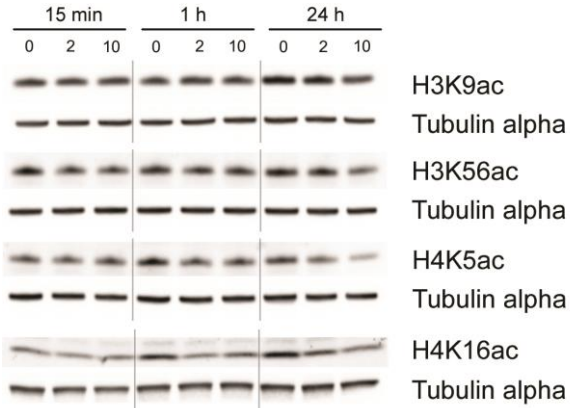


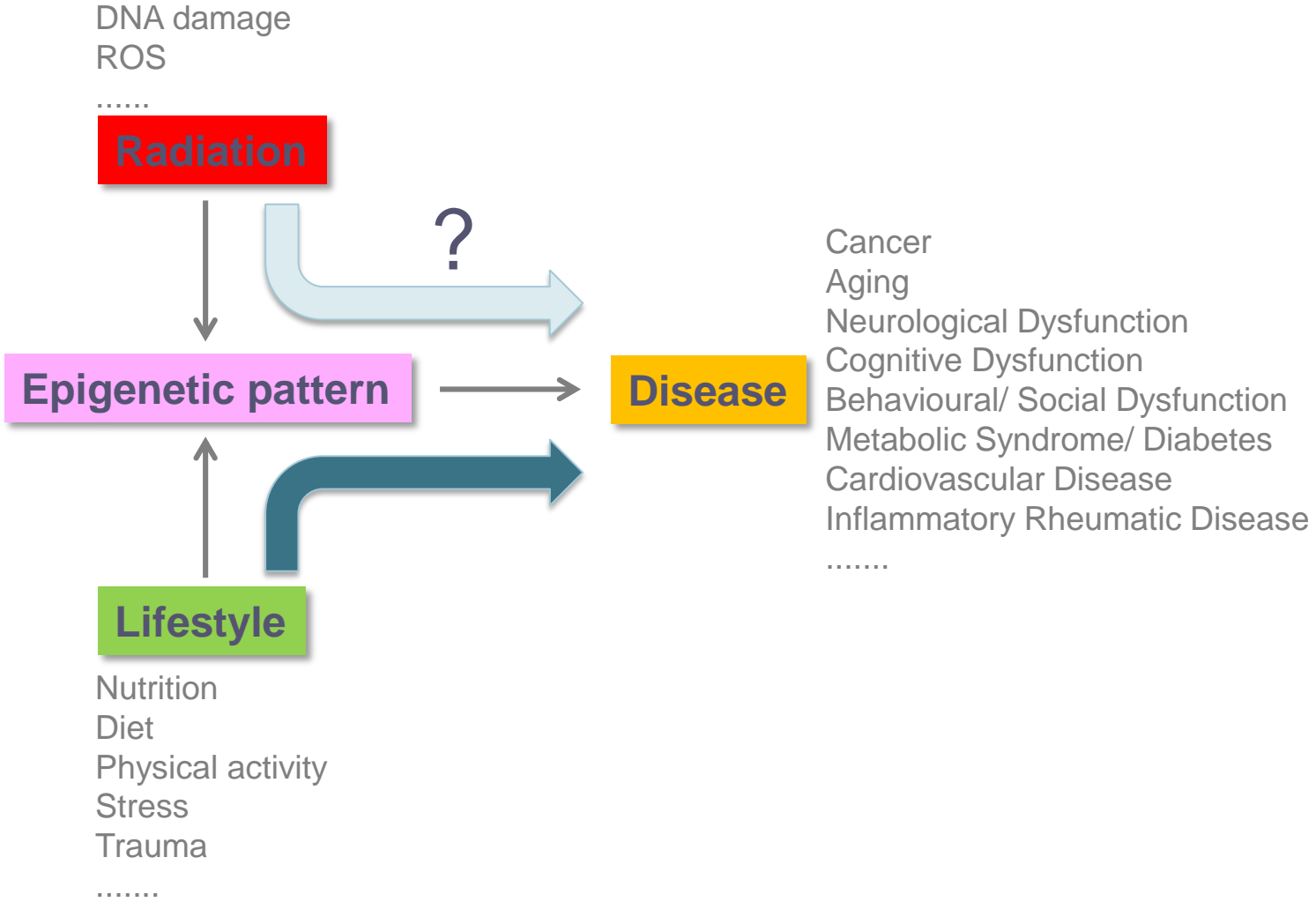
..

Radiation-induced long-term alterations of epigenetic patterns:

1. Left-over from repair (infrequent, at former damage site, random distribution)
2. Left-over from transcriptional response (infrequent, at radiation-responsive genes)
3. Result from radiation-induced alteration in enzyme activity, availability of co-factors or metabolism (frequent, global response, random distribution)

e.g. global loss of histone acetyl marks (Maroschik et al. 2014)





- Radiation-induced alterations in epigenetic patterns may lead to dysfunction and disease (in addition to genetic alterations)
- So far, little is known about dose-effect relationship and factors moderating the effects
- Lifestyle factors or therapeutical agents affecting epigenetic patterns may modulate the radiation response
- Low-level intervention by altering lifestyle factors may become a valuable strategy to reduce or reverse radiation-induced epigenetic alterations