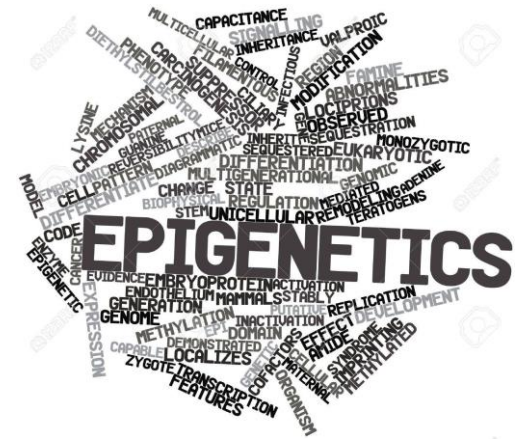
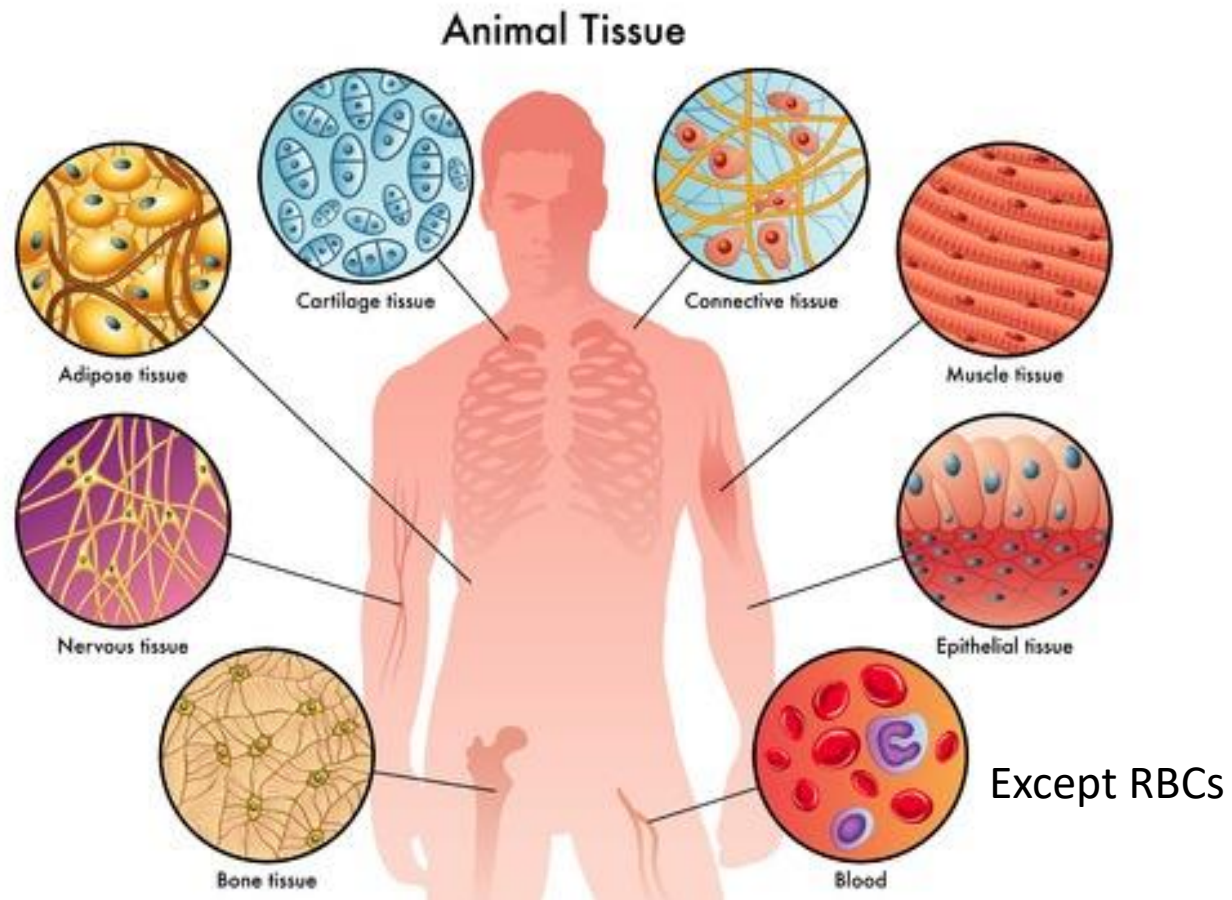


Lecture 3, Part 3

EPIGENETIC MECHANISMS OF CARCINOGENESIS



If we have the same DNA sequence in all our cells, how do we have different cell types with variations in function?



Epigenetics – a layer of control

- Heritable changes in gene expression not attributable to alternations in DNA sequence
- Epigenetic changes modify the activation of certain genes, but not the genetic code - sequence of DNA
- Common epigenetic changes:
 - DNA modification
 - Histone modification
 - ncRNA expression (functional RNA molecule, not translated to protein)

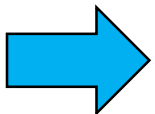
Dynamic process
modifications:
4 DNA
16 histone

Main epigenetic processes

- DNA methylation
 - Genome wide hypomethylation → transcriptional **activation** (oncogenes)
 - Promoter-specific hypermethylation → transcriptional **silencing** (tumor suppressor genes)
- Chromatin modifications
 - At histone lysine tails



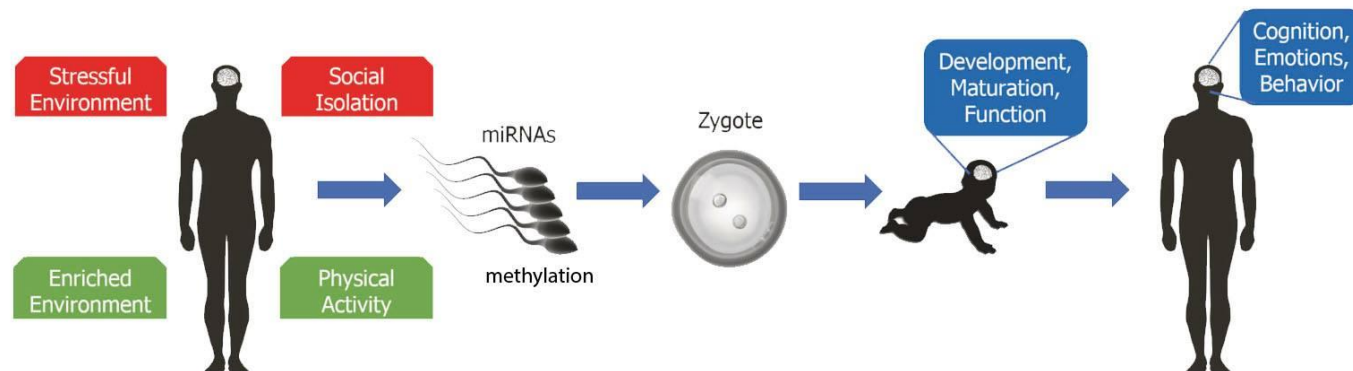
Activation and Silencing



Mediate reprogramming during development and maintenance of cell identity during the life of an organism

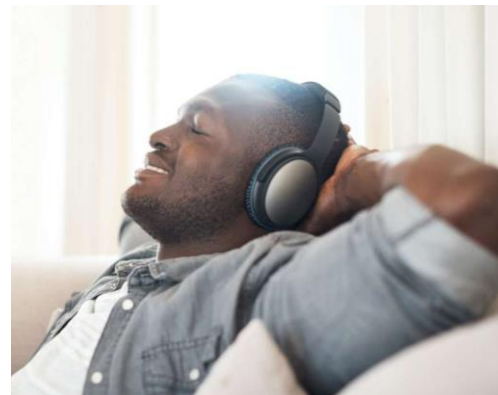
Epigenetic inheritance

- **Epigenetic inheritance** goes against the idea that **inheritance** happens only through transfer of the DNA code from parent to offspring.
- It means that a parents **epigenetic** tags can be passed down to future generations.
- Trans-generational epigenetic inheritance



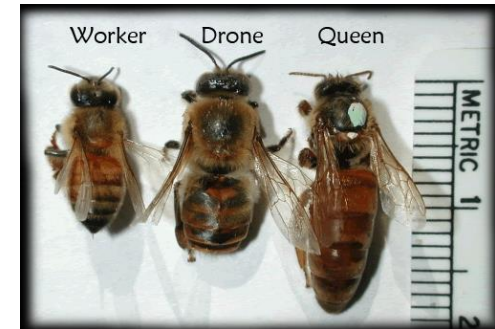
The changing epigenome

- Diet and environment are the biggest factors in epigenetic changes over lifespan

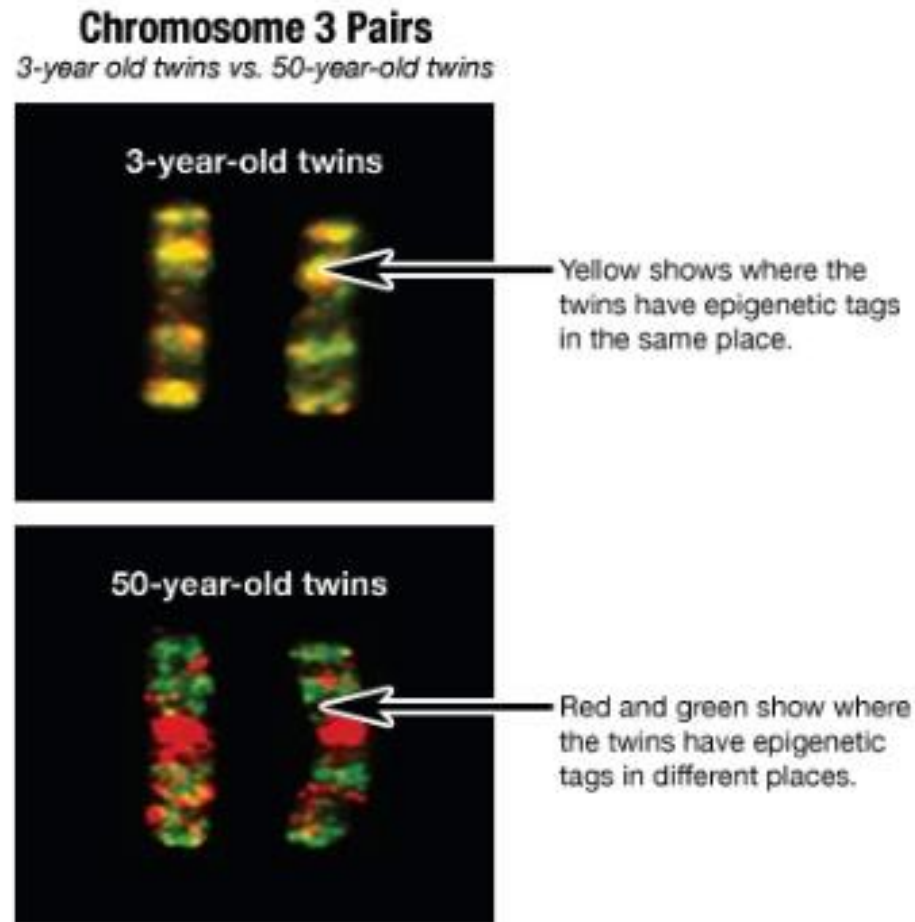


Nutrition and epigenetics

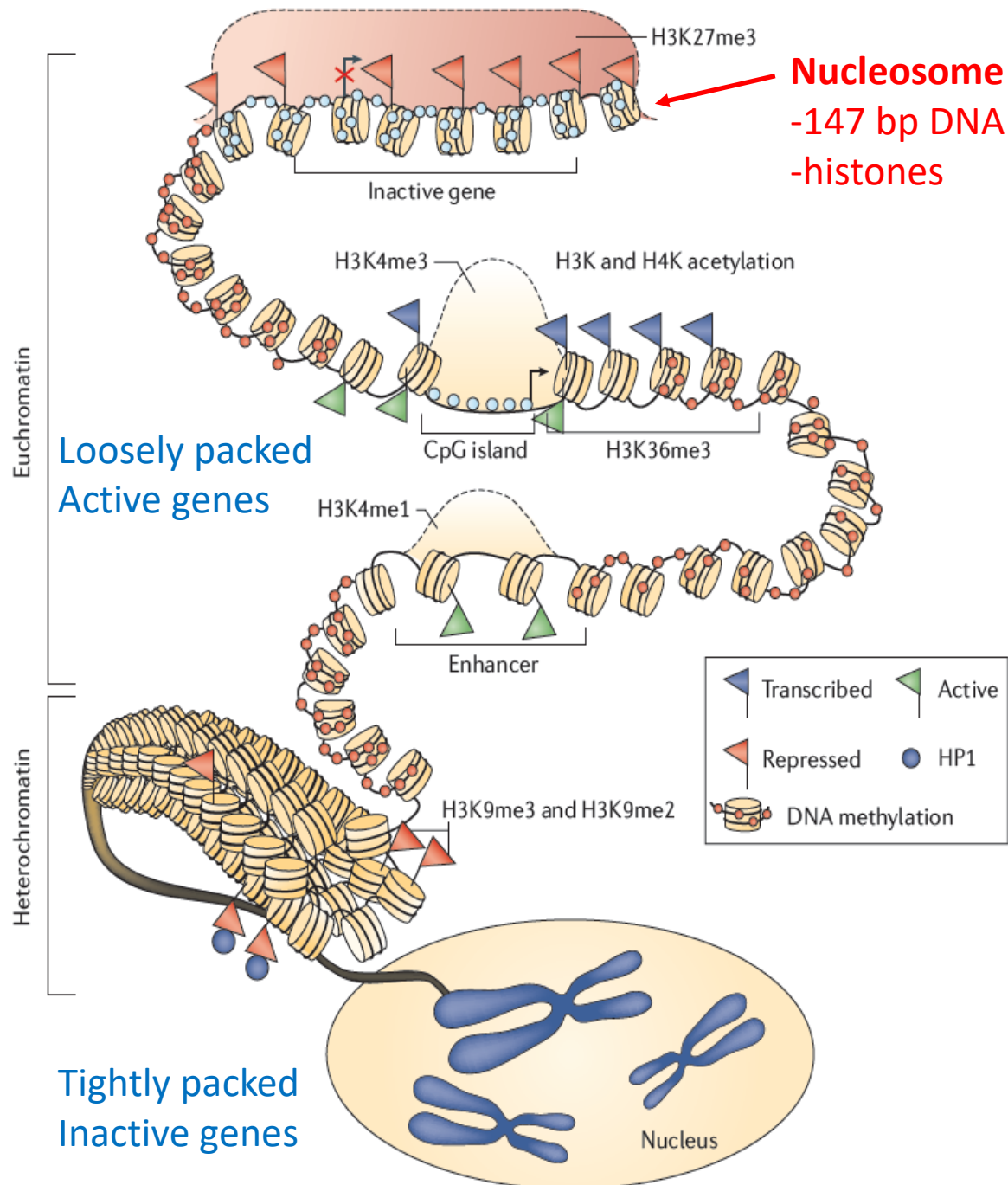
- What we can learn from bees:
- Queen bees and worker bees are genetically similar
- Worker bees are sterile, Queens are fertile
- Queen – fed royal jelly from larvae stage
 - Develops ovaries and large abdomen
- Workers – fed nectar and pollen
 - Inactive ovaries, sterile, smaller in size



Environment and epigenetics: Identical twins



Epigenome

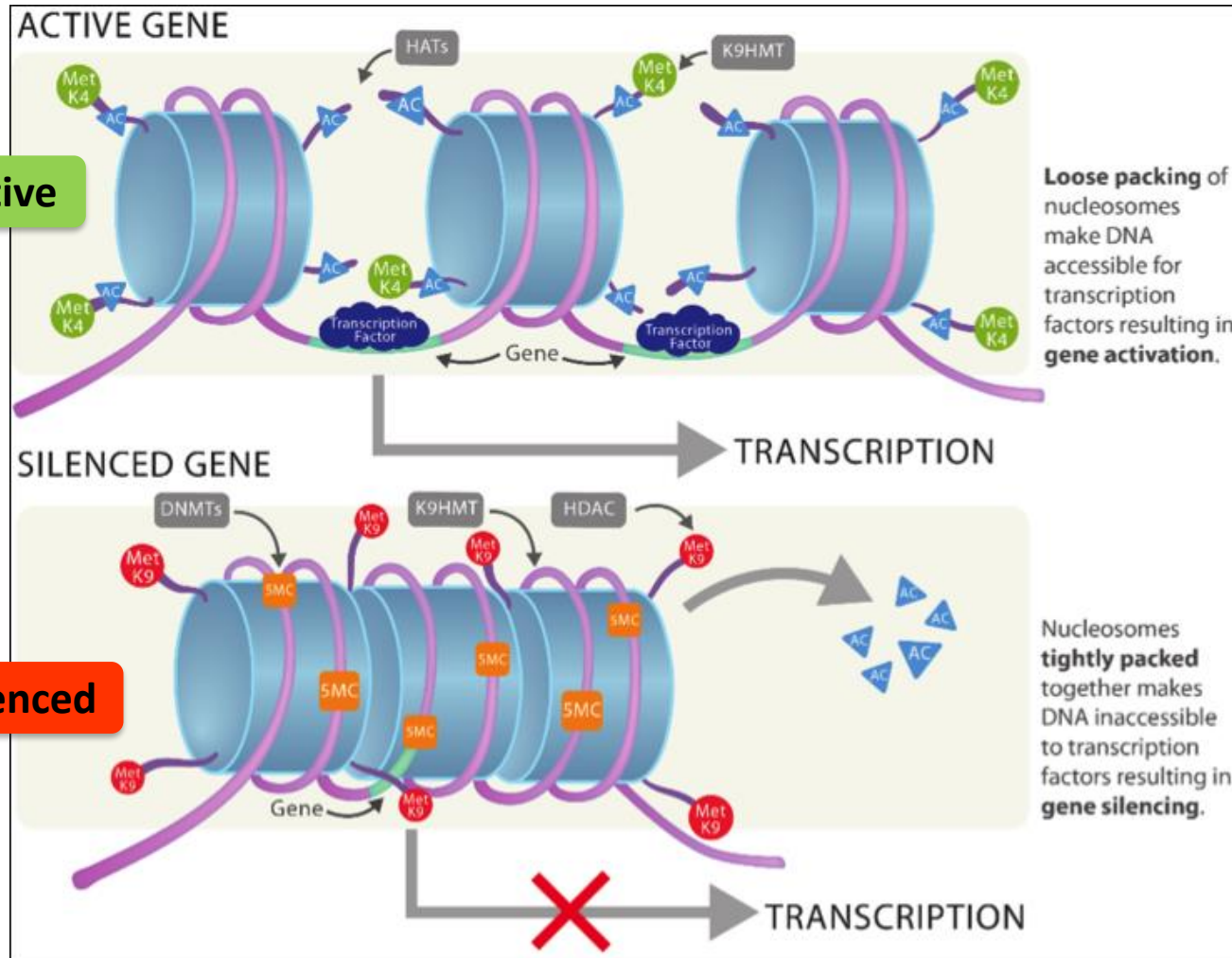


- Balanced state of chromatin, nucleosome positioning and DNA methylation
- Repressive vs enhancing modifications for histones and DNA
 - Methylation and acetylation of DNA and histones
- Bottom line for cancer:** altered DNA and histone modification status influences transcriptional regulation of oncogene and tumor suppressor genes

Epigenetic modifications

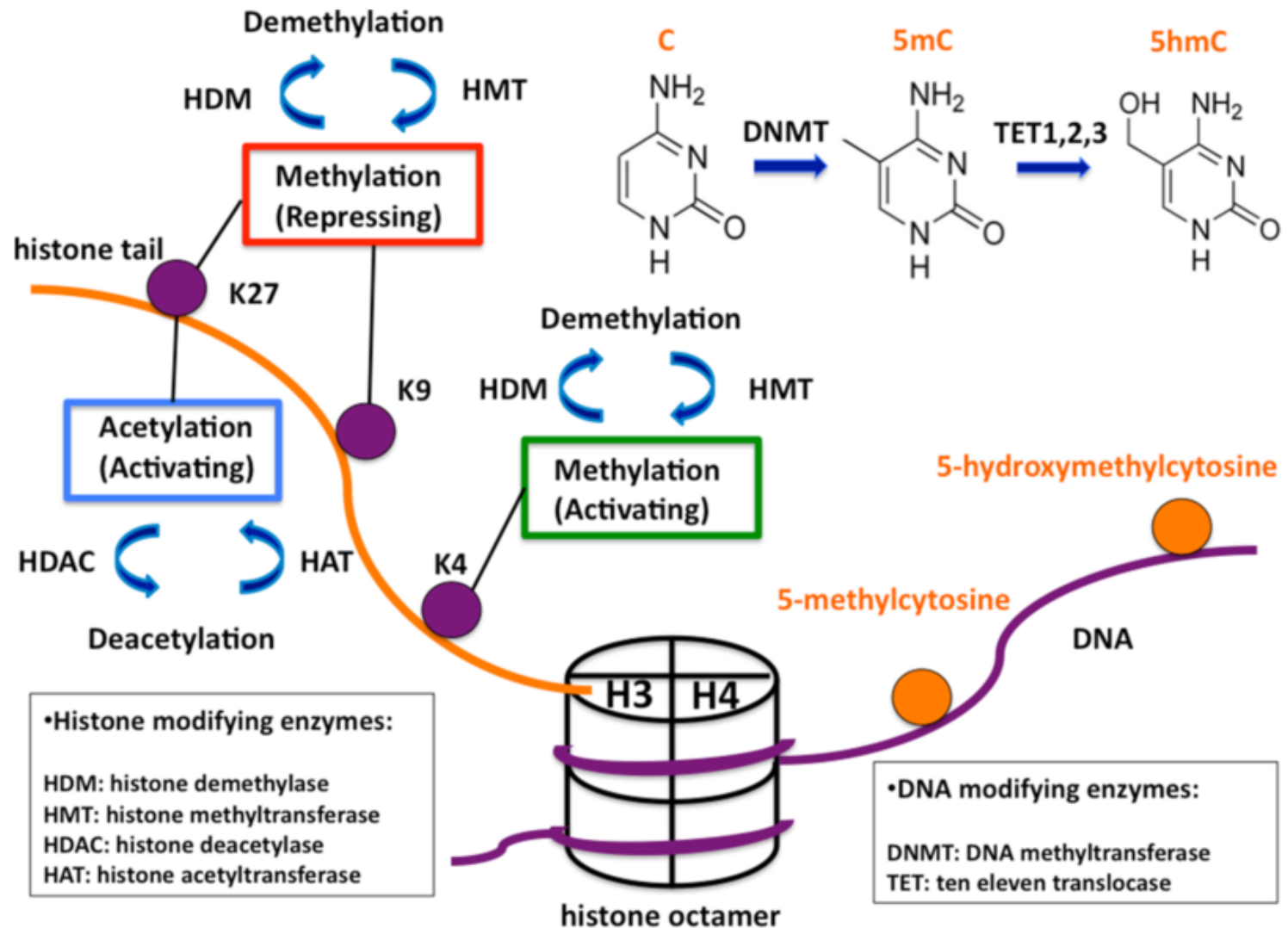
- DNA modifications = 4
- Histone modifications = 16
- Menti.com: histone acetylation

Histone modifications: 2 methylations with varying biological effects

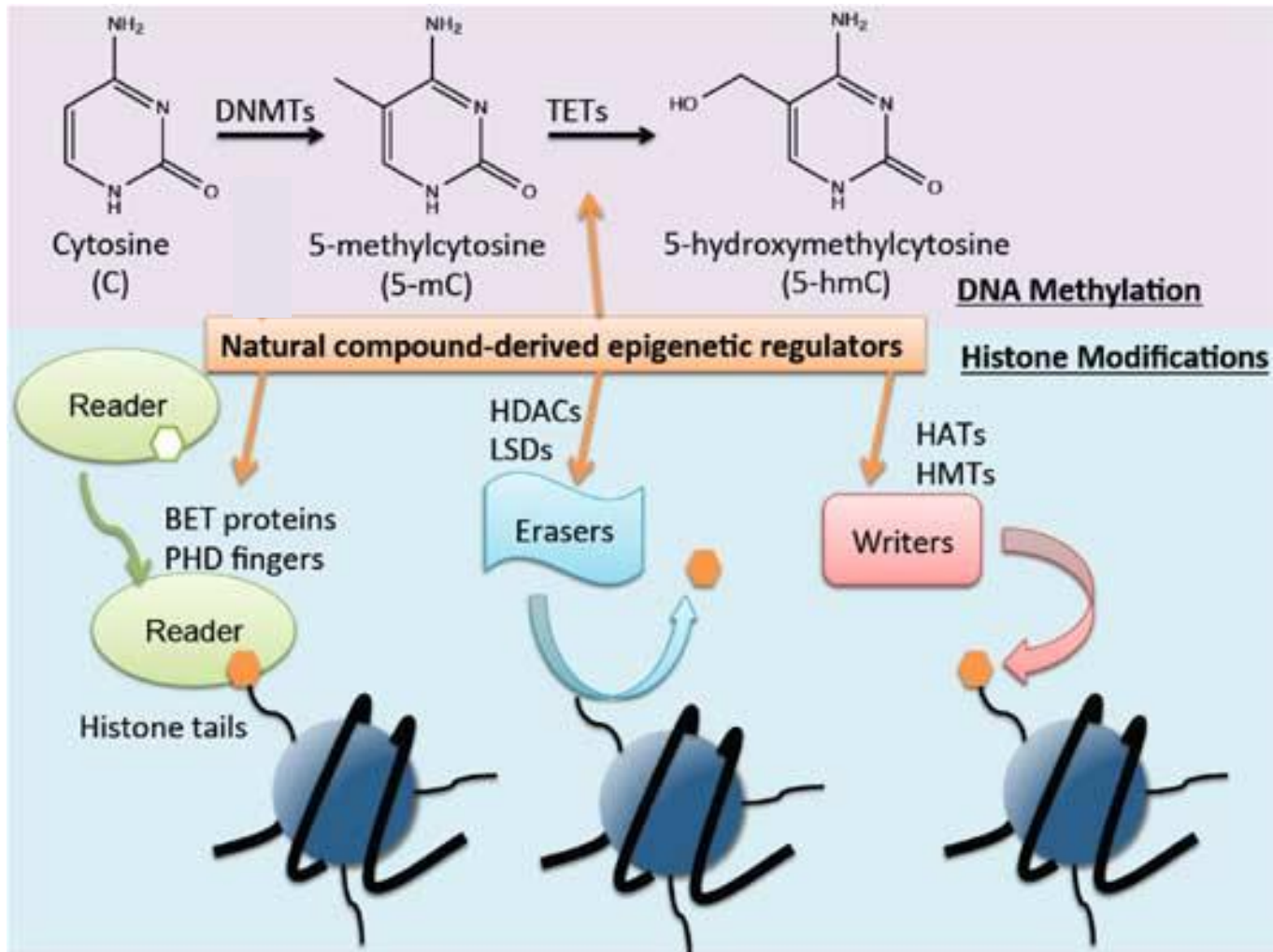


Histone methylation can be associated with either transcriptional repression or activation

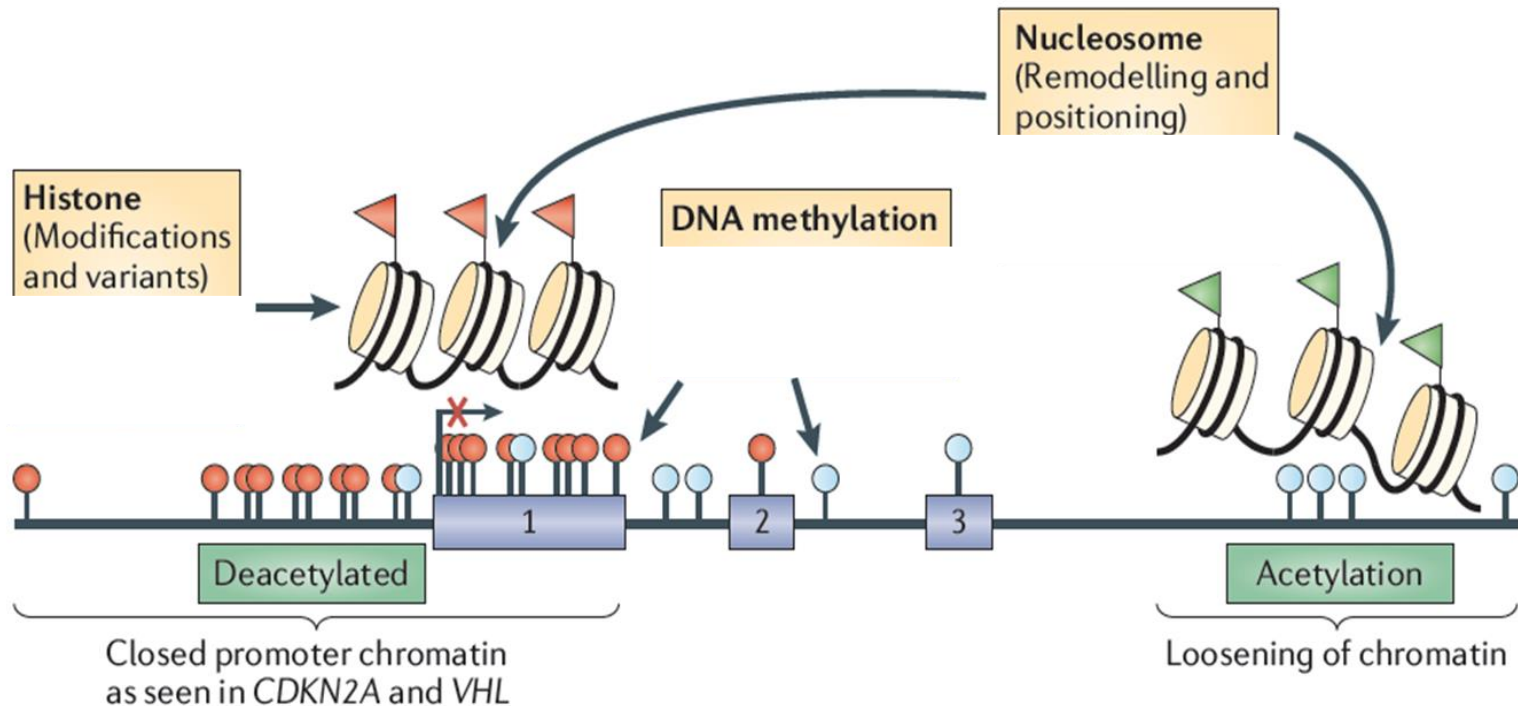
Epigenetic modifications are dynamic



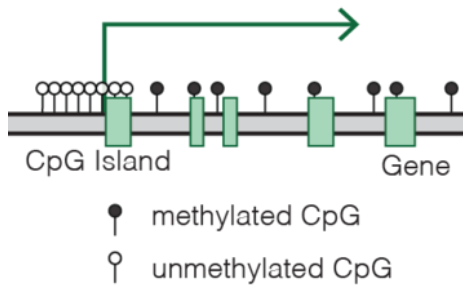
Writers, Readers and Erasers



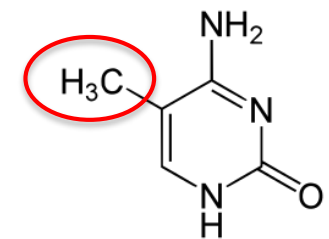
Cancer Epigenome (reprogramming)



- cancer epigenome is characterized by **global losses in DNA methylation** (pale blue circles)
- certain genes have **abnormal gains of DNA methylation** (red circles) and repressive histone modifications (red flags) in promoter region CpG islands (-> tumor suppressor regions)

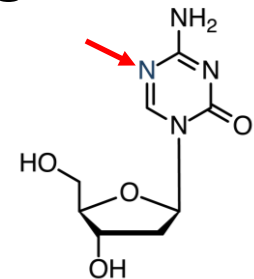


CpG Island



5-MethylC

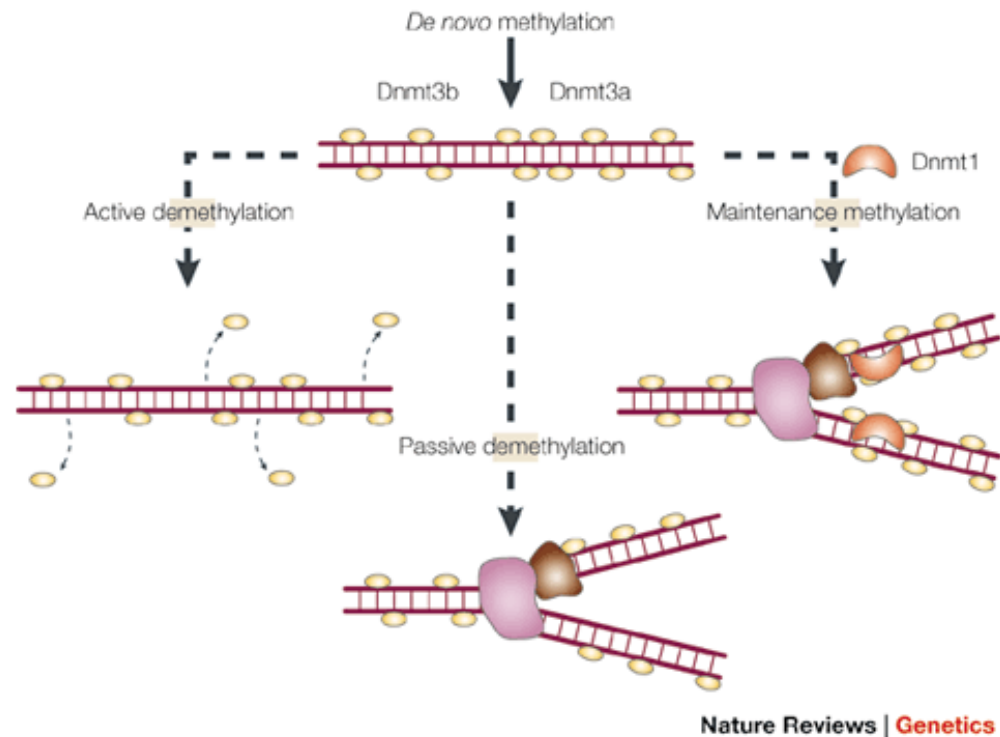
- DNA region of >500 bp that has a high CpG density
- CpG islands are found upstream of many mammalian genes
- DNA methylation often inhibits the transcription of genes, usually around a promoter region (CpG islands occur near many gene promoters)
- There are about 29,000 regions in the human genome
- Potential biomarkers for cancer
- Decitabine is a hypomethylating agent for the treatment of acute myeloid leukemia (AML) (inhibits DNMT methylation)



5-aza-2'-deoxycytidine
(decitabine)

DNA Methyltransferases (DNMT)

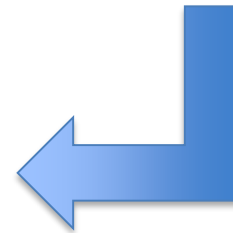
- DNA methylation occurs in the dinucleotide CpG
- Methyl groups added to C bases by the enzymes **DNMT3a** and **DNMT3b**
- When DNA is replicated, the methyl group on the template strand is recognized and a new one is introduced on the opposite (daughter) strand by the enzyme **DNMT1**
- **DNMT1** associated with the replication machinery



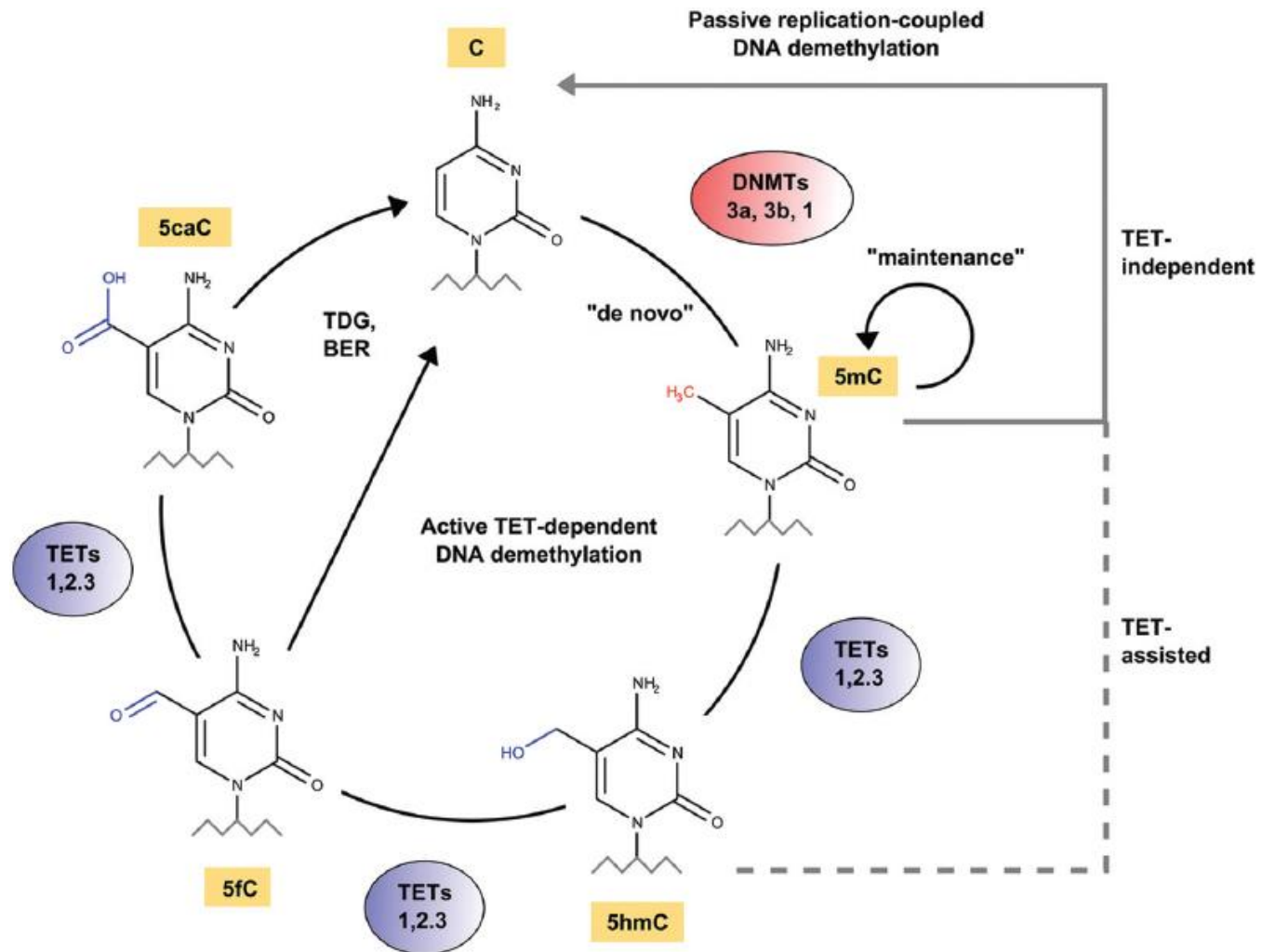
DNMT enzymes

- DNA methylation patterns tend to be maintained (maintenance methylation)
- Demethylation can occur in the absence of DNMT1 with:
 - continued rounds of DNA replication (passive demethylation)
 - Without DNA replication (active demethylation)

TET enzymes



Dynamic modifications for Cytosine



TET enzymes and cancer

- TET proteins regulate gene transcription by controlling 5-hmC, 5-formylC and 5-carboxyC levels
 - involved in modulating chromatin structure
- TET 2 is mutated in a wide variety of cancers, TET 1 and 3 mutations are rare
- TET 2 mutations impart a non-functional enzyme leading to methylation imbalance
 - e.g. hypermethylation at tumor suppressor genes
- For drug development it is difficult to directly target TET for cancer treatment because they are inactivated in cancer

Normal

Cancer

Epigenetics

- DNA methylation
- Histone modification
- Noncoding RNA

**Alteration
of epigenetic enzymes**

**Genome
instability**

Genetics

- Point mutation
- Deletion
- Amplification

