LEIDS UNIVERSITAIR MEDISCH CENTRUM

Leren lezen en schrijven met het epigenoom

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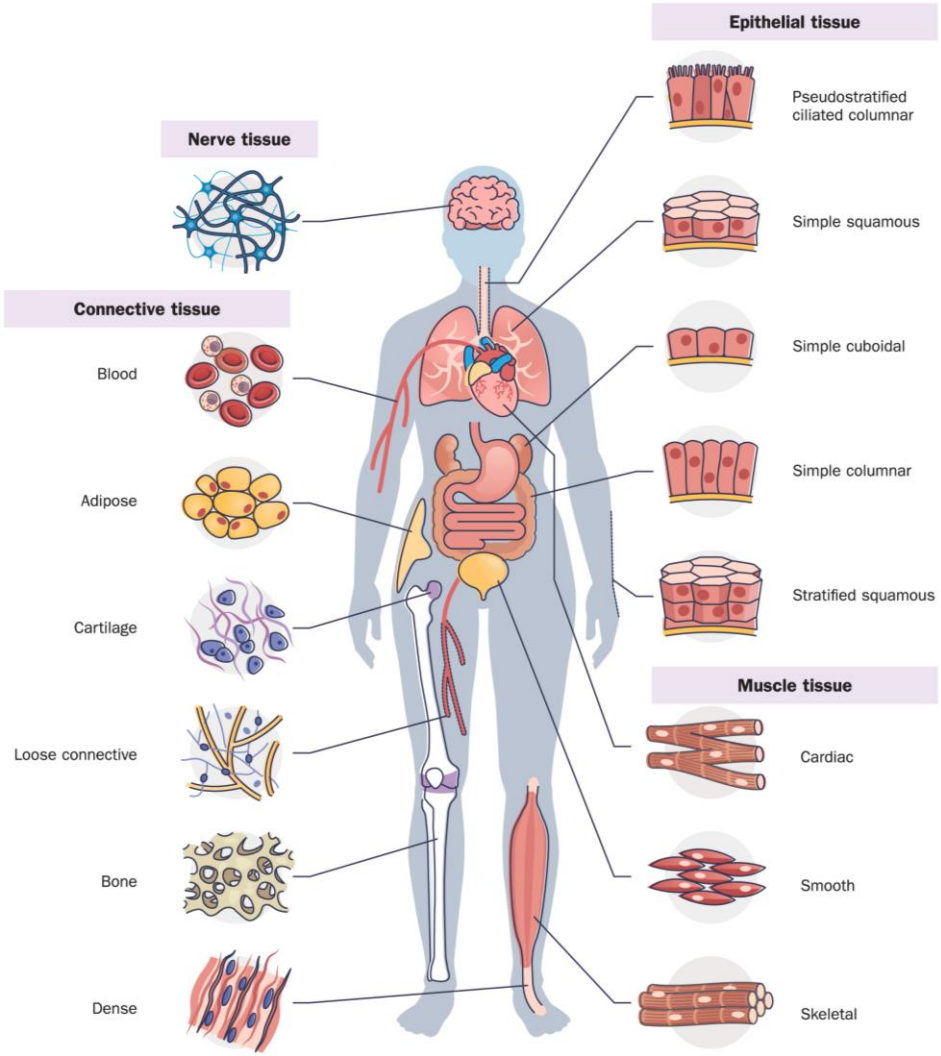
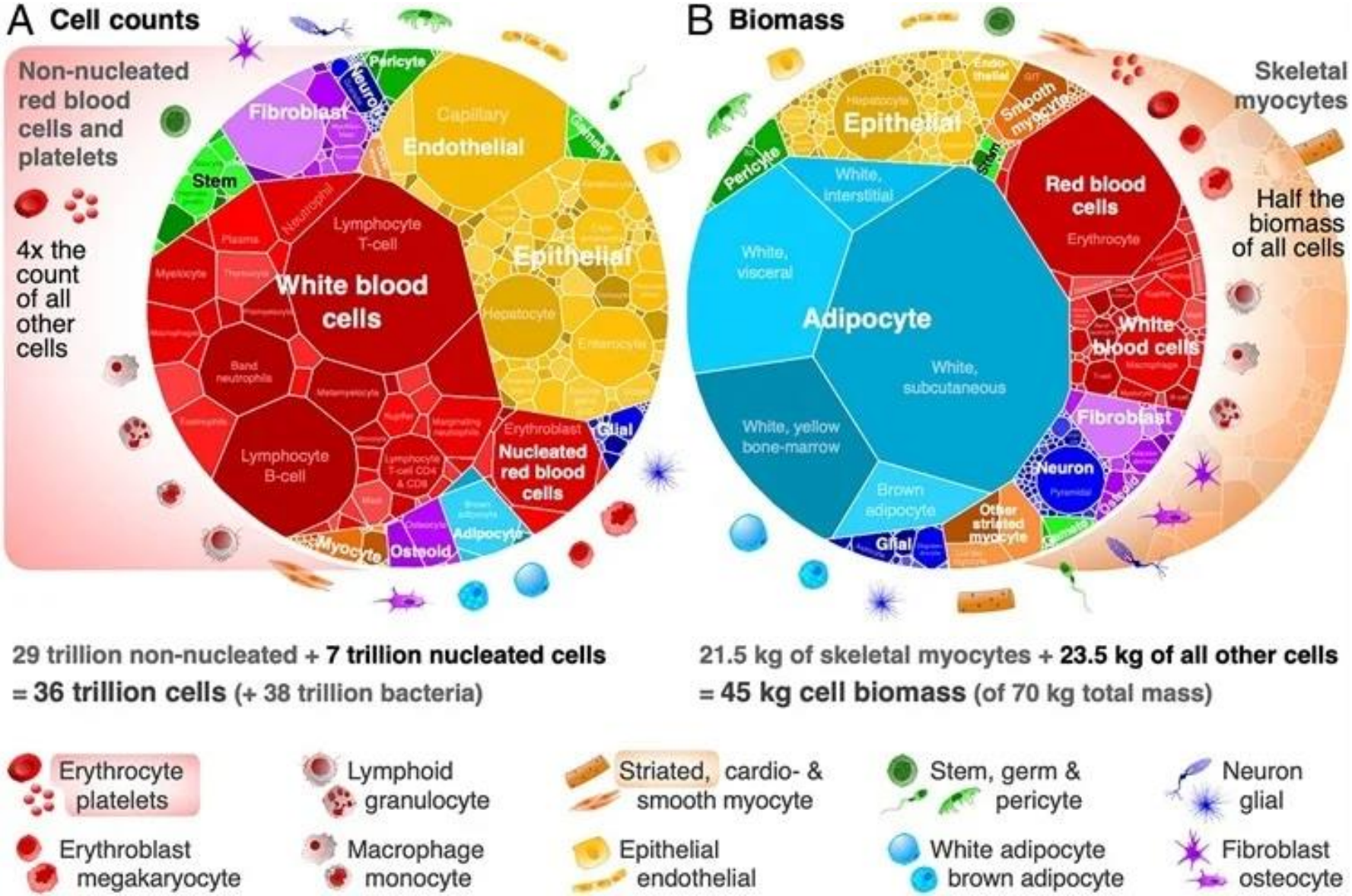
one genotype → many phenotypes



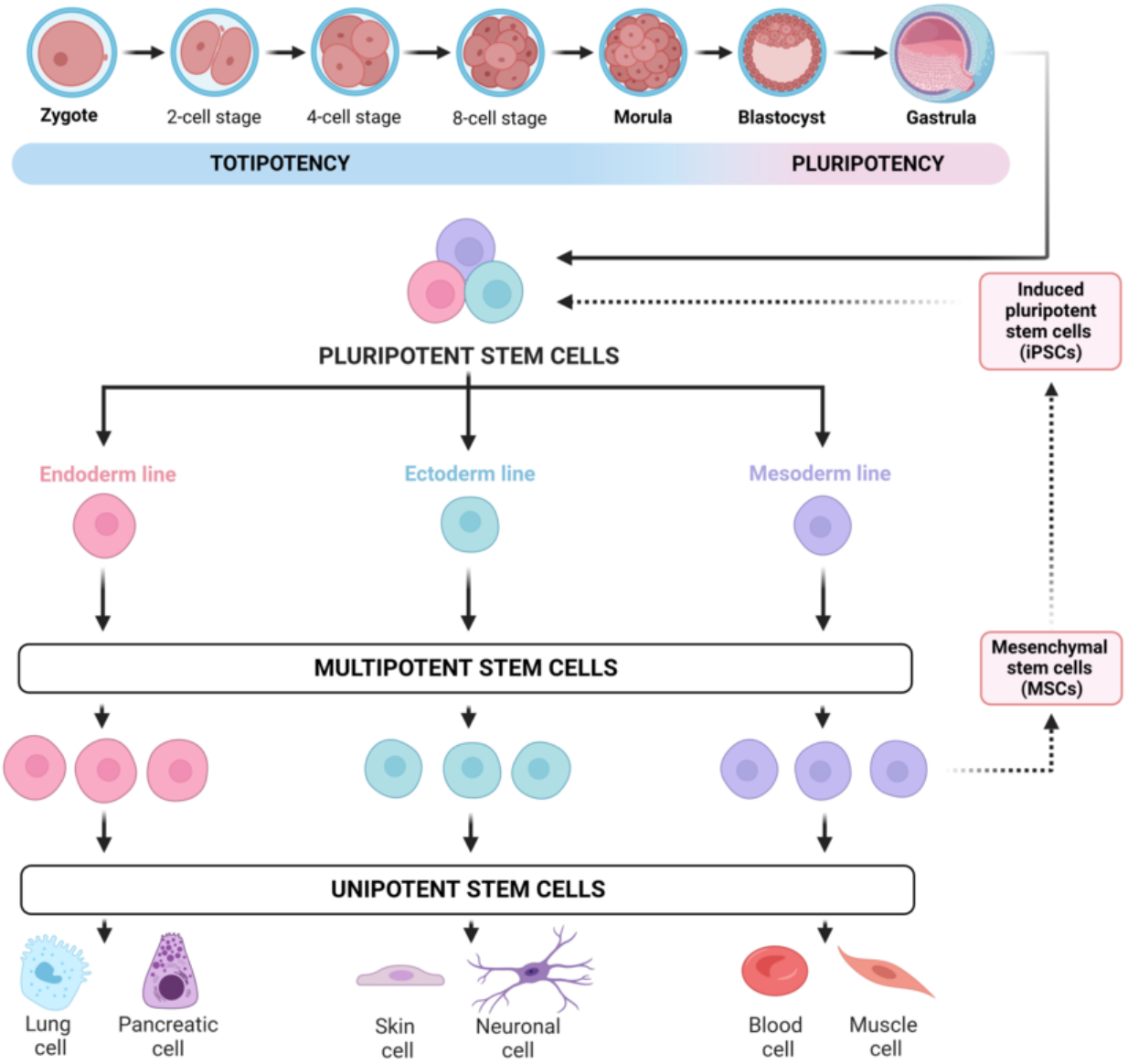
- The human body contains many different cell types
- These cell types contain basically the same genetic information except for germ cells (haploid), erythrocytes (anuclear) & cancer cells (aneuploid).
- Each human cell type expresses a unique part of the genome (housekeeping genes + cell type-specific genes).
- The phenotype of cells is affected by environmental factors, but the basic identity of each cell type is maintained throughout (healthy) life.
- Under normal conditions also the ratios between different cell types in human tissues/organs are very constant.

one genotype → many phenotypes

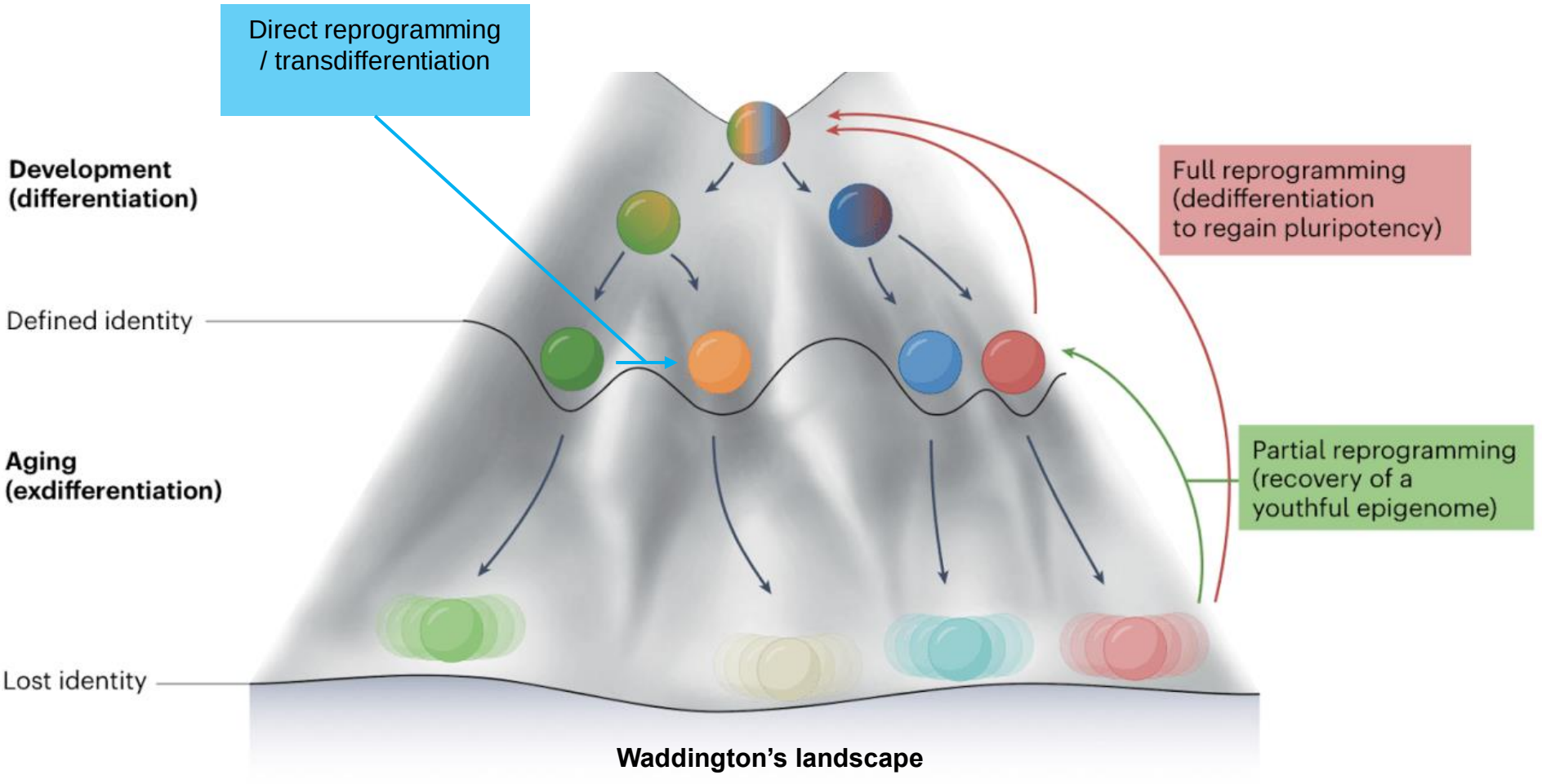


https://humancelltreemap.mis.mpg.de/

cell differentiation I



cell differentiation II



Waddington's landscape

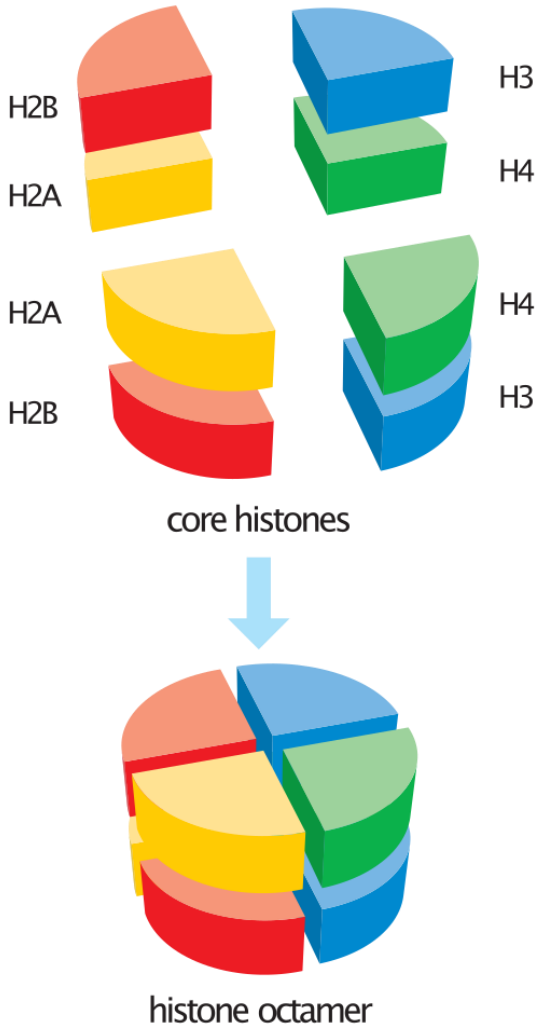
https://novoslabs.com/epigenetics-and-aging/

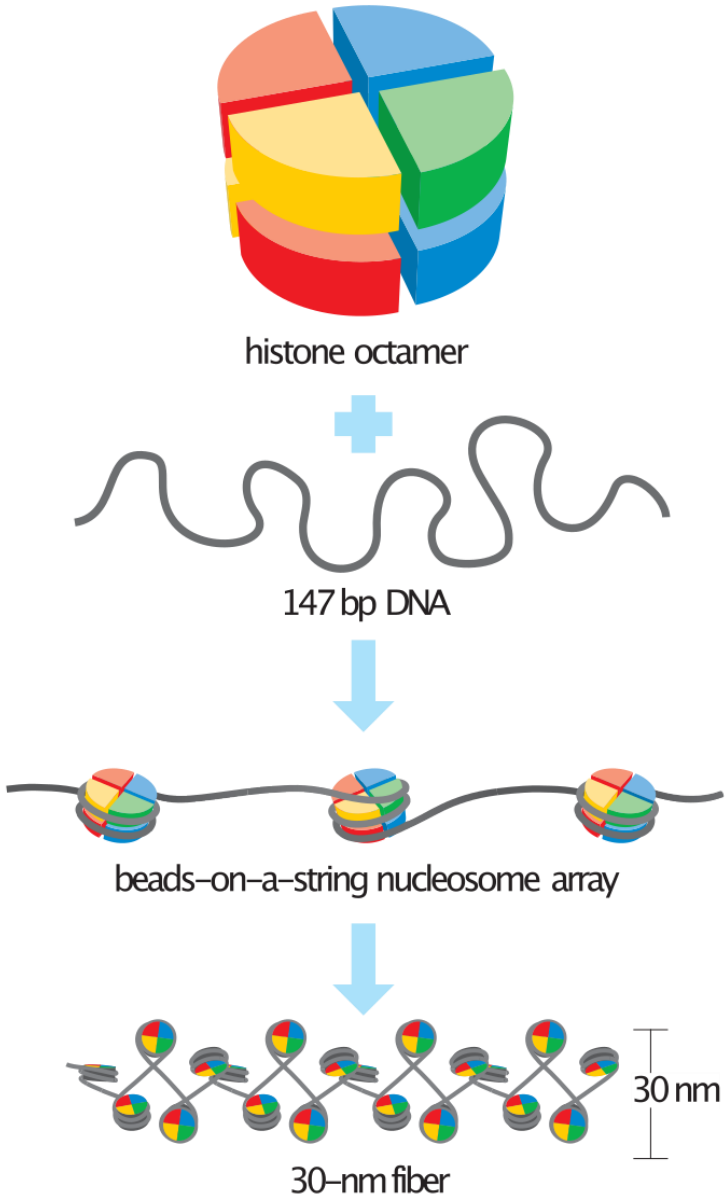
cell identity determinants

How is cell identity established and maintained?

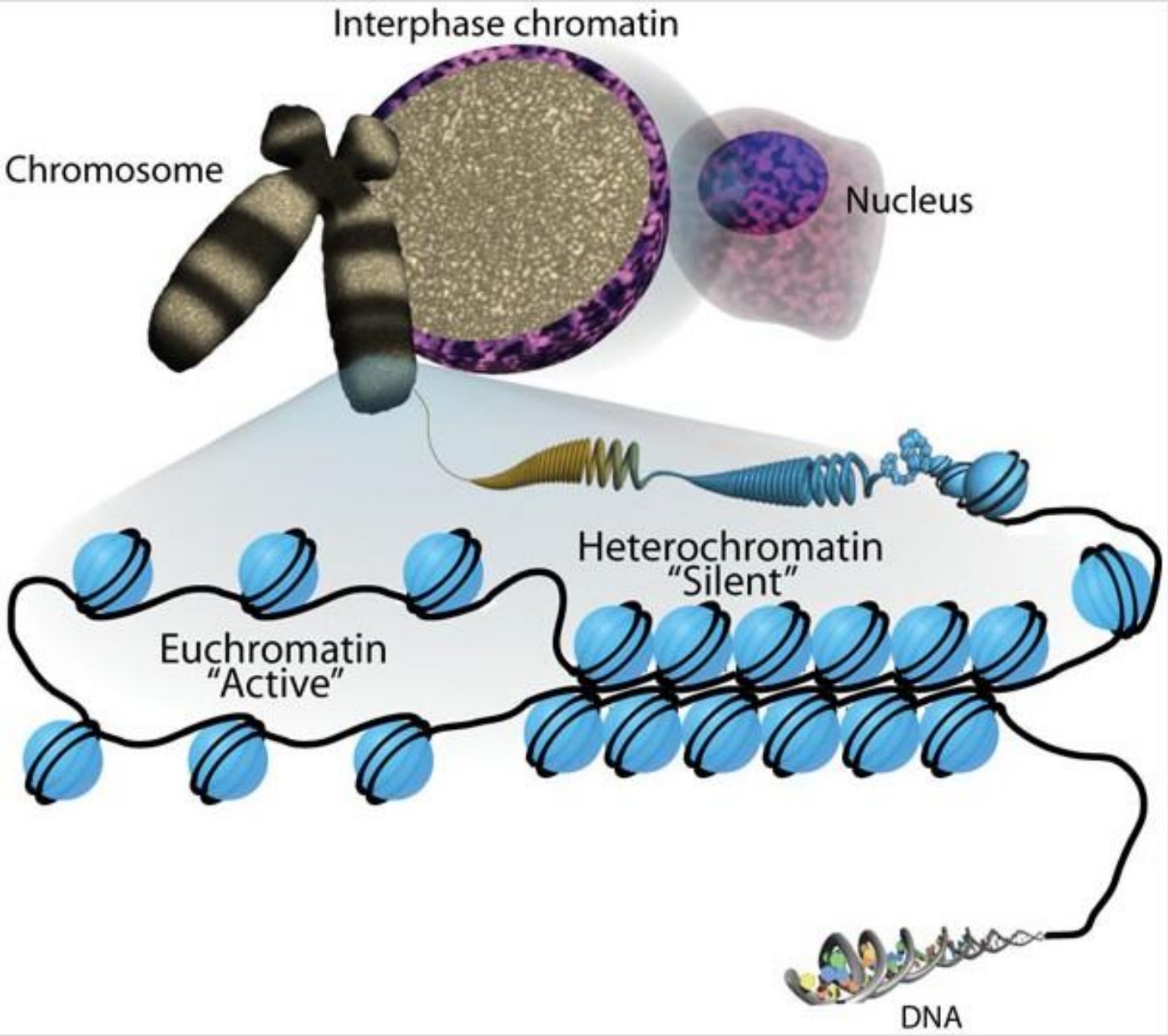
- environmental stimuli (→ cell signaling)
- transcription factors
- non-coding RNAs
- the epigenome

nucleosomes



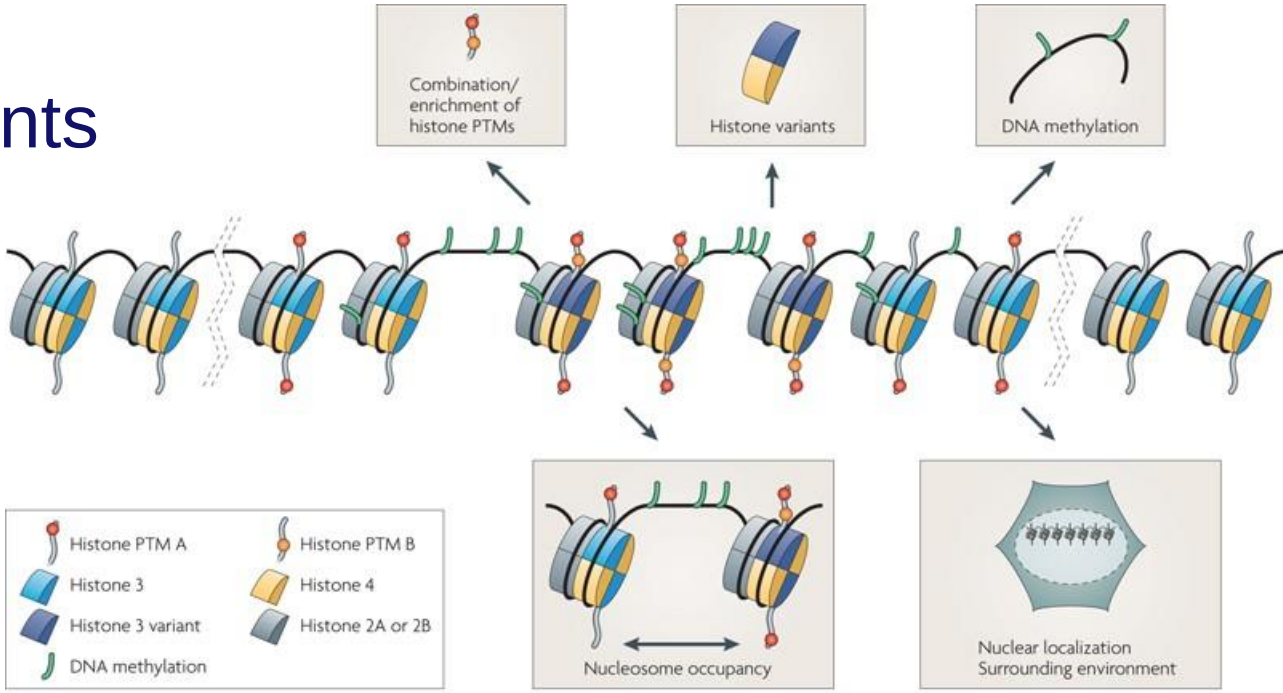


heterochromatin vs. euchromatin



epigenetic information

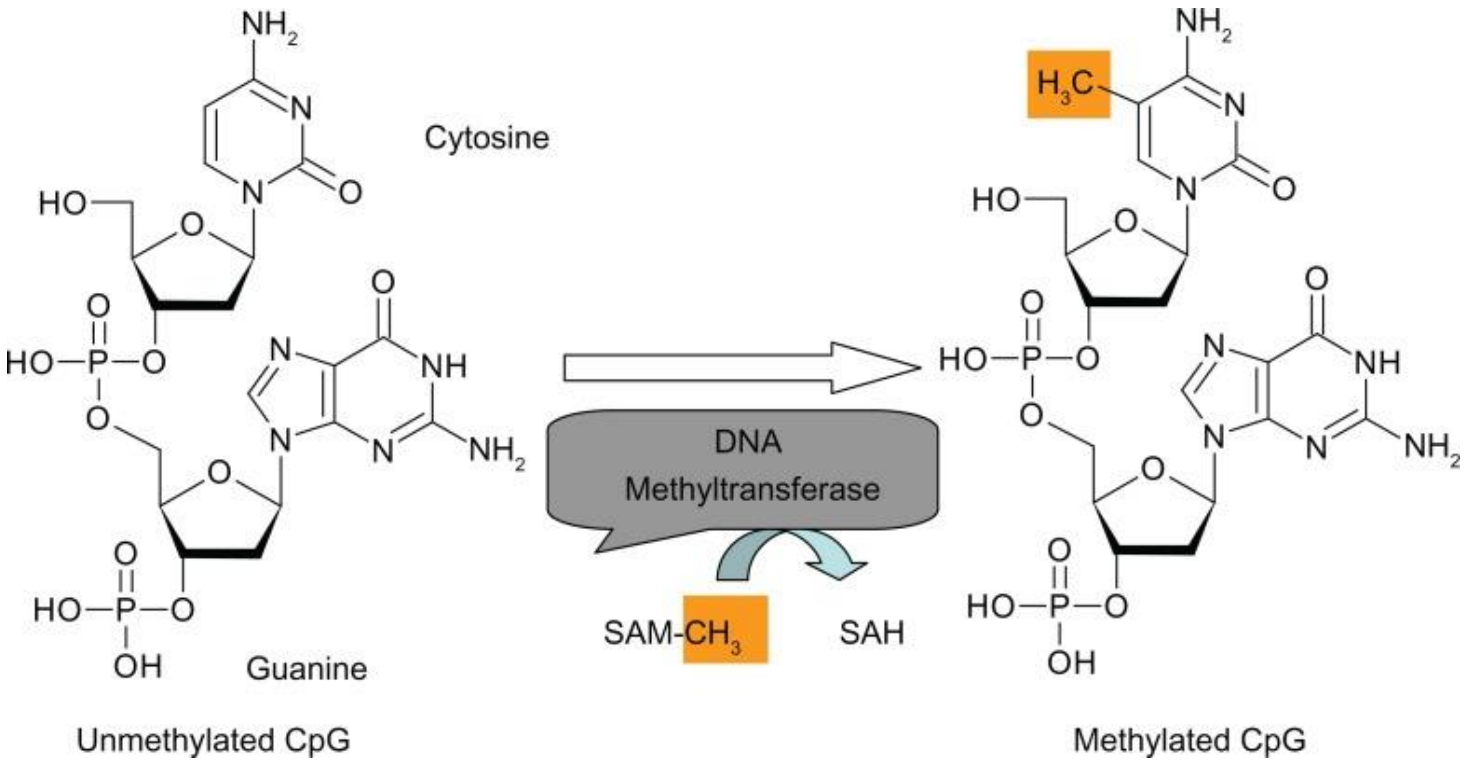
- DNA methylation
- histone posttranscriptional modifications (PMTs)
- chromatin architecture (nucleosome occupancy & looping)
- histone variants



Margueron & Reinberg. Nat Rev Genet 2010;11:285

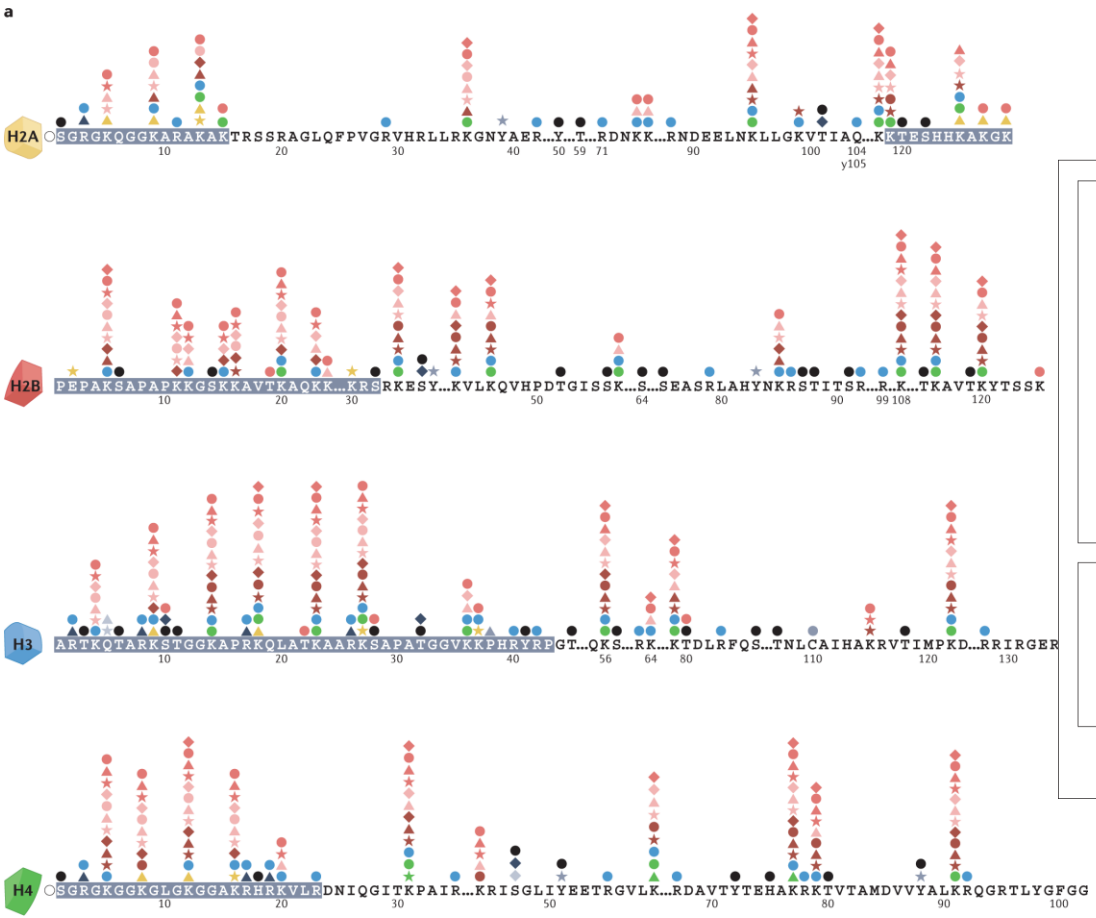
DNA methylation

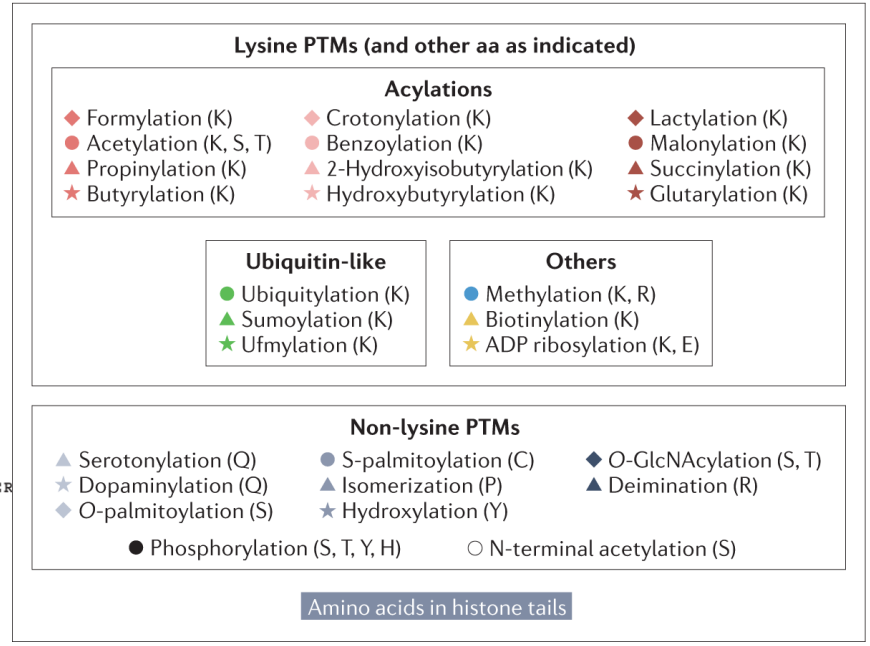
- Occurs at cytidine residues.
- Performed by DNA methyltransferase DNMT1, DNMT3A & DNMT3B.
- Methyl groups can be actively (methylcytosine dioxygenases TET1, TET2 & TET3 and base excision repair) or passively (DNA replication lost)
- Ageing alters genomic DNA methylation patterns towards pathogenic profiles.



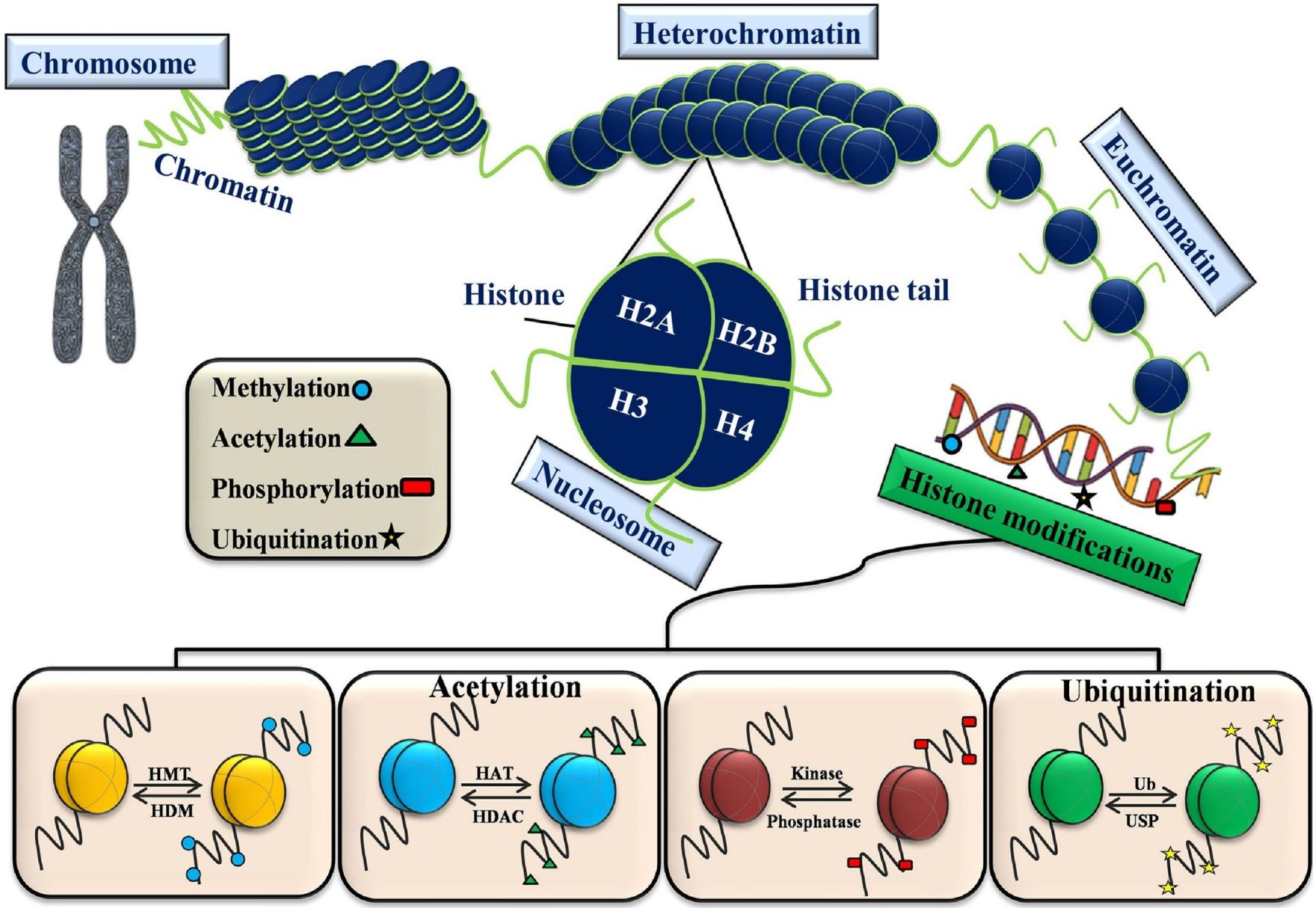
histone PTMs

- Histones can be modified at many positions by all kinds of PTMs, which either stimulates or represses gene expression.

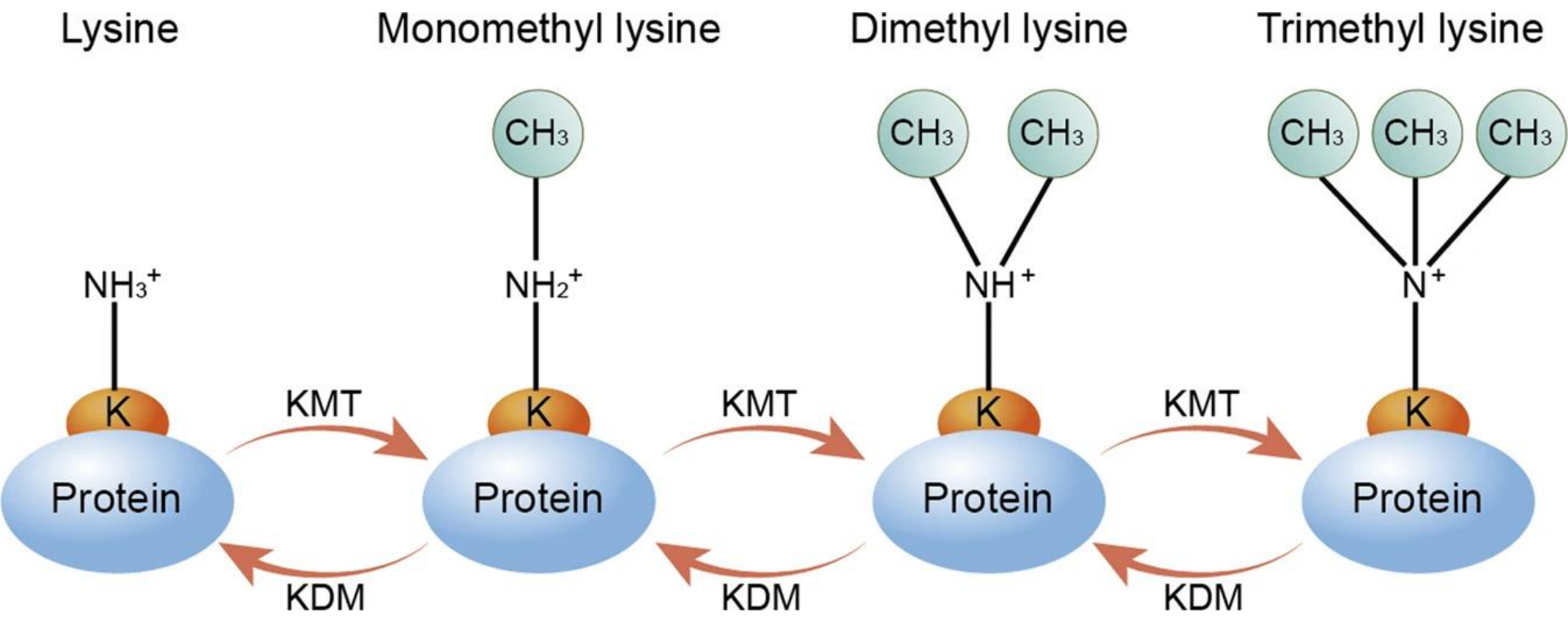




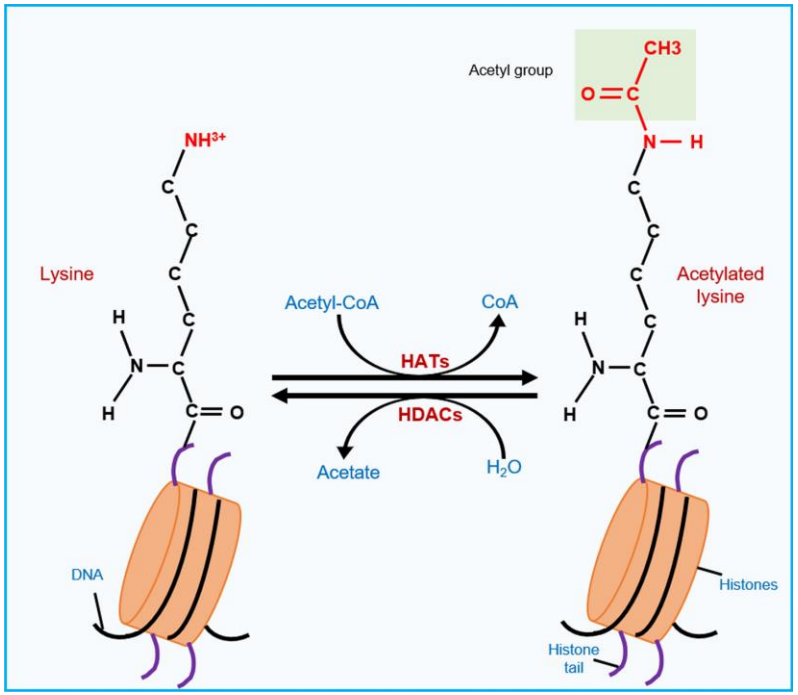
histone PTMs

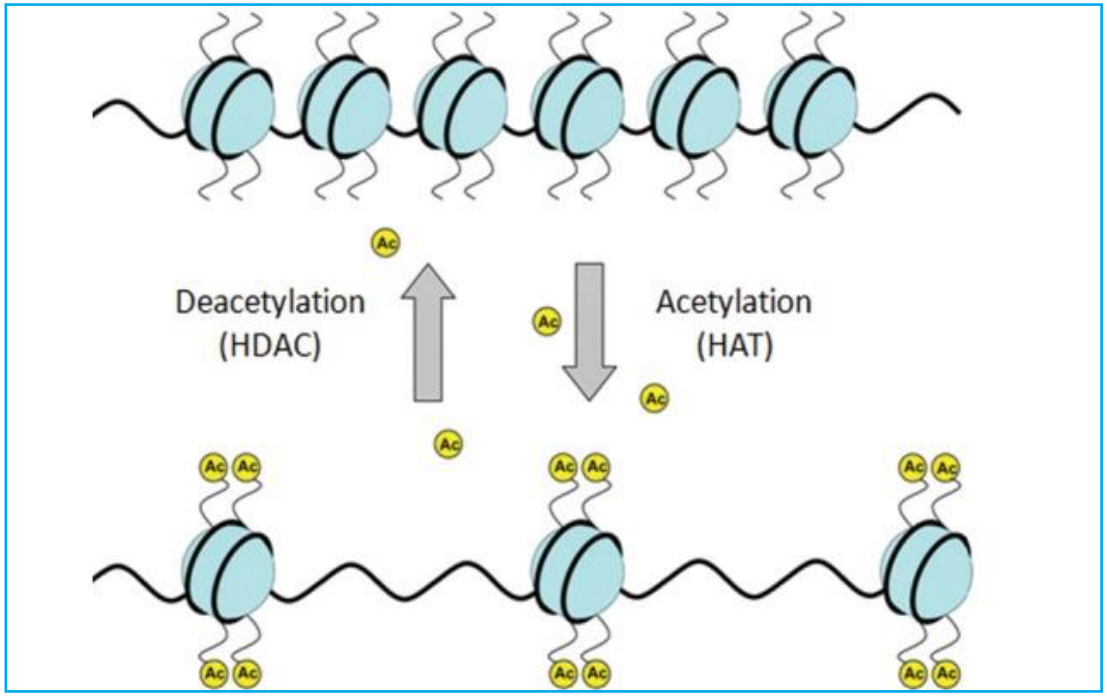


histone (de)methylation

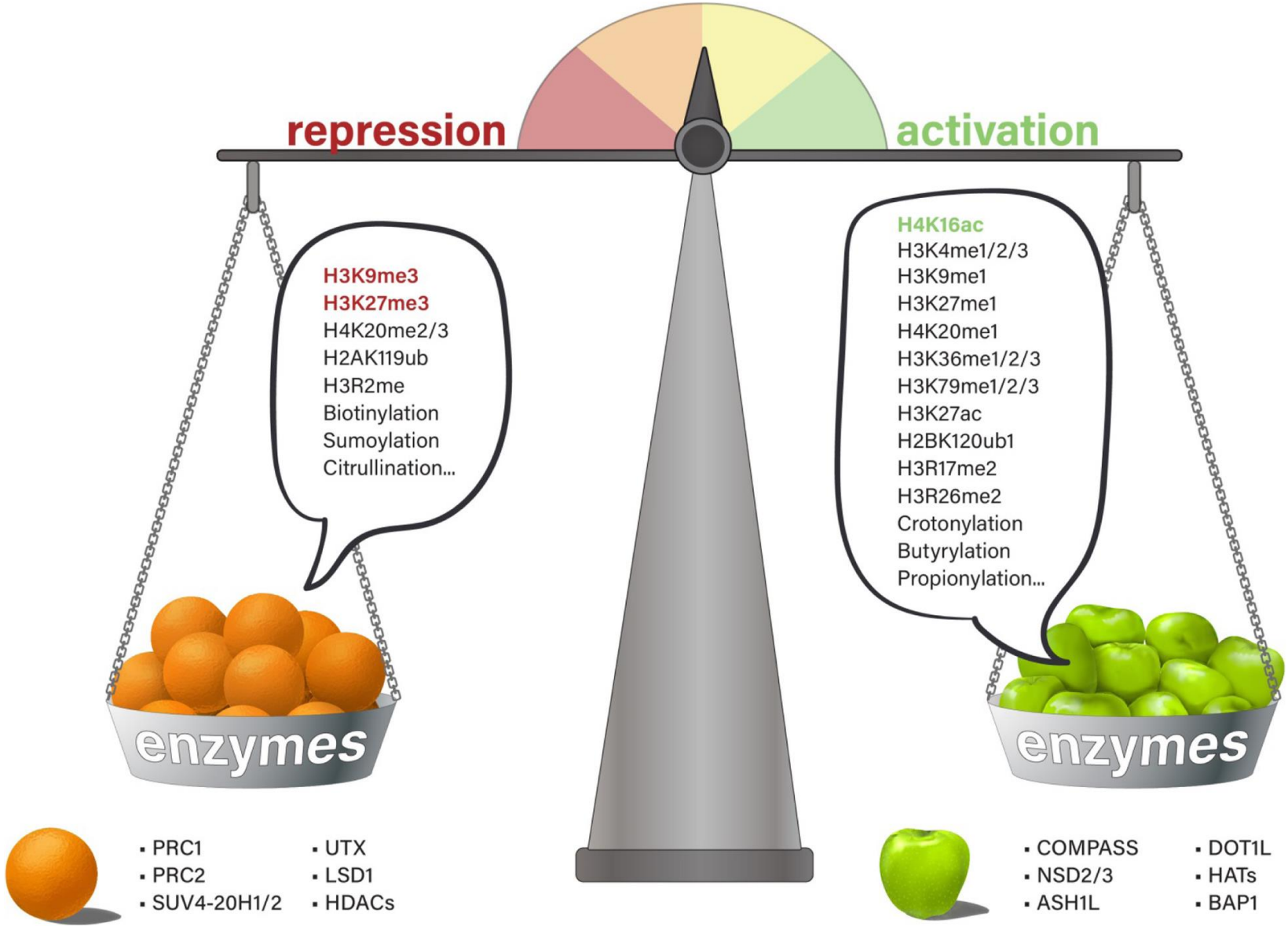


histone (de)acetylation



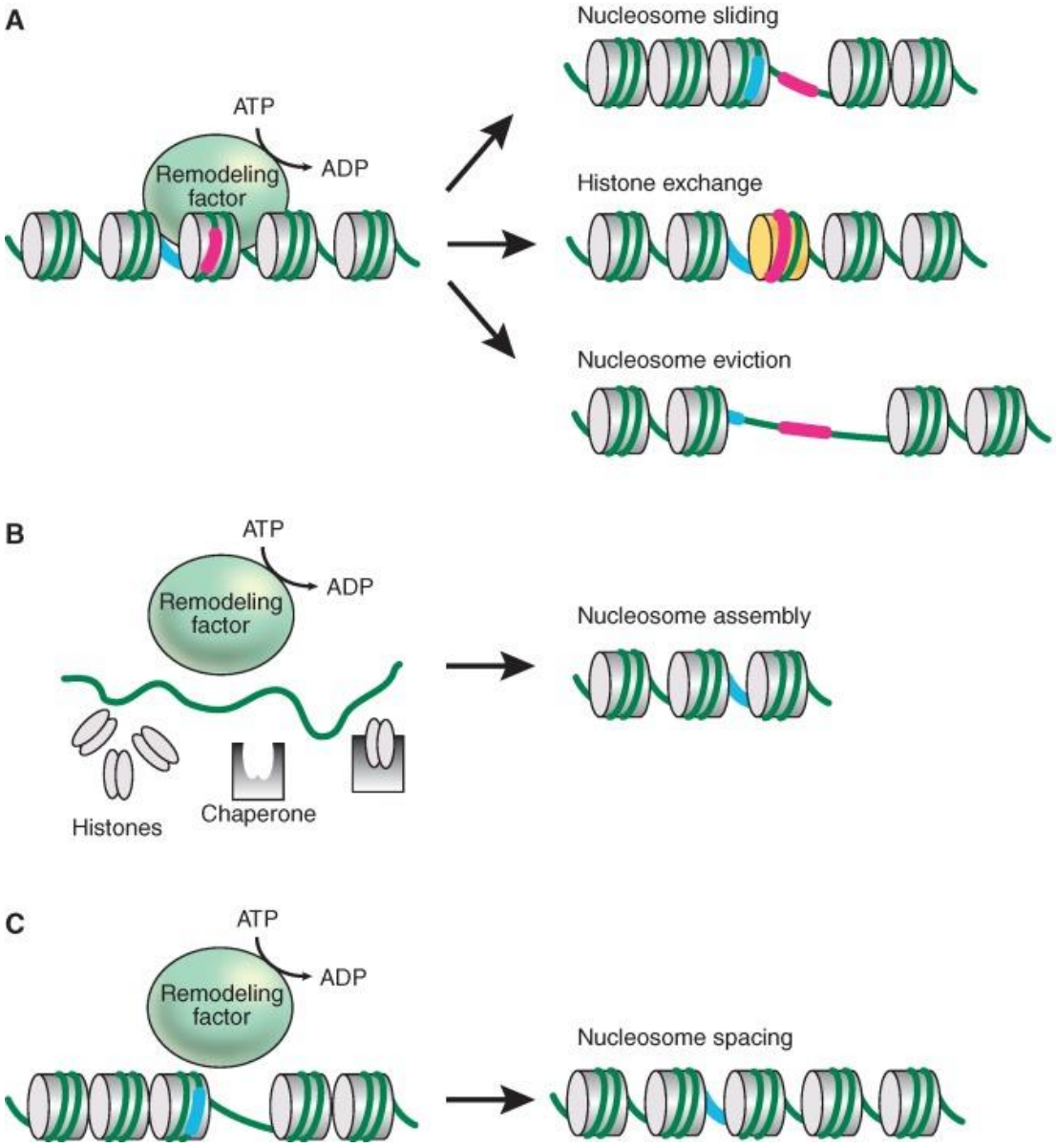


histone PTMs



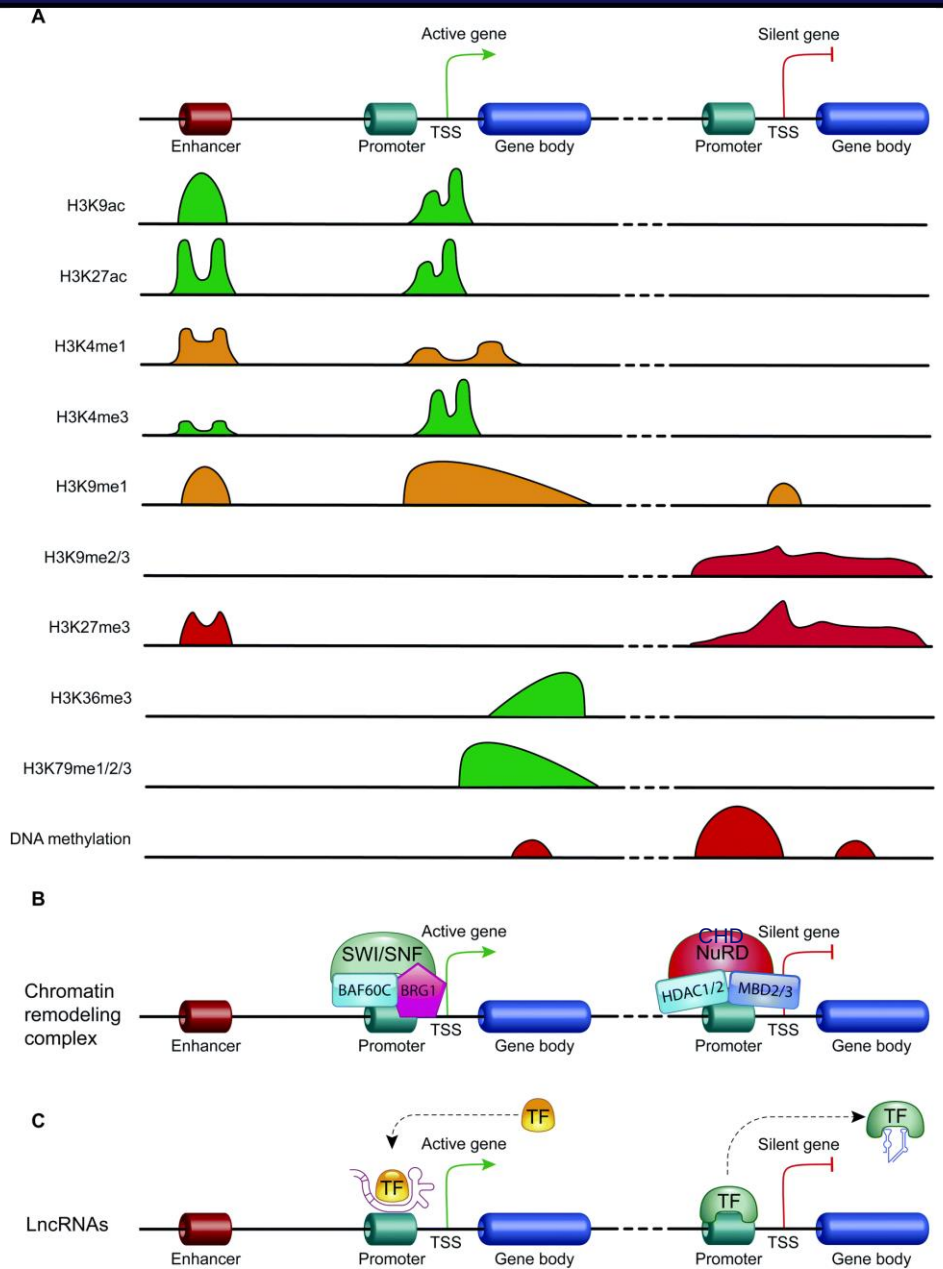
Zhao & Shilatifard. Genome Biol 2019;20(245

chromatin remodeling complexes

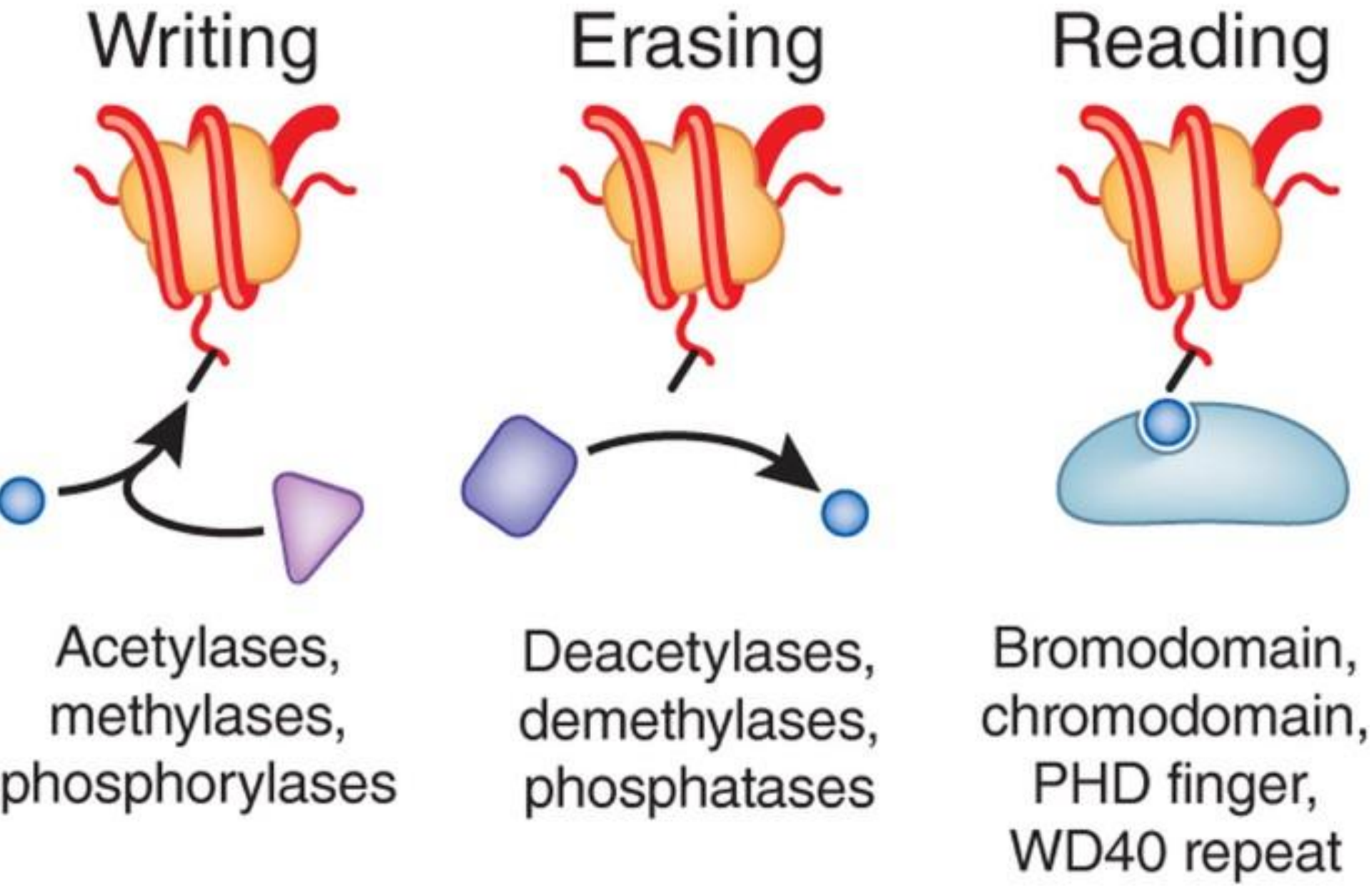


Becker & Workman. Cold Spring Harb Perspect Biol 2013;5:a017905.

epigenetic control of gene expression I



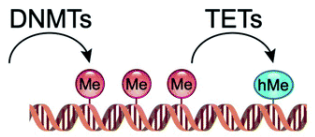
writers, erasers & readers



epigenetic control of gene expression II

DNA methylation

It consists in the addition of a methyl (Me) group to the fifth carbon of cytosine and occurs preferentially in genomic regions rich in C and G, called CpG islands.



It is catalyzed by **DNA methyltransferases** (**DNMTs**): **Dnmt3a** and **Dnmt3b** are involved in *de novo DNA* methylation, whereas **Dnmt1** is involved in the maintenance of DNA methylation.

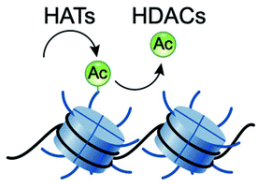
The removal of the methyl group from the DNA is catalyzed by: **AID/APOBEC-family cytosine deaminases** and/or **TET enzymes**.

EFFECTS ON GENE EXPRESSION

DNA methylation in promoter regions is involved in the repression of genes, while in the gene body is associated with active transcription.

Histone acetylation

It consists in the addition of an acetyl (Ac) group to the amino group of the lysine residues of histones H2B, H3 and H4.



It is catalyzed by **histone-acetyltransferases** (**HATs**), which use acetyl-CoA as cofactor.

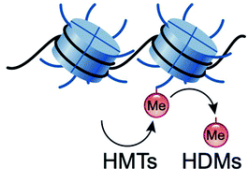
The removal of the acetyl group from histones is catalyzed by **histone-deacetylases** (**HDACs**).

EFFECTS ON GENE EXPRESSION

Histone acetylation is involved in transcriptional activation.

Histone methylation

It consists in the addition of one or more methyl (Me) groups on lysine or arginine residues which are preferentially localized on histone tails.



It is catalyzed by **histone-methyltransferases** (**HMTs**).

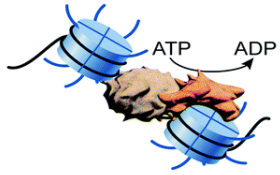
The removal of the methyl group from the histone tails is catalyzed by **histone-demethylases** (**HDMs**).

EFFECTS ON GENE EXPRESSION

Histone methylation is involved in the activation or repression of gene transcription, depending on the methylated residue of lysine or arginine, and on the degree of methylation.

ATP-dependent chromatin-remodeling complexes

They include multi-protein complexes that use the energy of ATP hydrolysis to locally alter the association of histones with DNA.



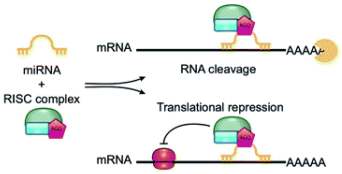
They can be divided into four classes, **SWI/SNF**, **ISWI**, **CHD** and **INO80**, on the basis of their ATPase subunits.

EFFECTS ON GENE EXPRESSION

ATP-dependent chromatin-remodeling complexes can act as transcription repressors, creating a highly compact chromatin structure, but can also promote gene expression by making chromatin open and accessible.

Non-coding RNAs

They include a variety of RNAs that are not translated into proteins and act transcriptionally and translationally by regulating gene expression.



They can be classified according to their length into:

- **short ncRNAs**, RNA molecules shorter than 200 nucleotides (e.g., miRNAs, siRNAs and PIWI-interacting RNAs);

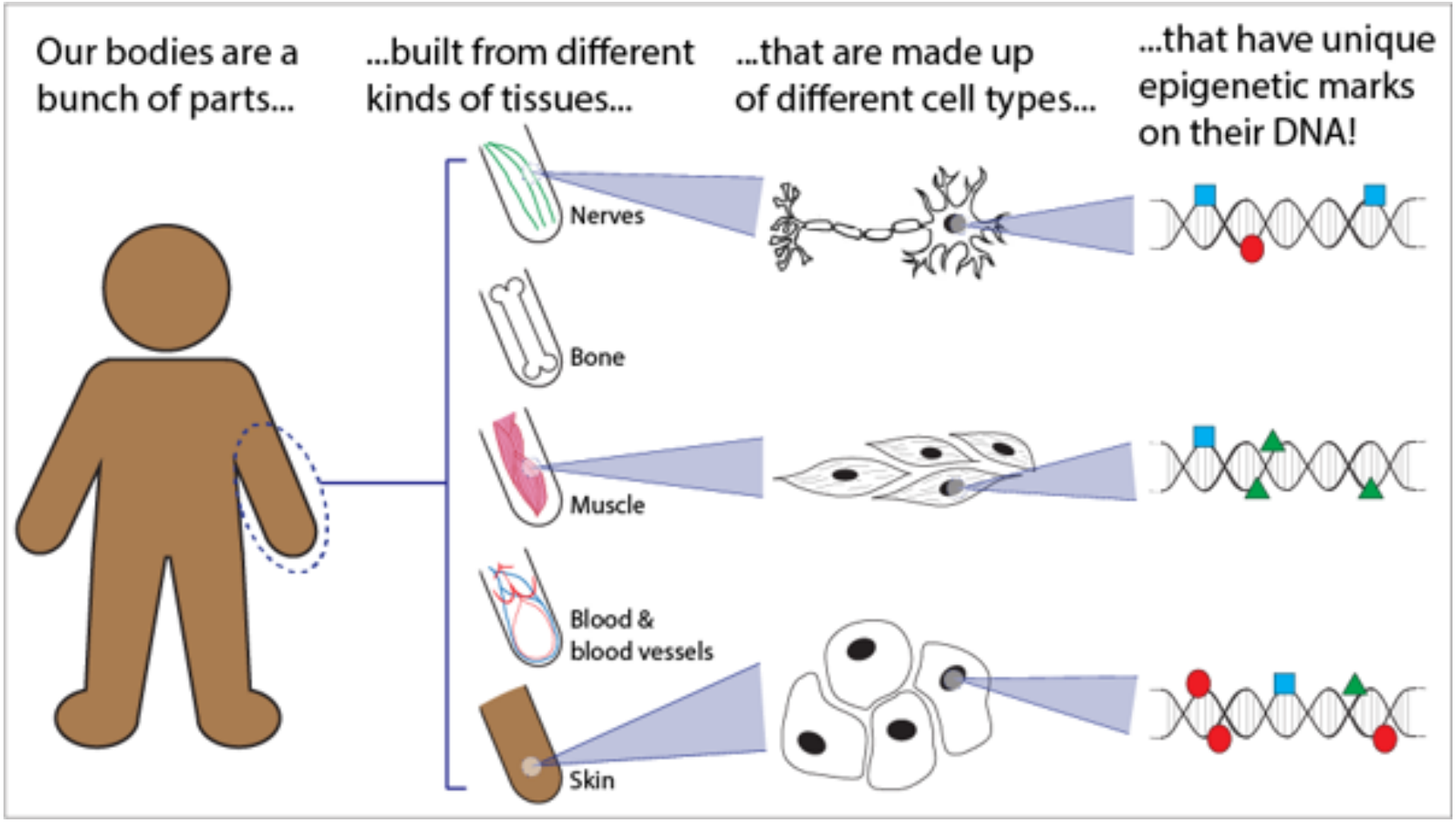
- **long ncRNAs**, RNA molecules longer than 200 nucleotides.

EFFECTS ON GENE EXPRESSION

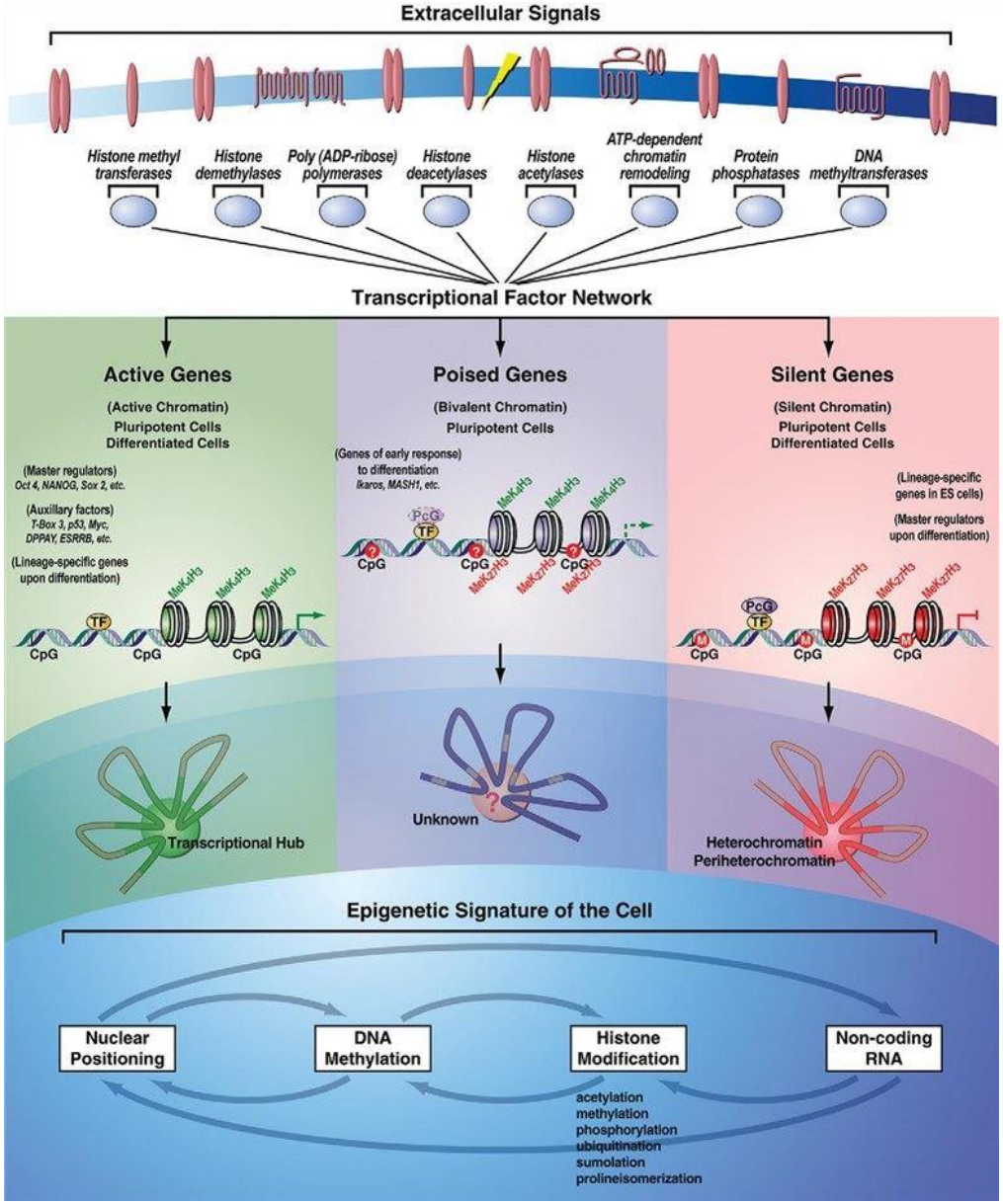
miRNAs regulate gene expression by binding to the 3'-UTR of targeted mRNAs, causing their degradation or preventing their translation into proteins.

cell type-specific epigenome

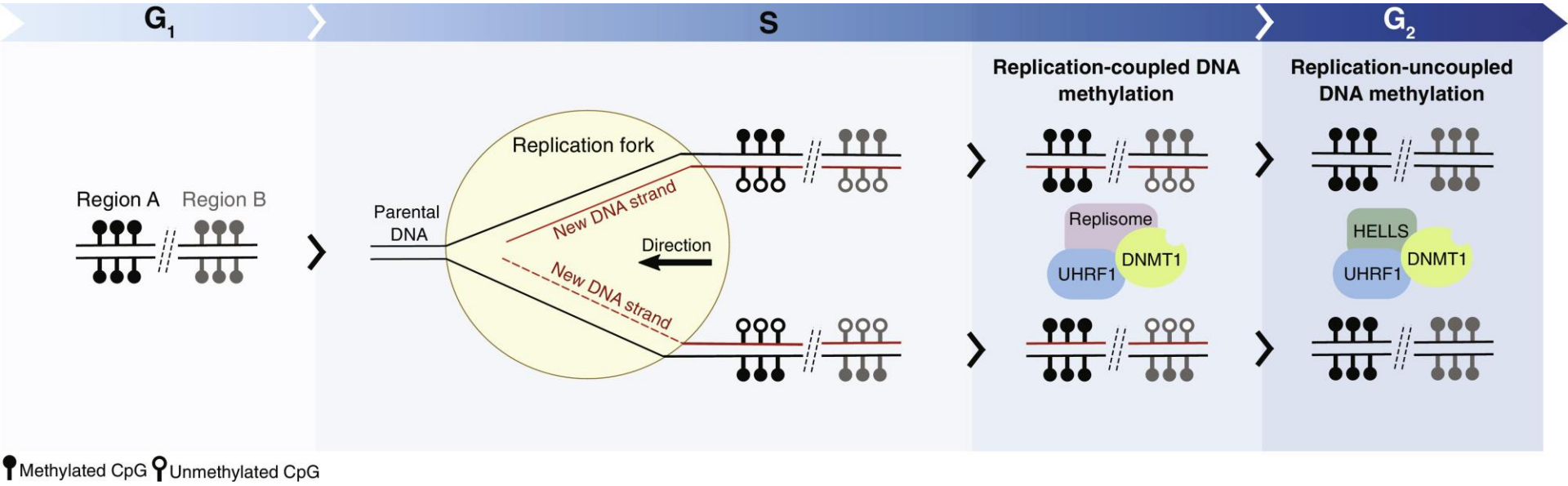
- Cell types-specific epigenome → cell type-specific gene expression profile (transcriptome) → cell type-specific properties (phenotype).



the environment instructs the epigenome

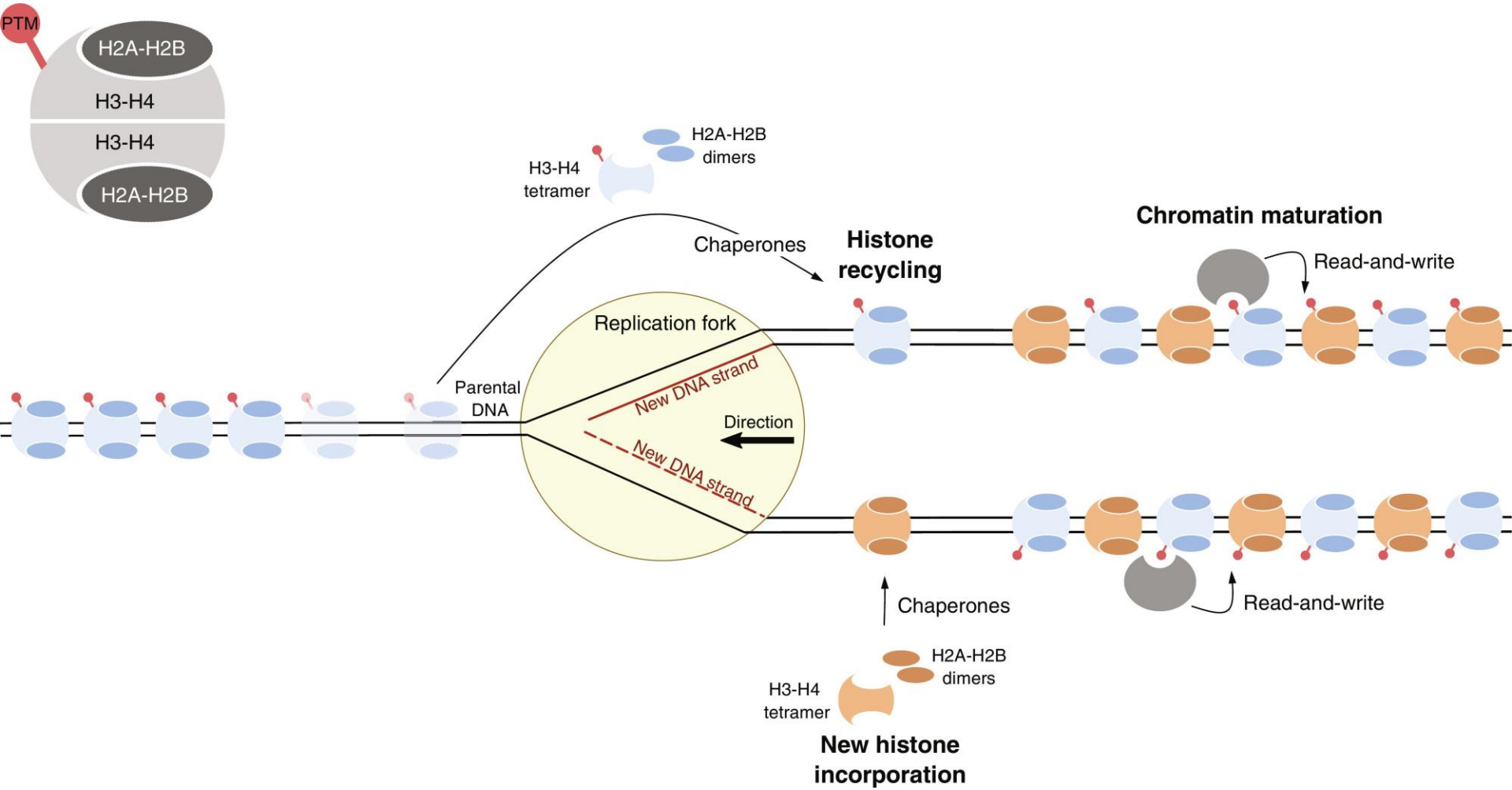


cell division & the epigenome



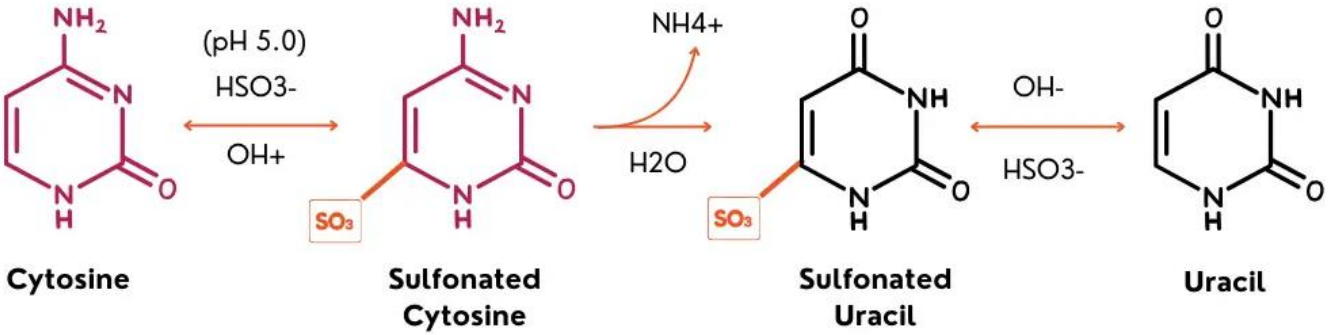
Espinosa-Martínez Sci Adv 2024;10:eadl3188

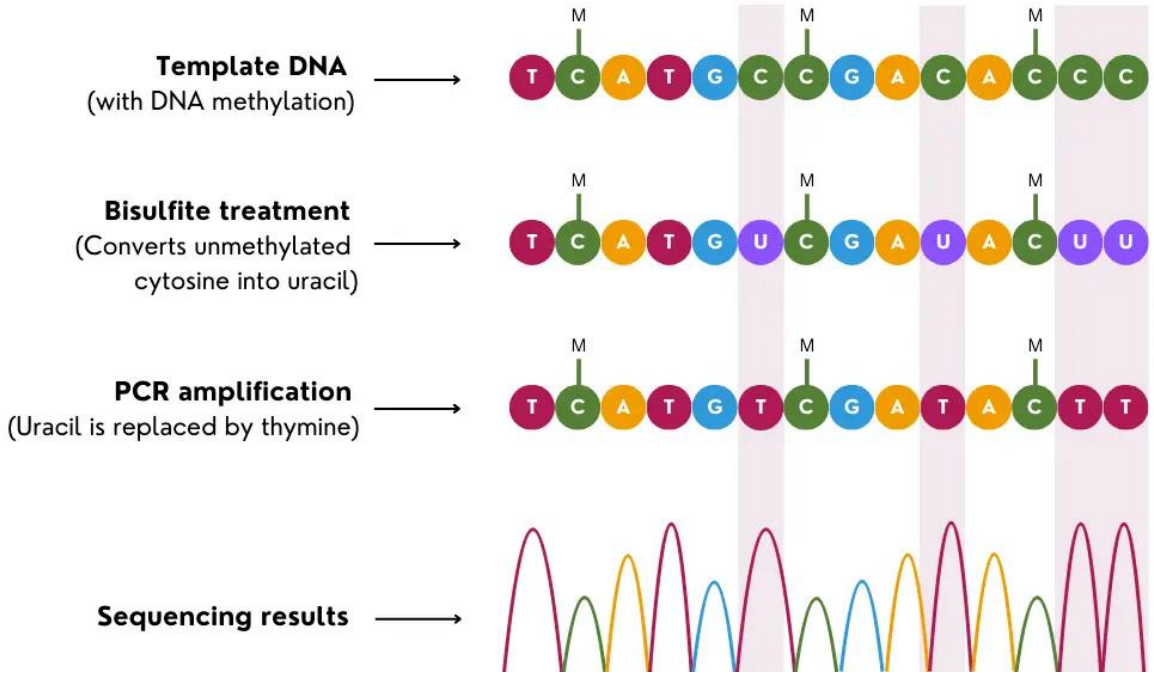
cell division & the epigenome



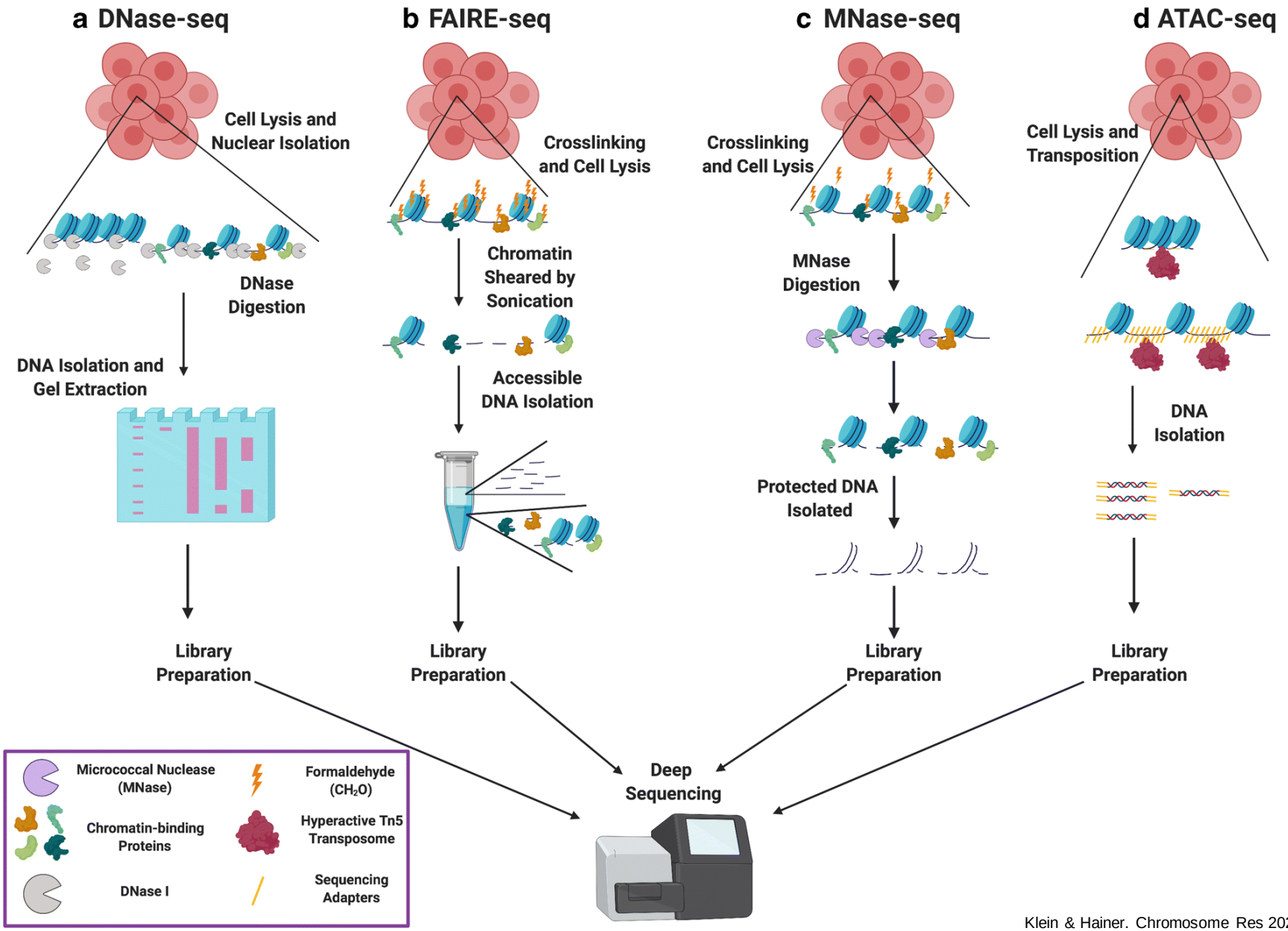
Espinosa-Martínez Sci Adv 2024;10:eadl3188

analysis of DNA methylation



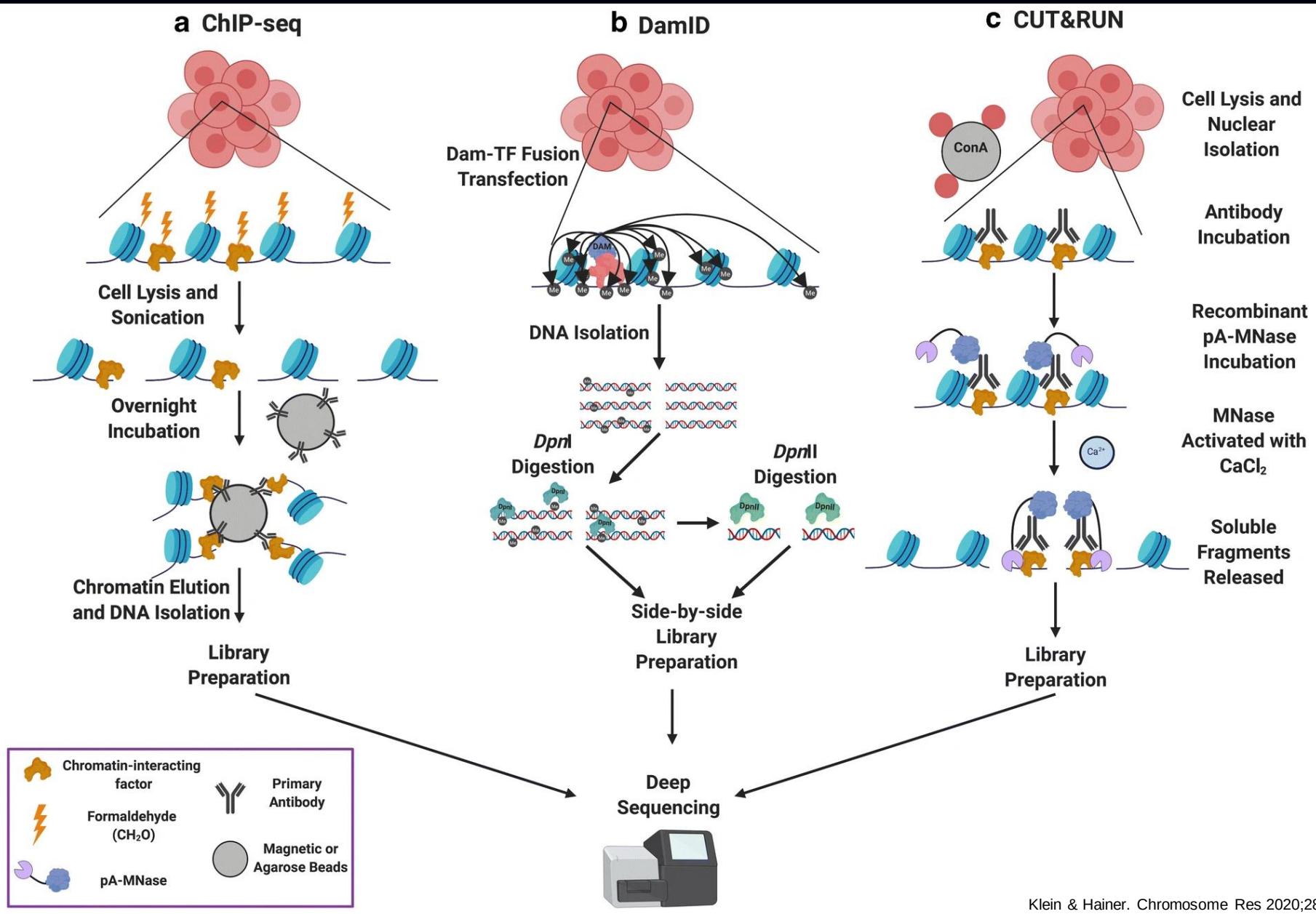


analysis of genome accessibility (euchromatin)



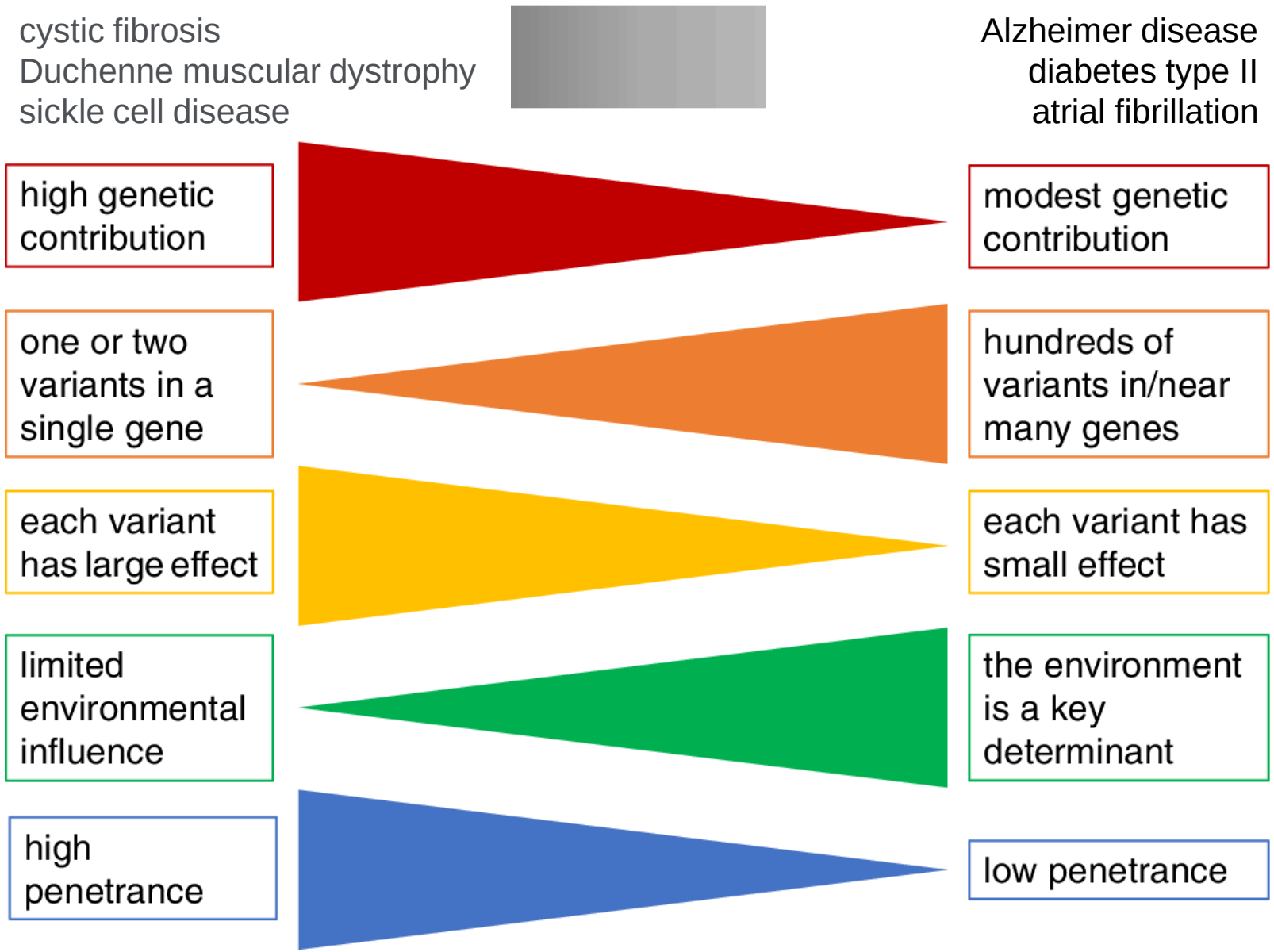
Klein & Hainer. Chromosome Res 2020;28:69

analysis of genome occupancy



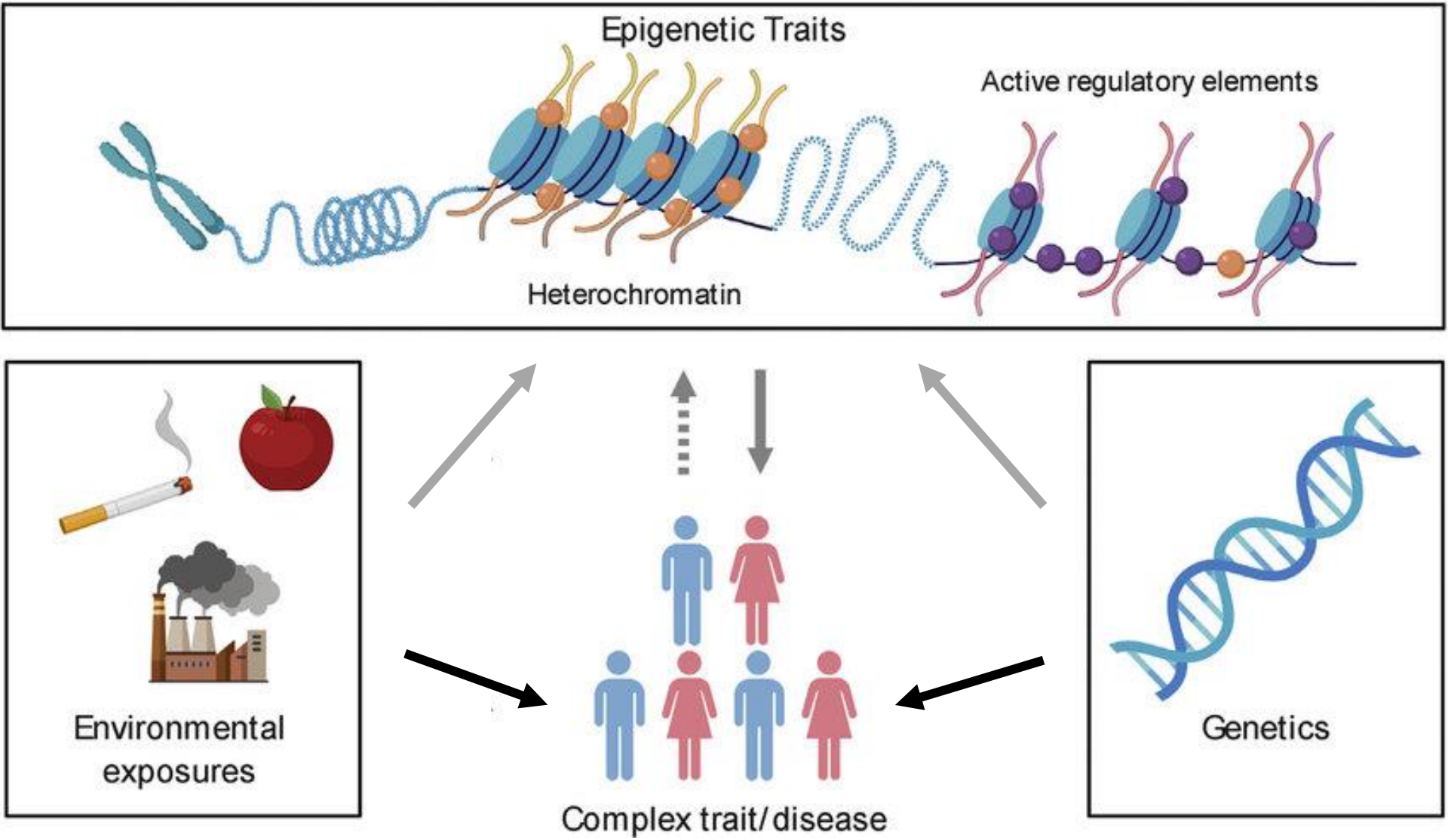
Klein & Hainer. Chromosome Res 2020;28:69

the epigenome & complex diseases I



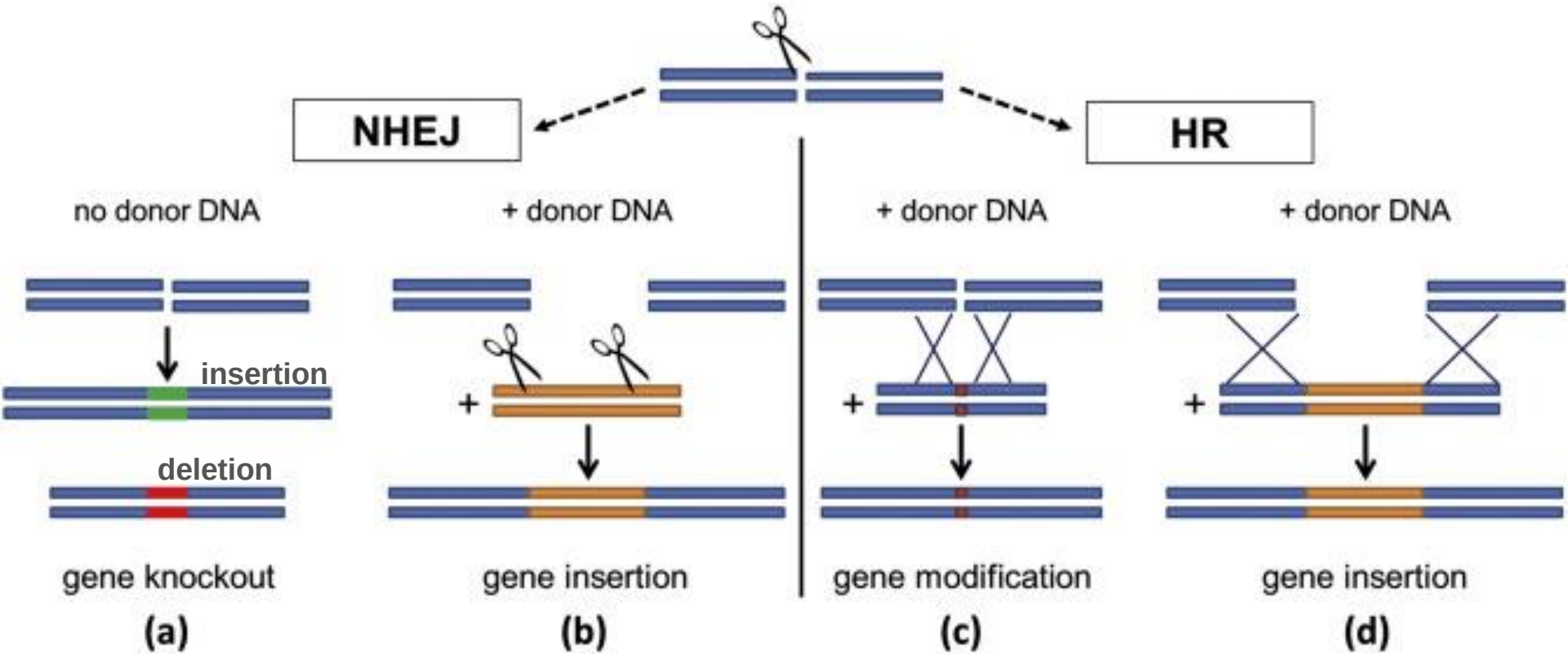
Sergouniotis. Camb Prism Precis Med 2023;1:e7

the epigenome & complex diseases II

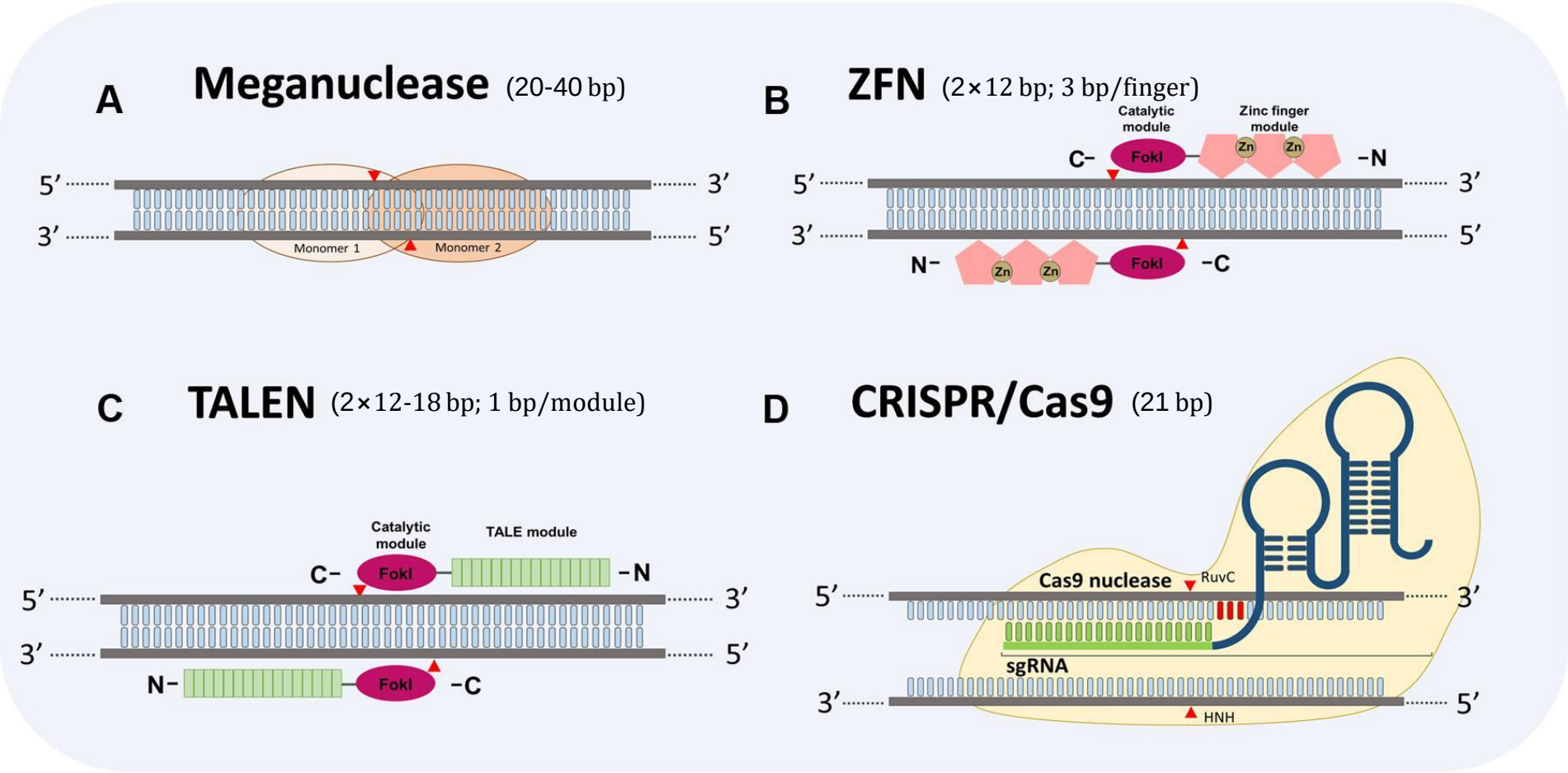


Allum Mol Metab 2020;38:100936

genome editing

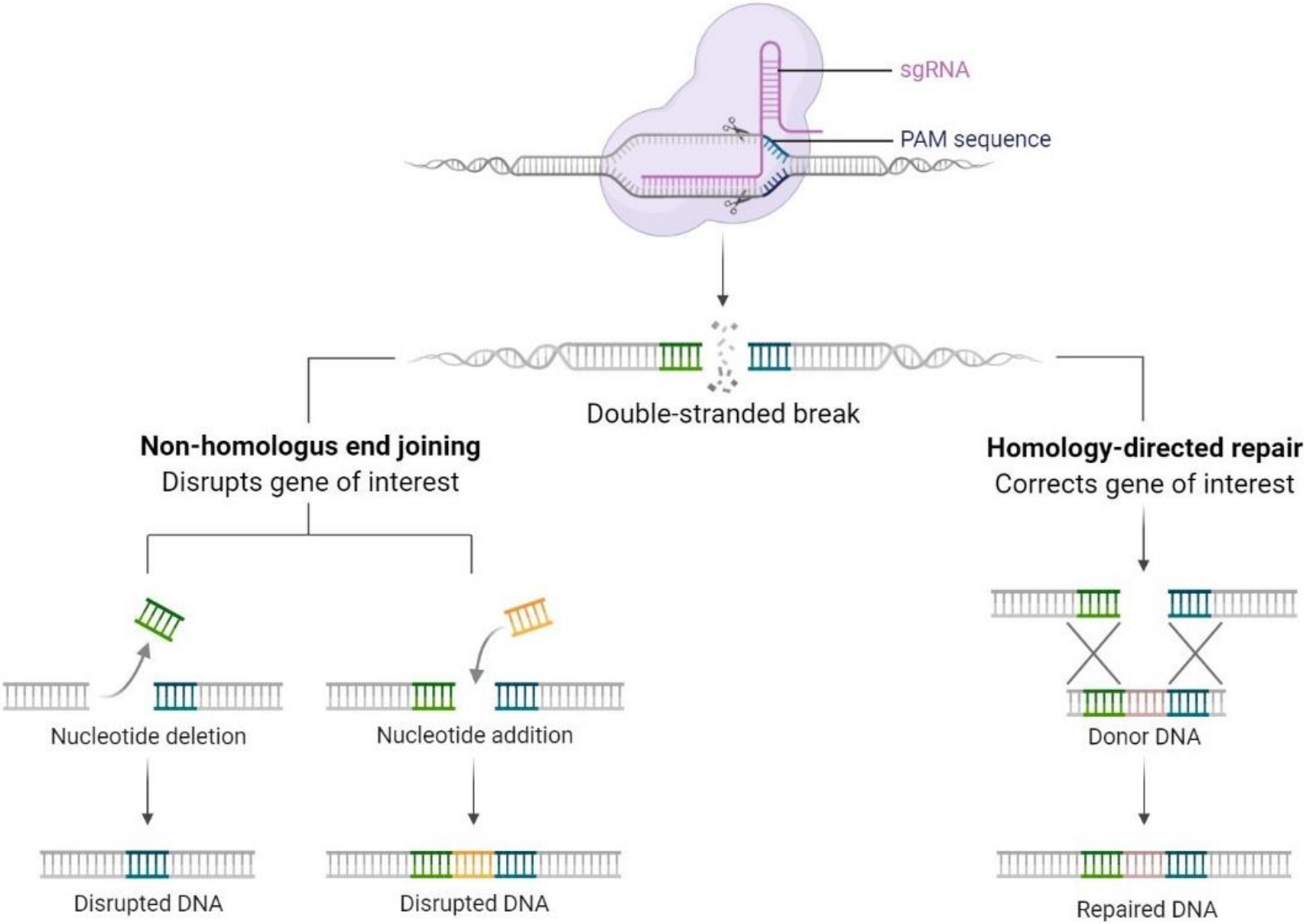


genome editing technology

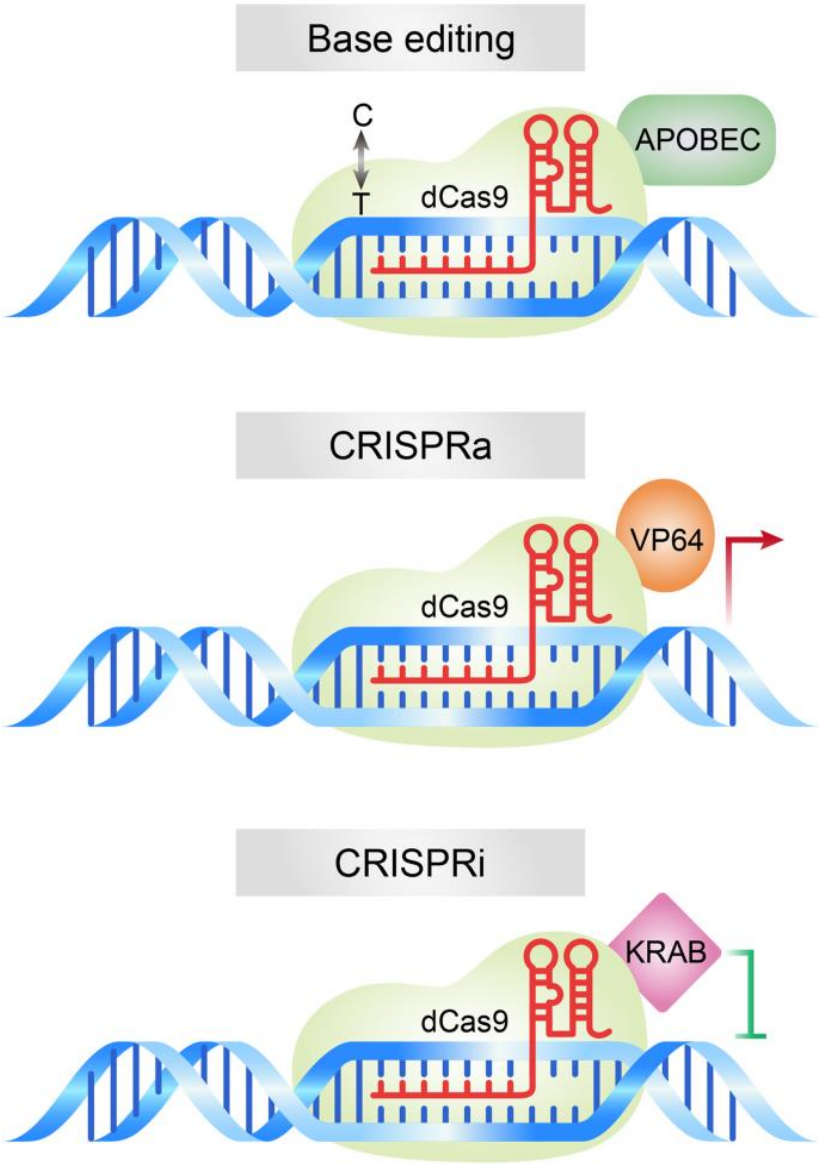


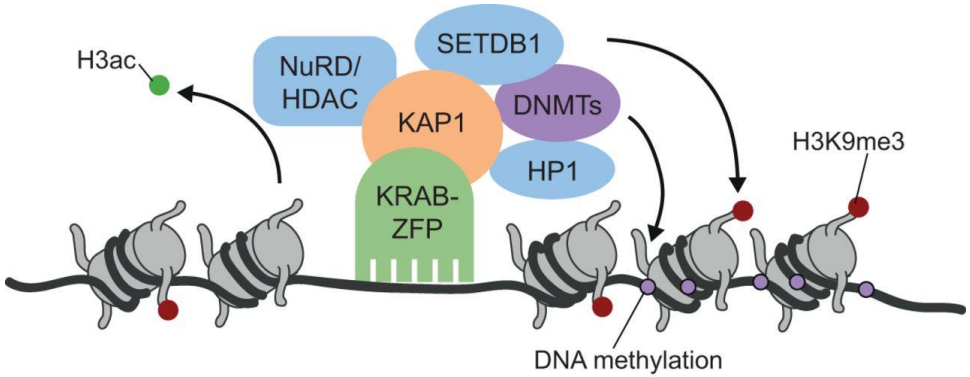
TALEN = Transcription Activator-Like Effector Nuclease; CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats

CRISPR/Cas9 genome editing



CRISPR/dCas9 (epi)genome editing

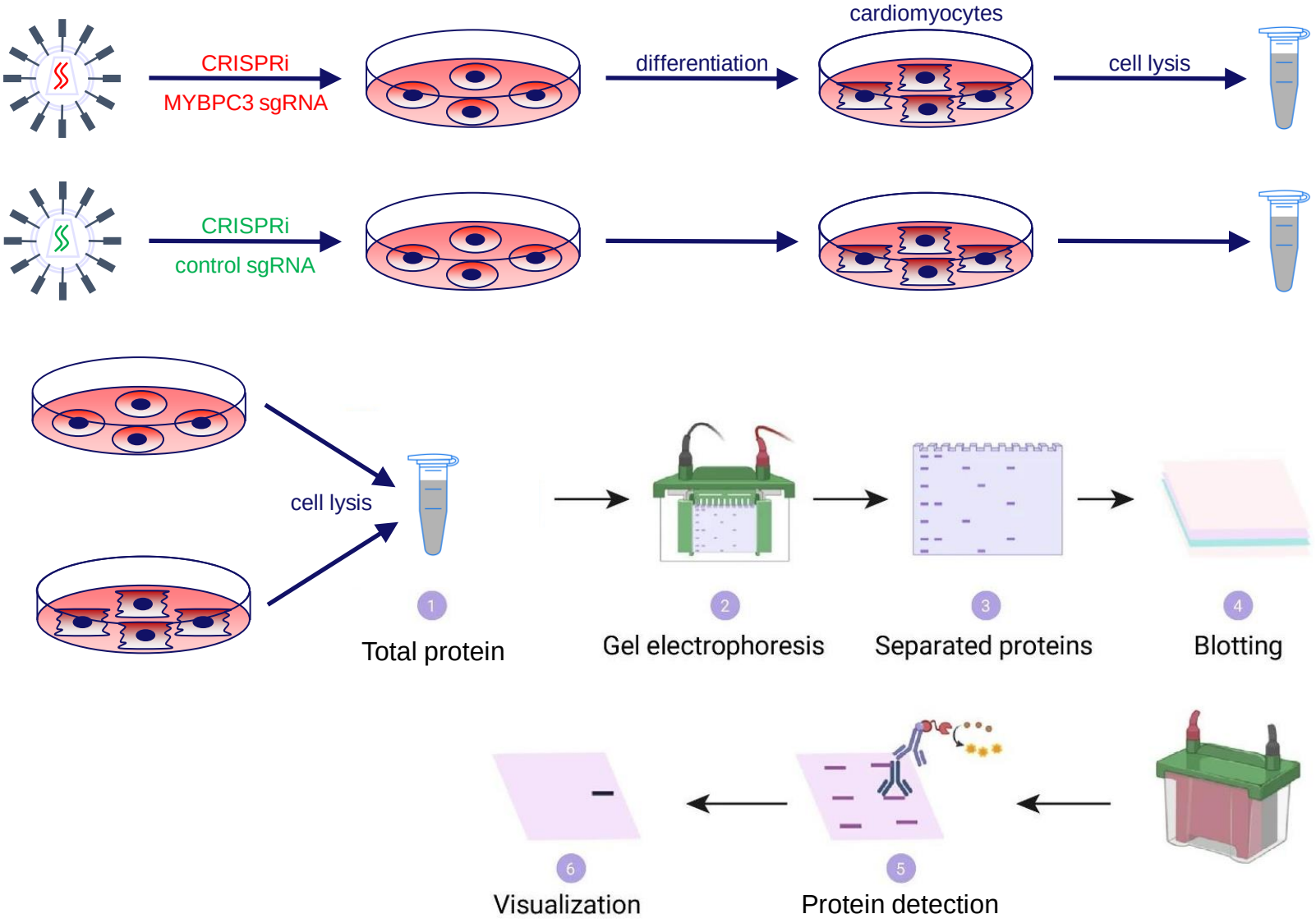




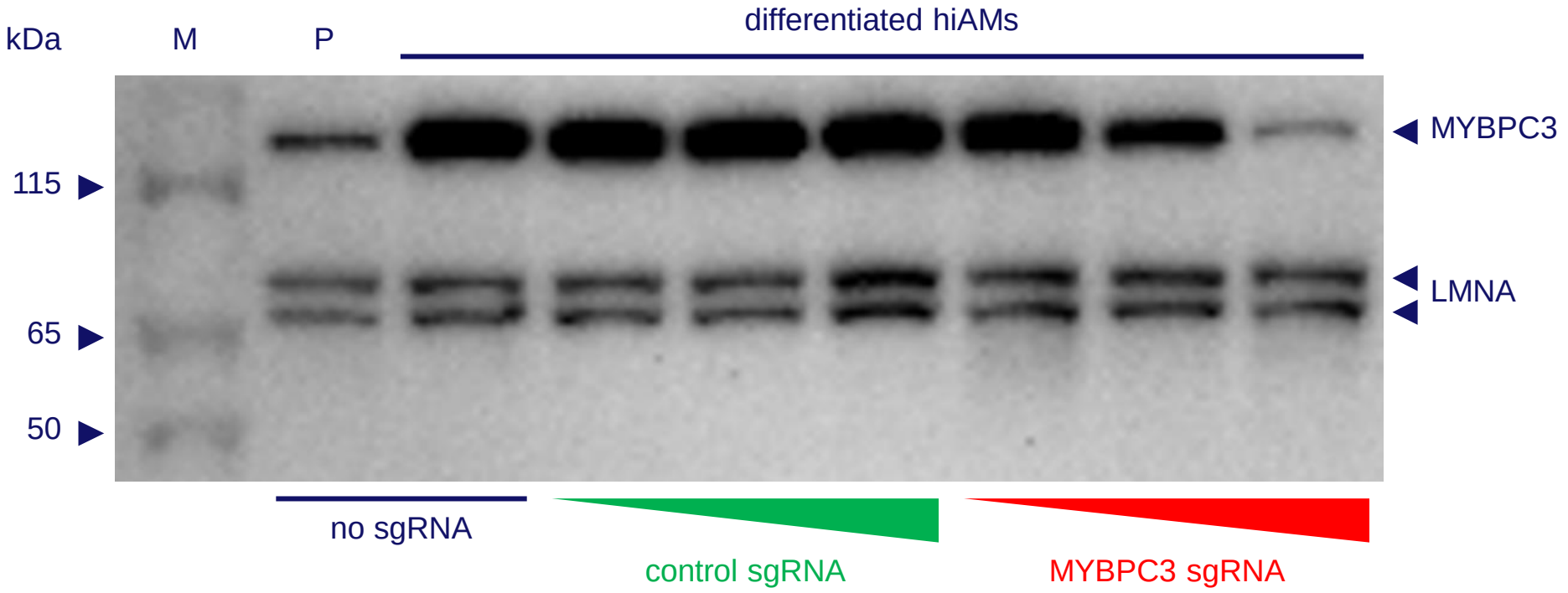
Zhang et al. Mol Cancer 2021;20:126

Ecco et al. Development 2017;144:2719

epigenome editing in the laboratory

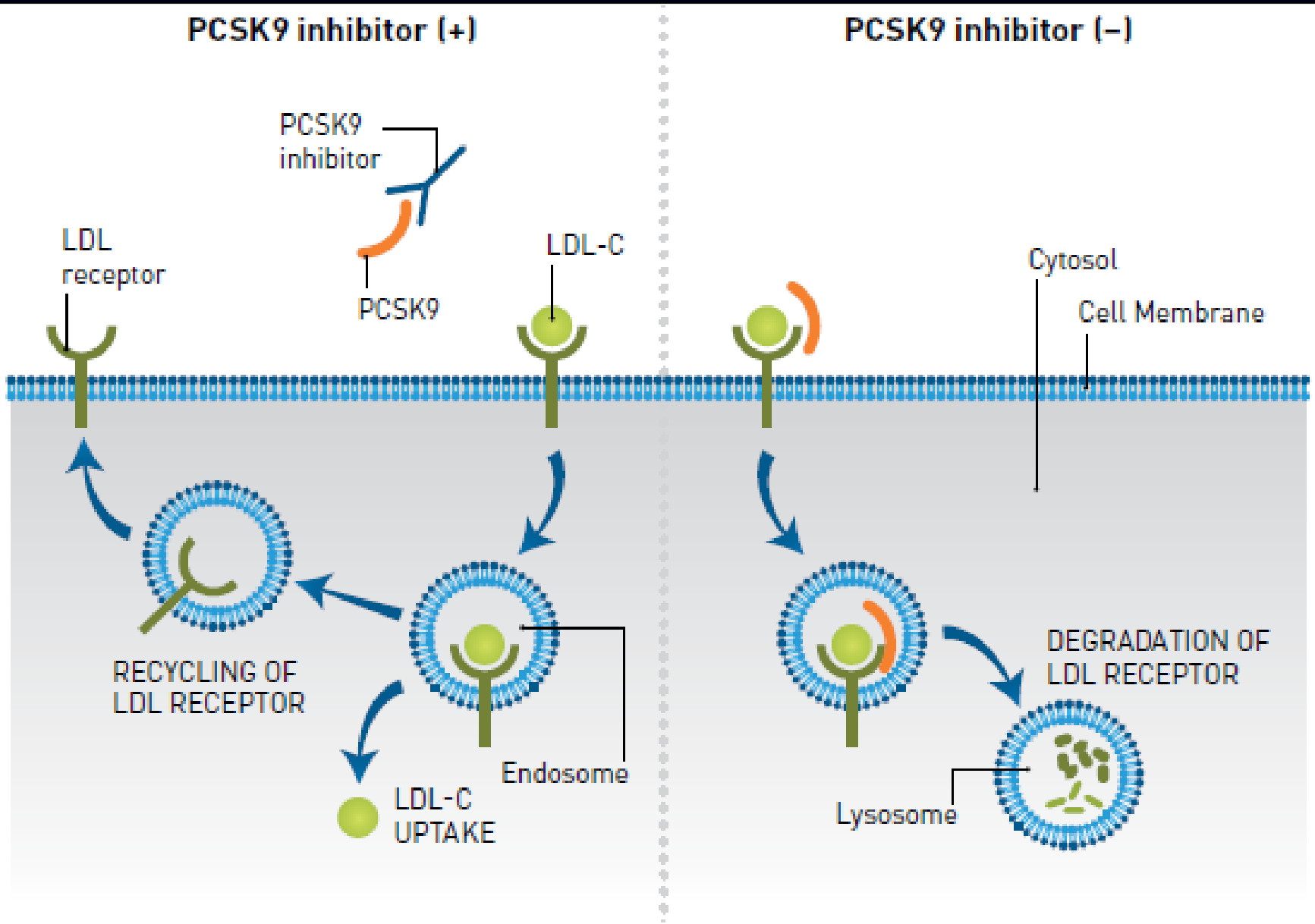


epigenome editing in the laboratory

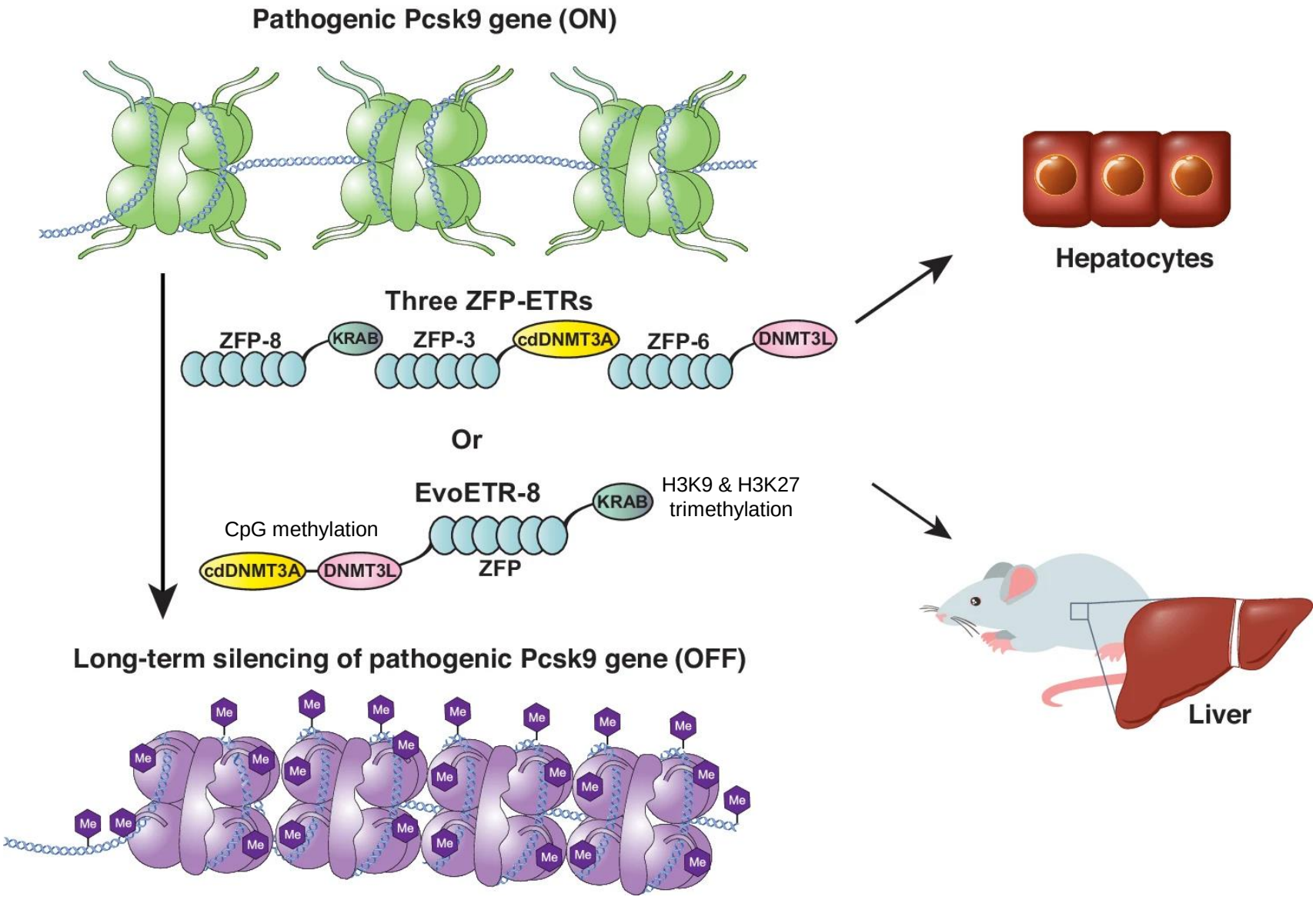


Liao et al. 2024: unpublished

LDL-C reduction via PCSK9 inhibition

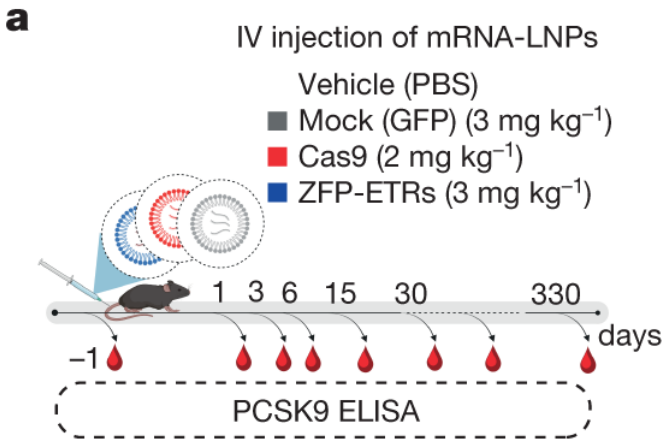


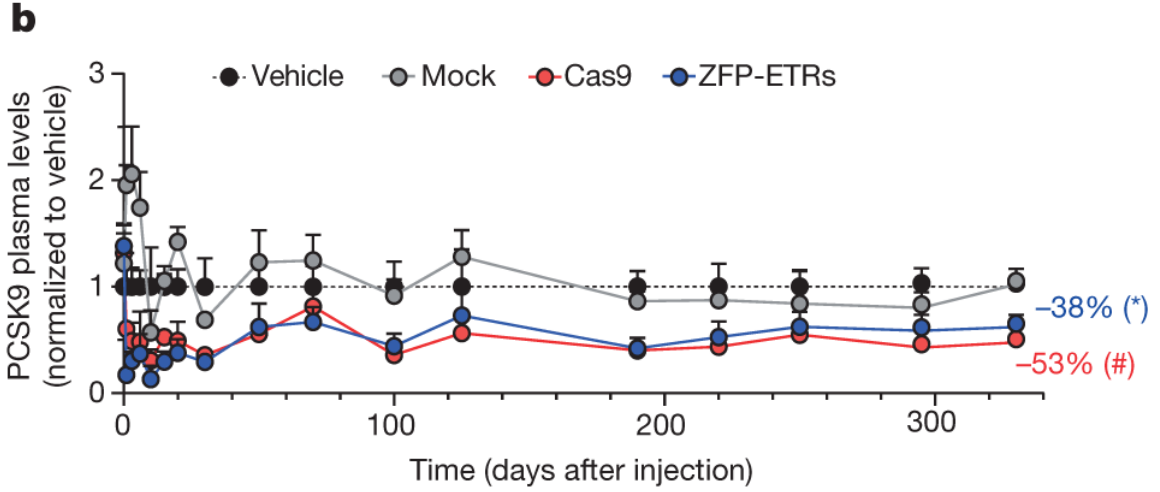
epigenome editing as therapy

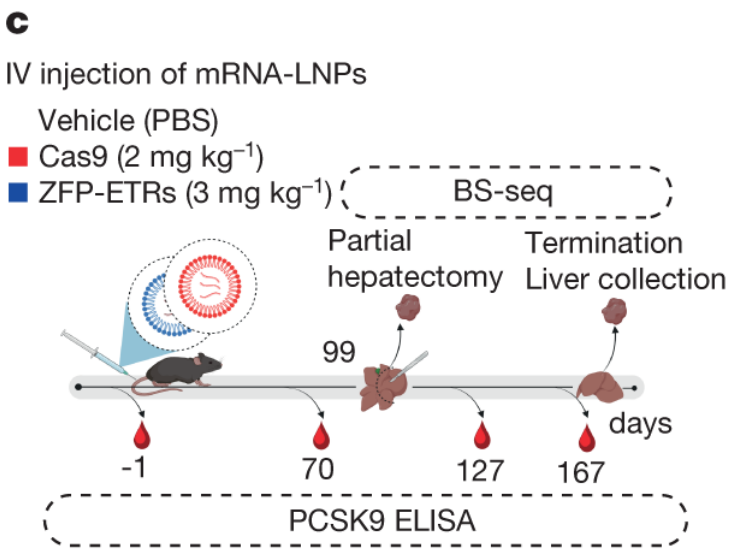


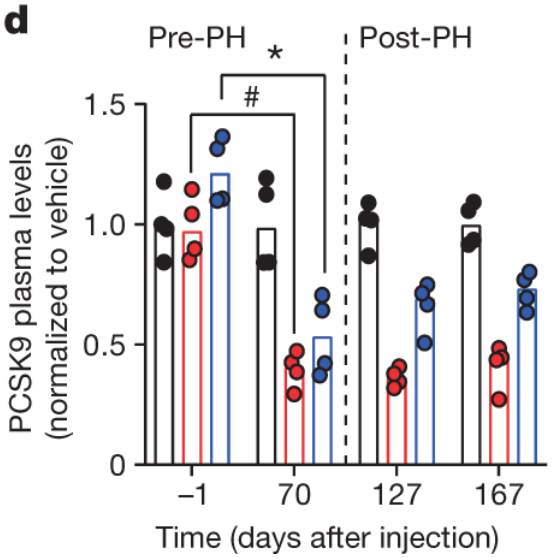
Cappelluti et al. Nature 2024;627:416

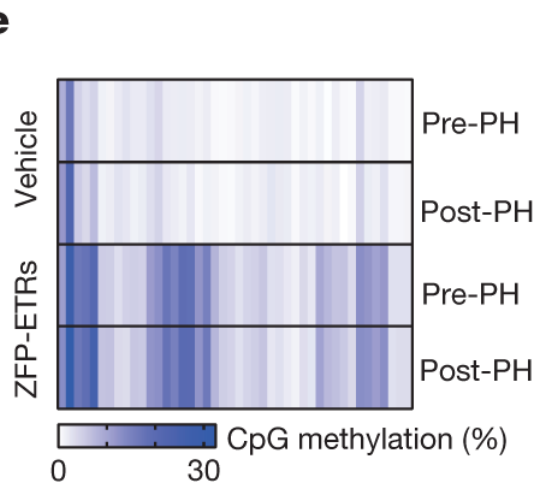
epigenome editing as therapy









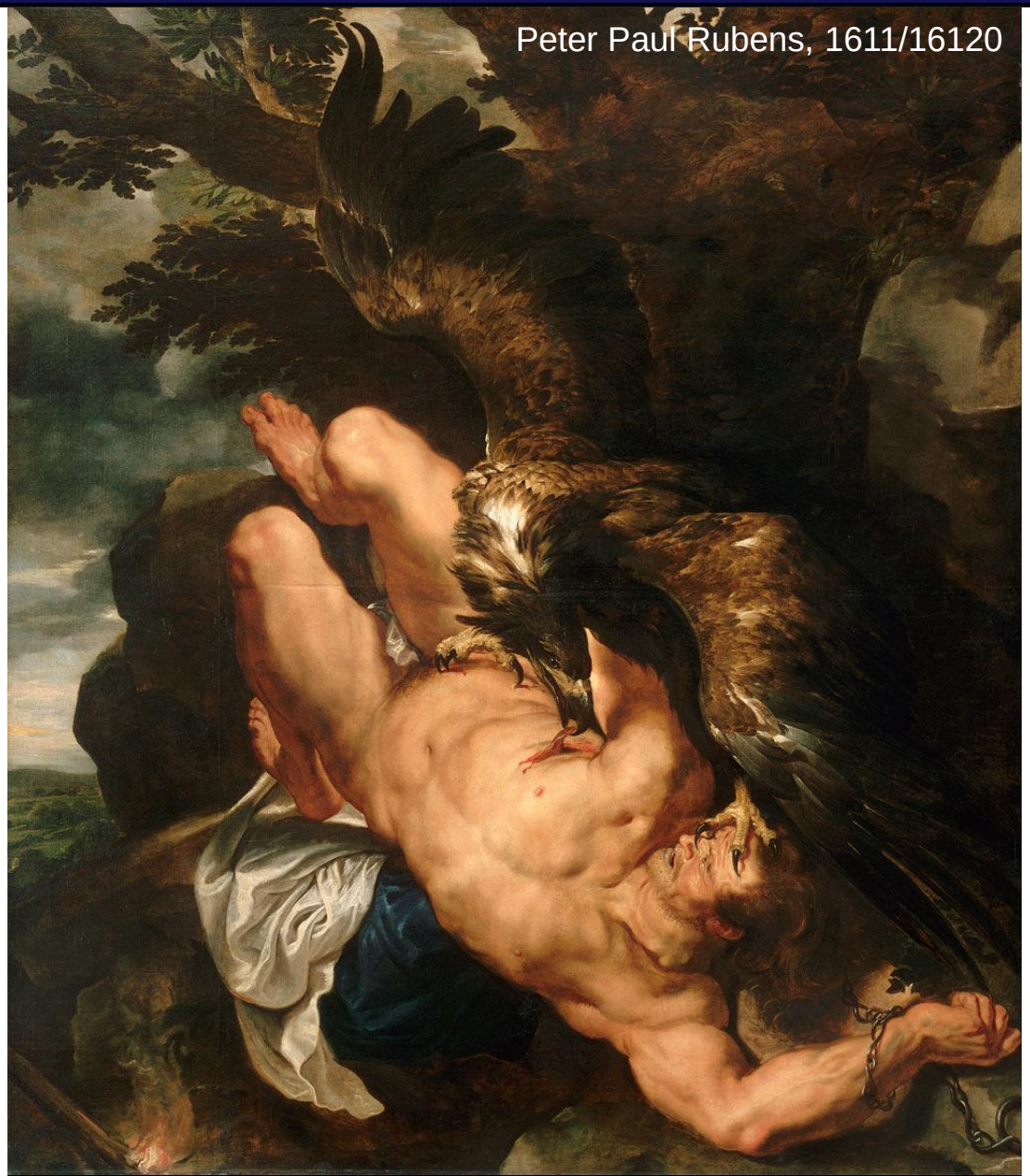


ETR: engineered transcription repressor
ZFP: zinc finger protein

LNP: lipid nanoparticle
PH: partial hepatectomy

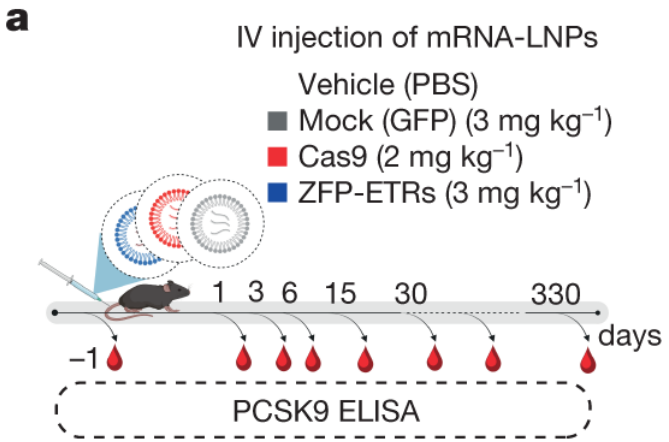
Cappelluti et al. Nature 2024;627:416

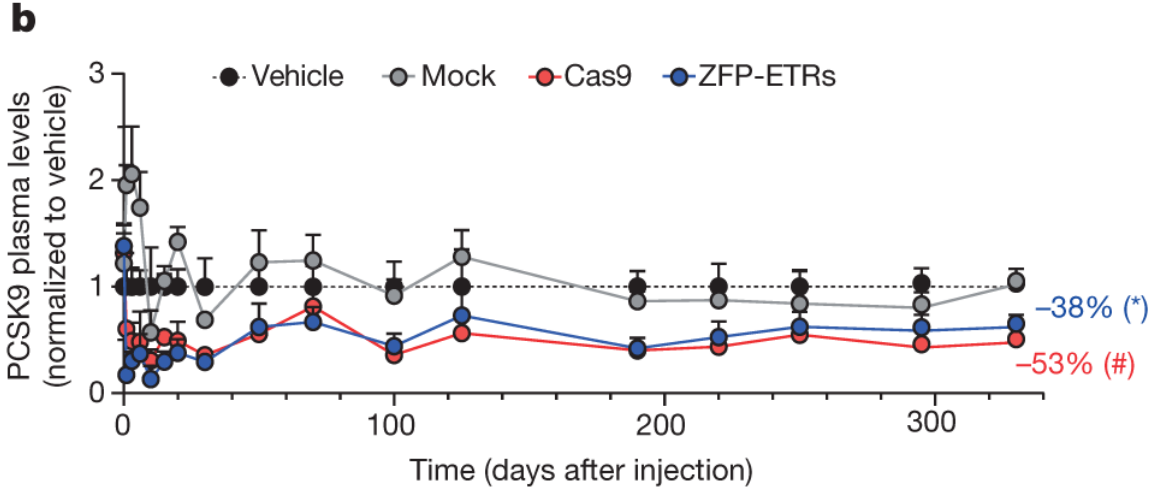
Prometheus Bound

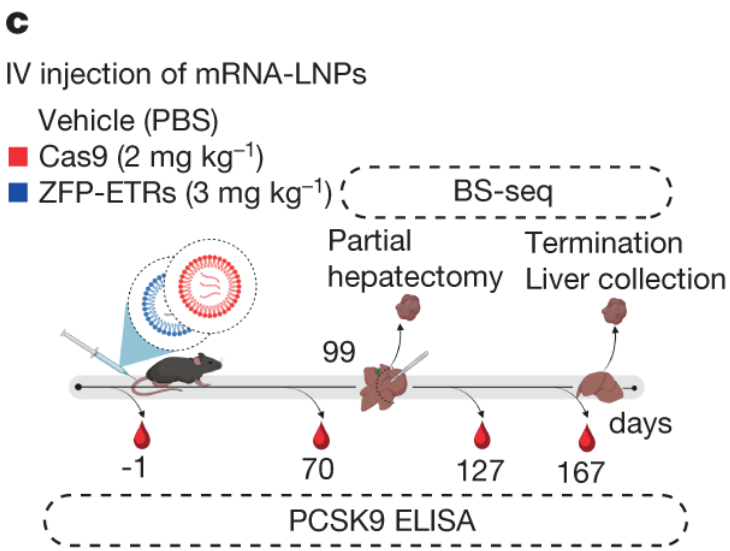


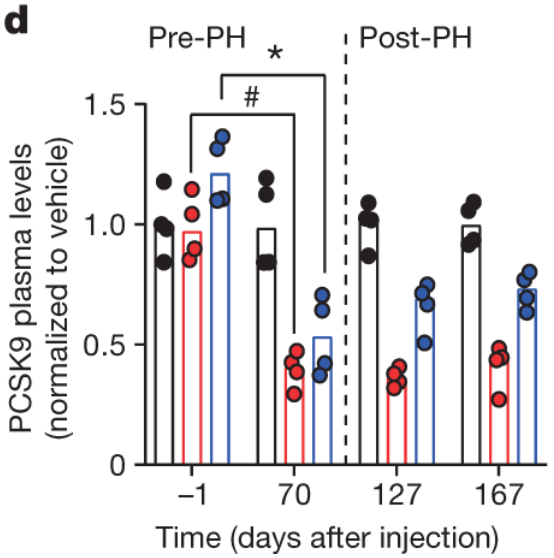
Peter Paul Rubens, 1611/16120

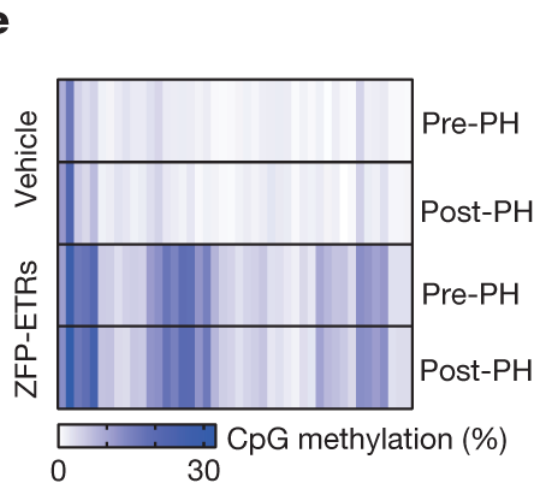
epigenome editing as therapy









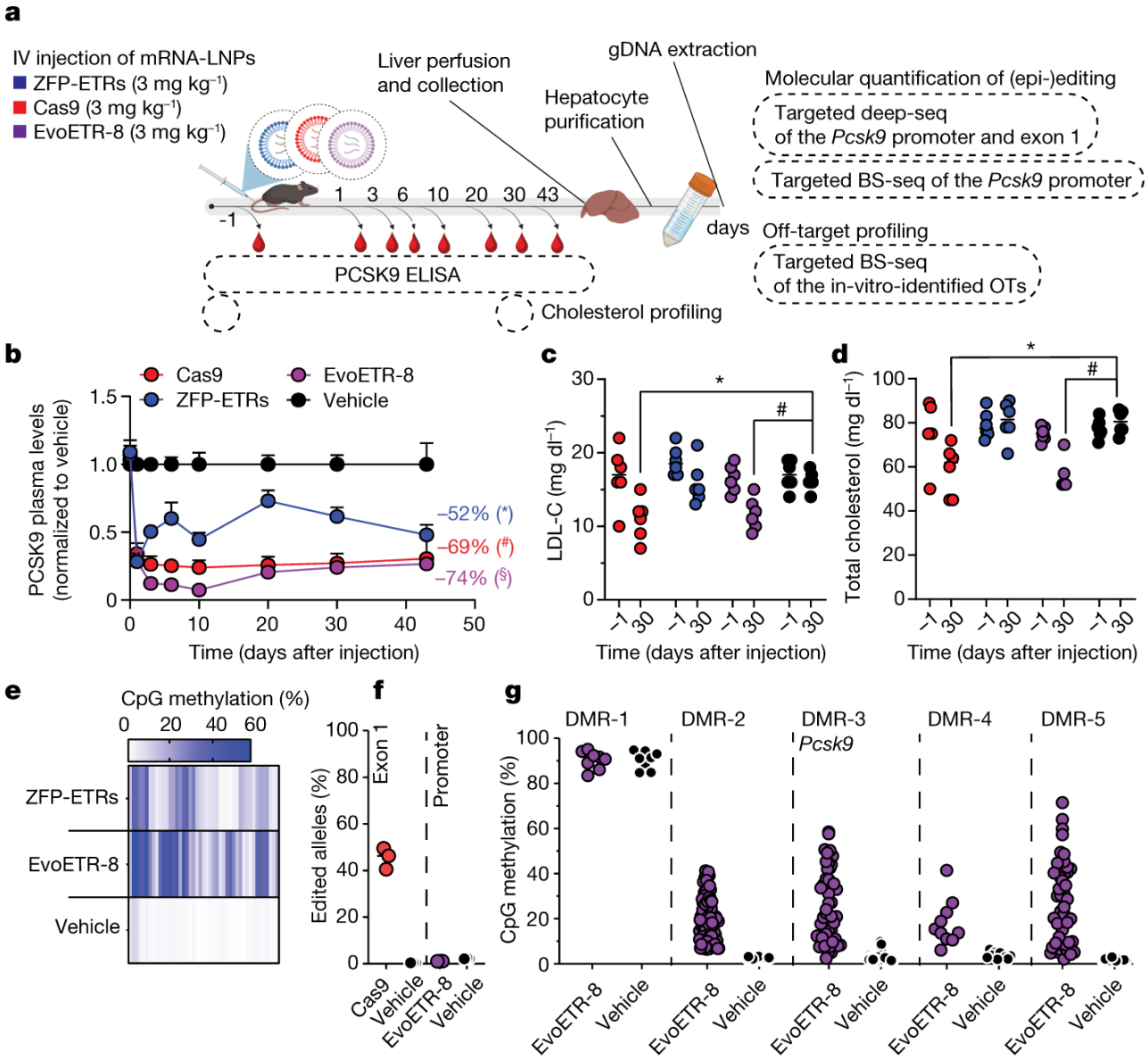


ETR: engineered transcription repressor
ZFP: zinc finger protein

LNP: lipid nanoparticle
PH: partial hepatectomy

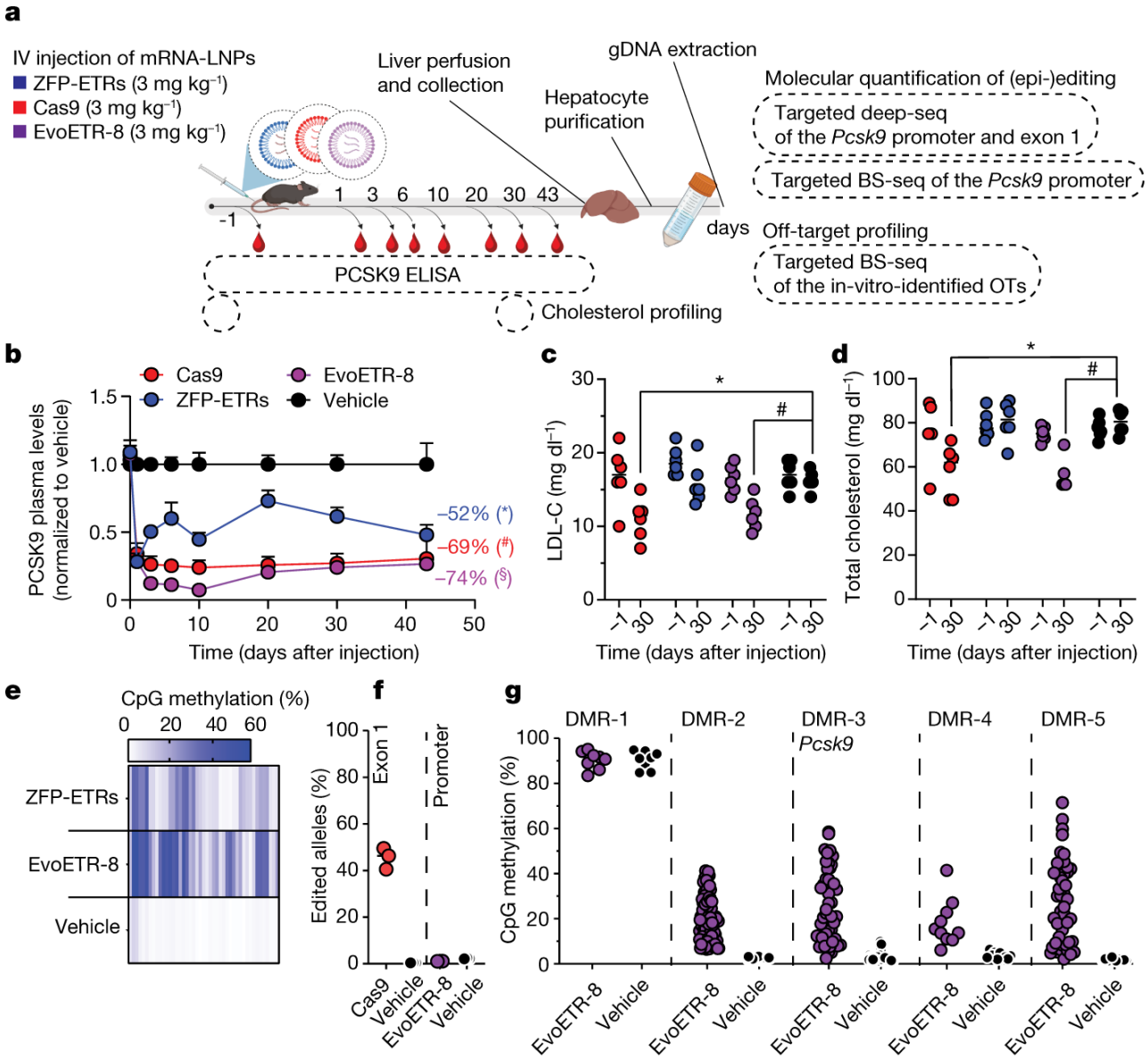
Cappelluti et al. Nature 2024;627:416

epigenome editing as therapy



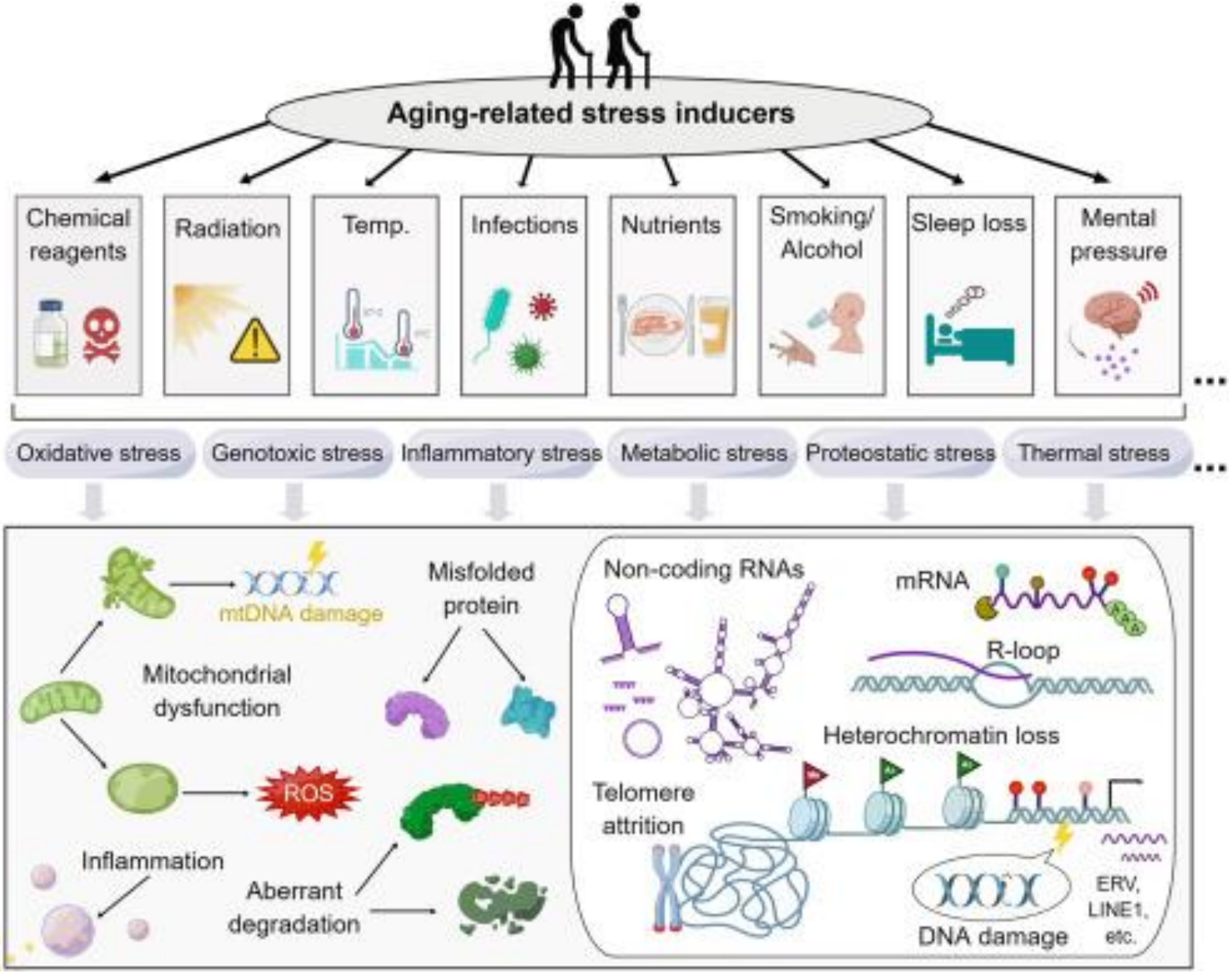
Cappelluti et al. Nature 2024;627:416

epigenome editing as therapy

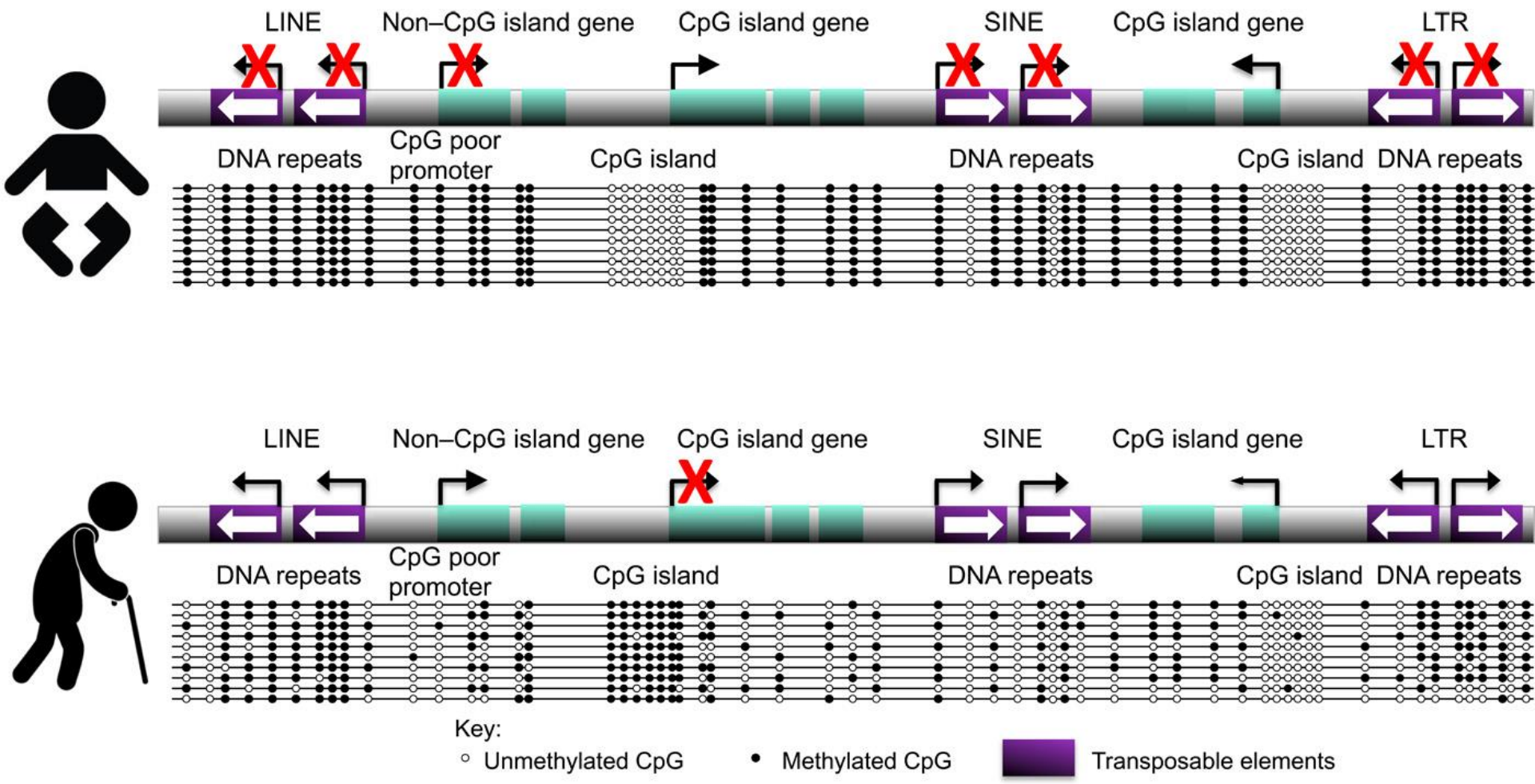


Cappelluti et al. Nature 2024;627:416

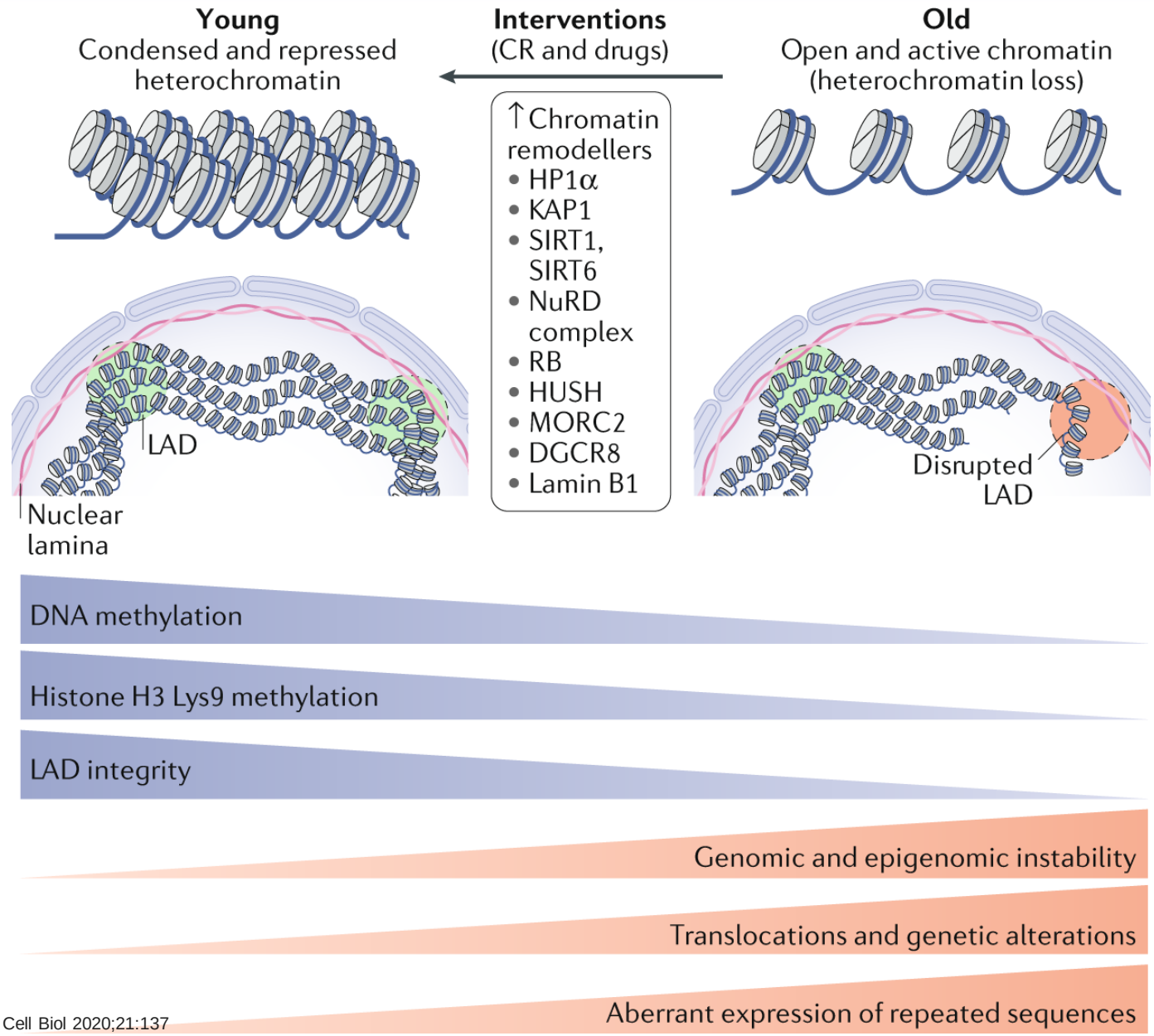
aging & the epigenome



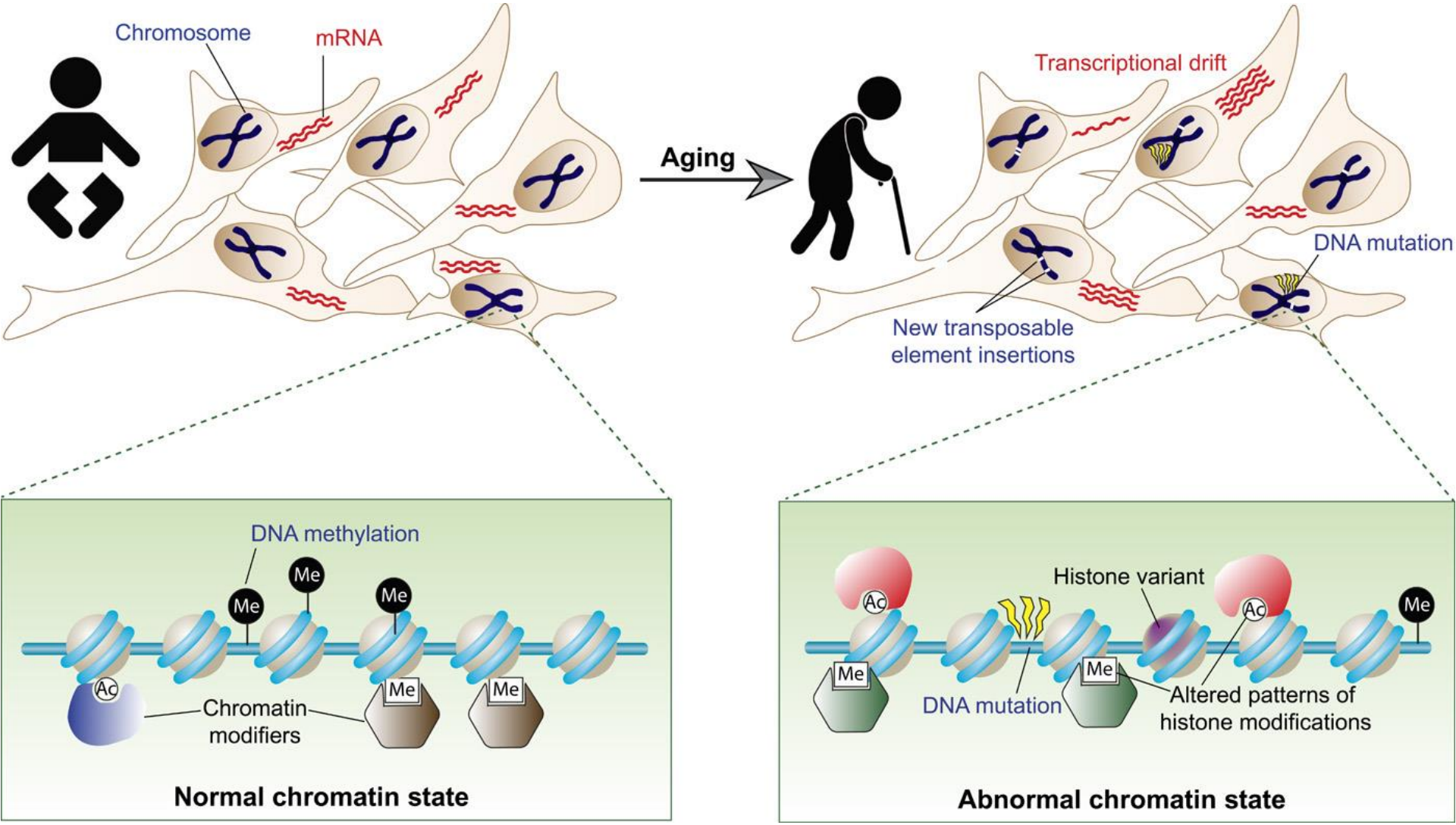
aging & the epigenome

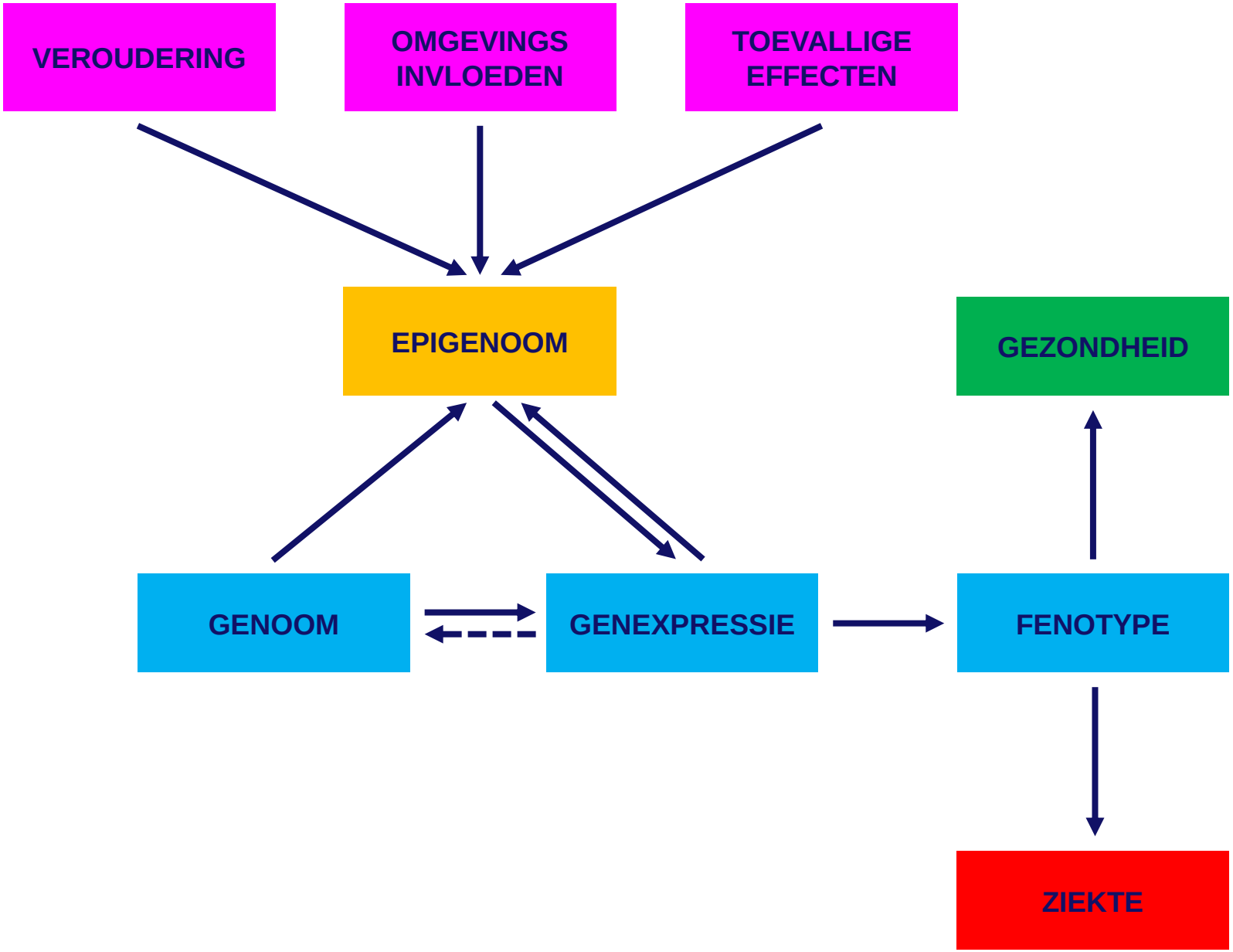


- global DNA hypomethylation → undesirable activation of transposable elements
- local DNA hypermethylation (i.p. GpC-rich promoters → undesirable gene silencing



Zhang et al. Nat Rev Mol Cell Biol 2020;21:137


Chromosome
mRNA
Aging
Transcriptional drift
DNA mutation
New transposable
element insertions
DNA methylation
Me
Ac
Chromatin
modifiers
Normal chromatin state
Histone variant
DNA mutation
Altered patterns of
histone modifications
Abnormal chromatin state


VERODUDERING
OMGEVINGS INVLOEDEN
TOEVALLIGE EFFECTEN
EPIGENOOM
GEZONDHEID
GENOOM
GENEXPRESSIE
FENOTYPE
ZIEKTE

questions

background information

https://www.youtube.com/watch?v=WgERHur3FMQ

https://www.youtube.com/watch?v=_6ZBVf6H_IA

https://www.youtube.com/watch?v=MD3Fc0XOjWk

https://www.youtube.com/watch?v=ebIpkw3XapE

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https://www.youtube.com/watch?v=gfAVIoSP_1c

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