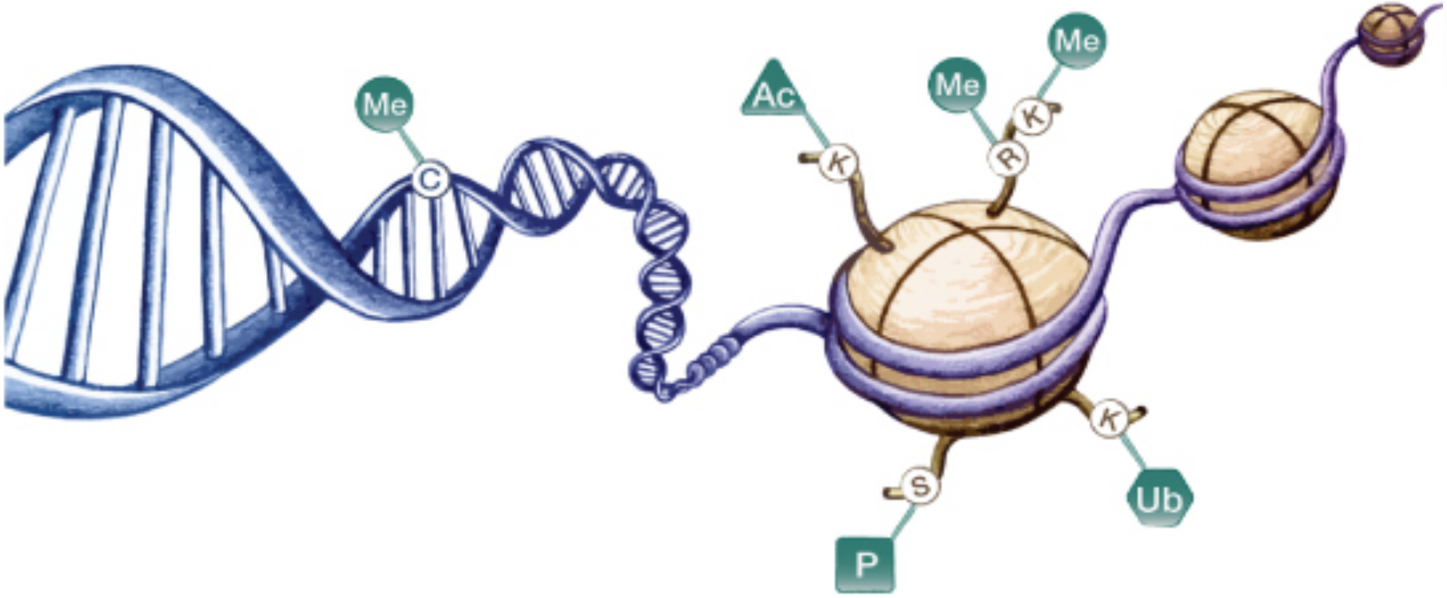
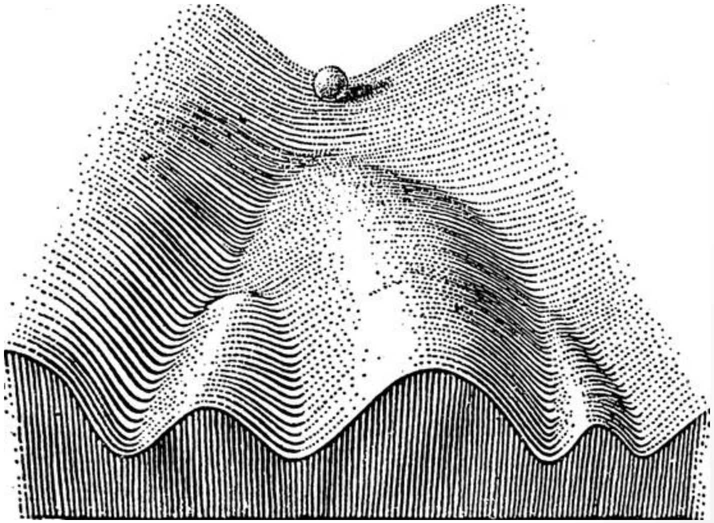


Intro to Epigenetics:

From Development to Cancer

Melissa Ko
Splash Fall 2013
mesako@stanford.edu

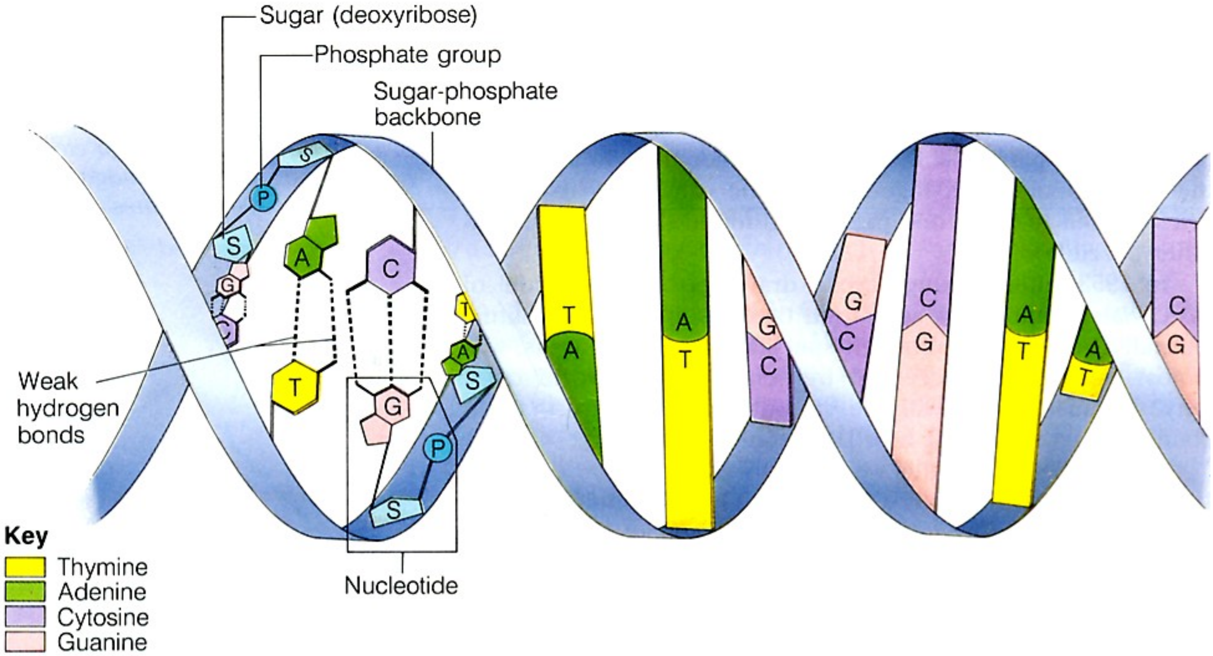


Today's Class Agenda:

- What is **epigenetics**?
  - How is information conveyed in cells?
  - Overview of chromatin structure regulation
  - How does epigenetics mediate development?
- What role does **epigenetics** play in **cancer**?
  - DNA hypermethylation
  - EZH2 histone methyltransferase mutations
  - SWI/SNF chromatin remodeler mutations

What is **epigenetics**?

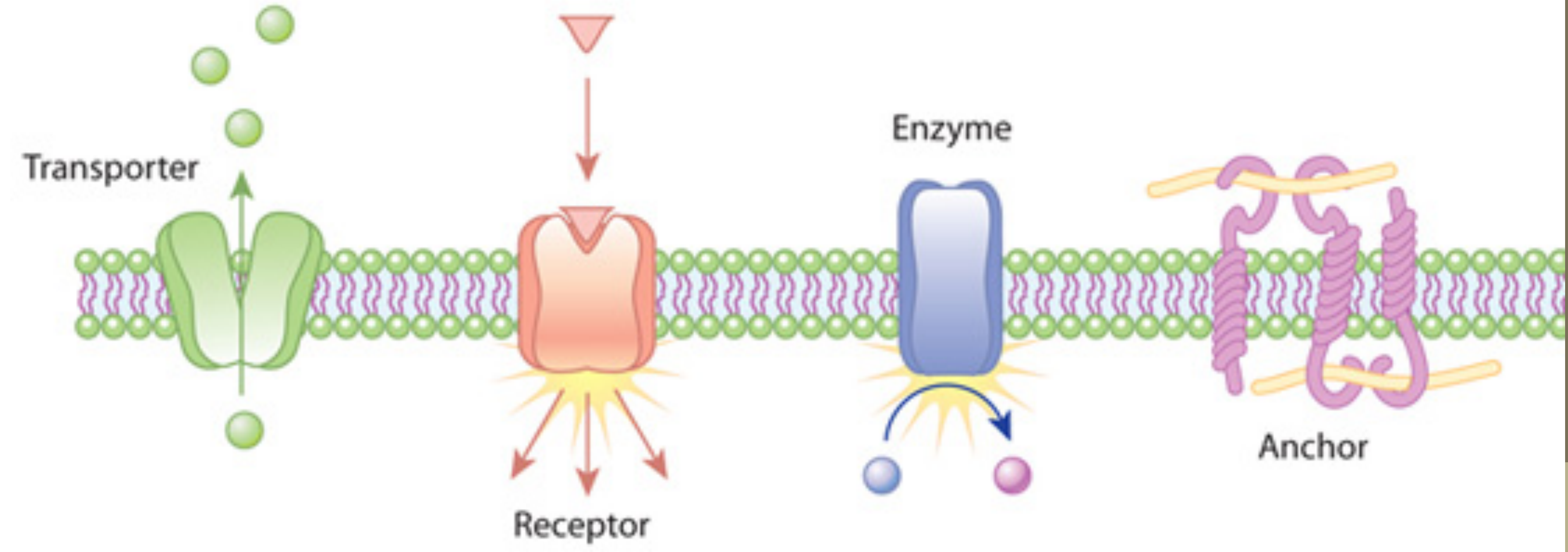
Biological information is stored in our DNA sequence in cells.



1 **TTGATTCAGAAGCCAGCCAGAG**CCCACAATACAGCTTCGAGTCATTACCT
51 CAGAAGATTTGTTTaATCTGTGGGGATGAAGCATCAGGCTGTCATTATGG
101 TGTCCTTACCTGTGGGAGCTGTAAGGTCTTCTTTAAGAGGGCAATGGAAG
151 GGCAGCACAACTACTTATGTGCTGGAAGATGACTGCATCGTTGATAAAAT
201 CGCAGAAAAAACTGCCCAGCATGTCGCCTTAGAAAGTGCTGTCAGGCTG
251 GCATGGTCCTTGGAGGTCGAAAATTTAAAAAGTTCAATAAAGTCAGAGTT
301 GTGAGAGCACTGGATGCTGTTGCTCTCCCACAGCCATTGGGCGTTCCAAA
351 TGAAAGCCAAGCCCTAAGCCAGAGATTCACTTTTTCACCAGGTCAAGACA
401 TACAGTTGATTCCACCACTGATCAACCTGTTAATGAGCATTGAACCAGAT
451 GTGATCTATGCAGGACATGACAACACAAAACCTGACACCTCCAGTTCTTT
501 GCTGACAAGTCTTAAT**CAACTAGGCGAGAGGCAACT**AATCCCGCGGCCAT
551 GGCGGCCGGGAGCATGCGACGTCGGGCCCAATTCGCCCTATAGTGAGTCG
601 TATTACAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCC

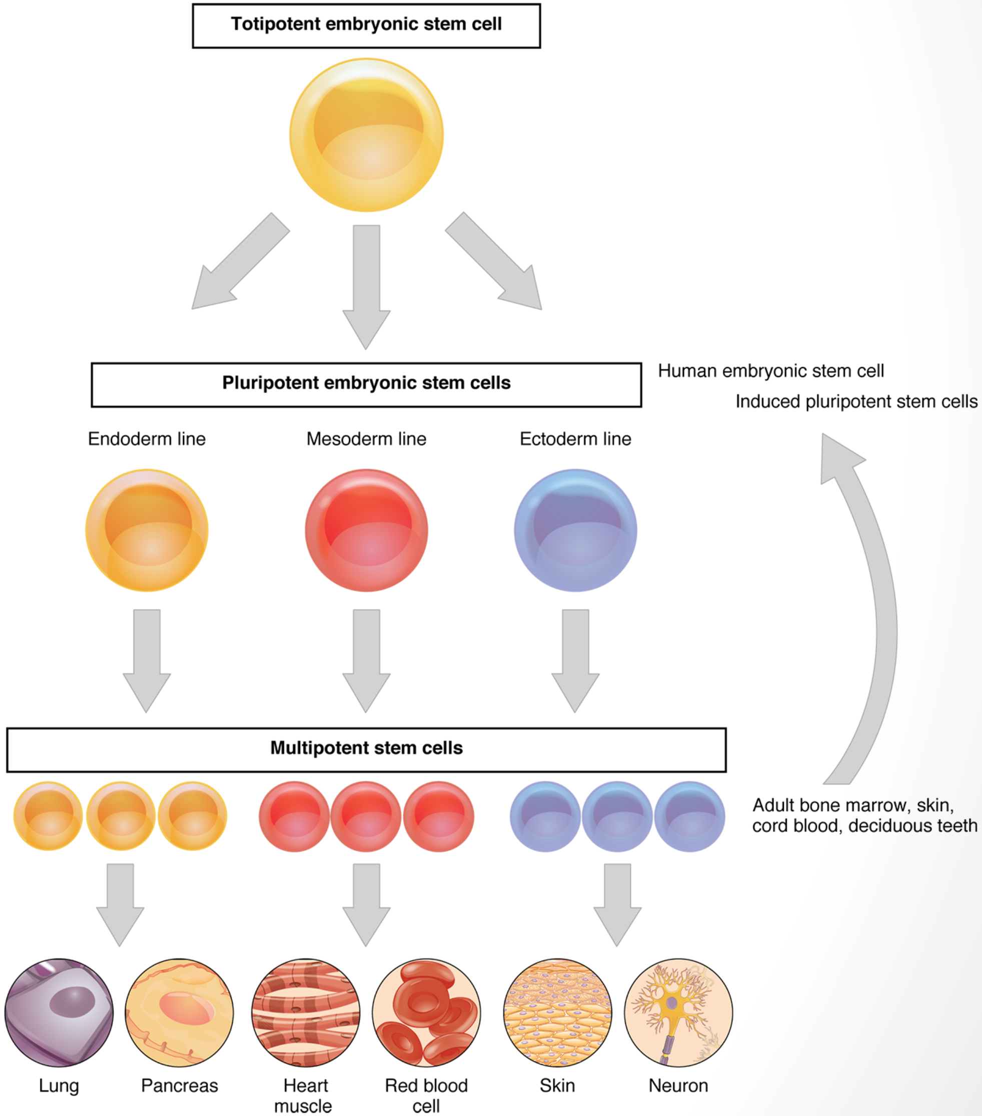
Biological information is stored in our DNA sequence in cells.

- produces **RNA** transcripts that act as instructions for building a diversity of functional **proteins**



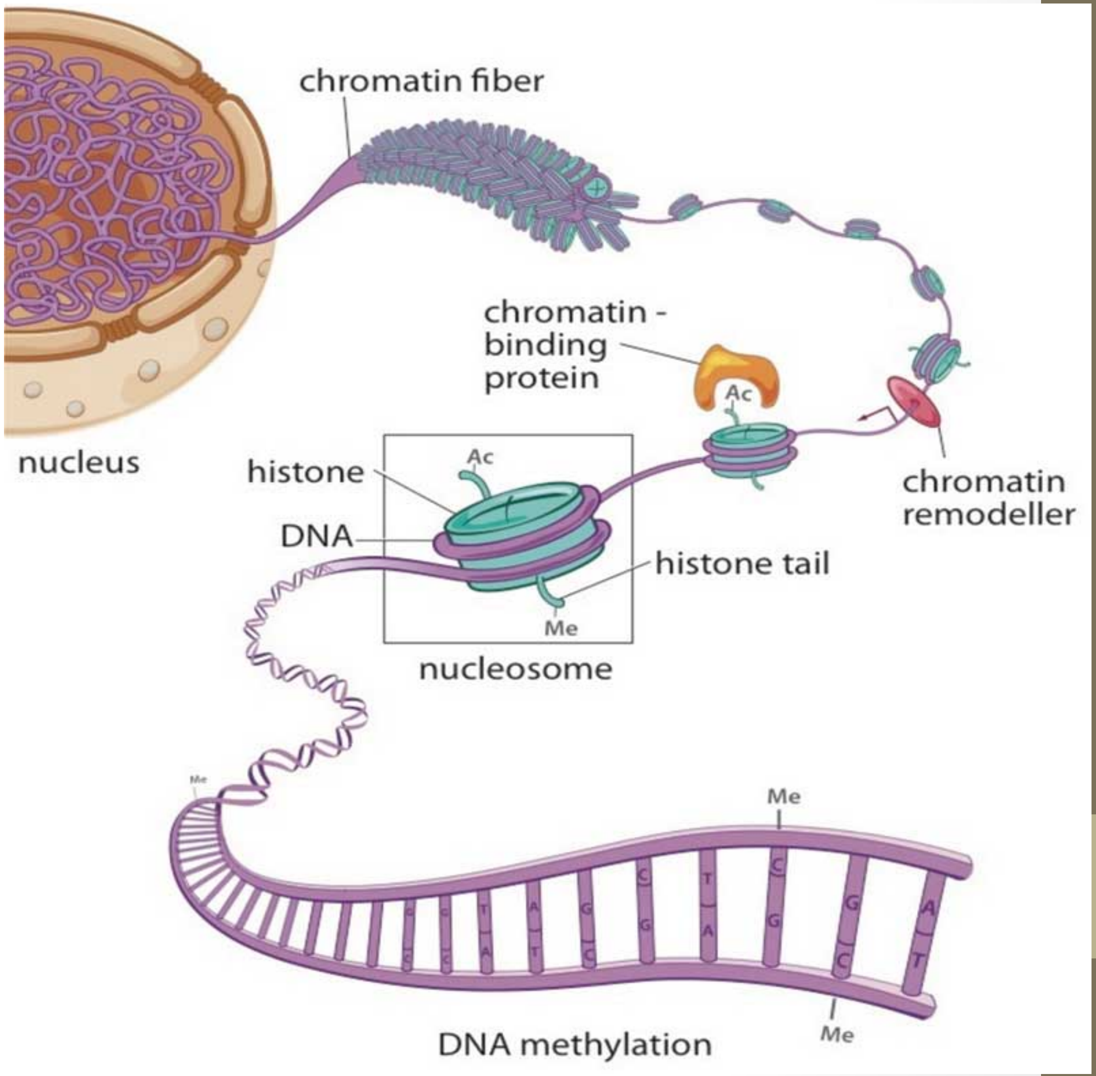
However, this cannot be the only form of information in cells.

- many **cell types** are found in the human body
- fulfill **different functions**, but have essentially the **same DNA**



Biological info is conveyed by the state of DNA/chromatin.

- information is embedded in **structure** of DNA besides sequence
- **chromatin** can have a certain structure in one cells, and a different one in another cell

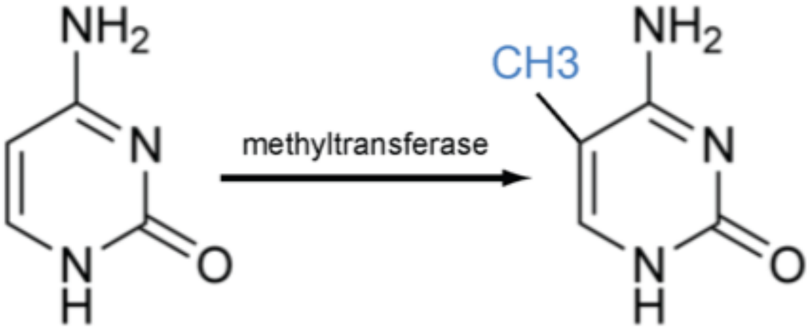


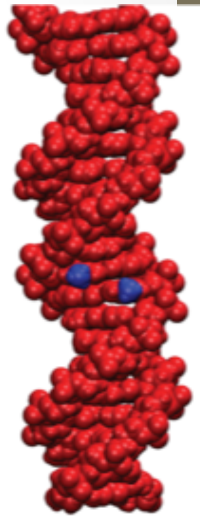
Chromatin structural changes make up epigenetic information.

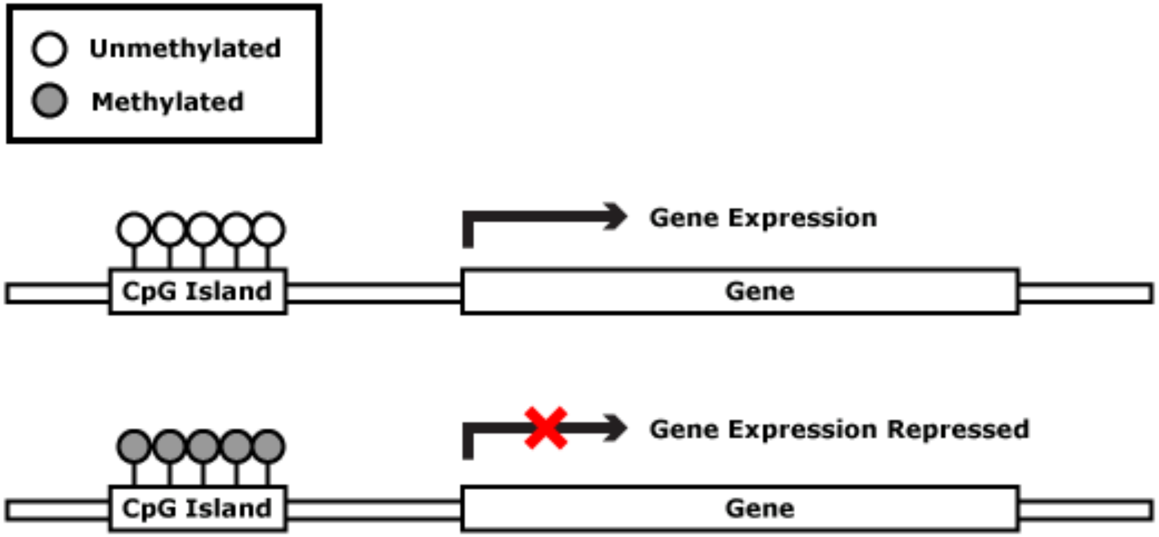
- Epigenetics are:
  - non-genetic cellular **memory/info**
  - **heritable** and usually self-perpetuating
  - **responsive** to inputs and **reversible**
- Epigenetics lead to:
  - changes in **gene expression**
  - changes in cell behavior or identity (**phenotype**)

DNA itself can be modified by methylation at cytosine bases.

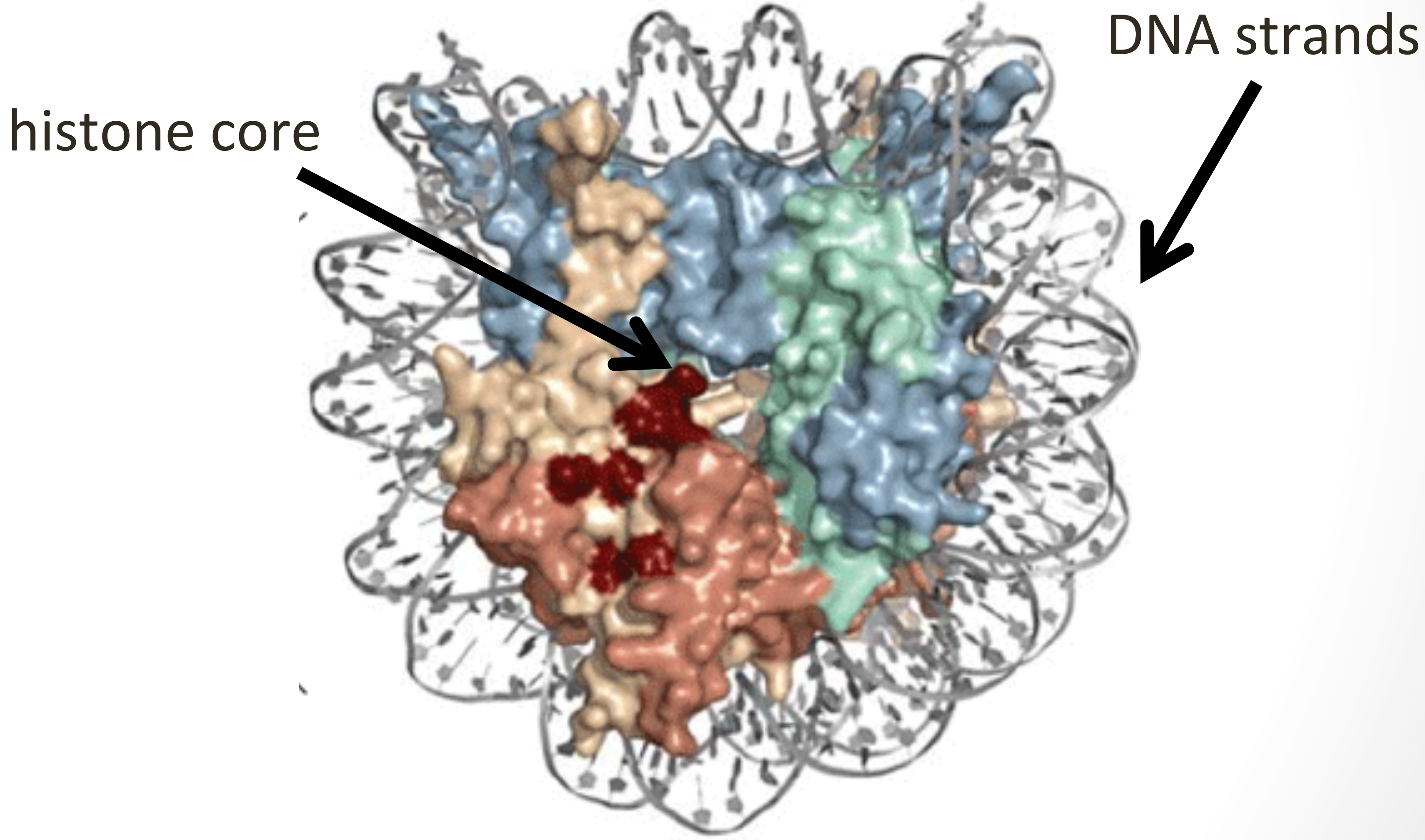
- **methyl** (CH_3) groups added at **cytosine** next to guanine (CpG)
- larger stretches of CpG found near promoters (**islands**)
- **repressive mark**





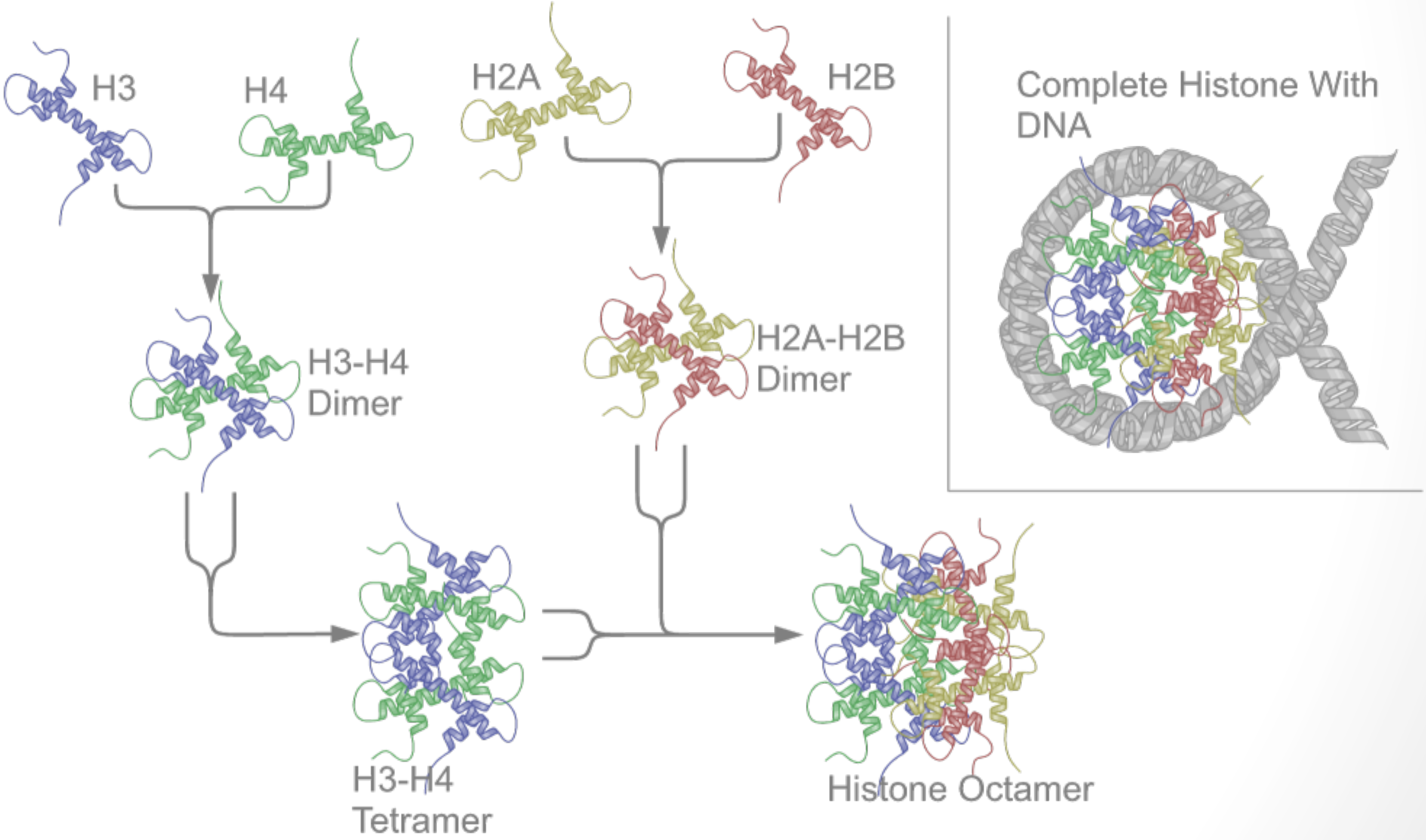


DNA associates with proteins (histones) to form chromatin.



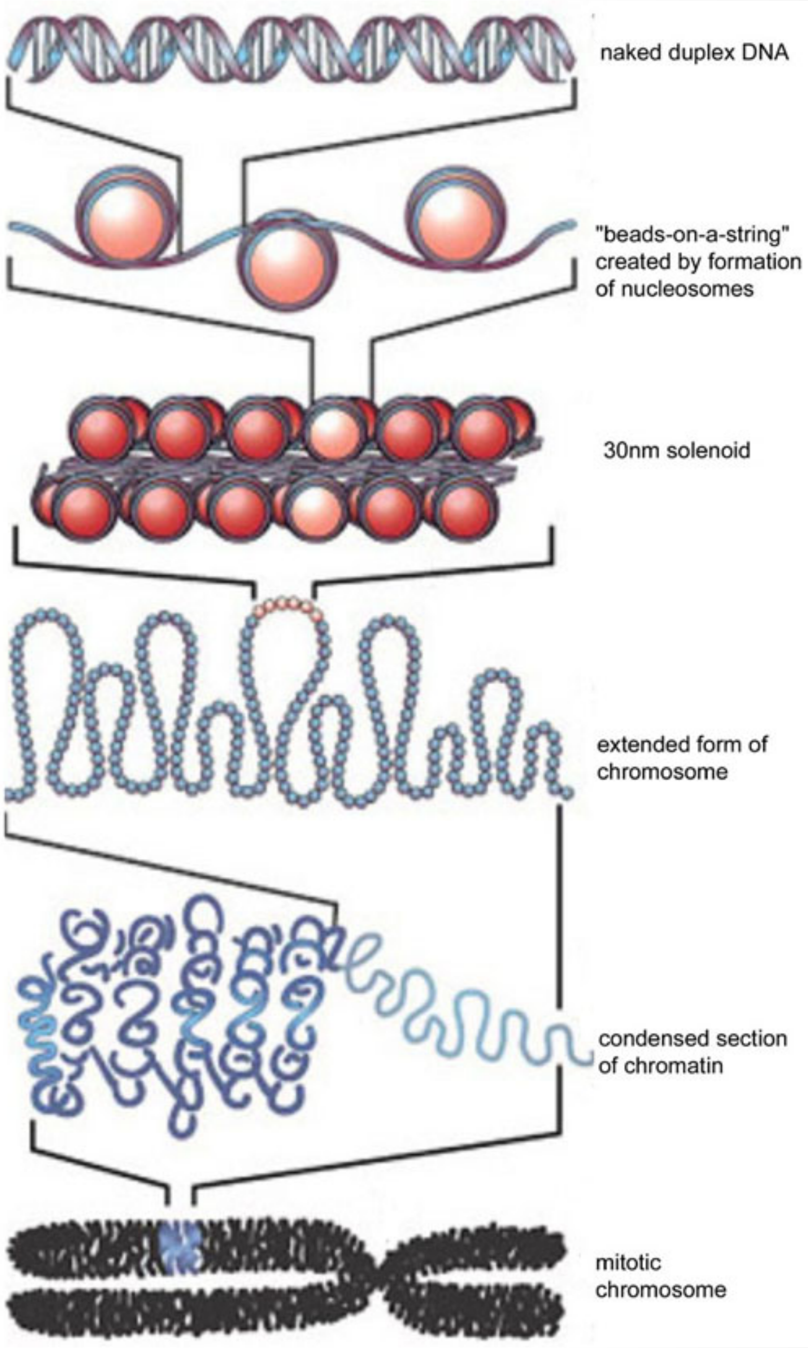
Combinations of histones make a “spool” for DNA to wind around.

- each protein (H3, etc.) is encoded by its own gene



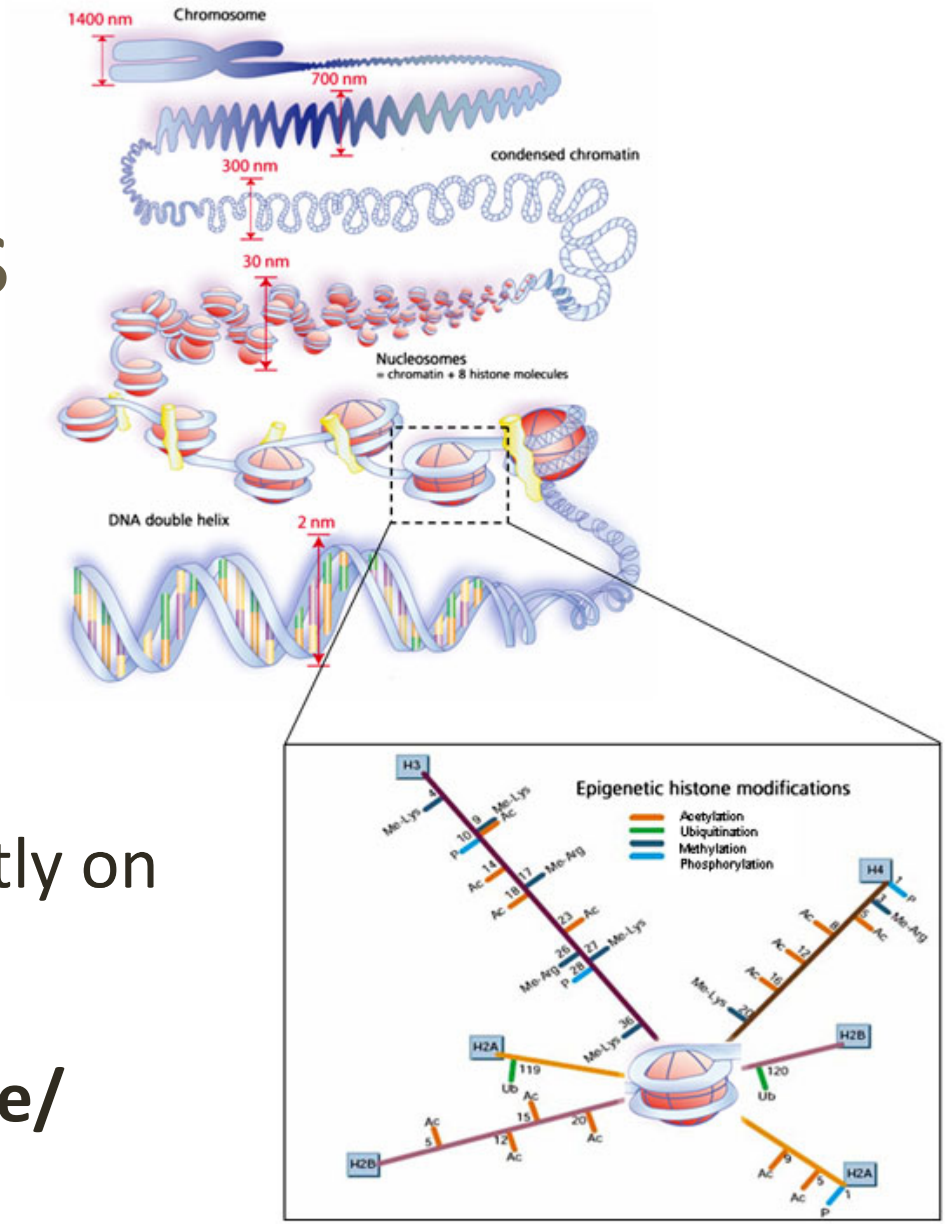
Chromatin has many levels of structure and compaction.

- DNA molecules, unwound, would have a length on the order of **meters**!
- cells are very small, so **coiling** is necessary

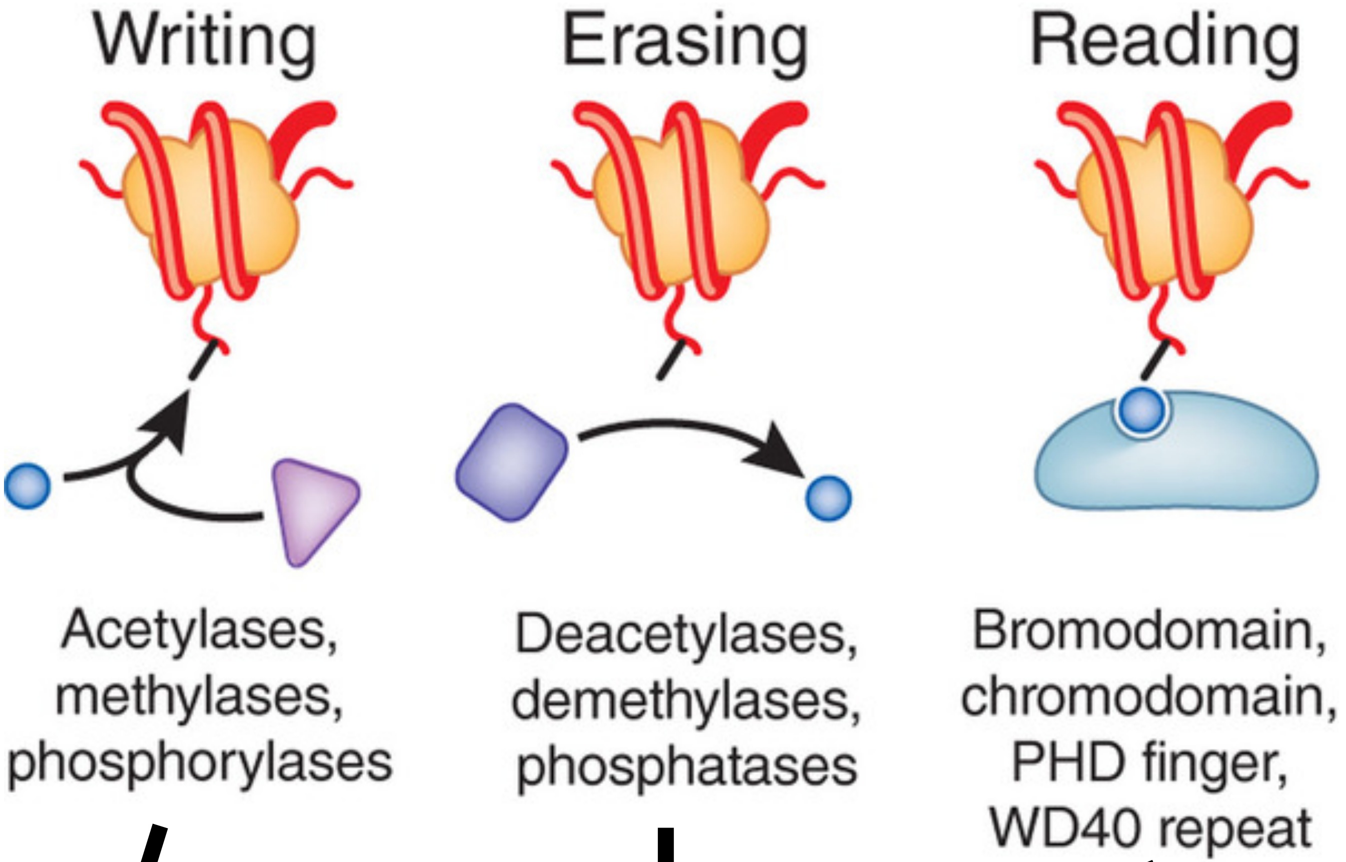


Histones can be chemically modified on tails exposed outside the inner DNA-protein core.

- **small tags** added covalently on mainly lysine residues
- these marks are **accessible/ readable** on the outside



Histone modifications work through three enzyme classes.

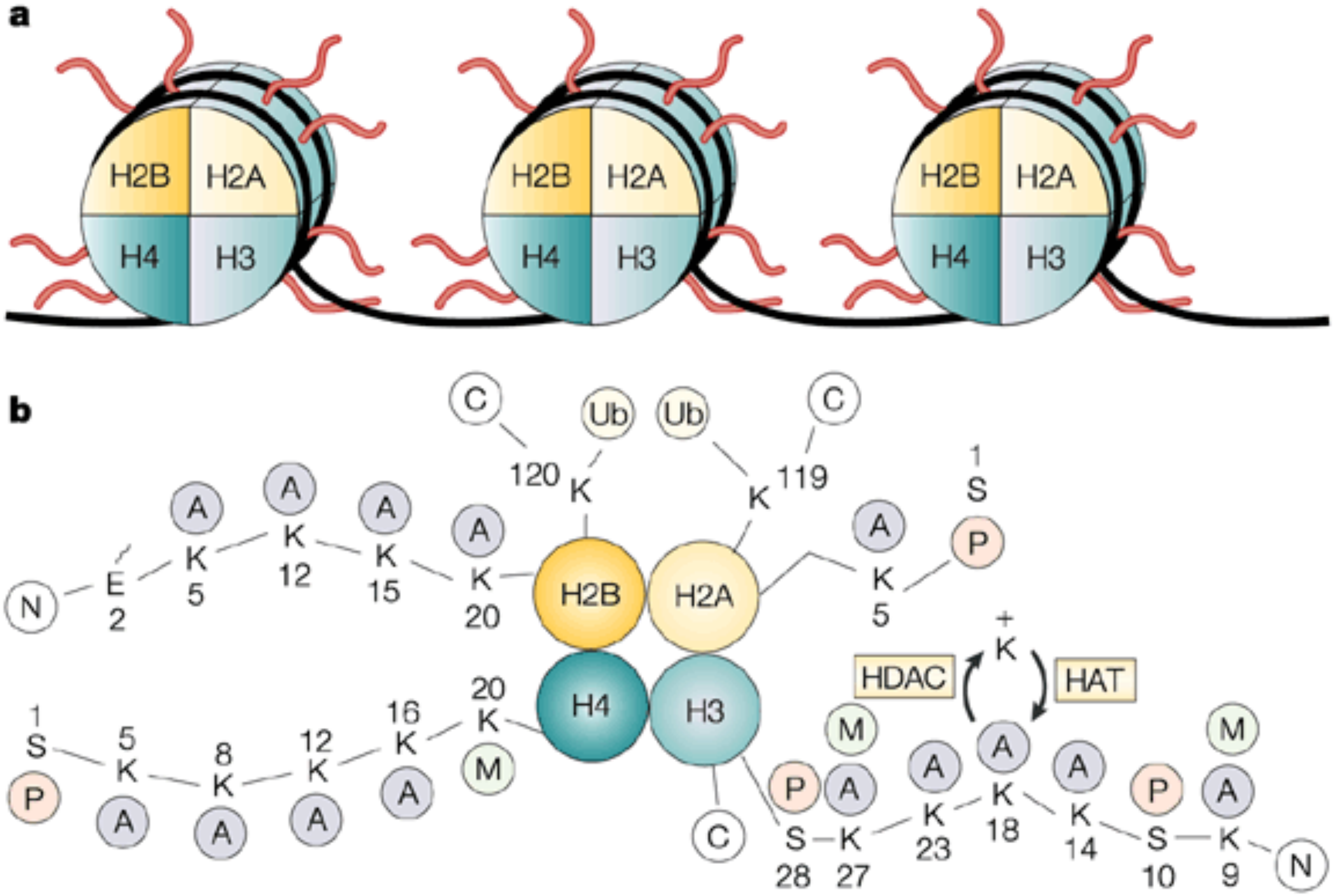


makes marks

removes marks

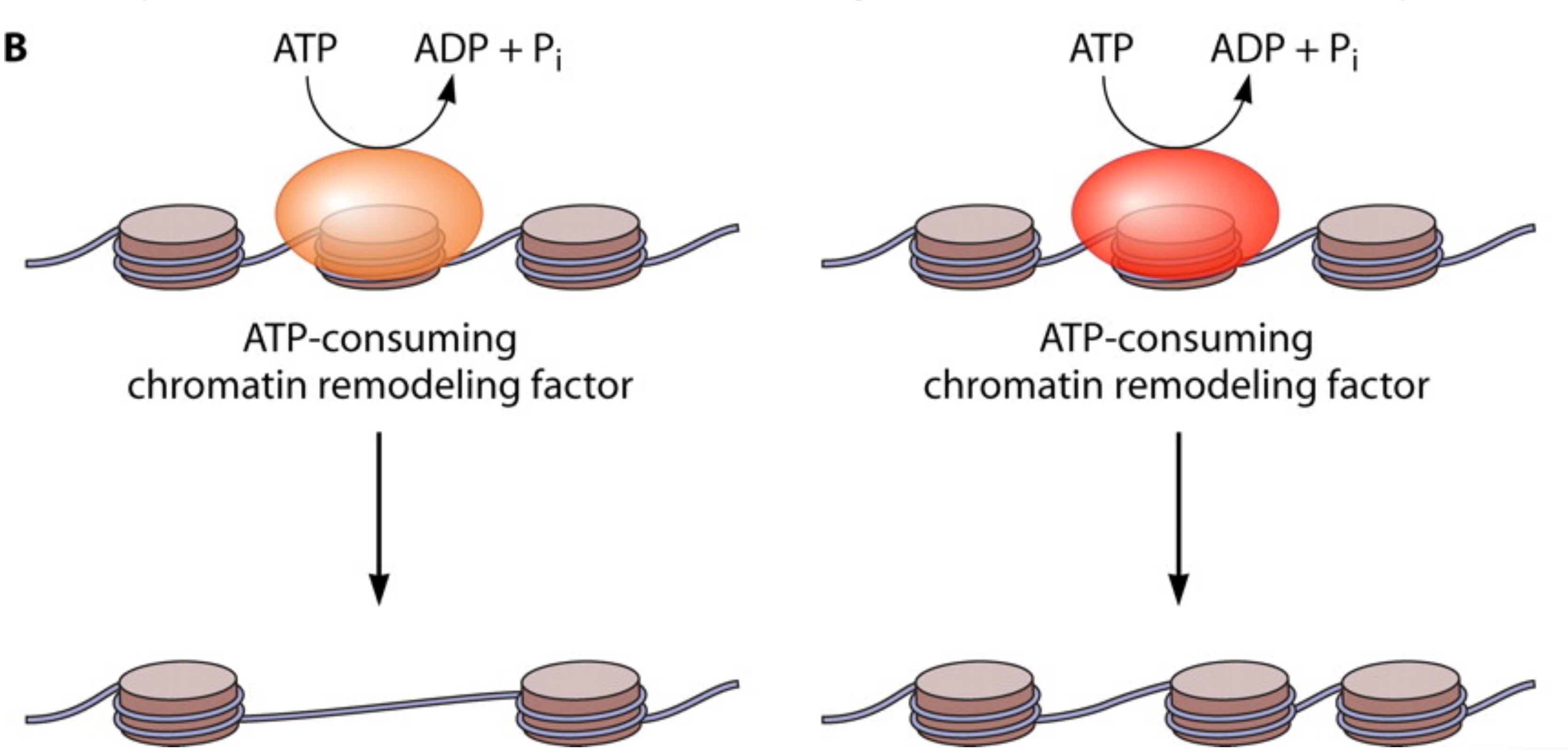
interprets marks

Different modifications convey different biological meaning.



Nature Reviews | Cancer

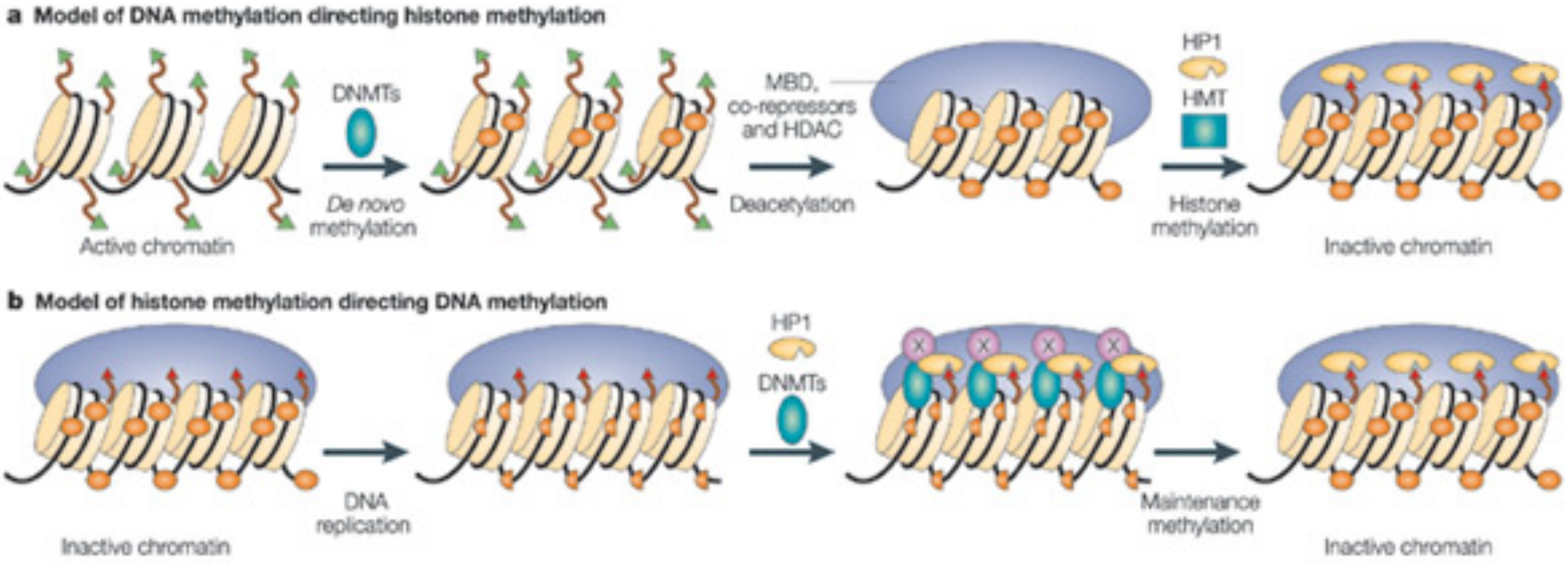
Nucleosome positioning is dynamic, affecting accessibility.



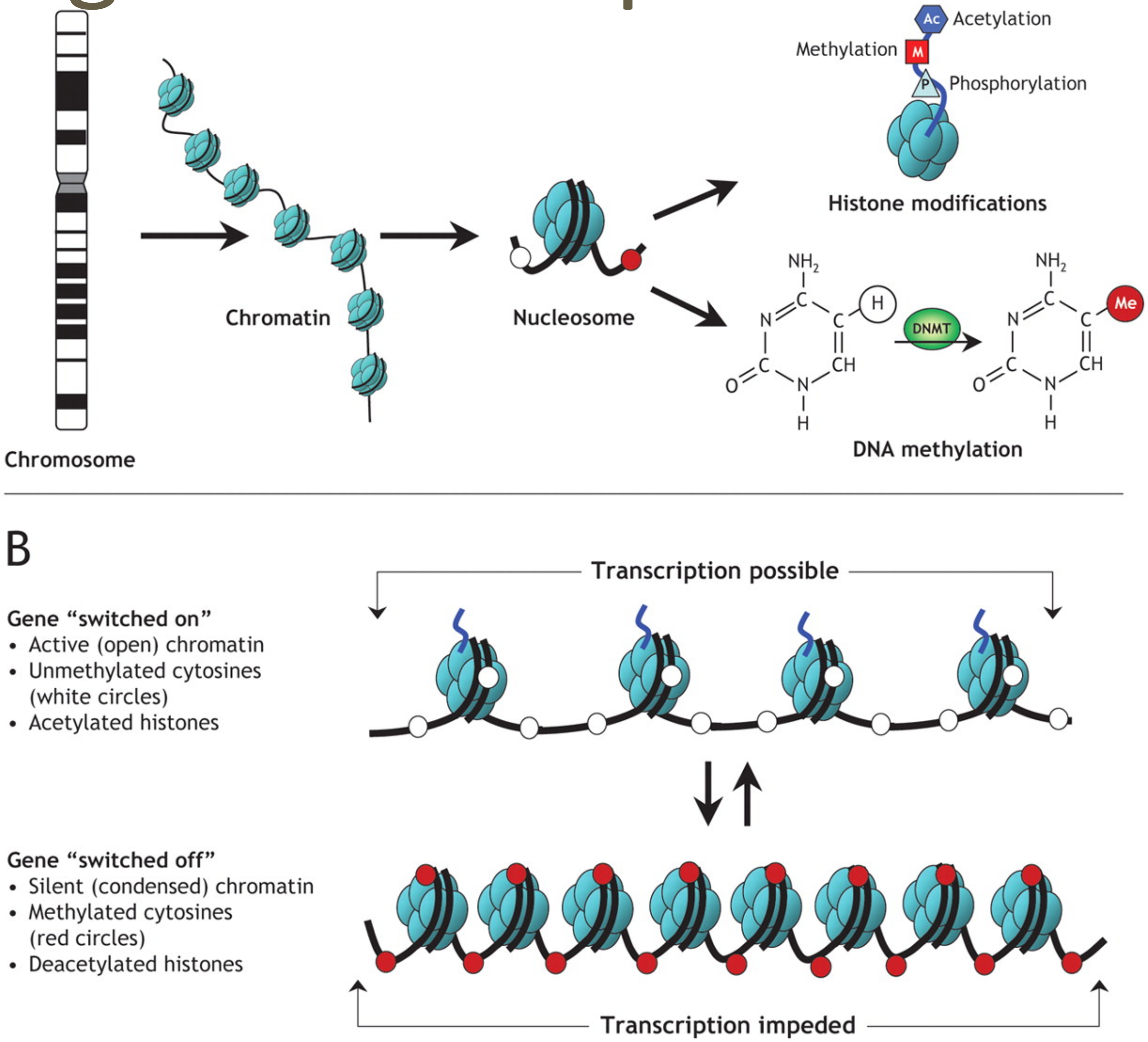
- **allows for gene expression**, by giving RNA polymerase (and other proteins) access

Epigenetic marks work together to change chromatin structure.

- one mark can cause chromatin to gain another
- repressive or activating marks can **cooperate**

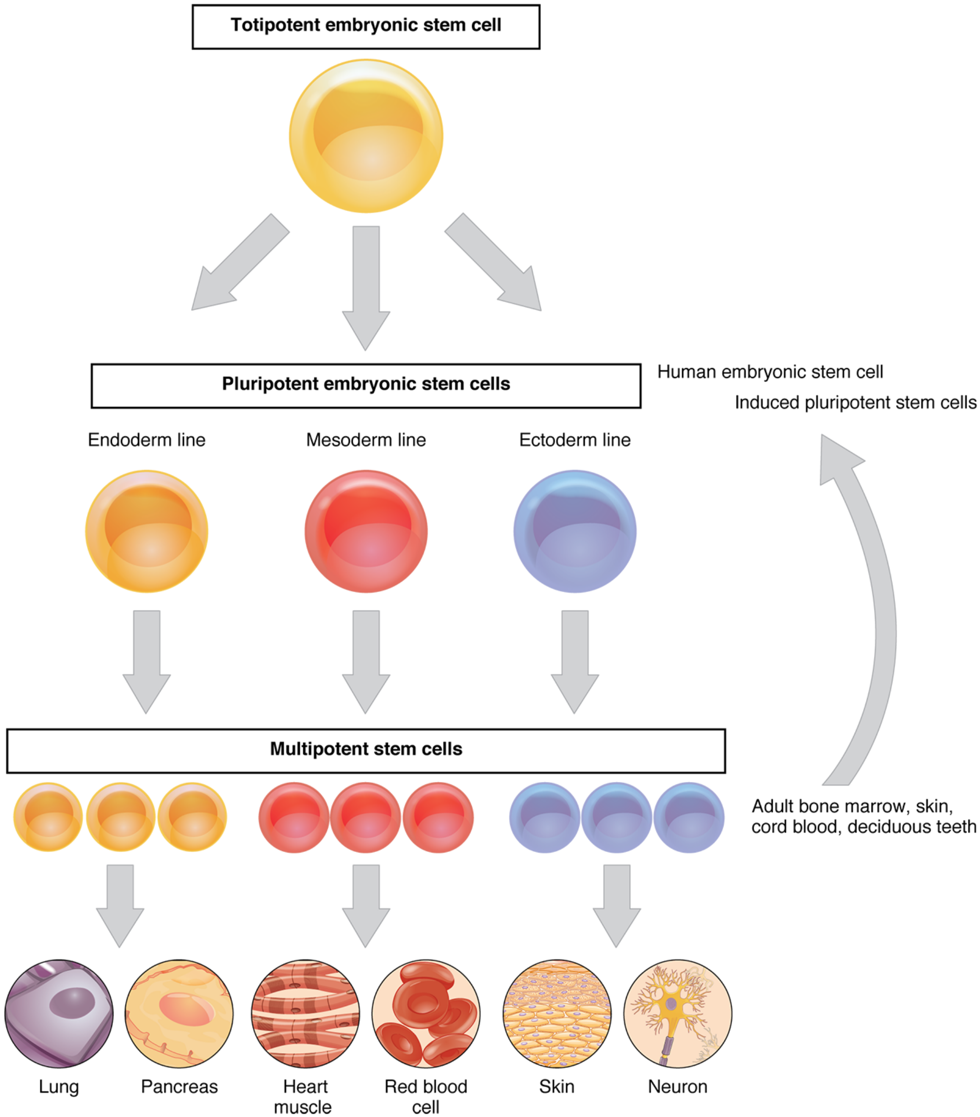


End result: epigenetics changes which genes are expressed.



Epigenetics "program" cells to follow certain instructions.

- a muscle cell will follow muscle cell **instructions** and make muscle proteins, but a neuron or a skin cell will not
- differences arise in the **epigenetics**, chromatin configuration, **not DNA**



Totipotent embryonic stem cell

Pluripotent embryonic stem cells

Human embryonic stem cell

Induced pluripotent stem cells

Endoderm line

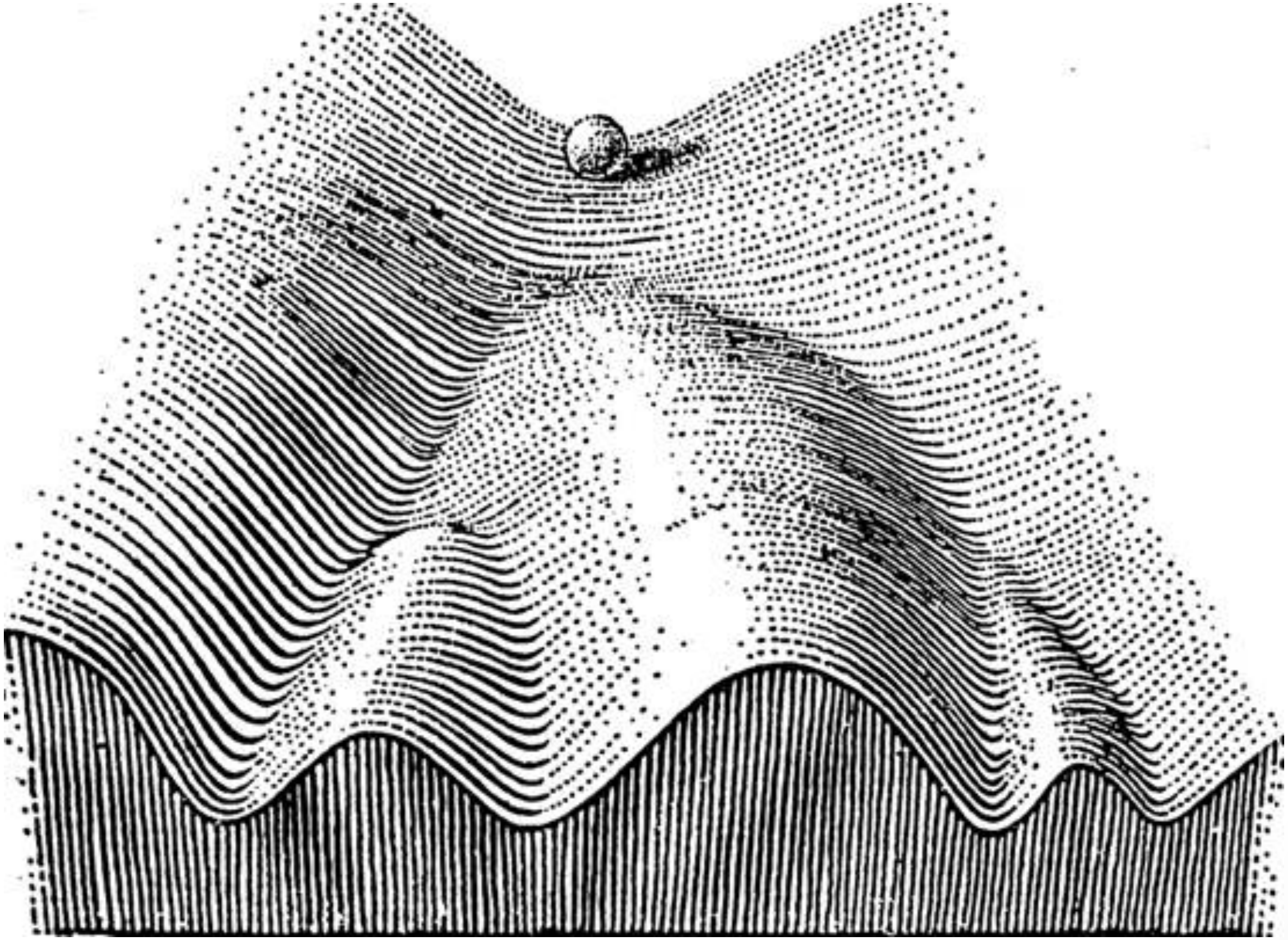
Mesoderm line

Ectoderm line

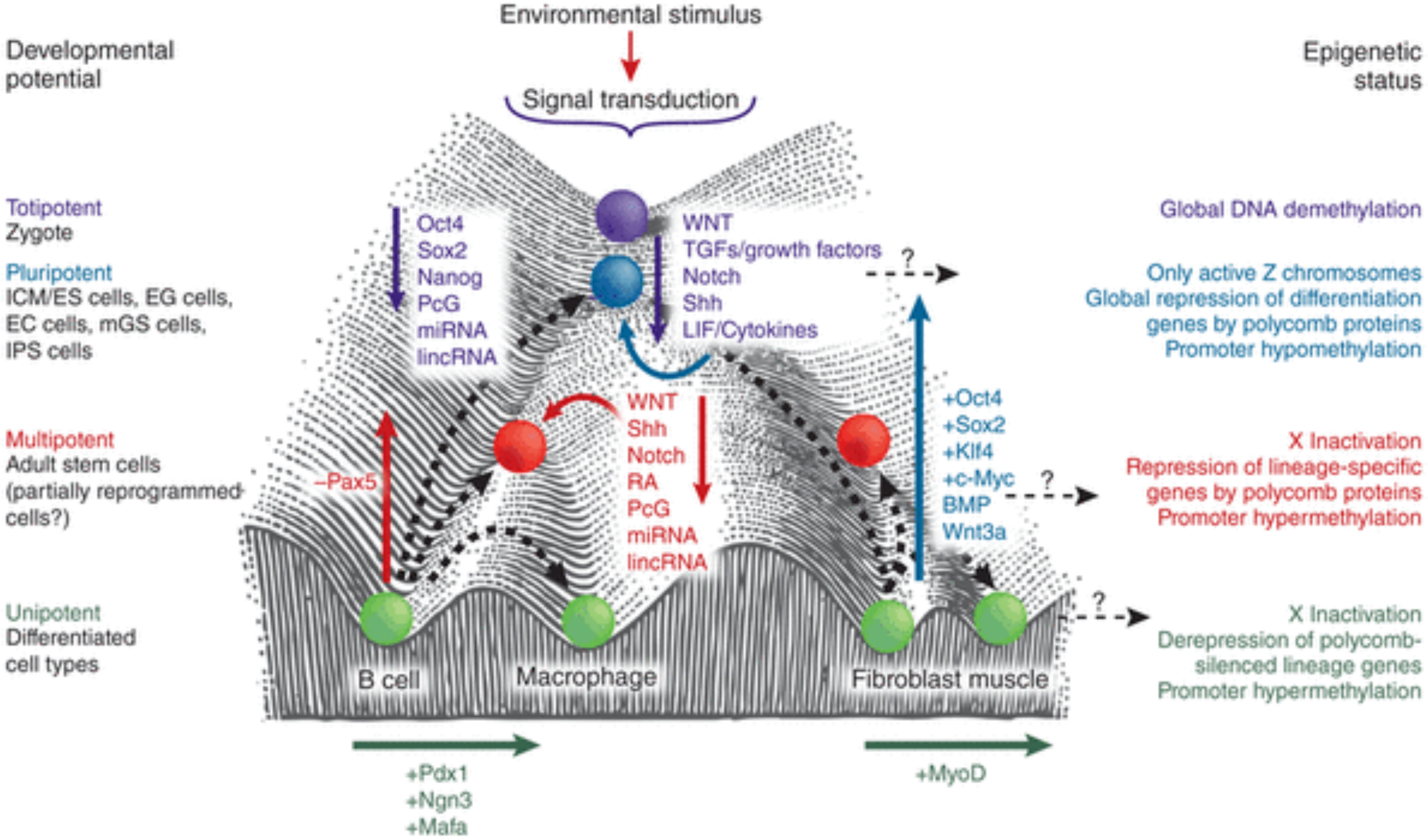
Multipotent stem cells

Adult bone marrow, skin, cord blood, deciduous teeth

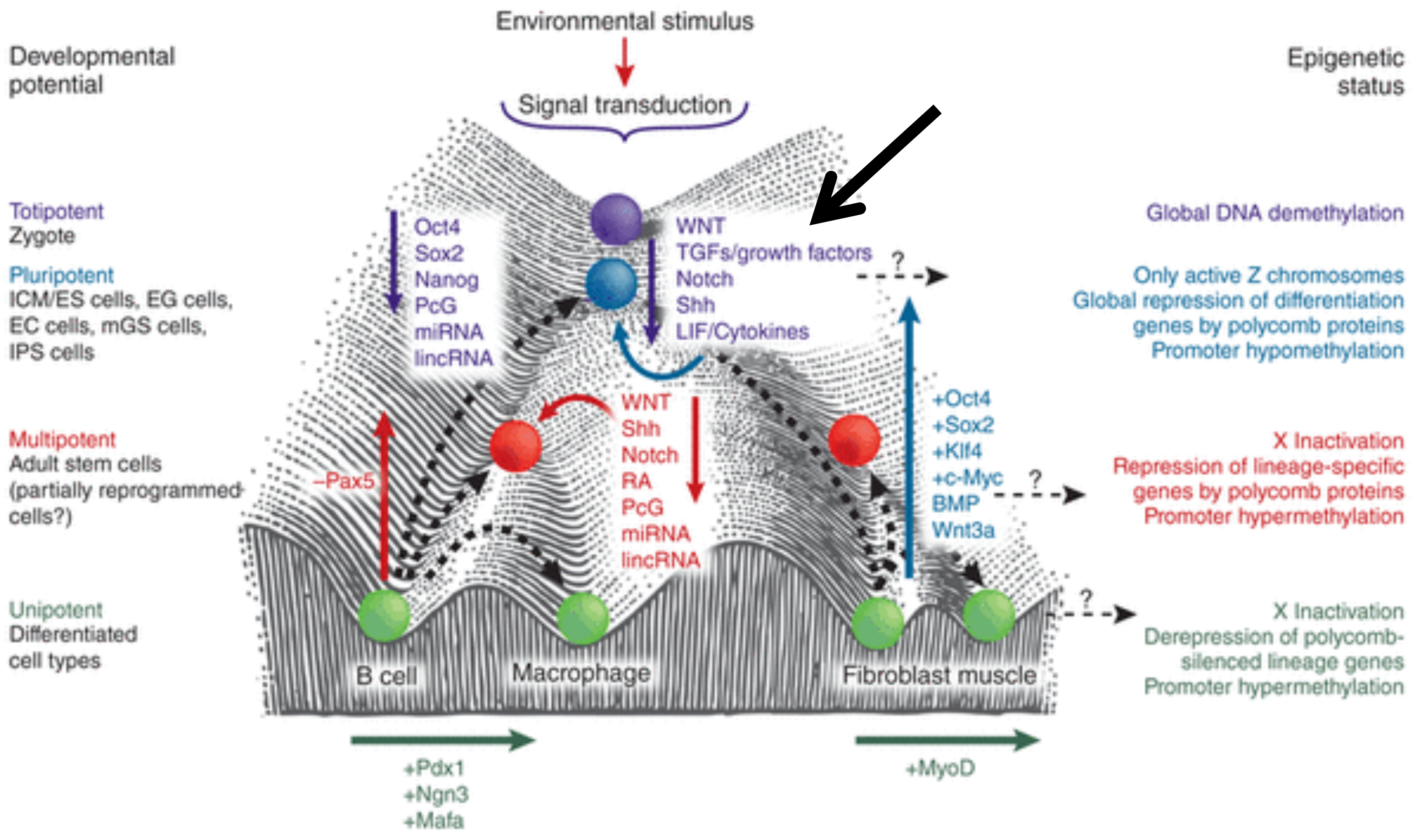
Epigenetic landscape shows cells falling into different lineages.



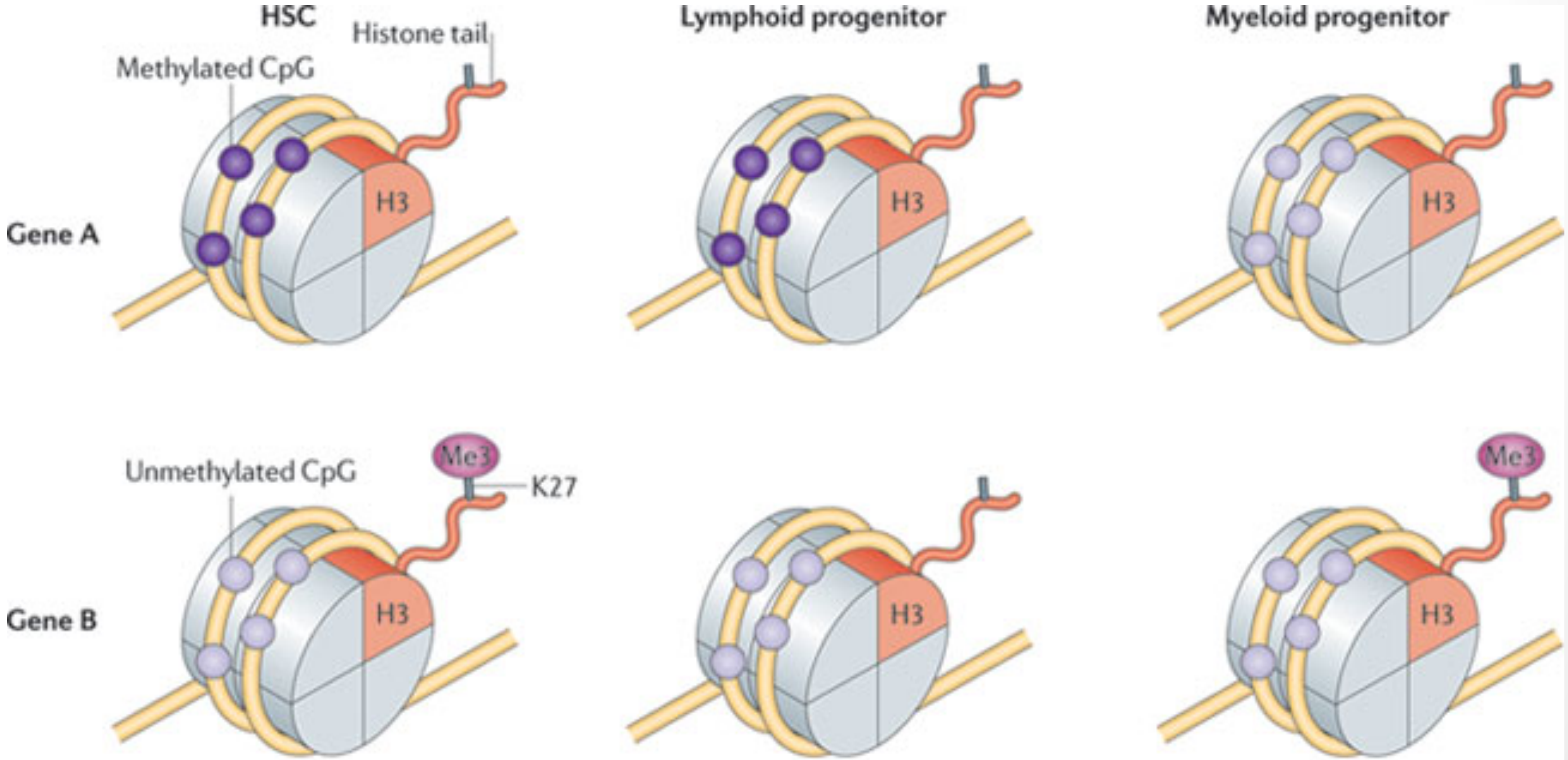
Epigenetic landscape shows cells falling into different lineages.



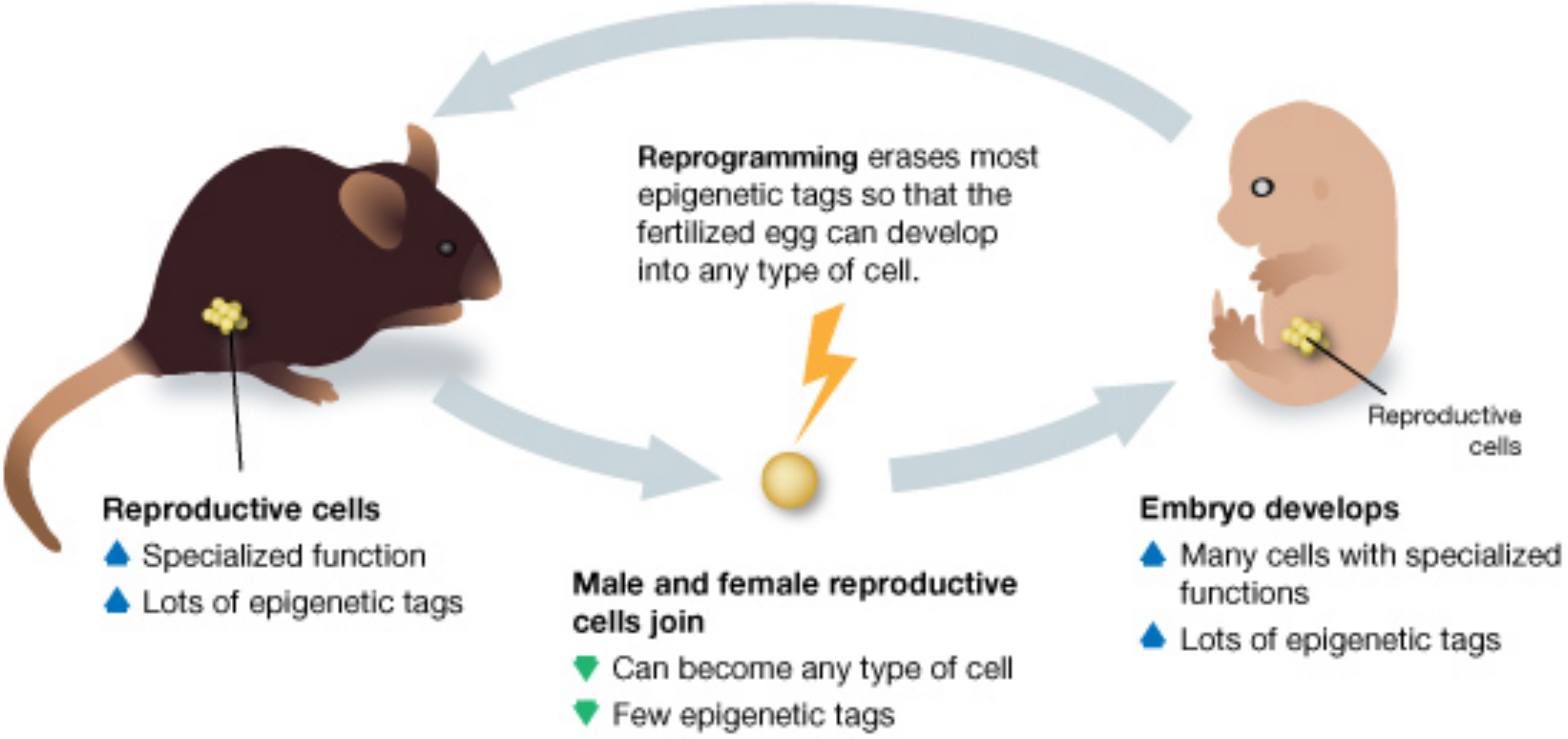
Inputs influence epigenetics and cause cells to differentiate.



Differentiated cells have marks to turn on type-specific genes and turn off unrelated genes.



Epigenetics plays a major role in development as cells take on roles.



Reprogramming erases most epigenetic tags so that the fertilized egg can develop into any type of cell.

Reproductive cells

- ▲ Specialized function
- ▲ Lots of epigenetic tags

Male and female reproductive cells join

- ▼ Can become any type of cell
- ▼ Few epigenetic tags

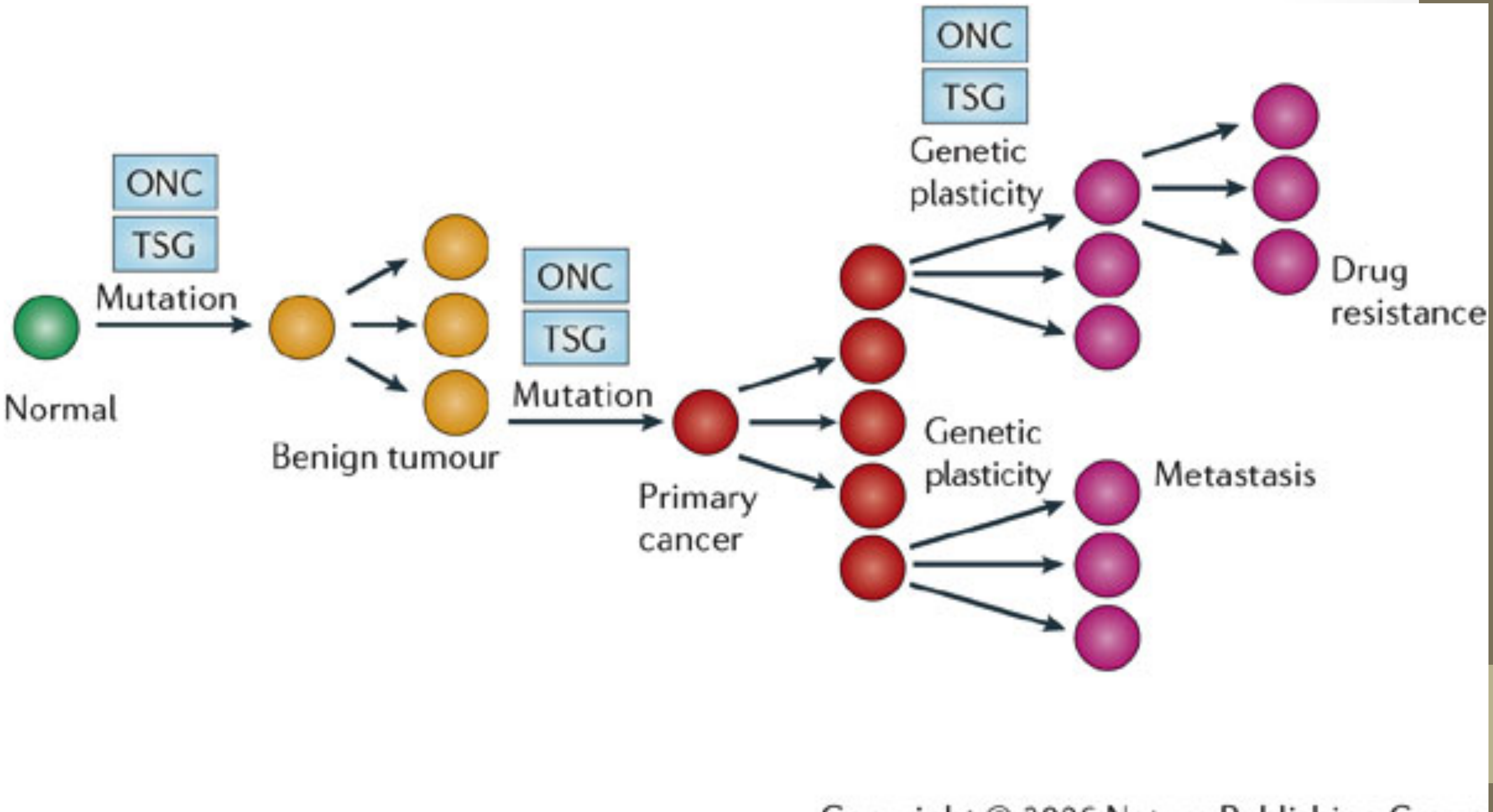
Reproductive cells

Embryo develops

- ▲ Many cells with specialized functions
- ▲ Lots of epigenetic tags

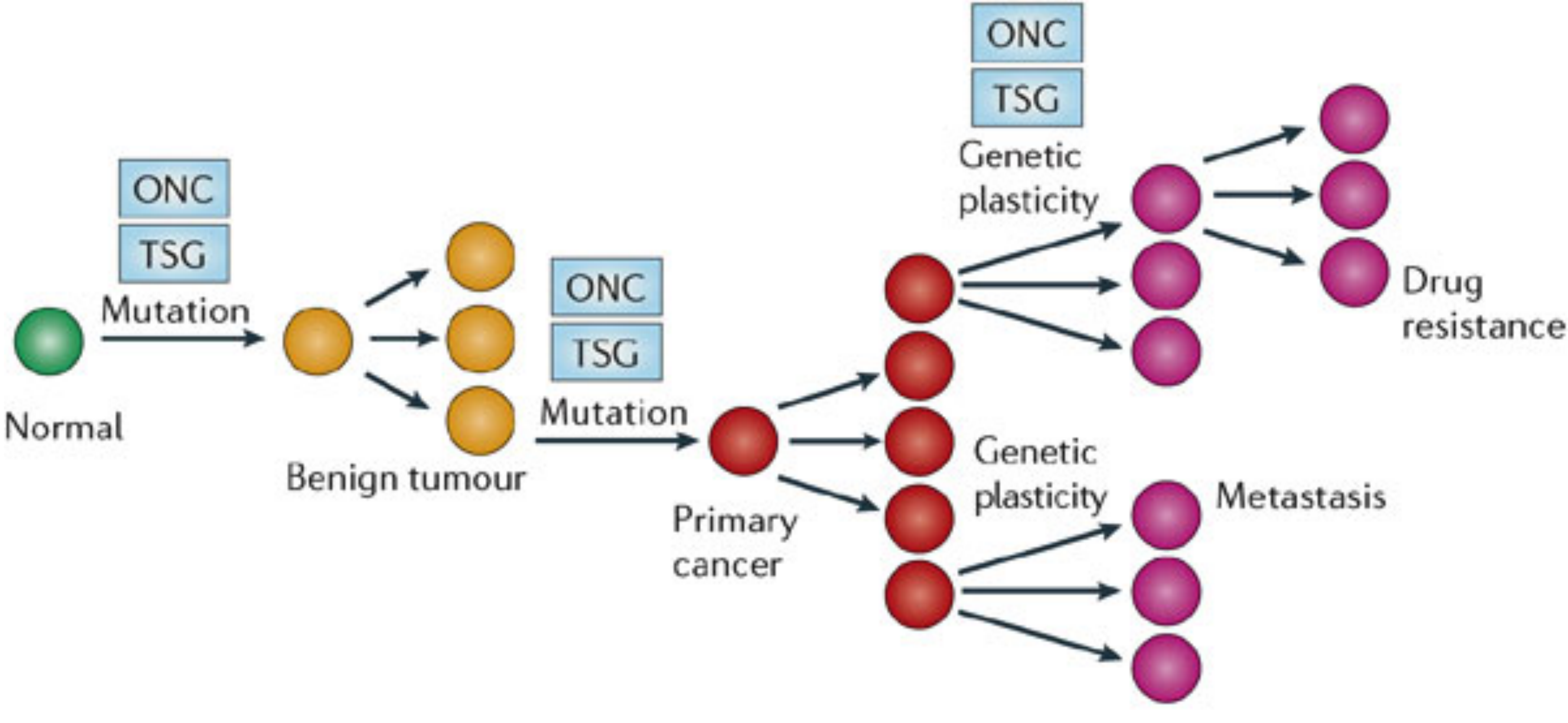
What role does **epigenetics** play in **cancer**?

Model of cancer has long focused on genetic changes from normal.



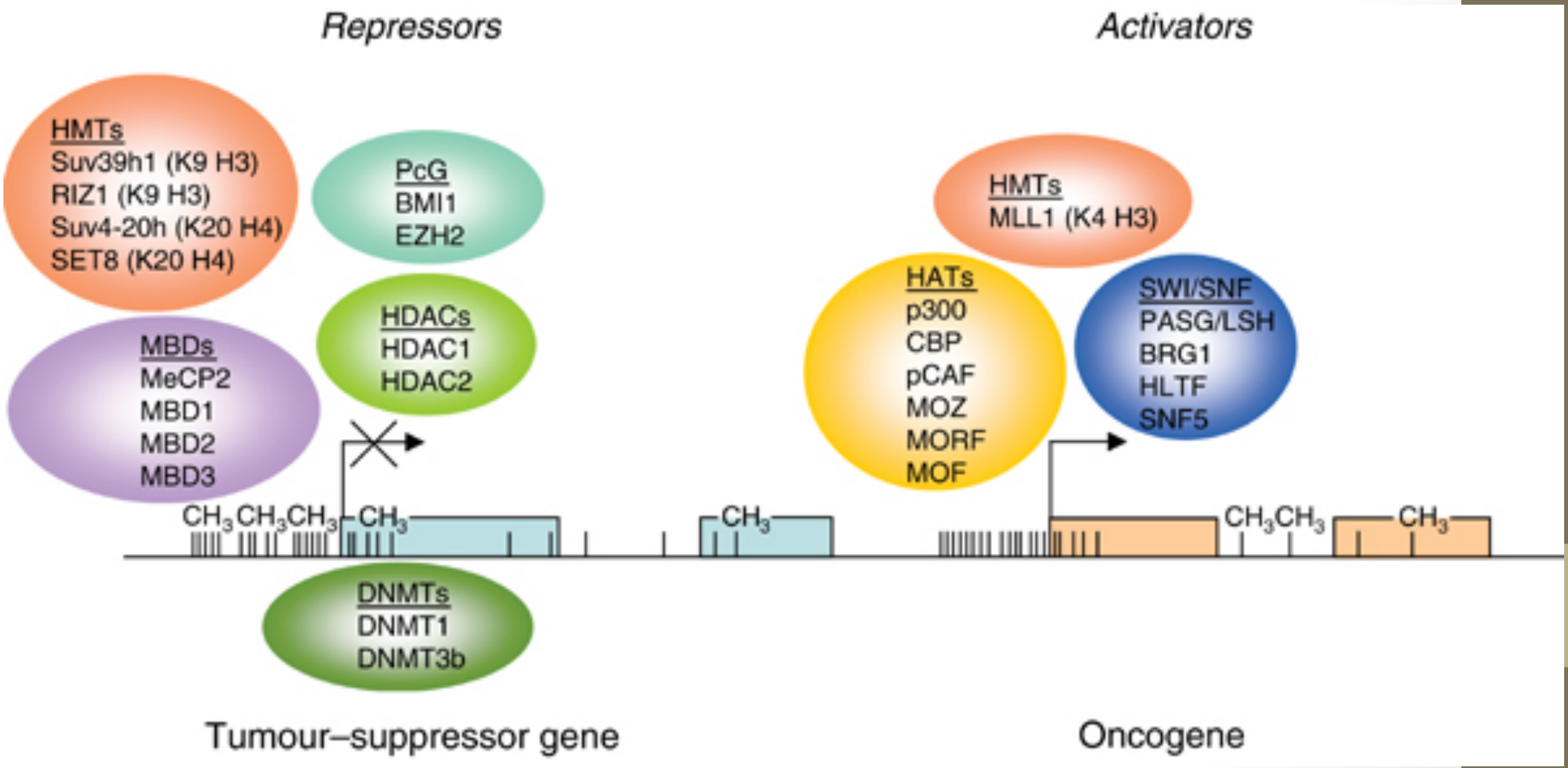
Nature Reviews | Genetics

But cancer also results from non-genetic gene expression changes.

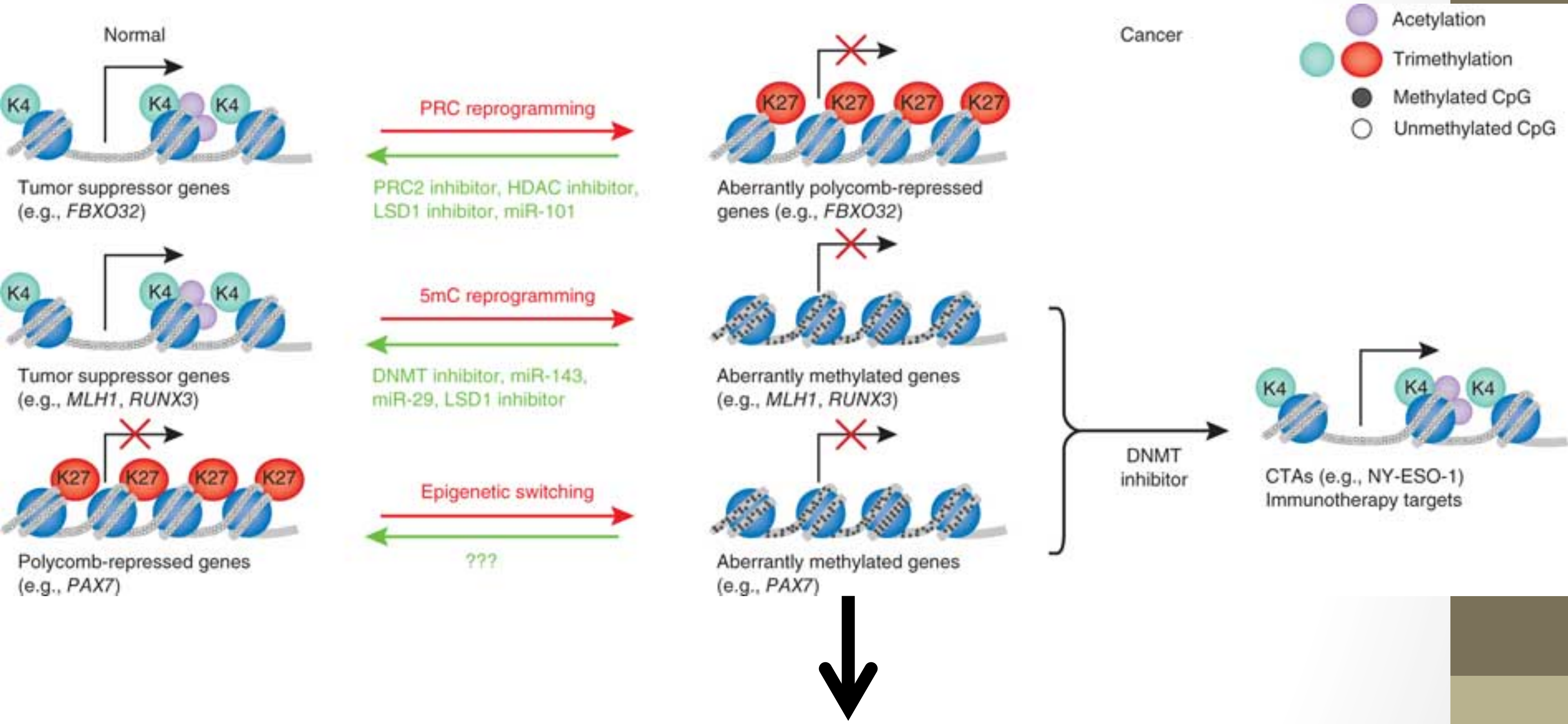


Nature Reviews | Genetics

Evidence has been found of epigenetic activators at oncogenes and repressors at TSGs.

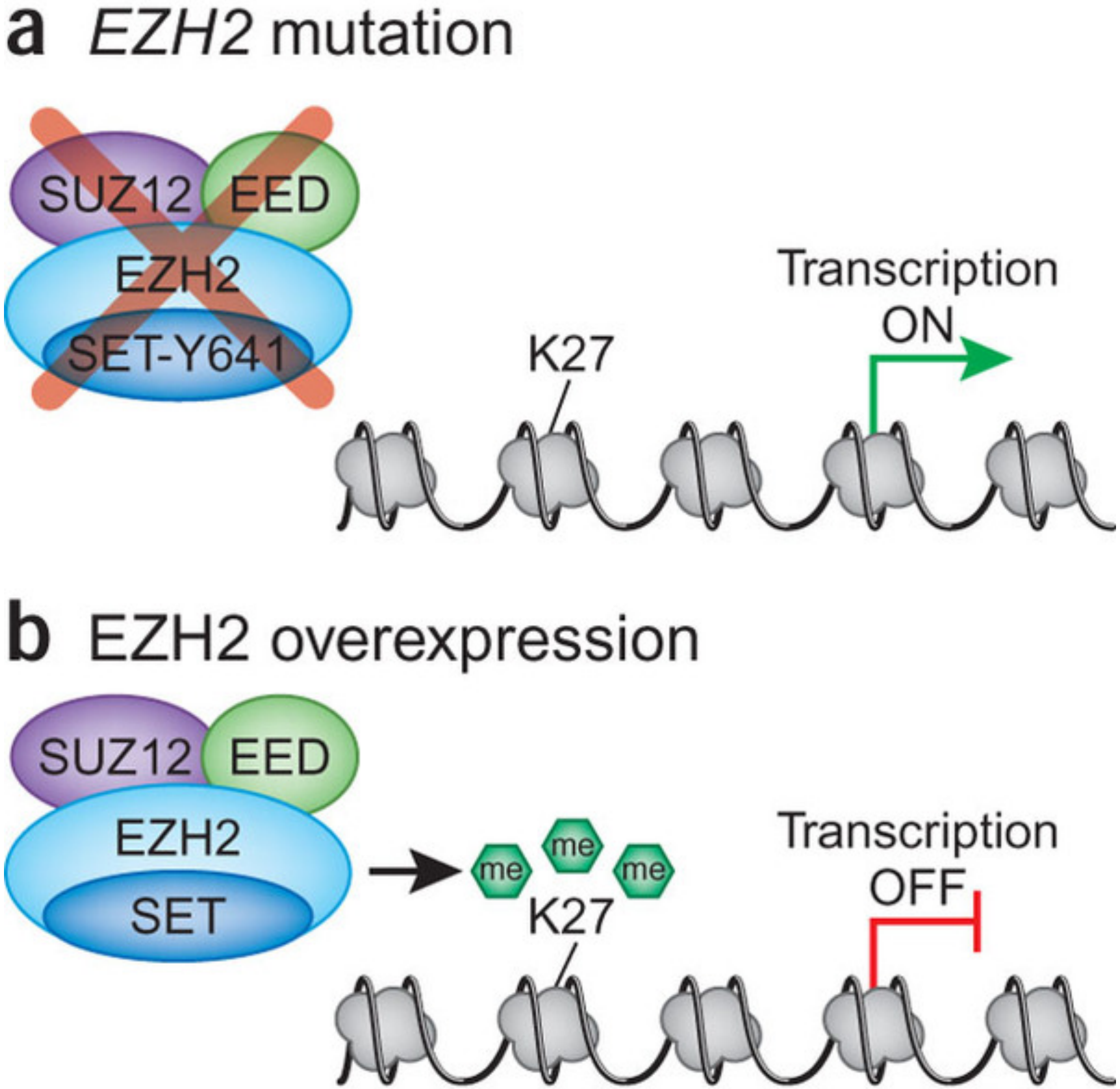


DNA hypermethylation at TSGs leads to cancer initiation.

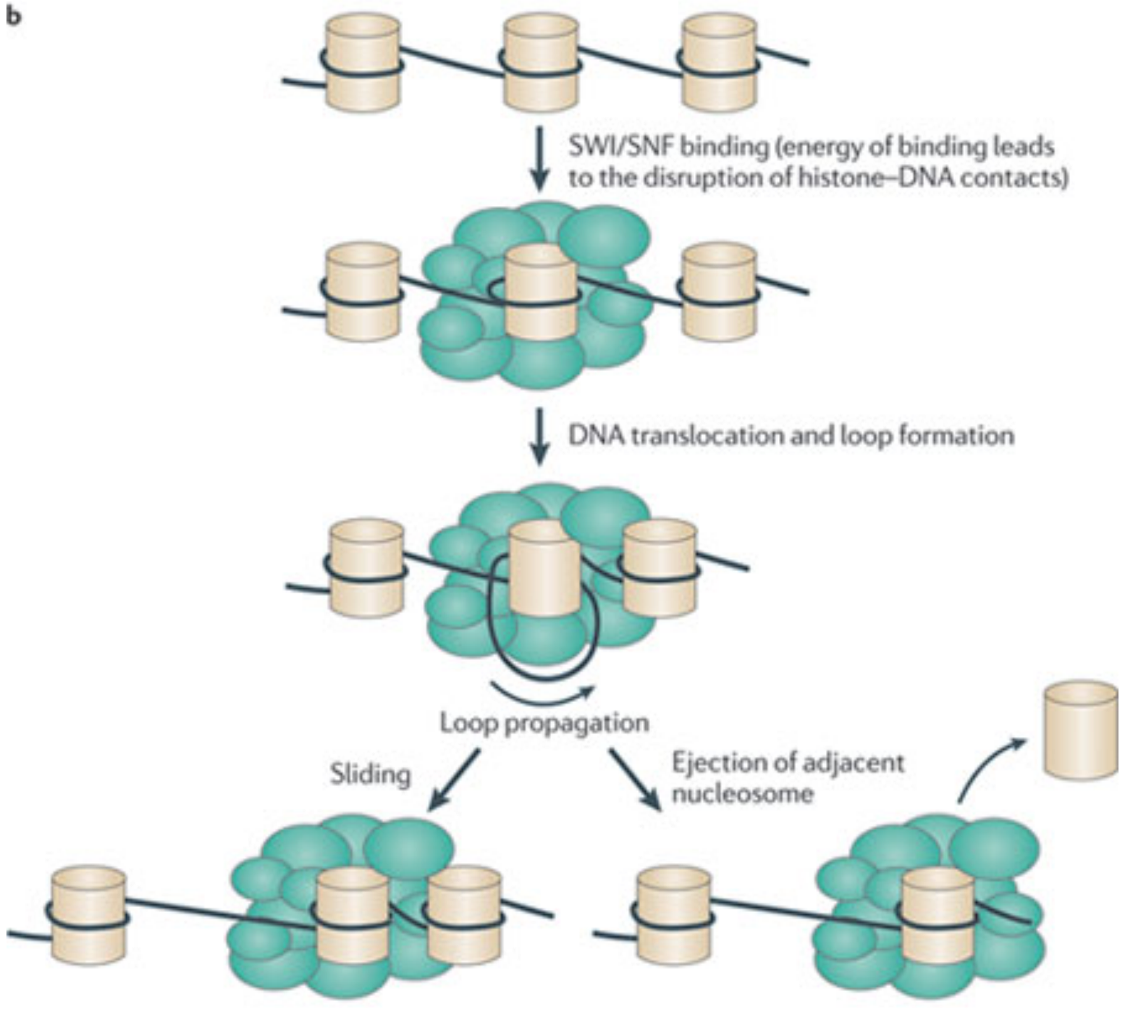


inactivation of **tumor suppressor genes**

EZH2 mutations causes aberrant widespread histone methylation.

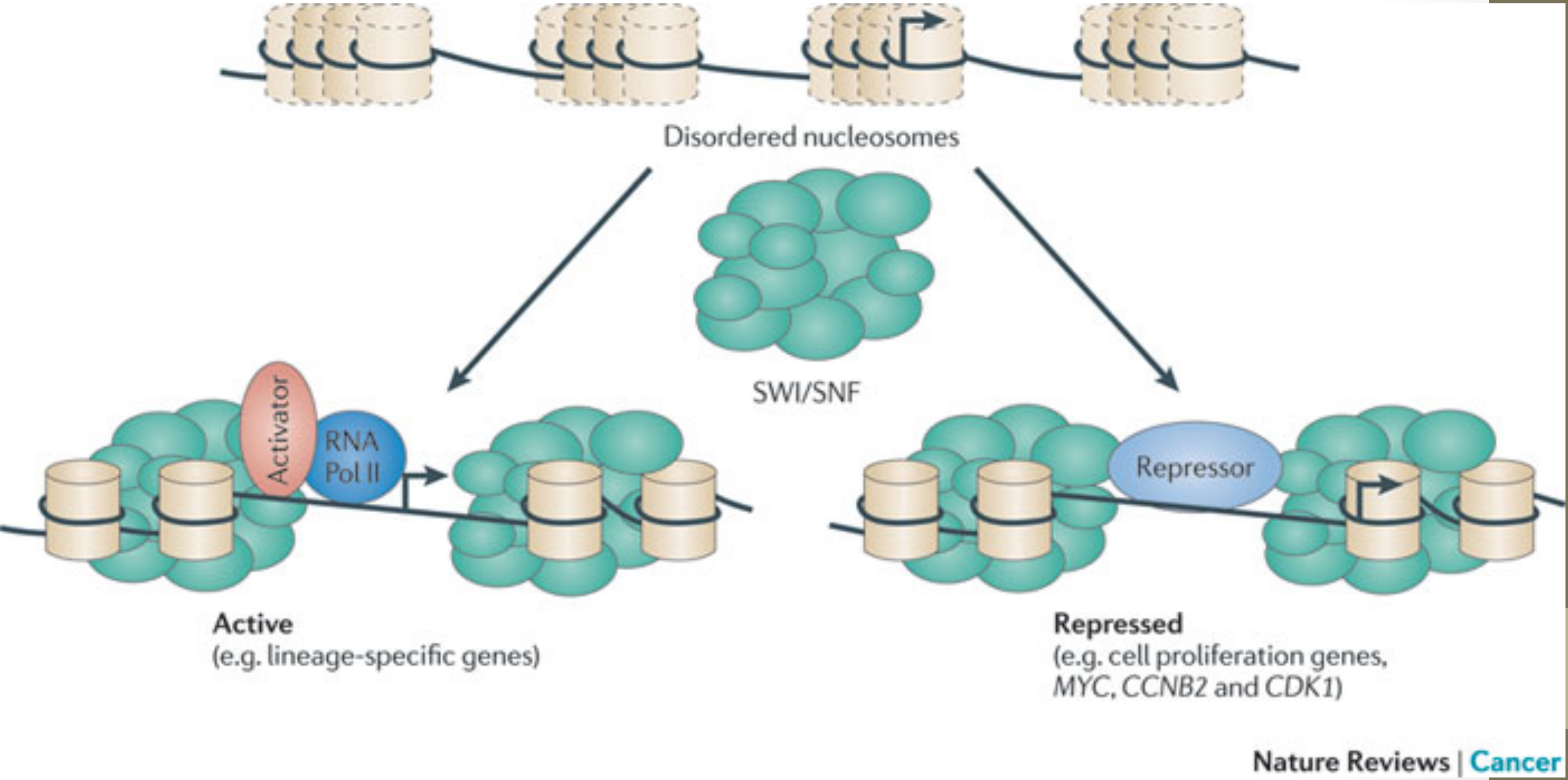


SWI/SNF complex moves nucleosomes to shape chromatin.



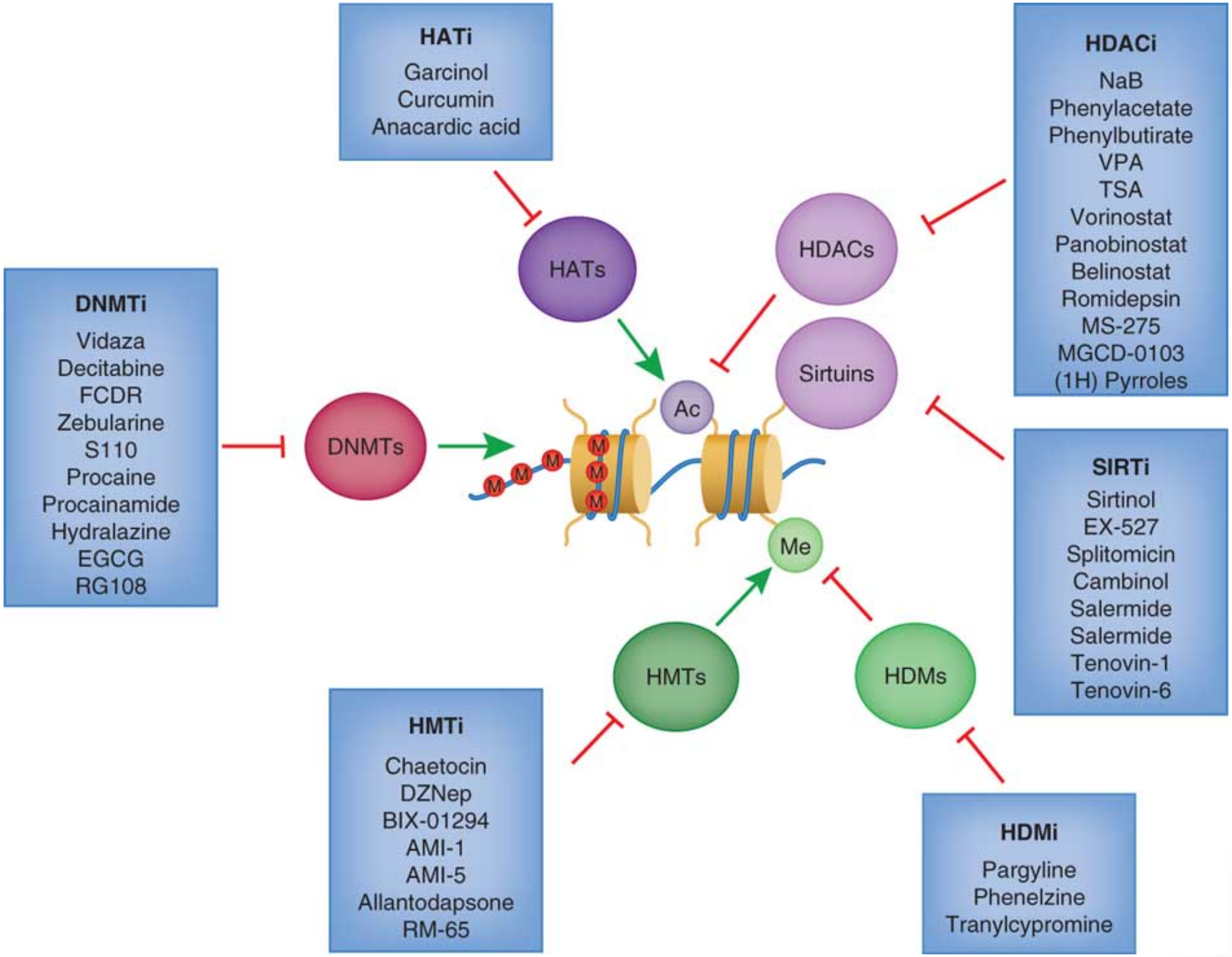
Nature Reviews | Cancer

Loss of SWI/SNF complex means a loss of repression of oncogenes.



Nature Reviews | Cancer

Epigenetic drugs are being explored as a new cancer therapy.



HATi
Garcinol
Curcumin
Anacardic acid

HDACi
NaB
Phenylacetate
Phenylbutirate
VPA
TSA
Vorinostat
Panobinostat
Belinostat
Romidepsin
MS-275
MGCD-0103
(1H) Pyrroles

DNMTi
Vidaza
Decitabine
FCDR
Zebularine
S110
Procaine
Procainamide
Hydralazine
EGCG
RG108

SIRTi
Sirtinol
EX-527
Splitomicin
Cambinol
Salermide
Salermide
Tenovin-1
Tenovin-6

HMTi
Chaetocin
DZNep
BIX-01294
AMI-1
AMI-5
Allantodapsone
RM-65

HDMi
Pargyline
Phenelzine
Tranylcypromine

Any Questions?

- feel free to email me at mesako@stanford.edu