Chromatin and epigenome in relation to embryogenesis and stem cell differentiation

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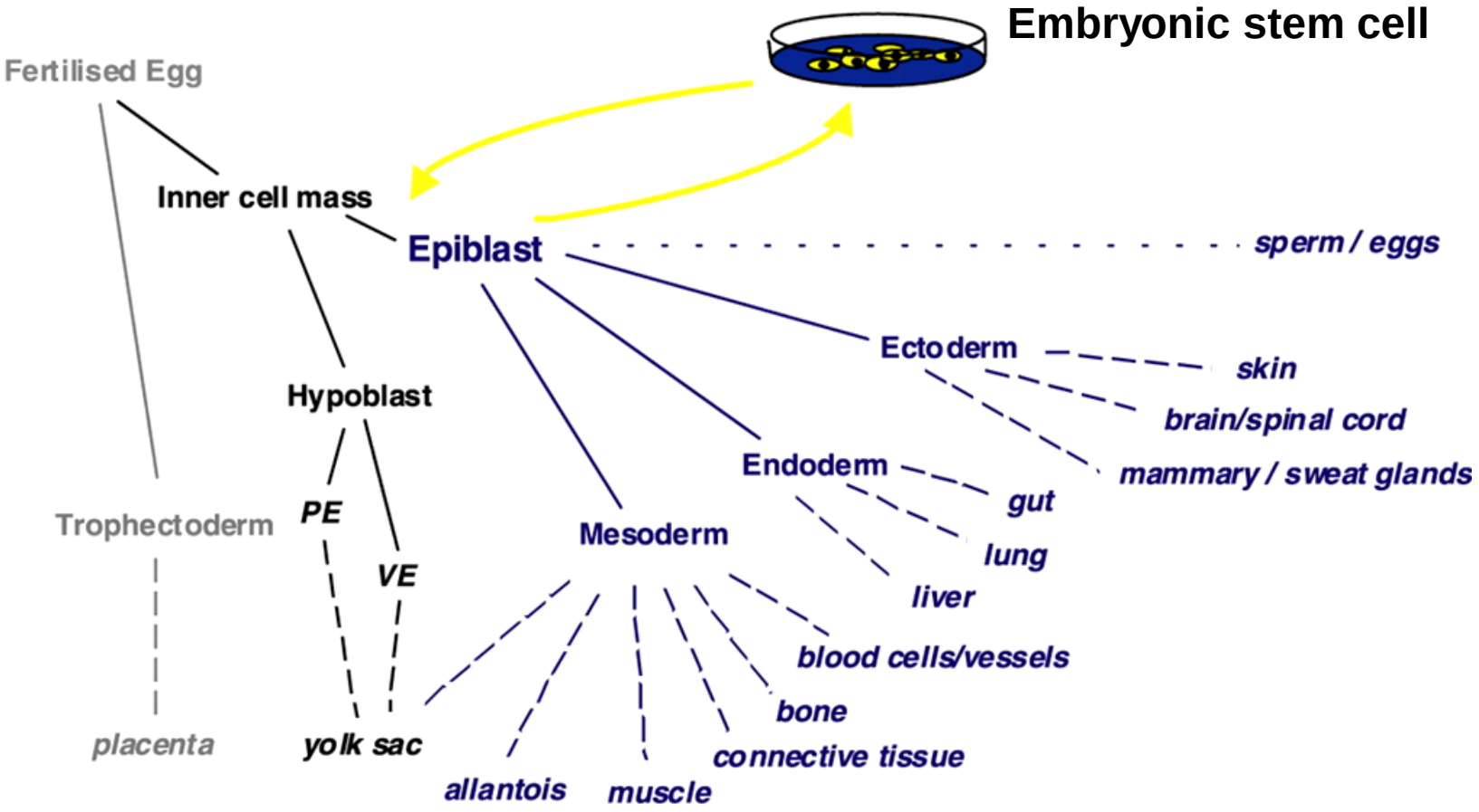
Cellular differentiation in the **embryo** and **stem cells**

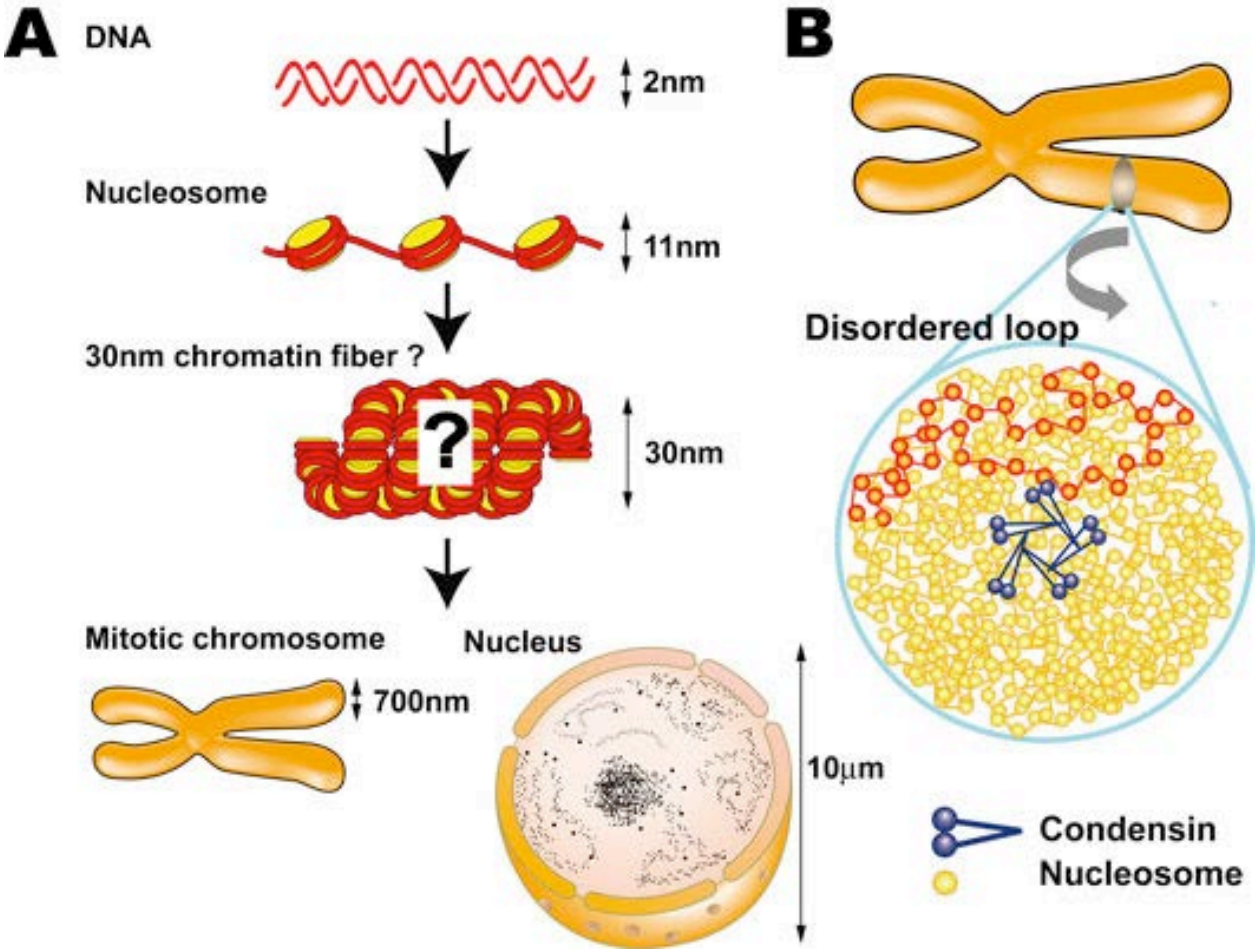


Question

- Chromatin and epigenome
  - Nucleosome dynamics
  - DNA methylation
  - Histone code

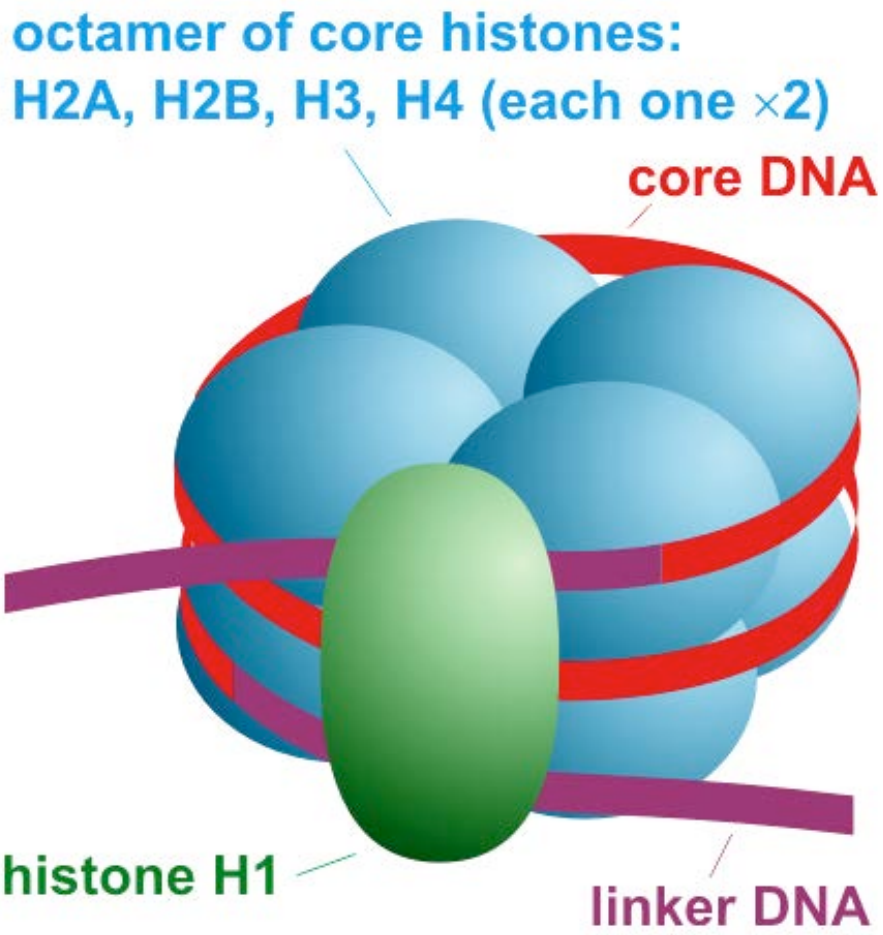
- How they contribute to embryogenesis and development?

Chromatin architecture

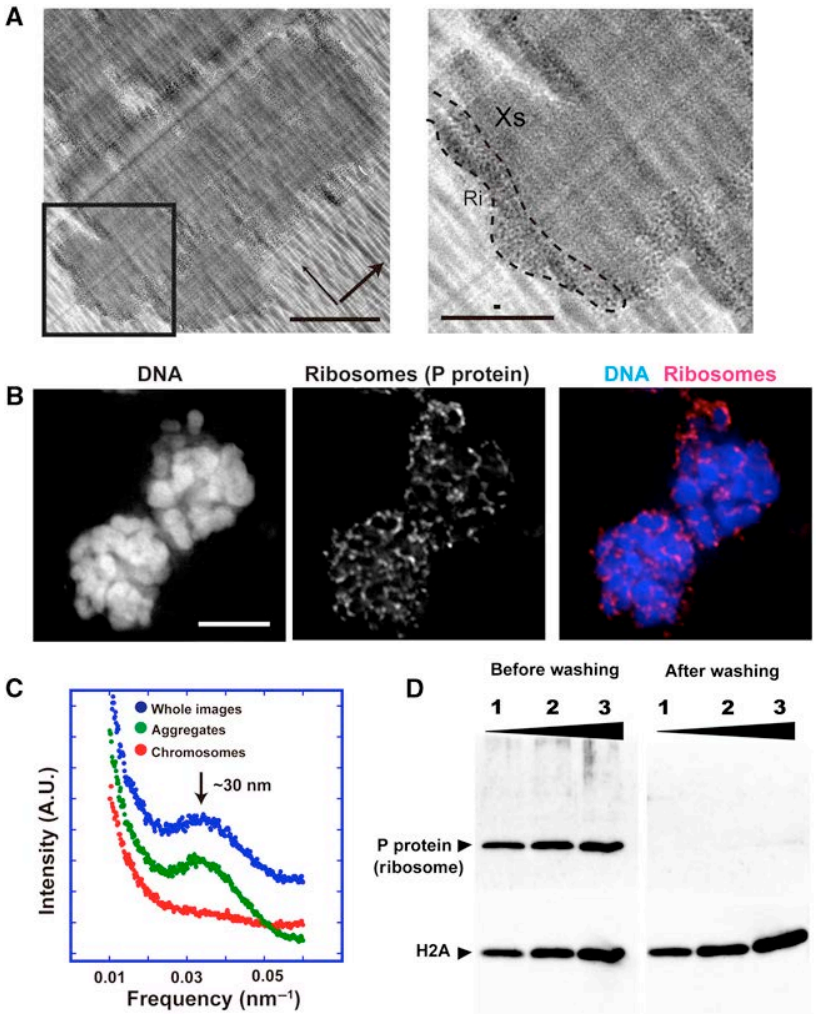


URL : http://www.nig.ac.jp/labs/MacroMol/index.html

Nucleosome

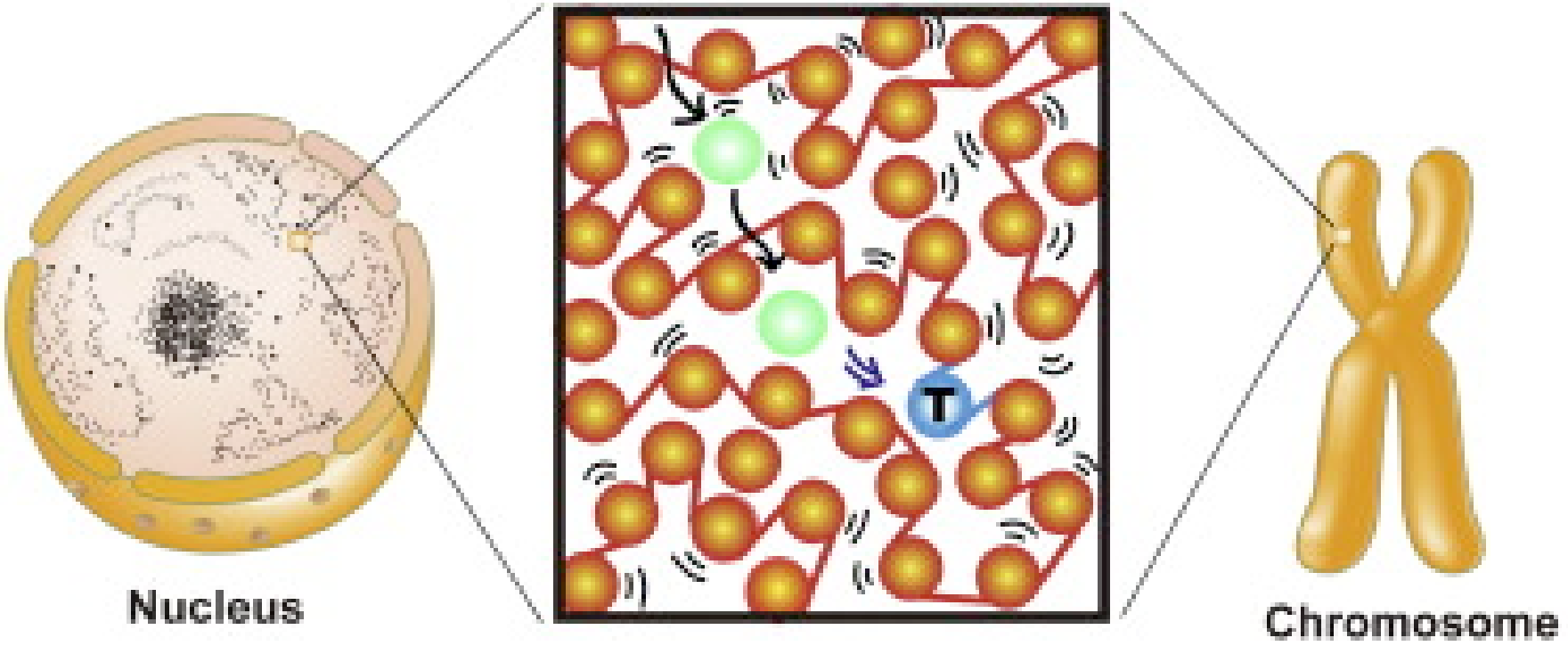

octamer of core histones:
H2A, H2B, H3, H4 (each one ×2)
core DNA
histone H1
linker DNA

Does 30 nm chromatin fiber exist? Ribosome aggregating around chromosomes leads to the 30nm peak



Nishino *et al.*, 2012, EMBO J

Local Nucleosome Dynamics Facilitate Chromatin Accessibility



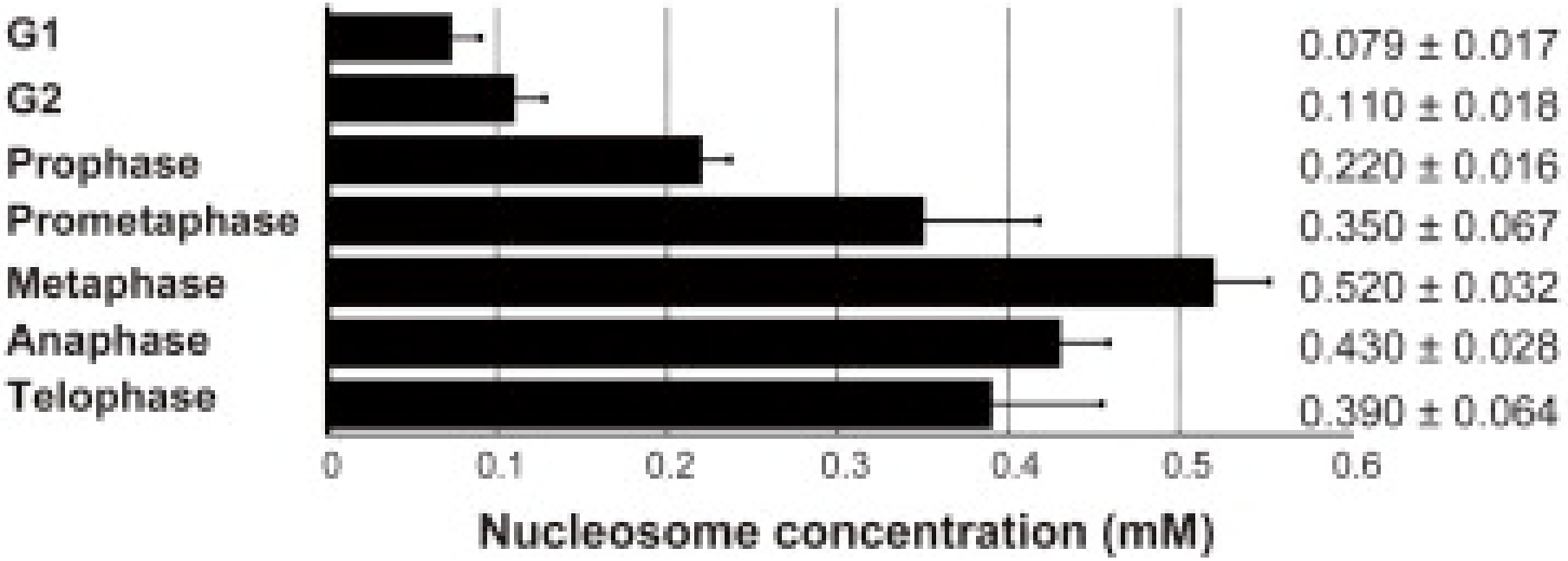
Nucleosome (fluctuates by Brownian motion)

Diffusing protein (e.g. transcription factor)

T Target for the diffusing protein

URL : http://www.nig.ac.jp/labs/MacroMol/index.html

Nucleosome concentrations in mammalian cell's nuclei



Hihara *et al.,* 2012, Cell Rep

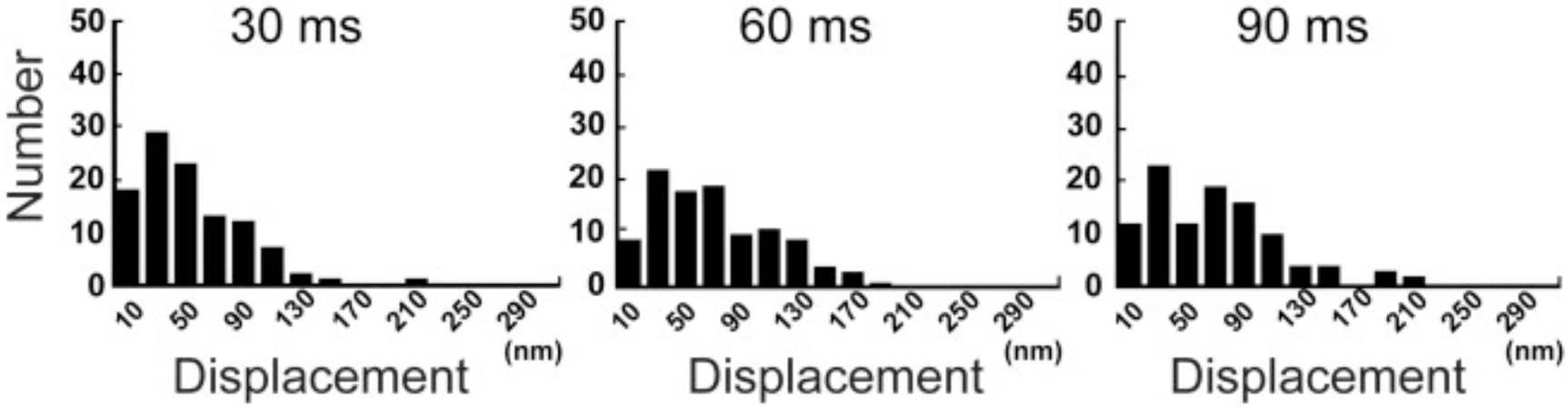
Nucleosome concentration in interphase chromatin and mitotic chromosomes

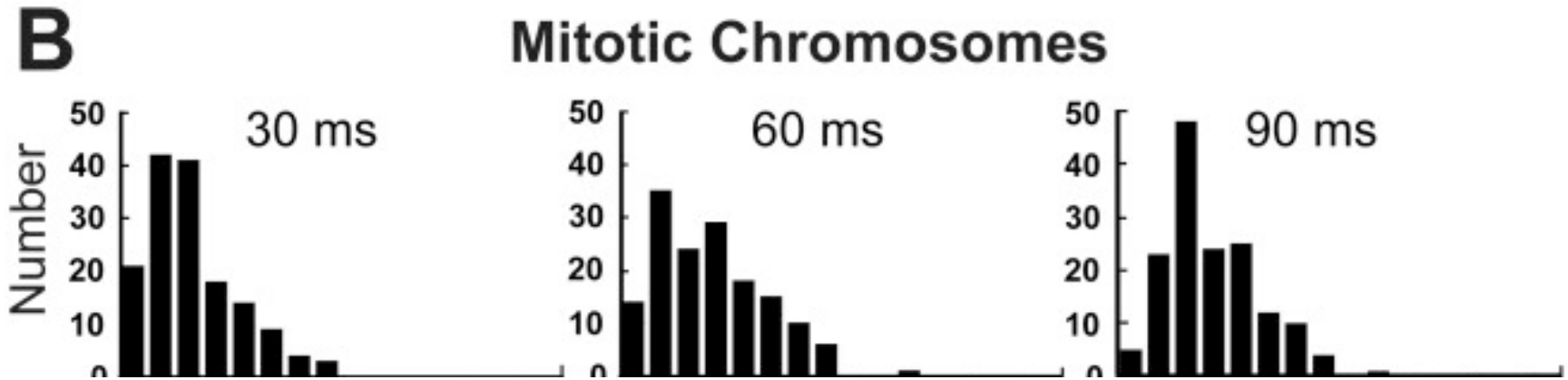
- Interphase nuclei: ~0.1 mM (not evenly distributed in the nucleus)

- Mitotic chromosome ~0.5 mM

(Results are consistent among fluorescence-based measurements, EM-based measurements)

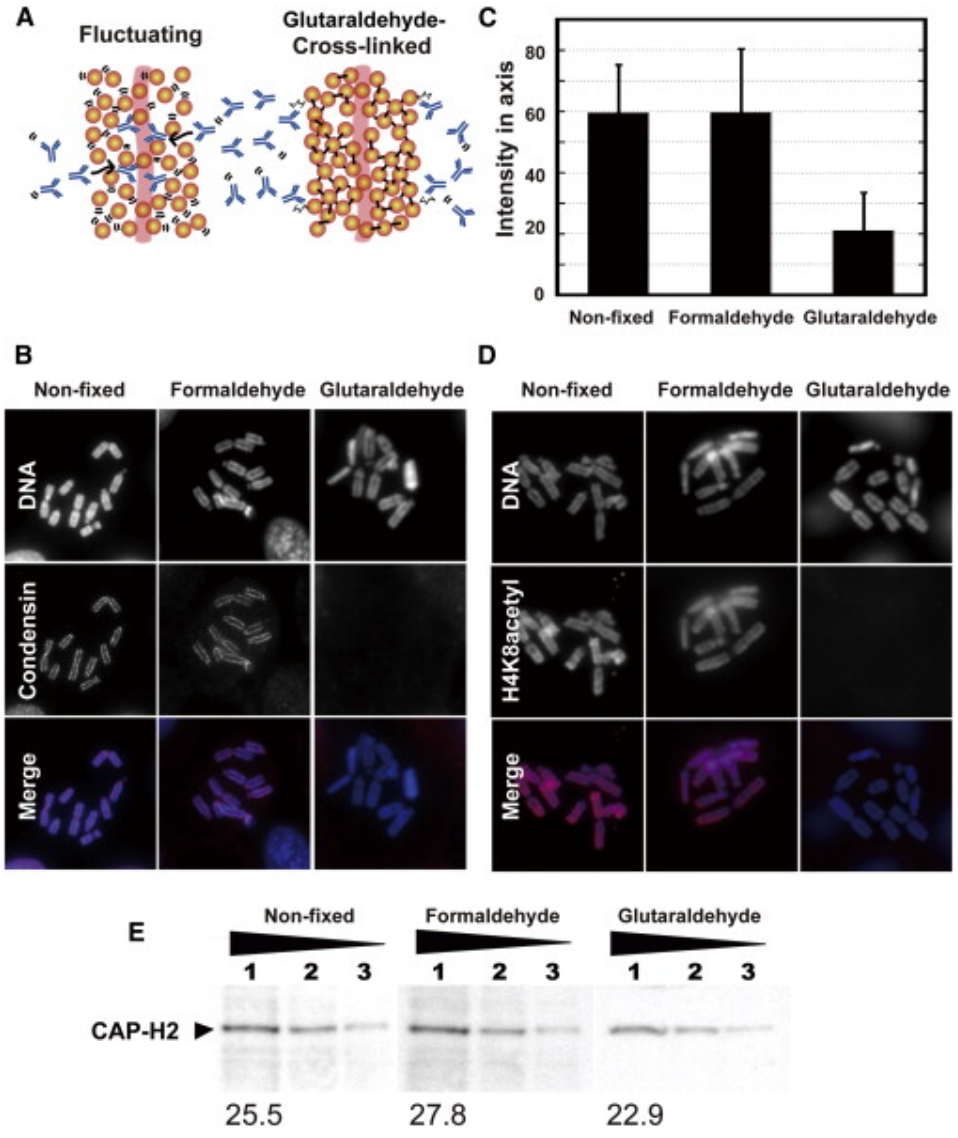
Displacement of single nucleosome by Brownian motion in live mammalian cells



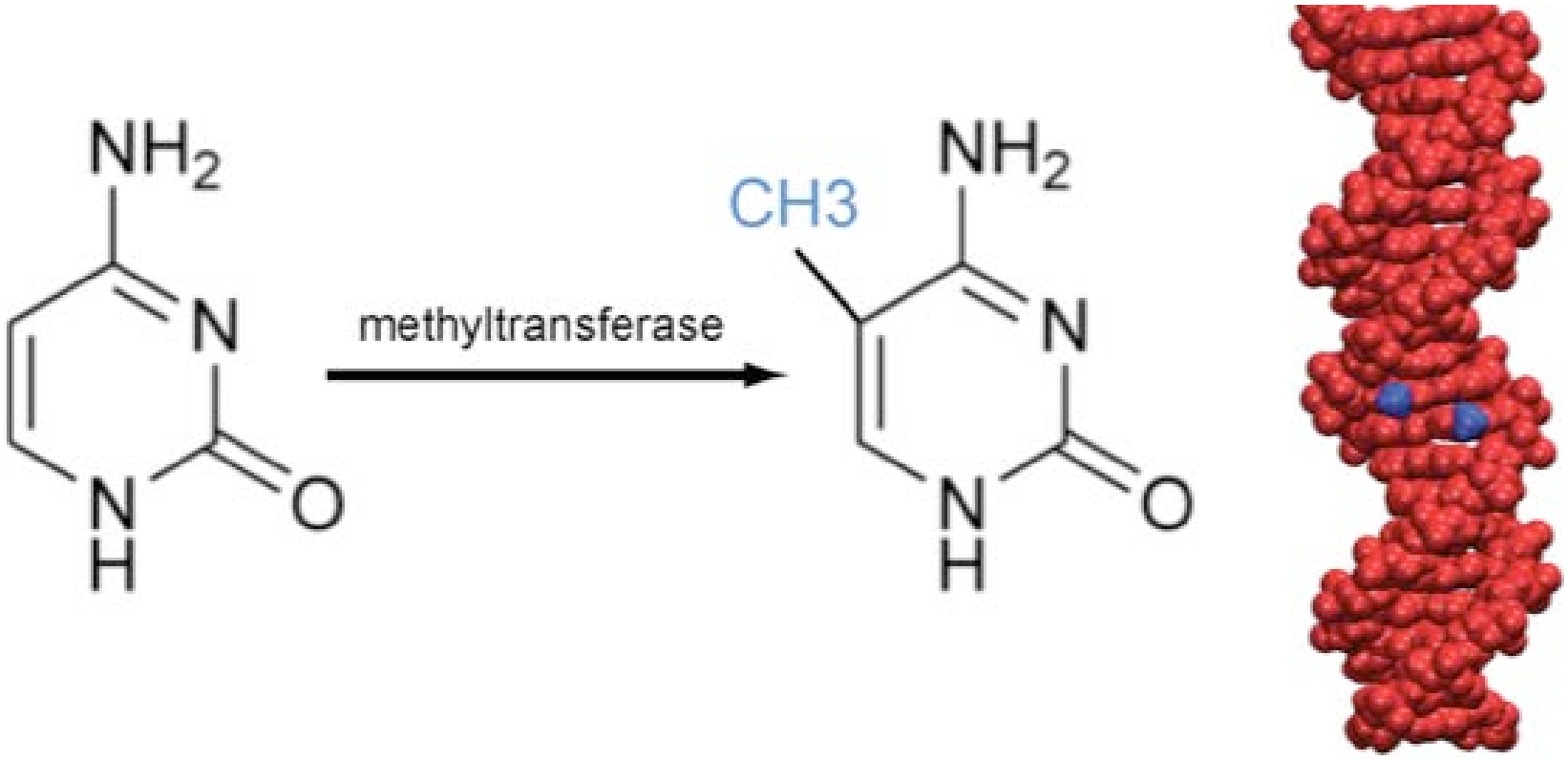


Hihara *et al.,* 2012, Cell Rep

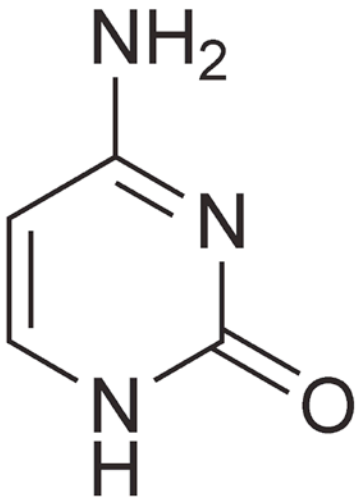
Protein accessibility in mitotic chromosome



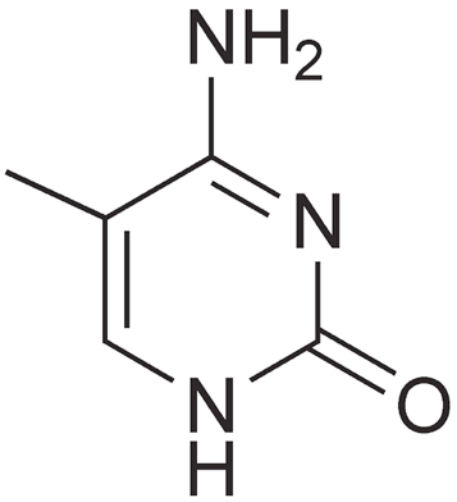
DNA methylation



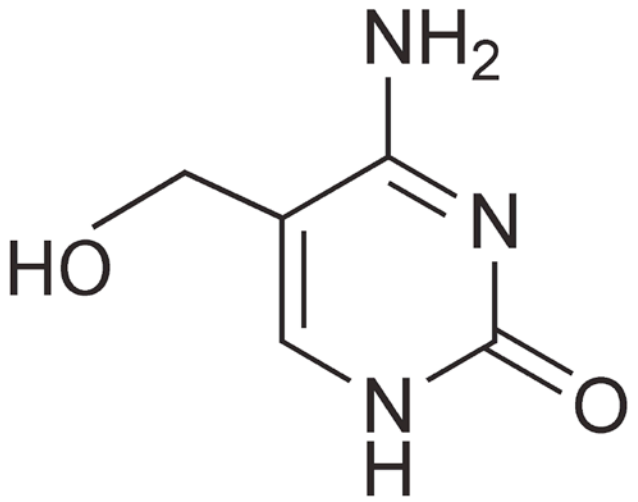
Cytosine, methylcytosine and hydroxymethylcytosine



Cytosine

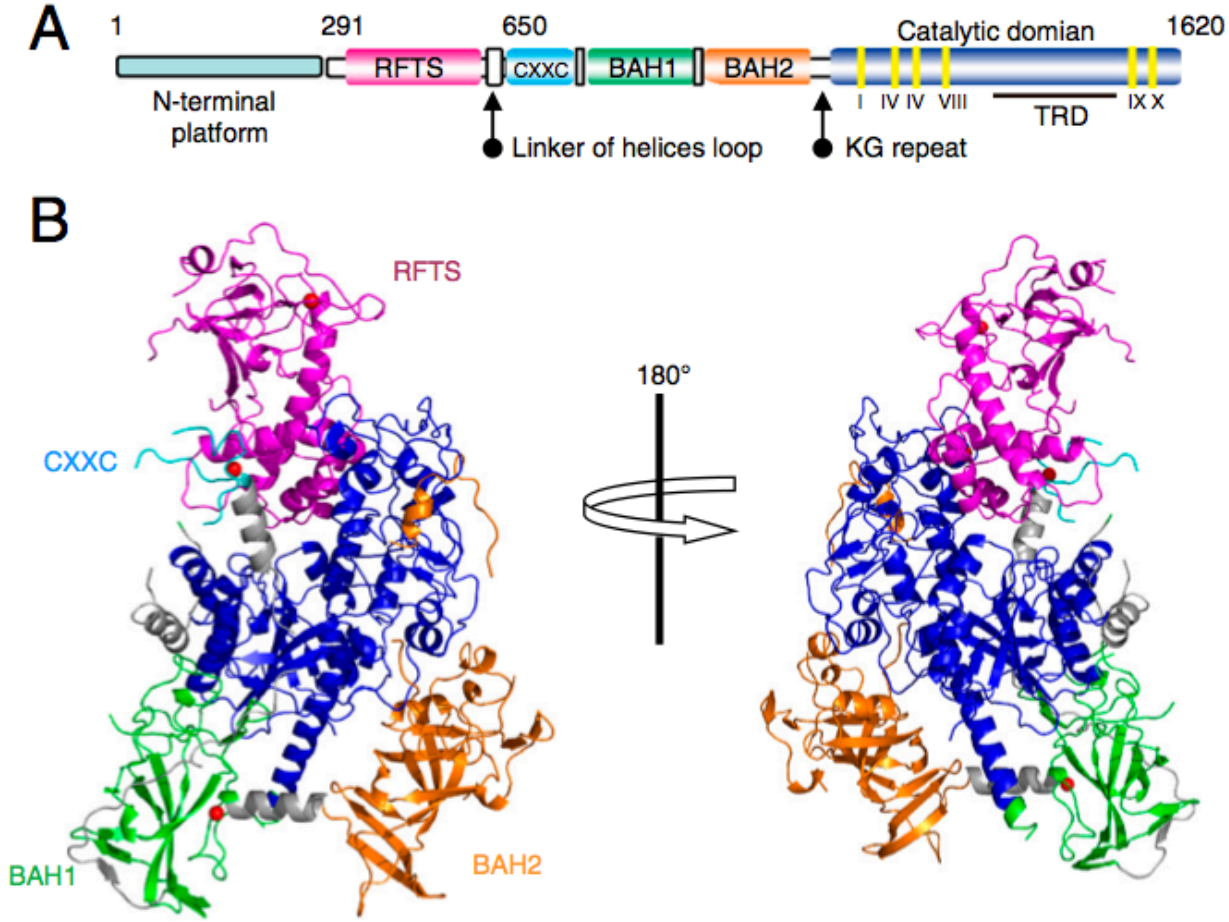


Methylcytosine

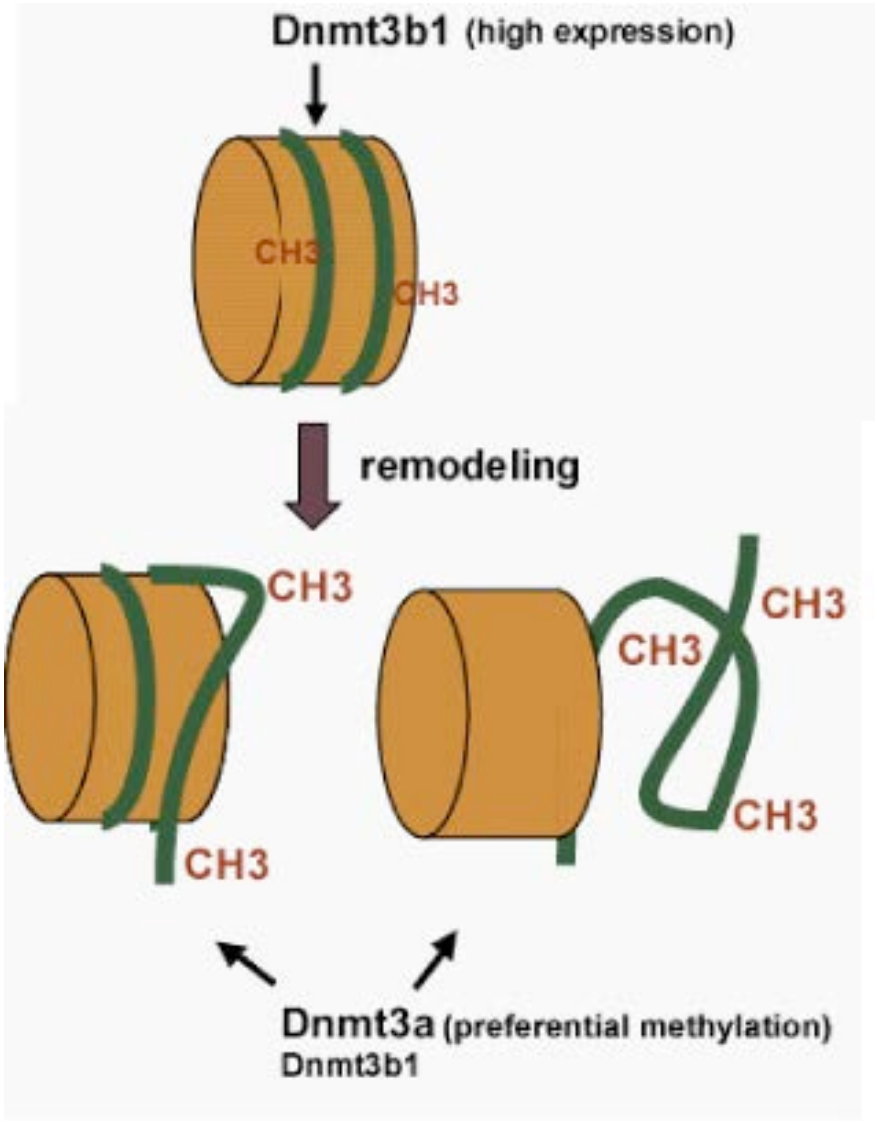


Hydroxymethylcytosine

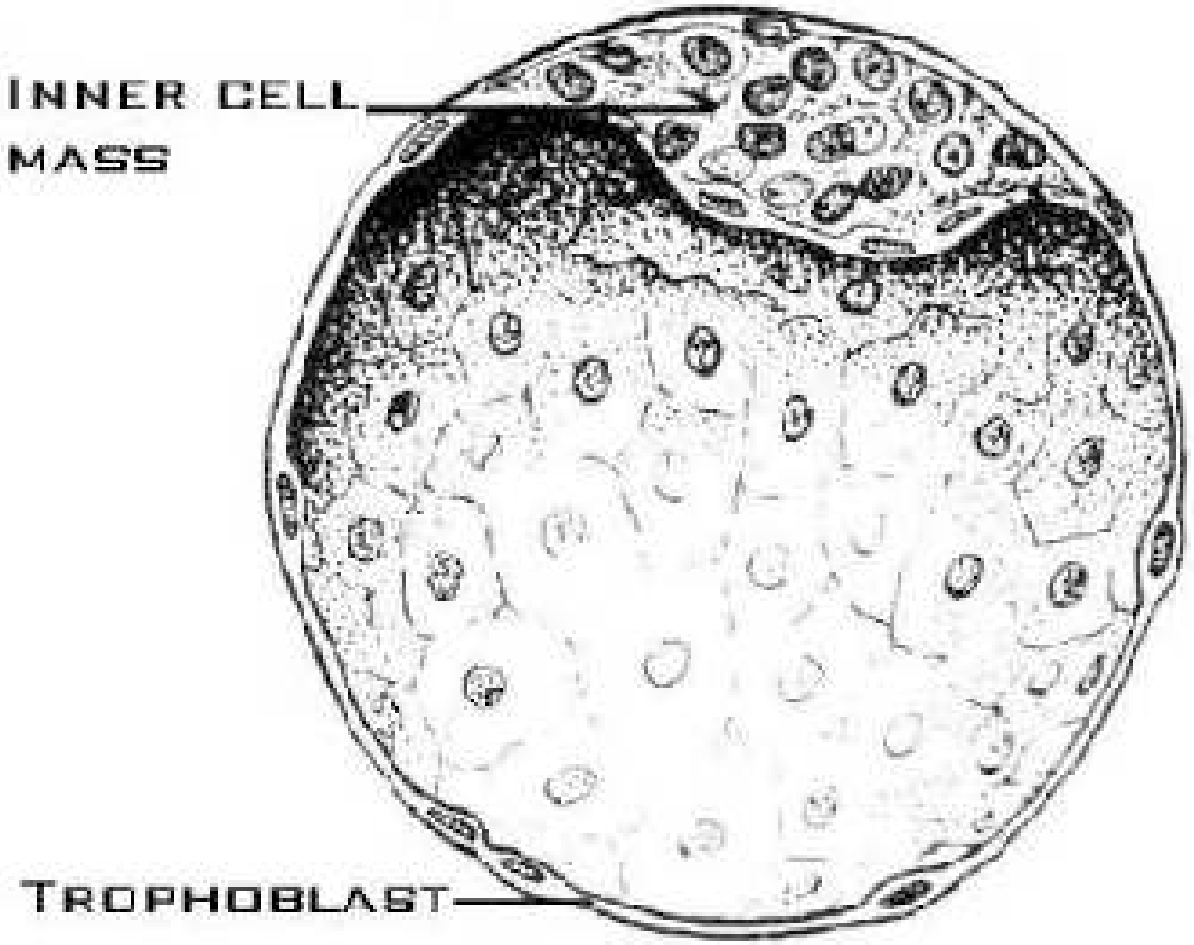
Maintenance DNA methyltransferase: Dnmt1



De novo DNA methyltransferases: Dnmt3a and 3b

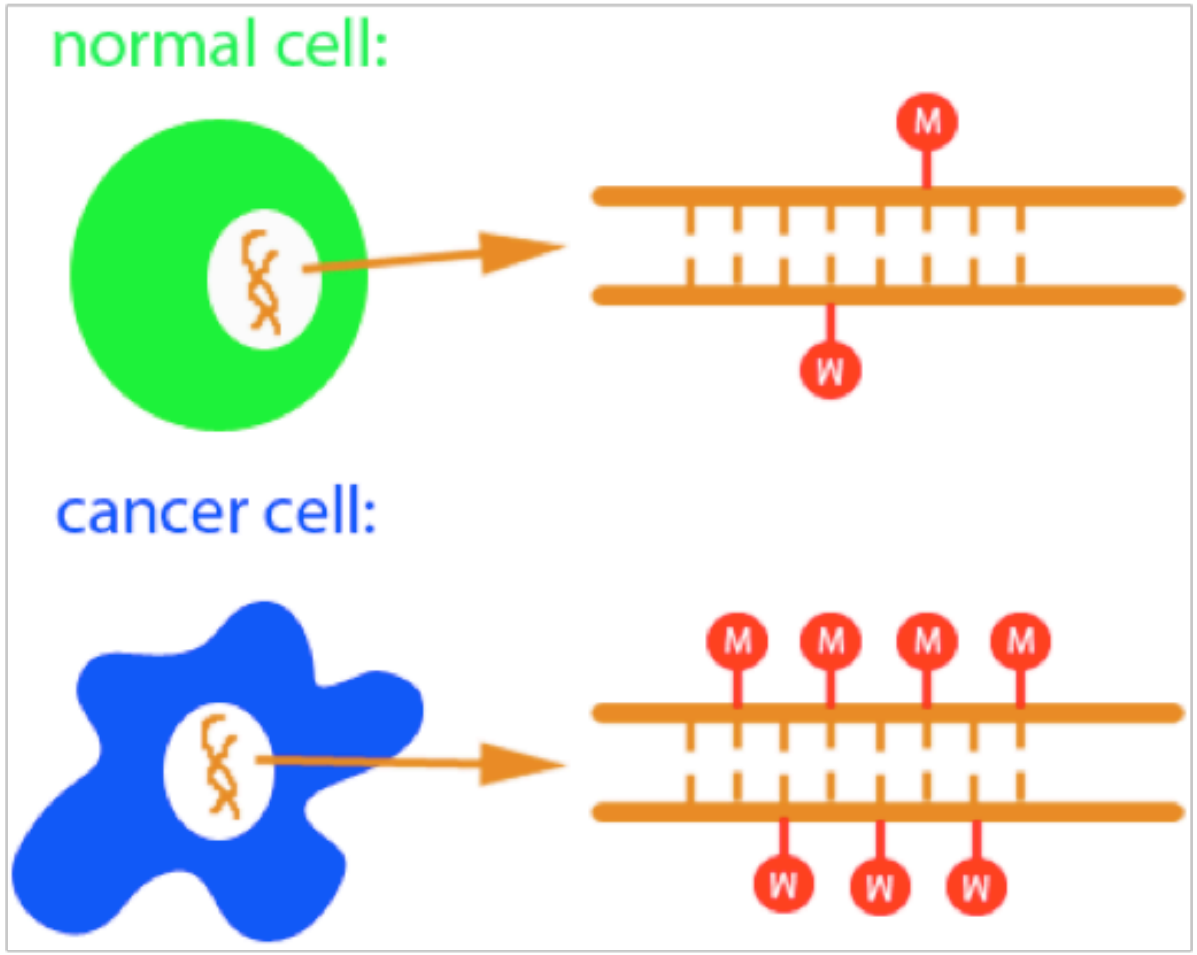


Dnmt1-/- mouse ES cells transdifferentiate into trophectoderm

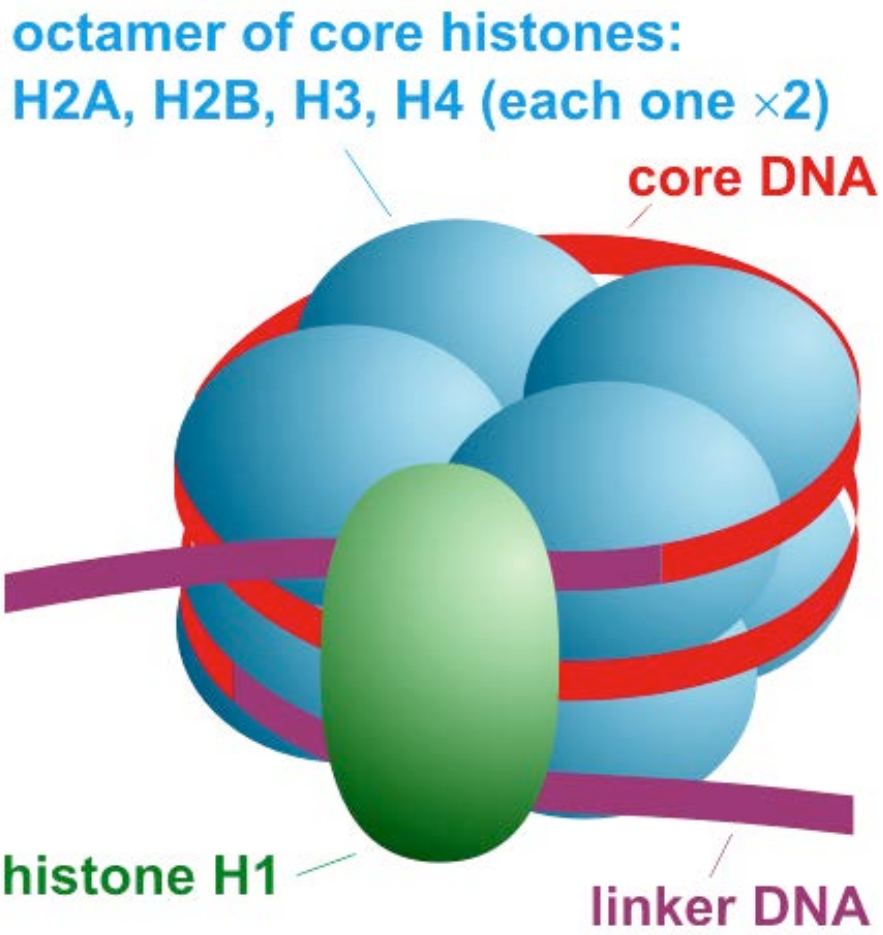


Ng *et al.,* 2008, Nat Cell Biol

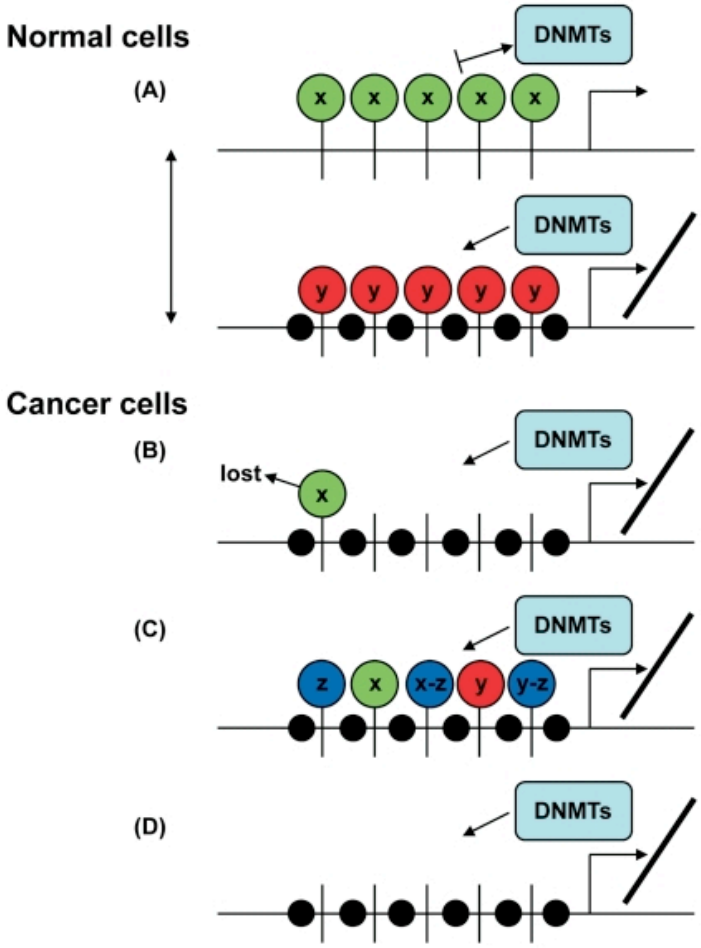
DNA hypermethylation in cancer cells



Histone modifications



How the histone code may direct DNA methylation during development and carcinogenesis



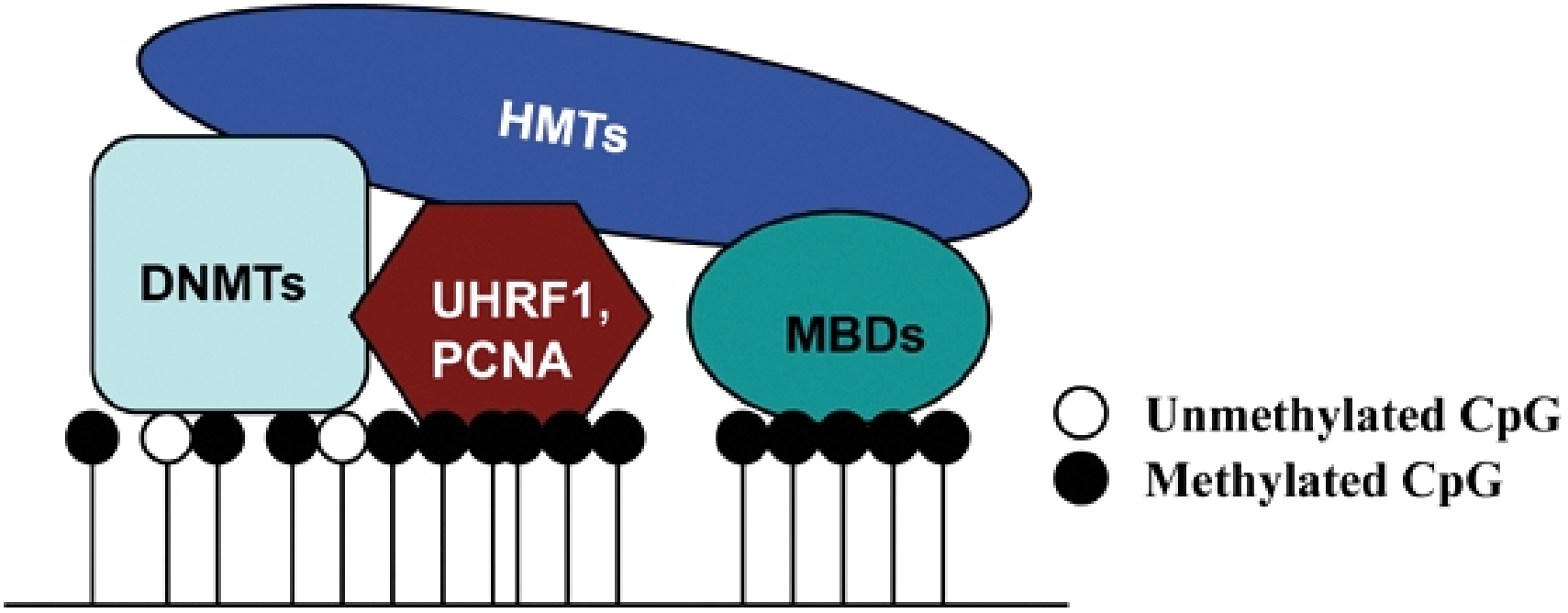
x: transcription-activating histone marks
e.g. H3K4me3

y: transcription-repressing marks
e.g. H3K8me, H3K27me

z: aberrant acquisition of a new mark

Jin *et al.,* 2011, Genes Cancer

How the histone code may rely on the DNA methylation machinery for direction



Jin *et al.,* 2011, Genes Cancer

DNA methylation and selective expression of the genome

- Does not apply to all organisms, e.g. plants and nematodes, which have RNAi-based gene silencing instead

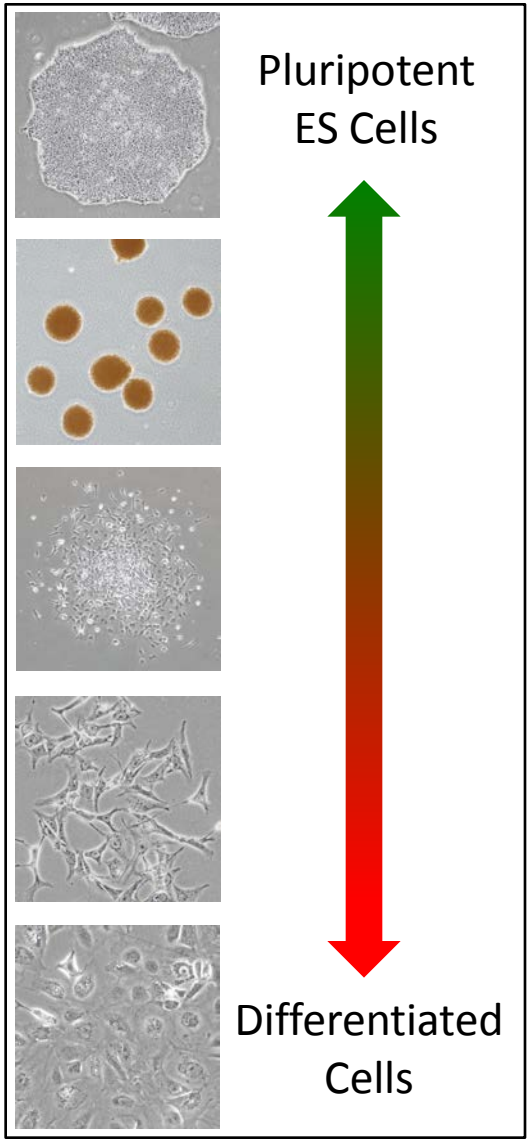
- How does DNA methylation lead to gene-specific transcriptional regulation?

Some open questions

- Cause and effect relationship between “the epigenetics” and development?
- Sequence-specificity of the epigenetic mechanisms? Epigenetic code or other mechanism?
- Possibility that “the epigenetics” are epiphenomena of development?

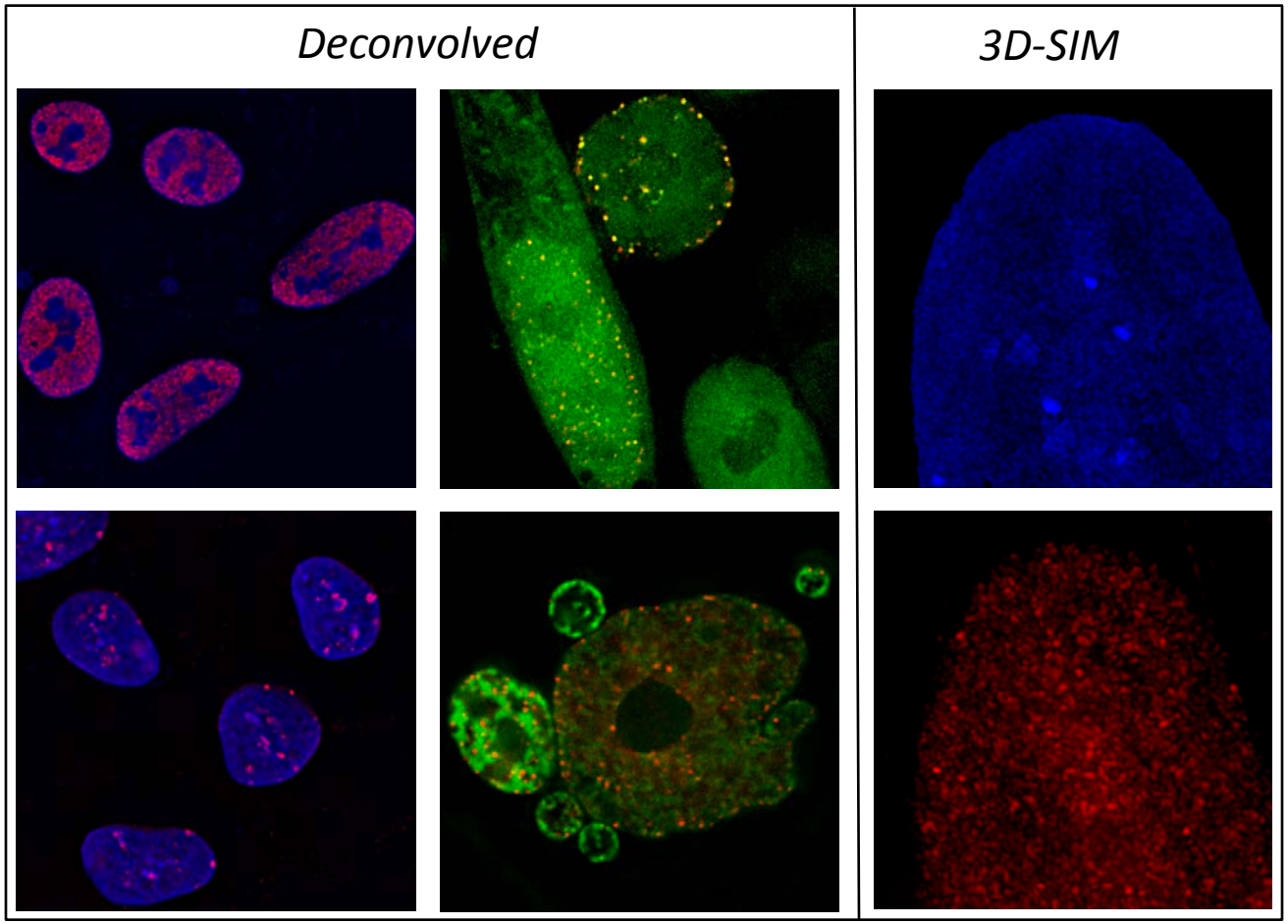
Imaging the epigenome of human pluripotent stem cells with high/super resolution fluorescence microscopy

Kai Lu, Peter M. Carlton (iCeMS, Kyoto University)



Chromatin & Epigenome

- DNA methylation
- Histone modifications



3D structured illumination (3D-SIM) microscopy
Imaging chromatin in stem cells