Your Genes and Your Health

http://bio84.stanford.edu/

Epigenetics

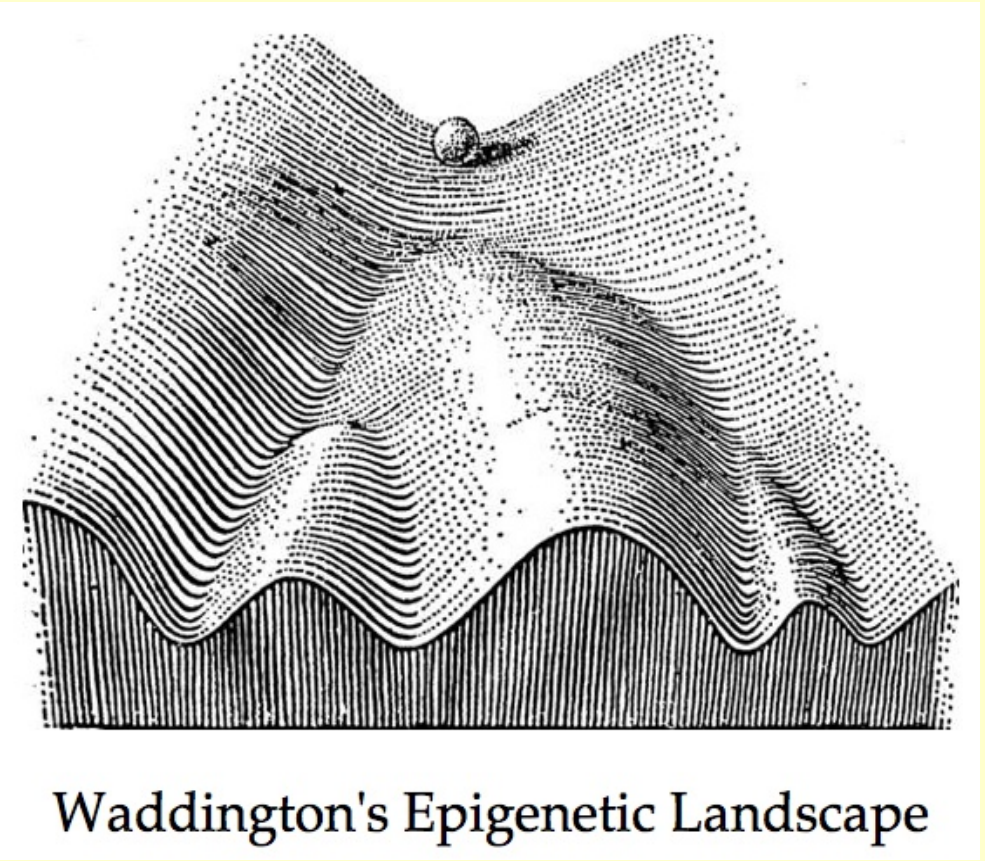
http://bio84.stanford.edu/08%20miRNA%20&%20Epigenetics.htm

Doug Brutlag, Professor Emeritus
Biochemistry and Medicine (by courtesy)
Stanford University School of Medicine

What is Epigenetics?

- C.H. Waddington coined the term epigenetics to mean above or in addition to genetics to explain differentiation.
- How do different adult stem cells know their fate?
  - Myoblasts can only form muscle cells
  - Keratinocytes only form skin cells
  - Hematopoietic stem cells only become blood cells
  - But all have identical DNA sequences.

C.H. Waddington



Waddington's Epigenetic Landscape

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- Modern definition is non-sequence dependent inheritance.
- How can identical twins have different natural hair colors?

Identical Twins with Different Hair Color

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- How can a single individual have two different eye colors?

An Individual with Two Different Eye Colors

"Diego"

An Individual with Two Different Eye Colors

"Josie Too"

A Woman with Two Different Eye Colors

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- How can identical twin liter mates show different coat colors?

Coat Colors of Genetically Identical Agouti Mice Liter Mates

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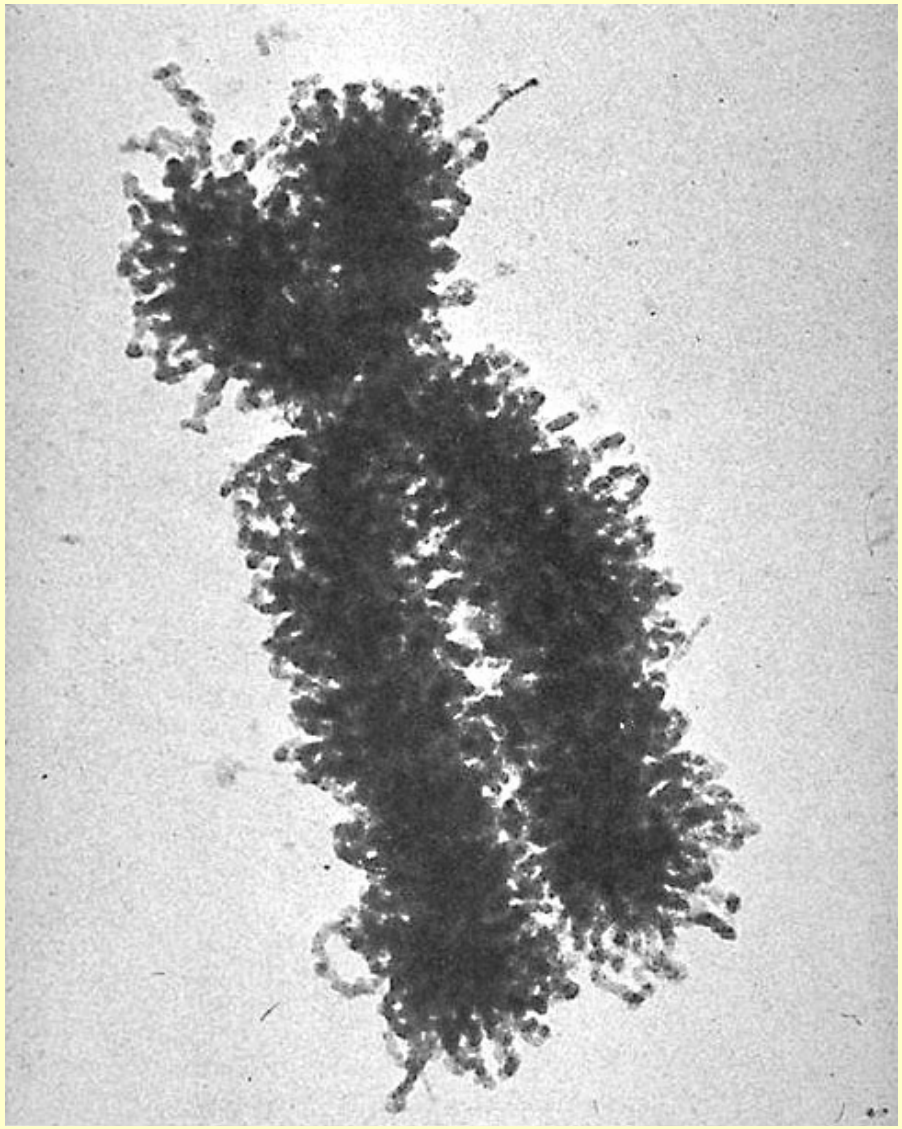
- How can identical twin liter mates show different coat colors?
- How can females express only one X chromosome per cell?
- How can acquired traits be passed on to offspring?
- Some changes in gene expression that are, in fact, heritable!

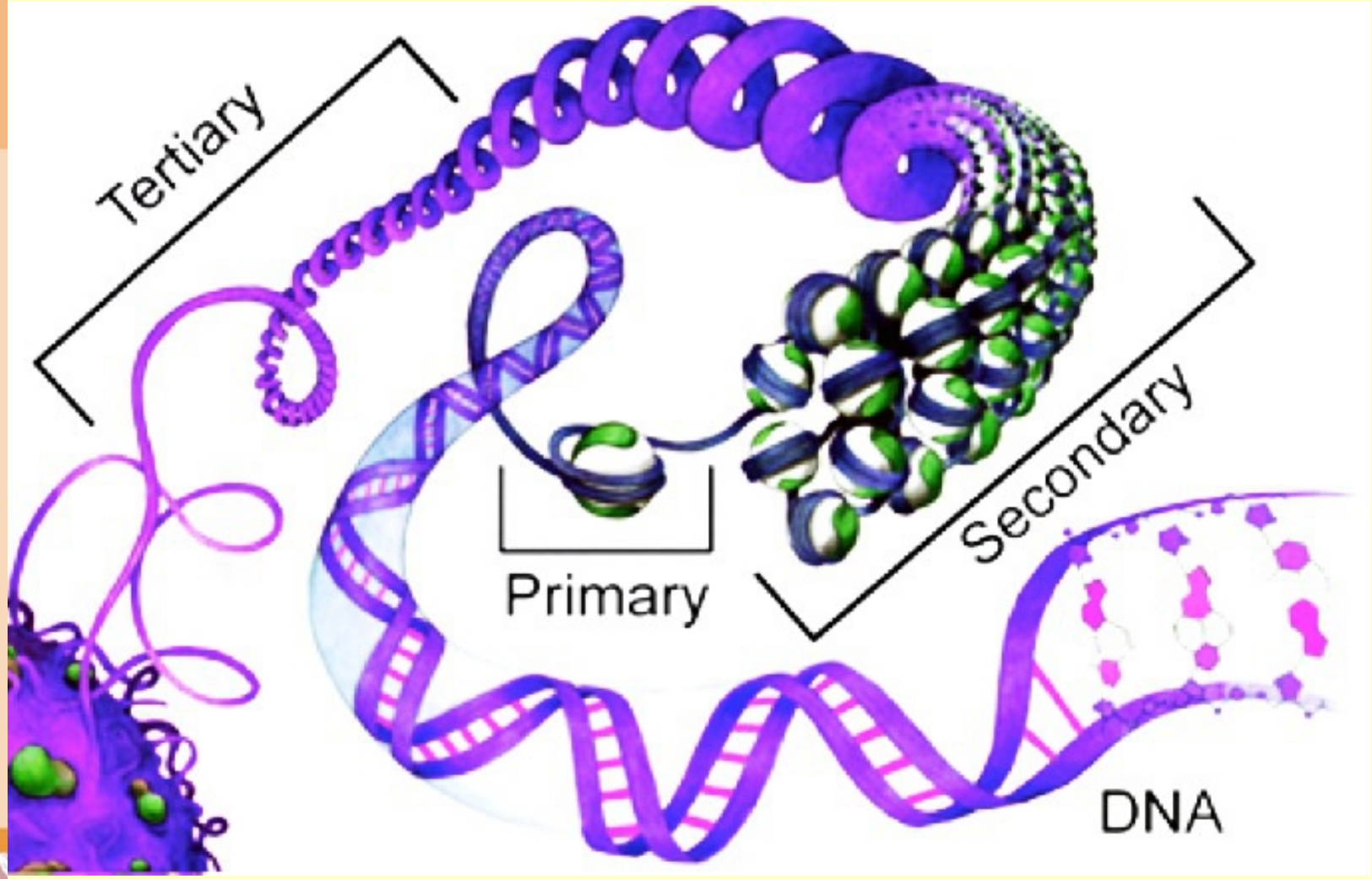
What is Epigenetics?

- Nova Show on Epigenetics
- http://www.teachersdomain.org/asset/biot09_vid_epigenetics/

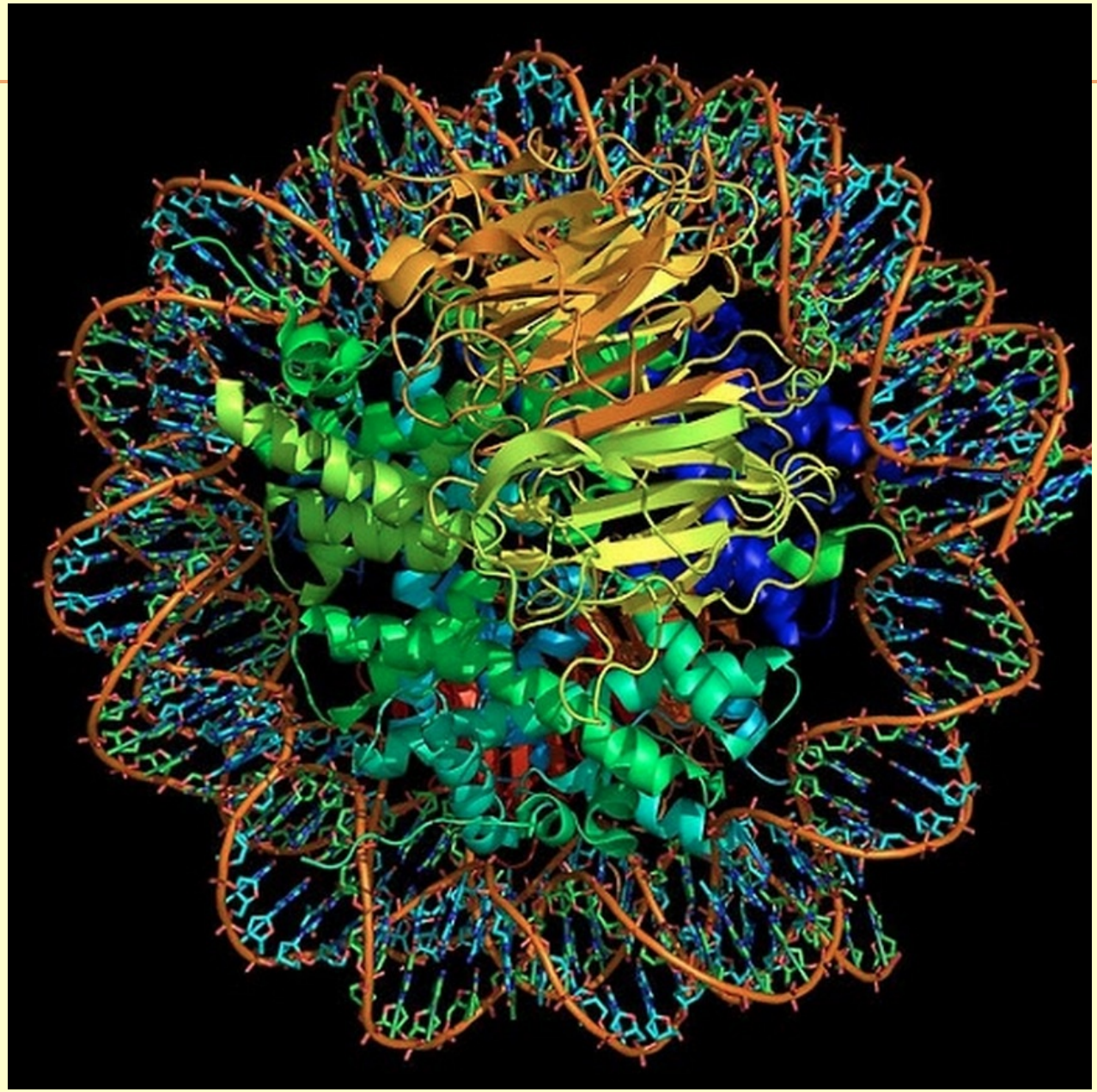
Human Mitotic Chromosome



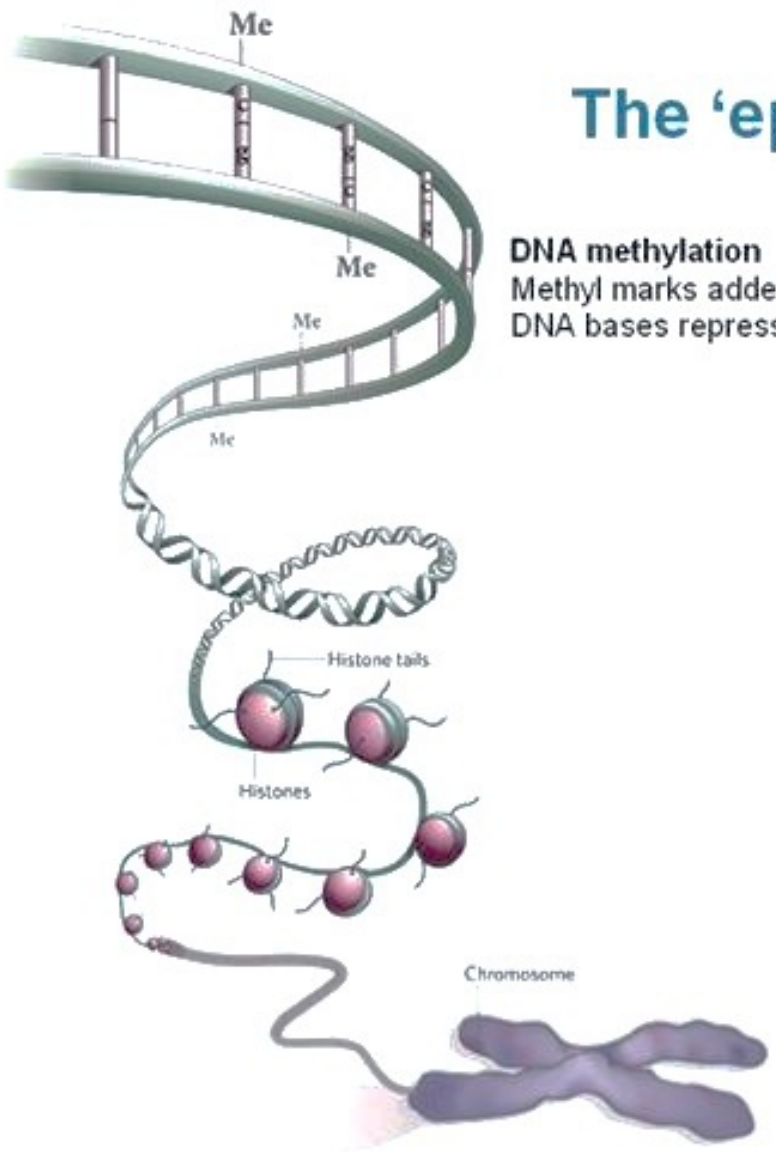
Three Levels of Folding of DNA in Chromatin



Nucleosome Core Structure



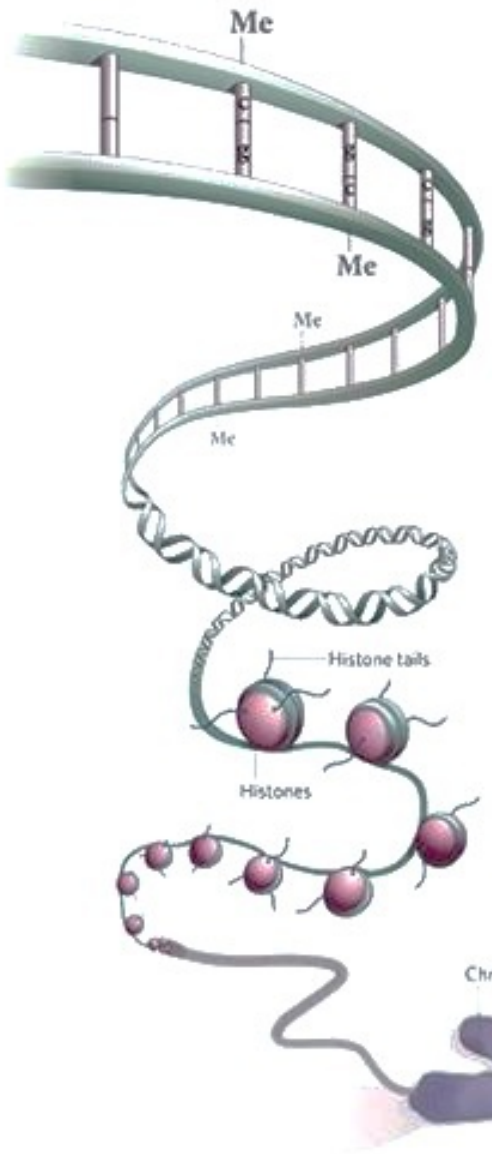
DNA Methylation & the Epigenetic Code



The 'epigenetic' code

DNA methylation
Methyl marks added to certain
DNA bases repress gene activity

DNA Methylation & Histone Modifications Form the Epigenetic Code

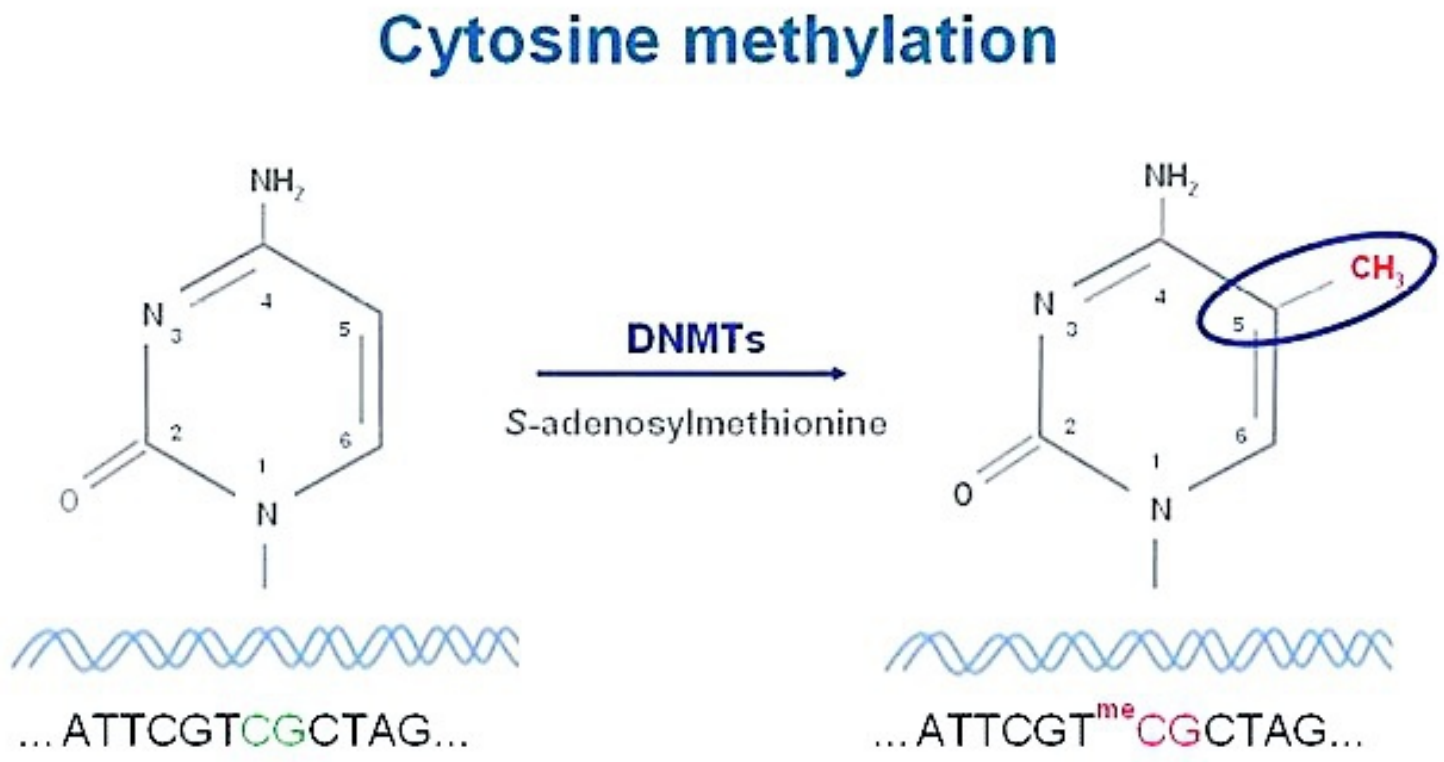


The 'epigenetic' code

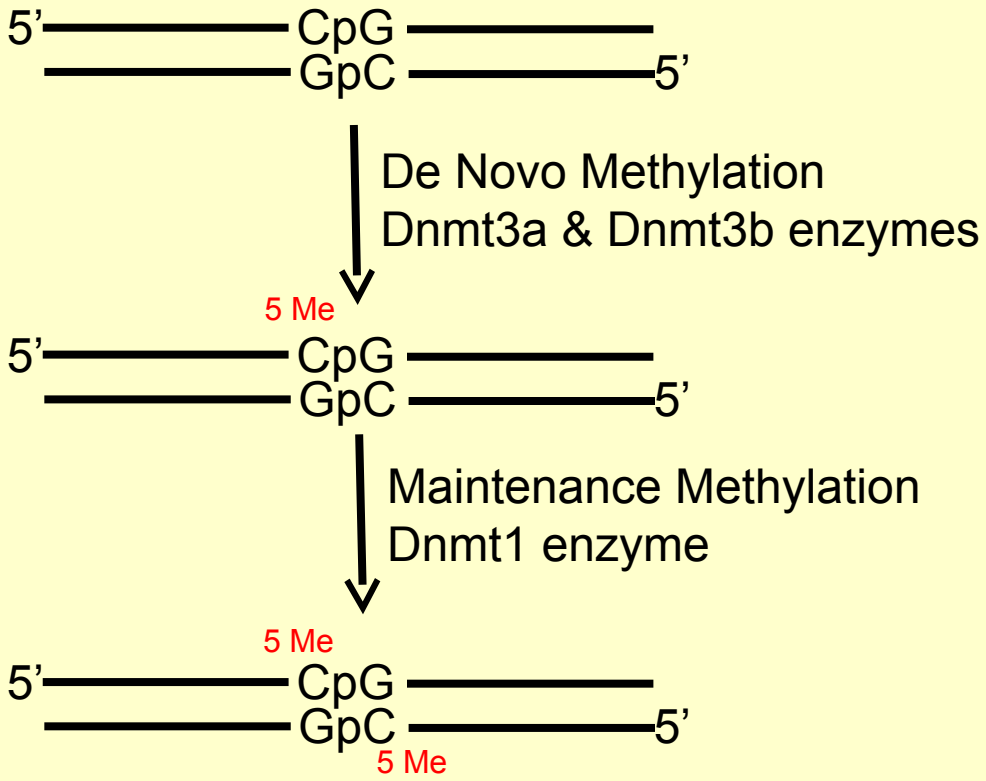
DNA methylation
Methyl marks added to certain DNA bases repress gene activity

Histone modification
A combination of different molecules can attach to the "tails" of proteins called histones, These alter the activity of the DNA wrapped around them

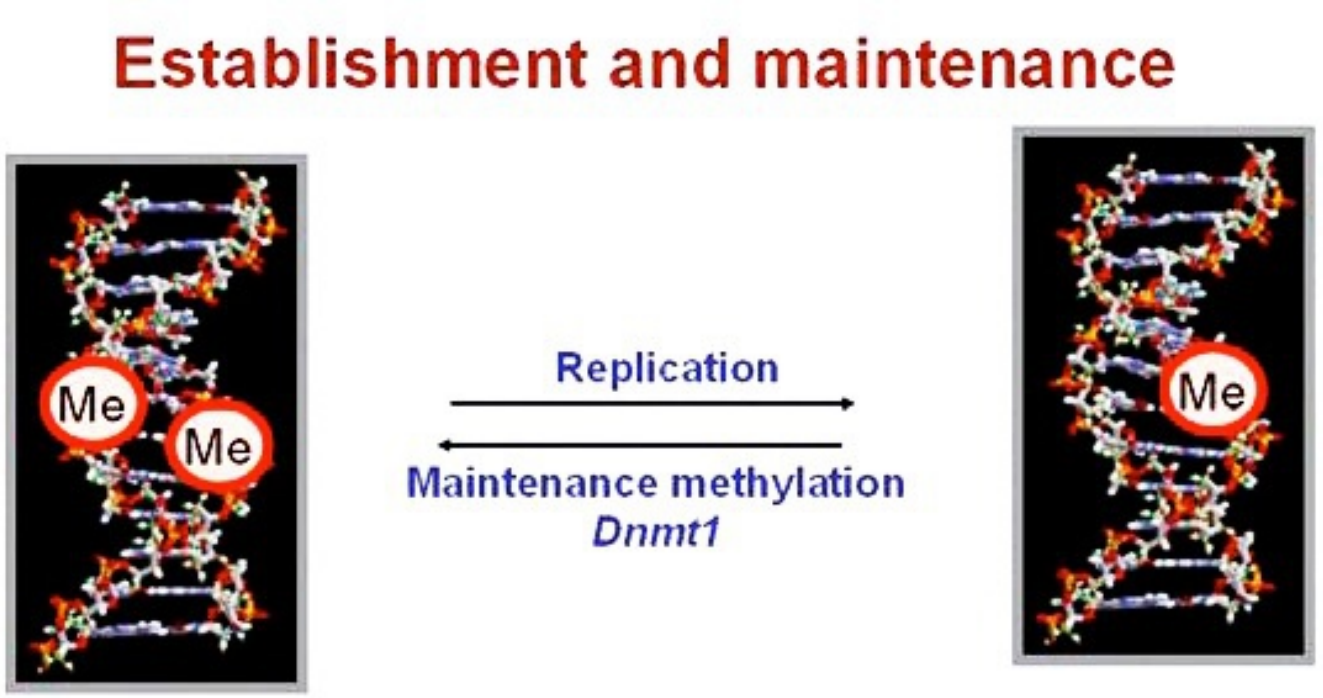
Methylation of Cytosine in DNA



Only Cs in CG sequences are Methylated

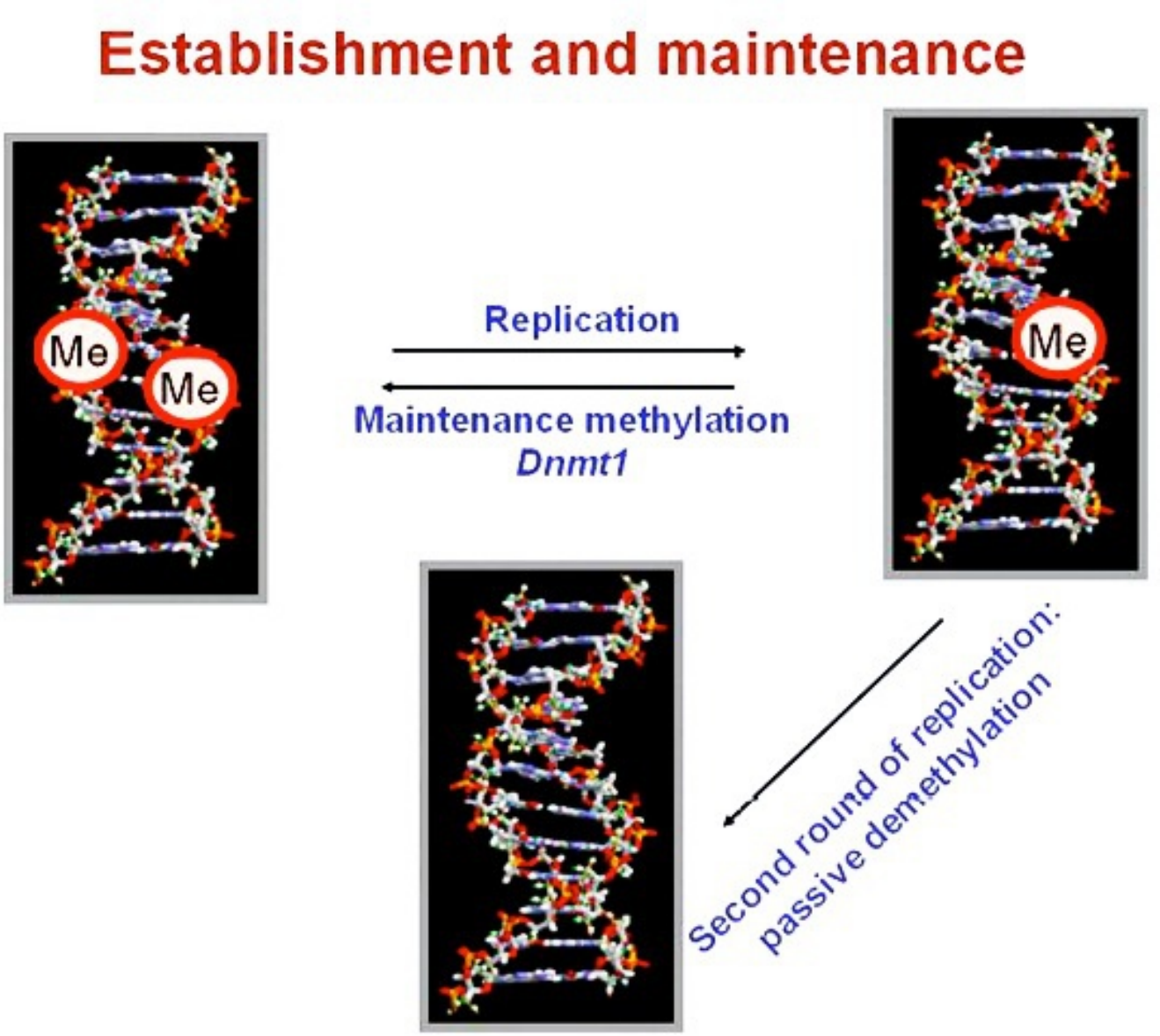


Maintenance of Cytosine Methylation



Alex Meissner, Henry Stewart Talks

Passive Demethylation of 5-Methyl-Cytosine



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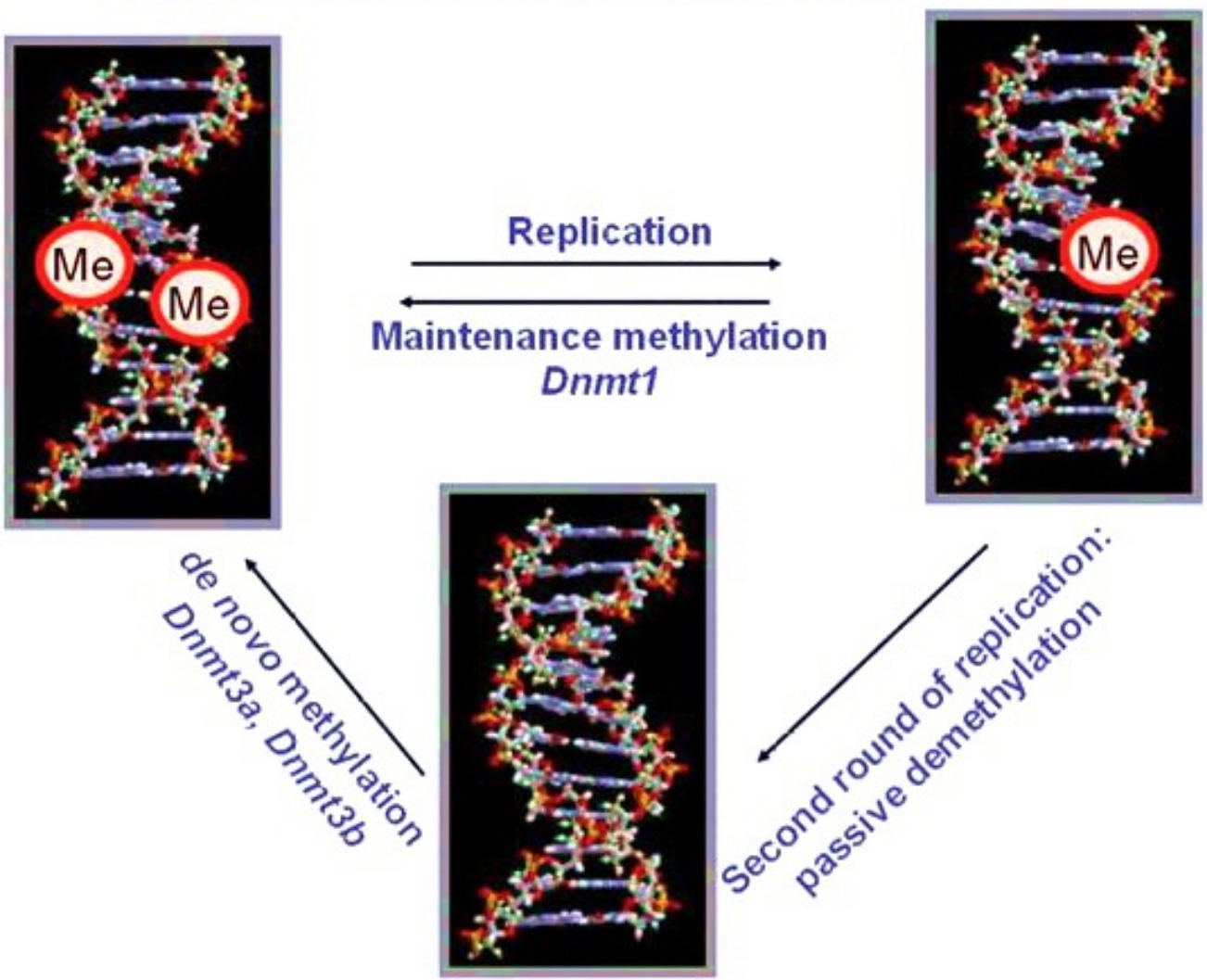
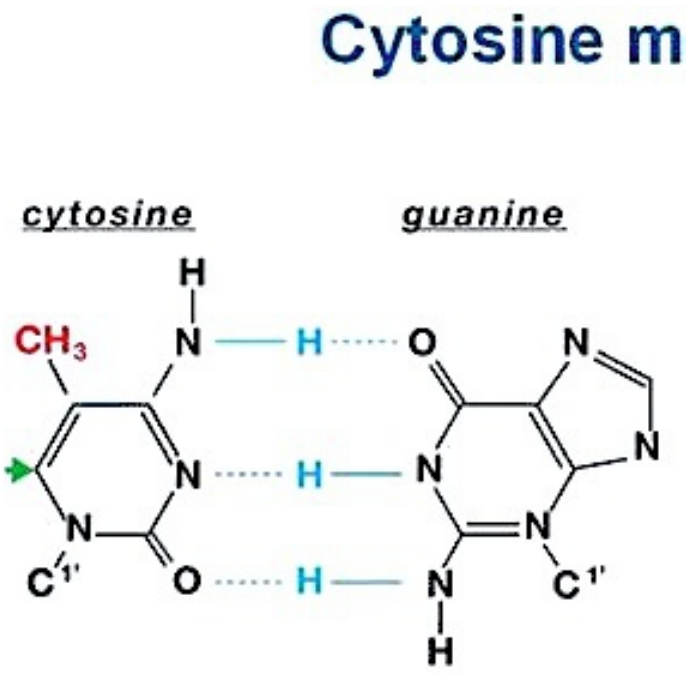
Establishment and Maintenance of Cytosine Methylation



Alex Meissner, Henry Stewart Talks

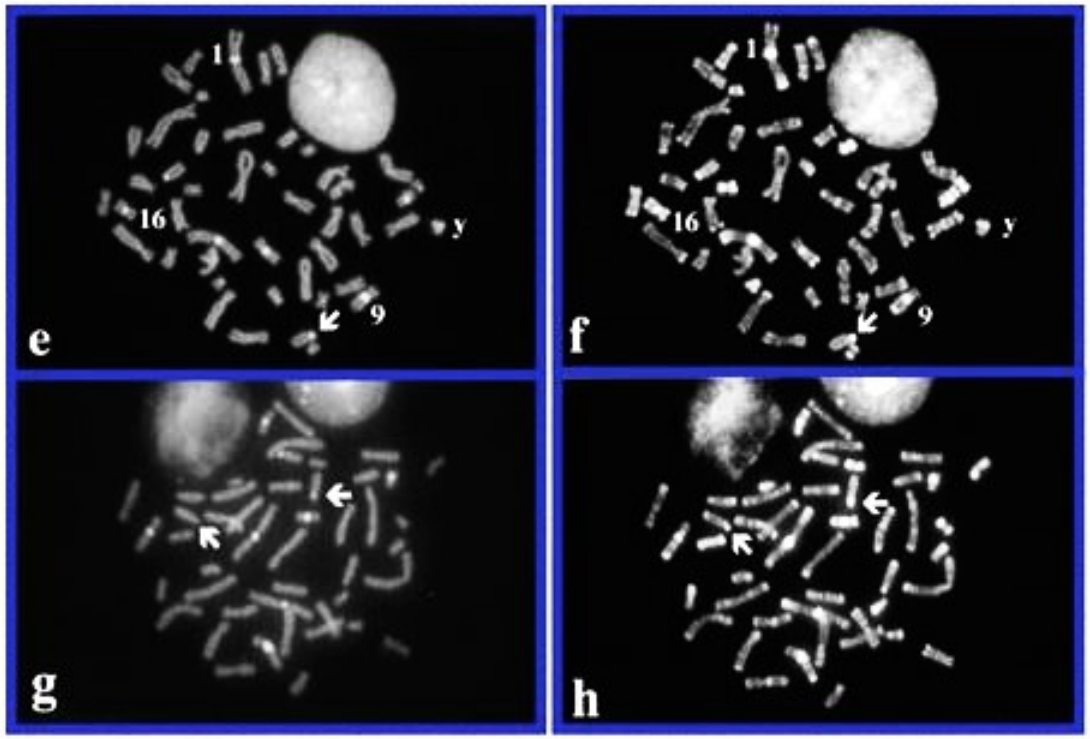
5-Methyl Cytosine in DNA



5-Methyl Cytosine is Found in Heterochromatic Regions

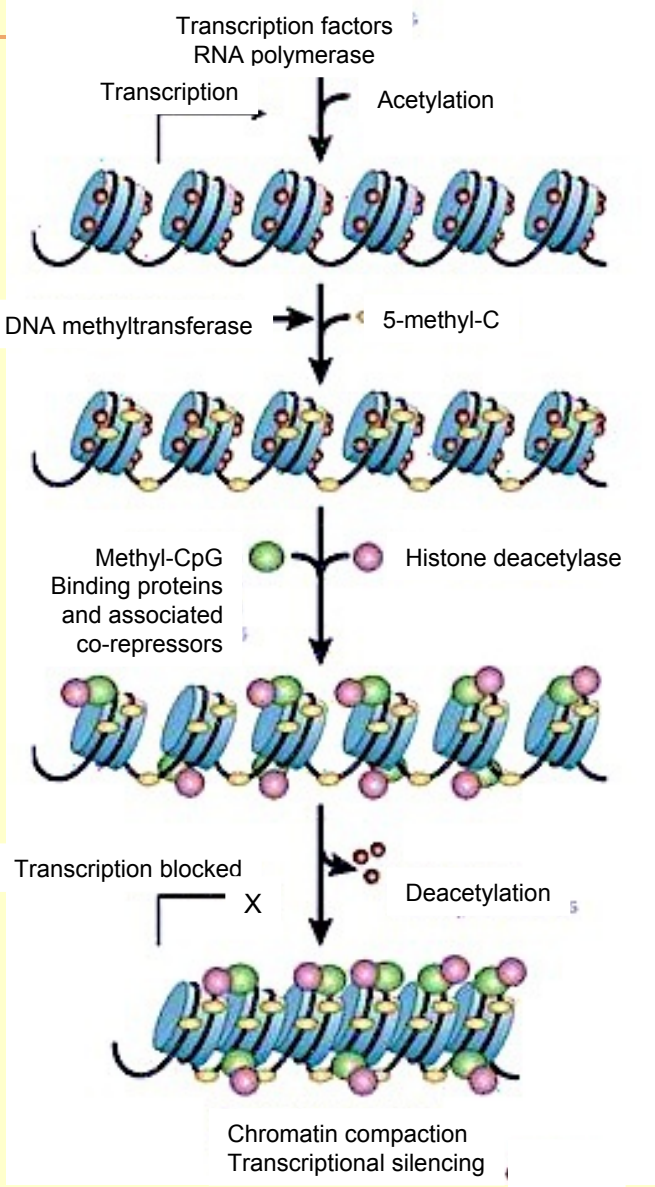
The distribution of cytosine methylation in mammals

- Heterogeneity visible at cytogenetic scale
- Associated with heterochromatic regions



PMID 9609658

Cytosine Methylation Maintains Inactive-Condensed Chromatin State



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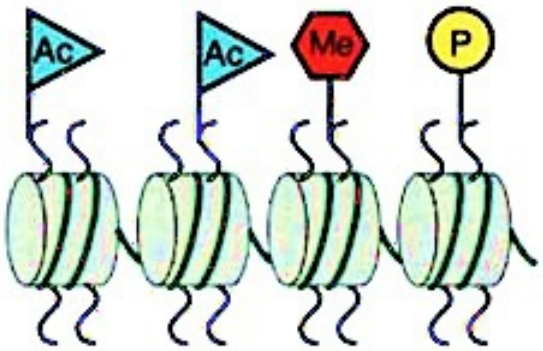
Structure & Epigenetics of Euchromatin versus Heterochromatin

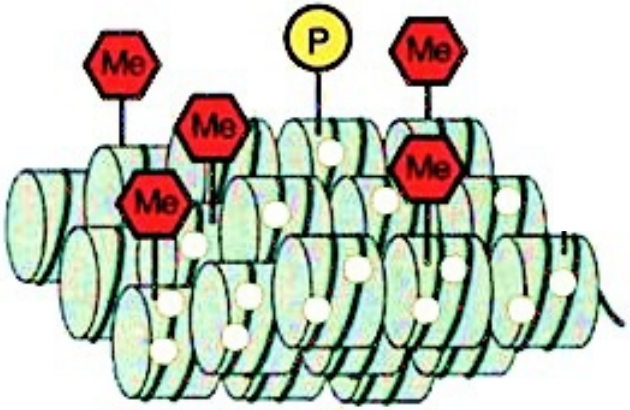
DNA methylation and histone modifications help to compartmentalize the genome into domains of different transcriptional potentials

Euchromatin



- High histone acetylation
- Low DNA methylation
- H3-K4 methylation

Heterochromatin



- Low histone acetylation
- Dense DNA methylation
- H3-K9 methylation

Paula Vertino, Henry Stewart Talks

Histone Code

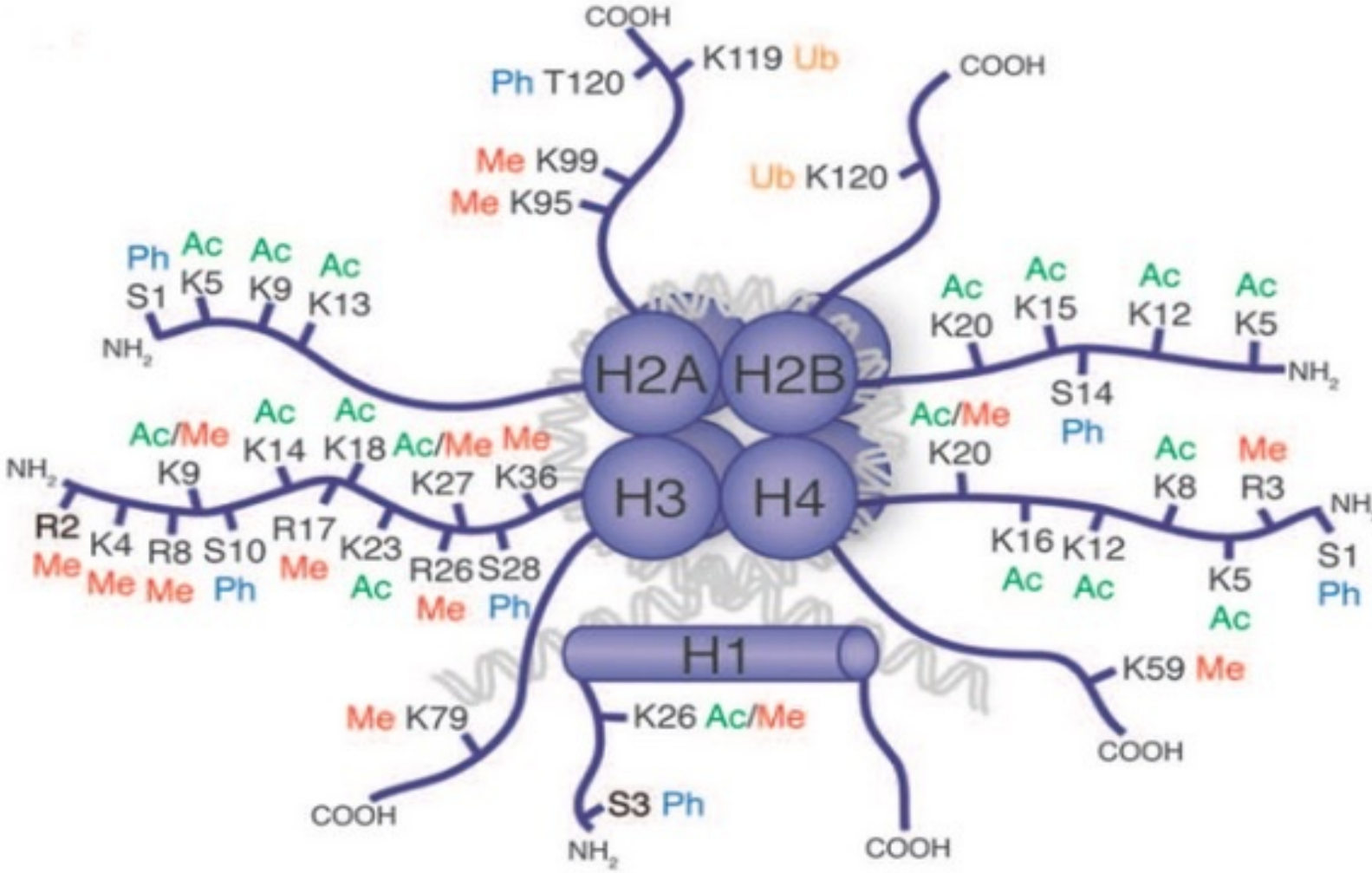
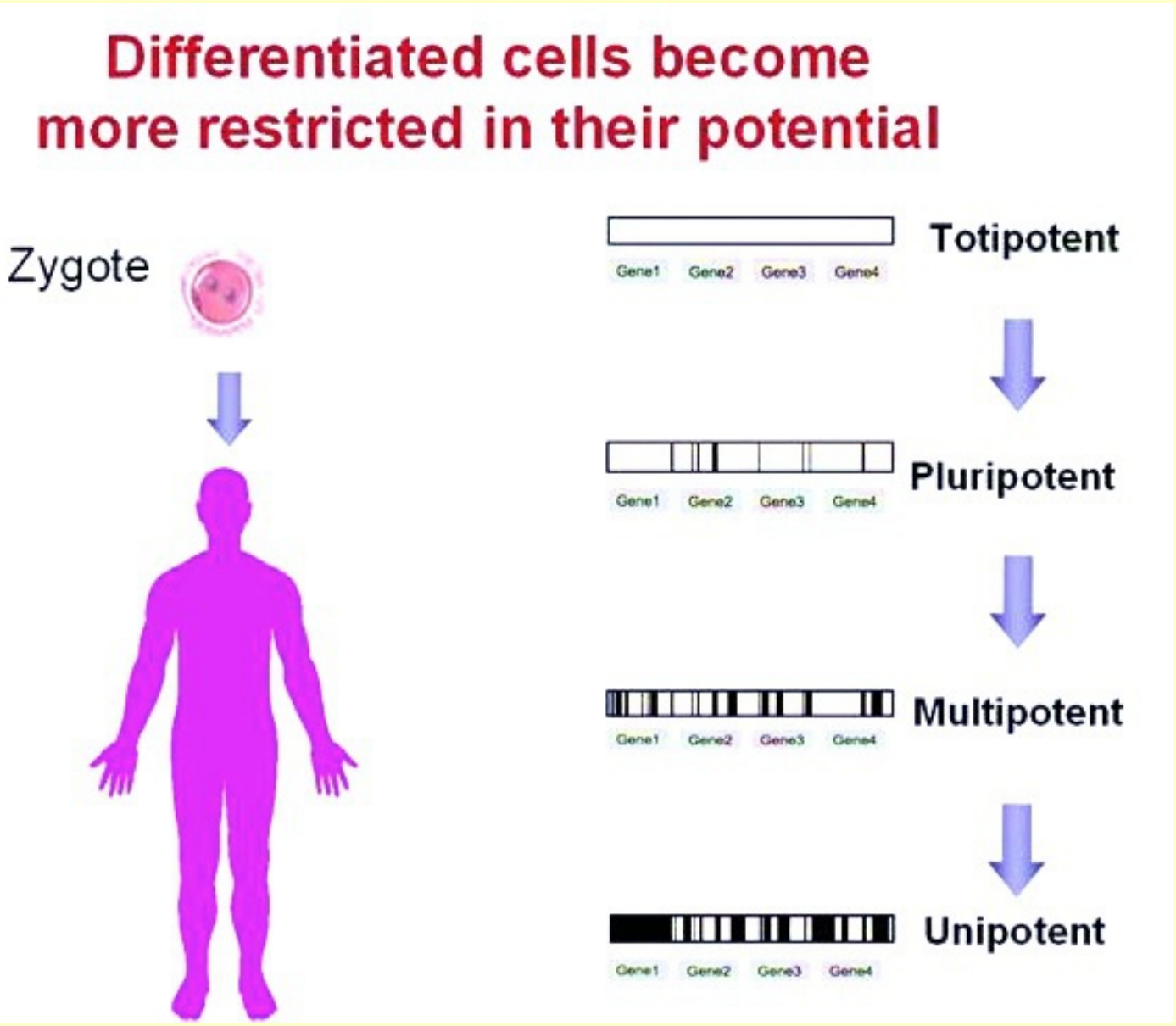


FIGURE 4.

Nucleosome with histone posttranslational modifications (Adapted from 1)

"Pluripotent Stem Cells", book edited by Deepa Bhartiya and Nibedita Lenka

Methylated DNA from Zygote to Adult



Alex Meissner, Henry Stewart Talks

Methylated DNA from Zygote to Adult

ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGAT
GTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACC
AGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTAACA
TAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGATGTT
TTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACCAGT
AGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTTTATTAT
AGGACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCAT
GATGTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATG
ACCAGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTA
ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATACAGCACCATACCATGAT

How is the diversity of cell types created and maintained in multi-cellular organisms?

ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGAT
GTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACC
AGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTAACA
TAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGATGTT
TTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATGACCAGT
AGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTTTATTAT
AGGACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCAT
GATGTTTTTATTACCAGGATGATCACCATTGGGTACCATTTACCAGGATTACACAGTTTTAGATG
ACCAGTAGCTATTAGAGGATTTTAAATTTATTTAGGATTTTATGGGATTGATAAAGGGAGATTTA
ACATAGACATACACACTGTTGATTAGGGAGATAGTGACAGATCCATTACAGCACCATACCATGAT

Alex Meissner, Henry Stewart Talks

DNA Methylation Differentiates Totipotent Embryonic Stem Cells from Unipotent Adult Stem Cells

Pluripotent cell

ctggaggtgcaatggctgtcttgtcctggcctt
ggacatgggctgaaatactgggttcacccatat
ctaggactctagacgggtgggtaagcaagaact
gaggagtggccccagaaataattggcacacgaa
cattcaatggatgttttaggctctccagaggat
ggctgagtgggctgtaaggacaggccgagaggg
tgcagtgccaacaggctttgtggtgcgatgggg
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ggttgtcctgtccagacgtccccaacctccgtc
tggaagacacaggcagatagcgctcgcctcagt
ttctcccacccccacagctctgctcctccaccc
acccaggggggcggggccagaggtcaaggctaga
gggtgggattggggagggagaggtgaaaccgt
cctaggtgagccgtctttccaccaggcccccgg
ctcggggtgcccaccttccccatggctggacac

Unipotent cell

Ctggaggtgcaatggctgtcttgtcctggcctt
ggacatgggctgaaatactgggttcacccatat
ctaggactctagacgggtgggtaagcaagaact
gaggagtggccccagaaataattggcacacgaa
cattcaatggatgttttaggctctccagaggat
ggctgagtgggctgtaaggacaggccgagaggg
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tggaagacacaggcagatagcgctcgcctcagt
ttctcccacccccacagctctgctcctccaccc
acccaggggggcggggccagaggtcaaggctaga
gggtgggattggggagggagaggtgaaaccgt
cctaggtgagccgtctttccaccaggcccccgg
ctcggggtgcccaccttccccatggctggacac

Alex Meissner, Henry Stewart Talks

DNA Methylation Differentiates Totipotent Embryonic Stem Cells from Unipotent Adult Stem Cells

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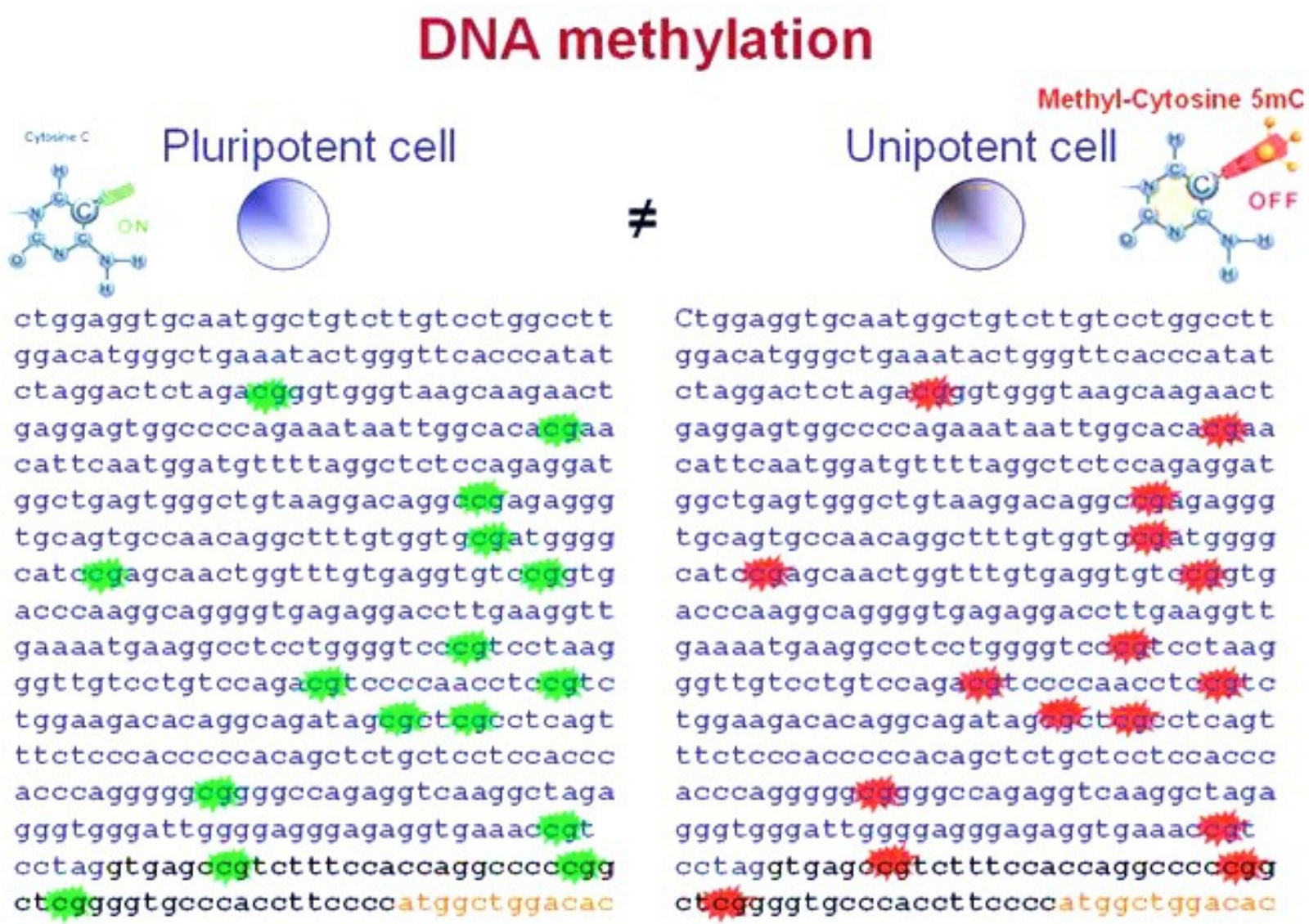


Alex Meissner, Henry Stewart Talks

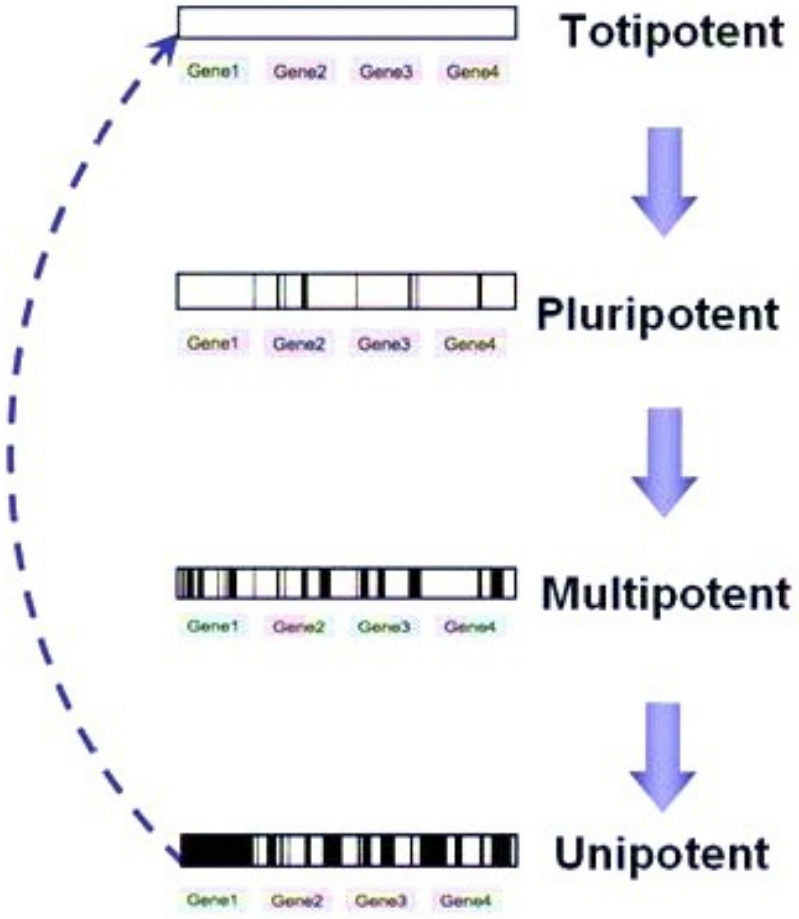
Differentiated Cells can Become Totipotent

Nuclear transplantation demonstrates nuclear equivalence

Briggs and King, 1952
Gurdon, 1960s

"Dolly"

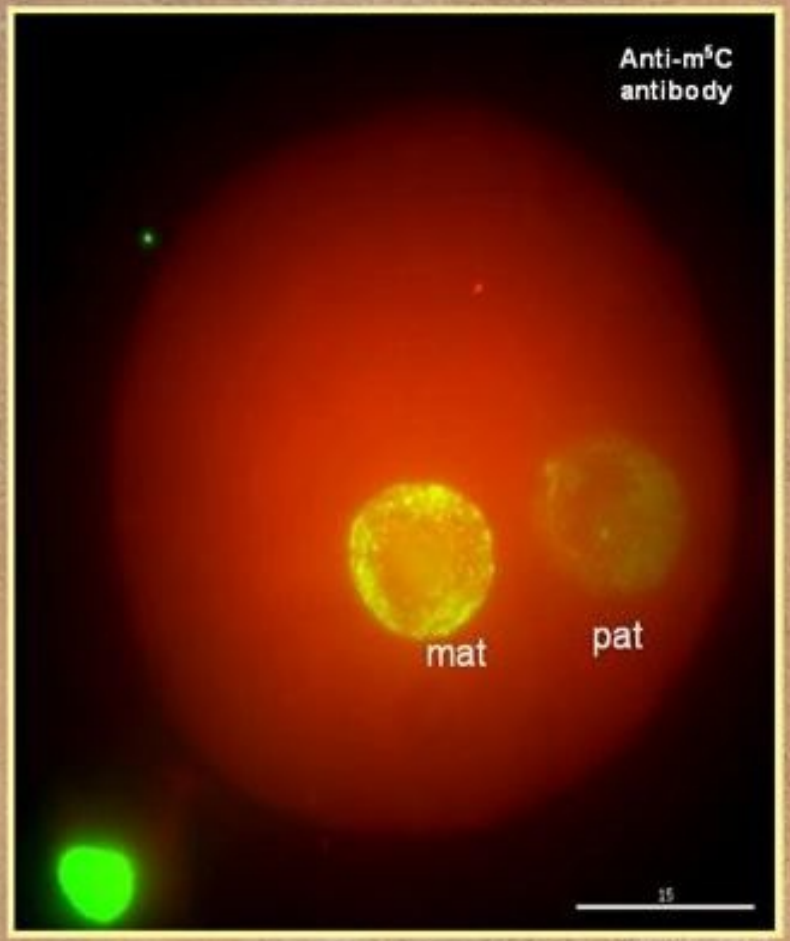
Differentiated cells maintain the potential to generate an entire organism

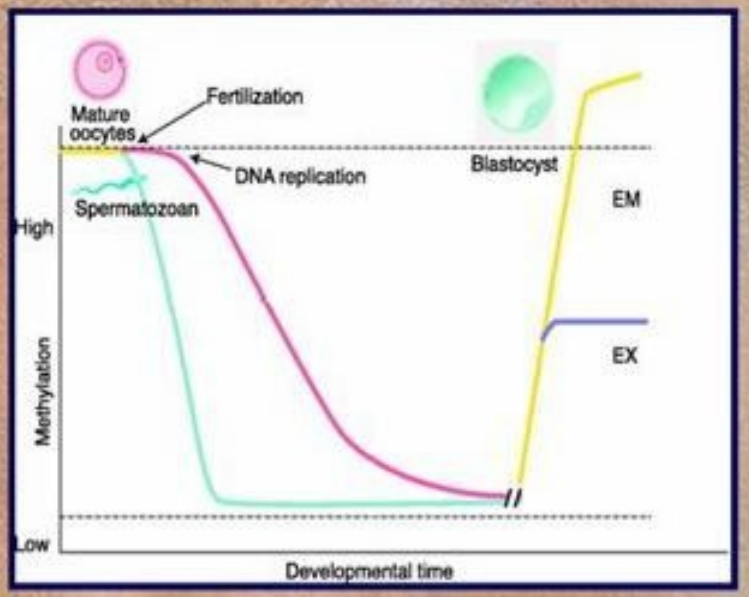


Alex Meissner, Henry Stewart Talks

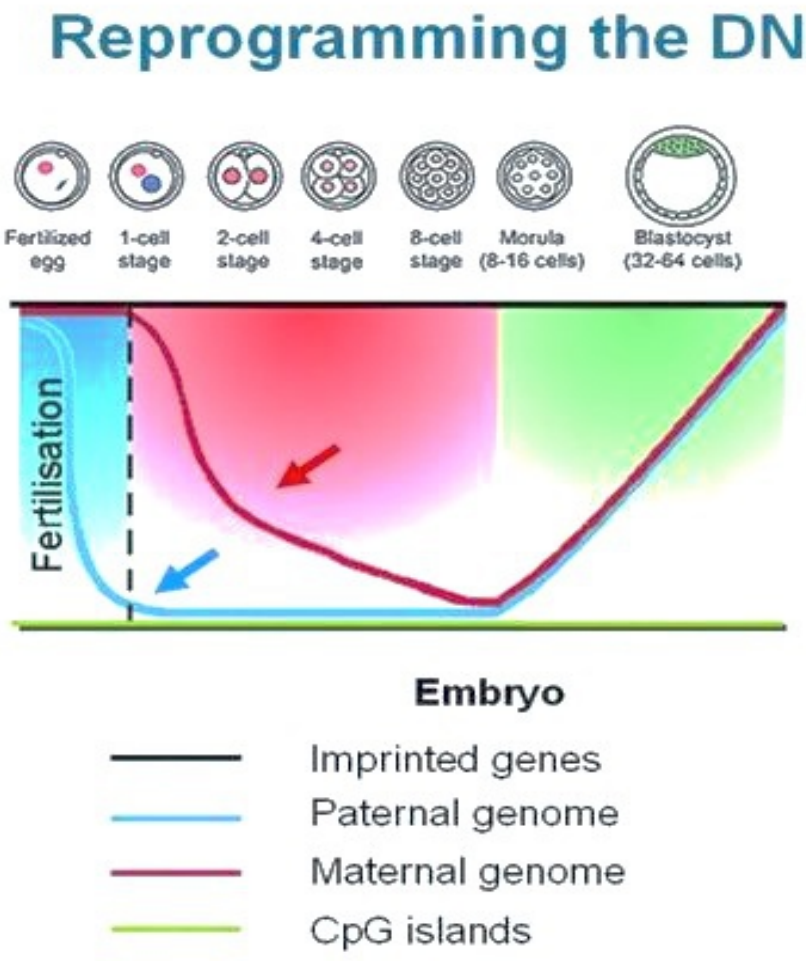
Demethylation of the Paternal Genome

De-methylation of the paternal pronucleus in the one-cell embryo of mouse





Methylation Changes During Development



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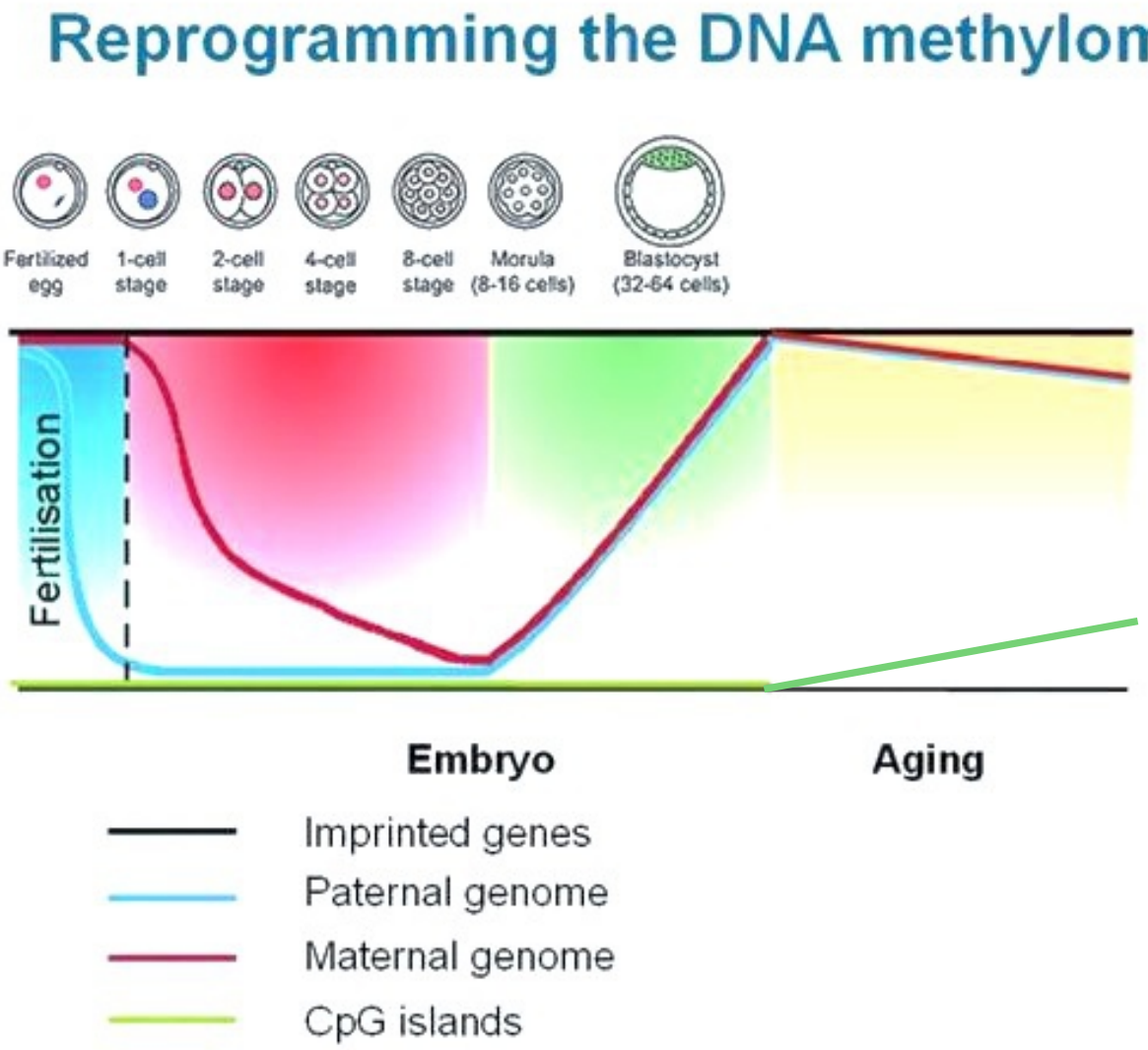

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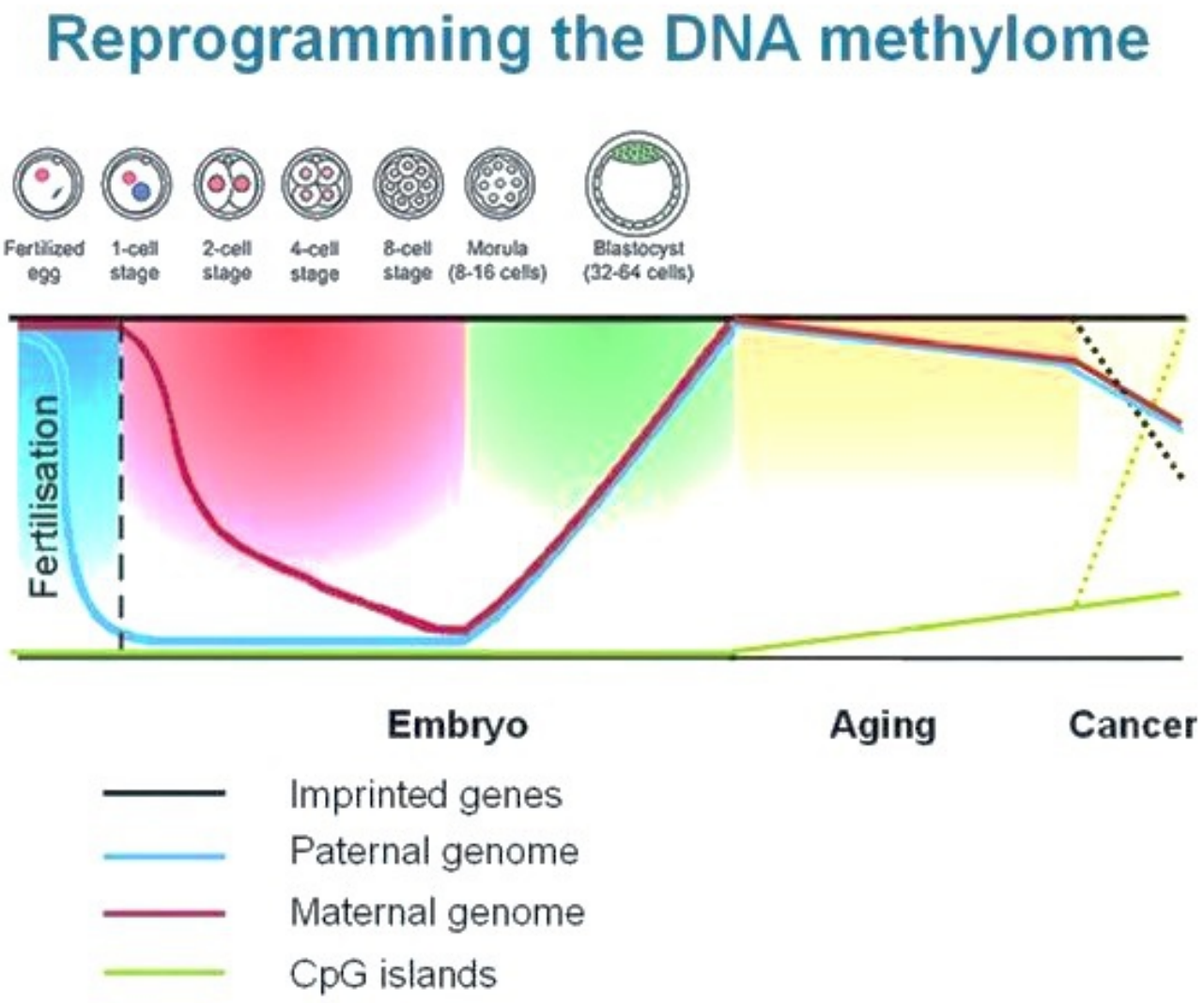
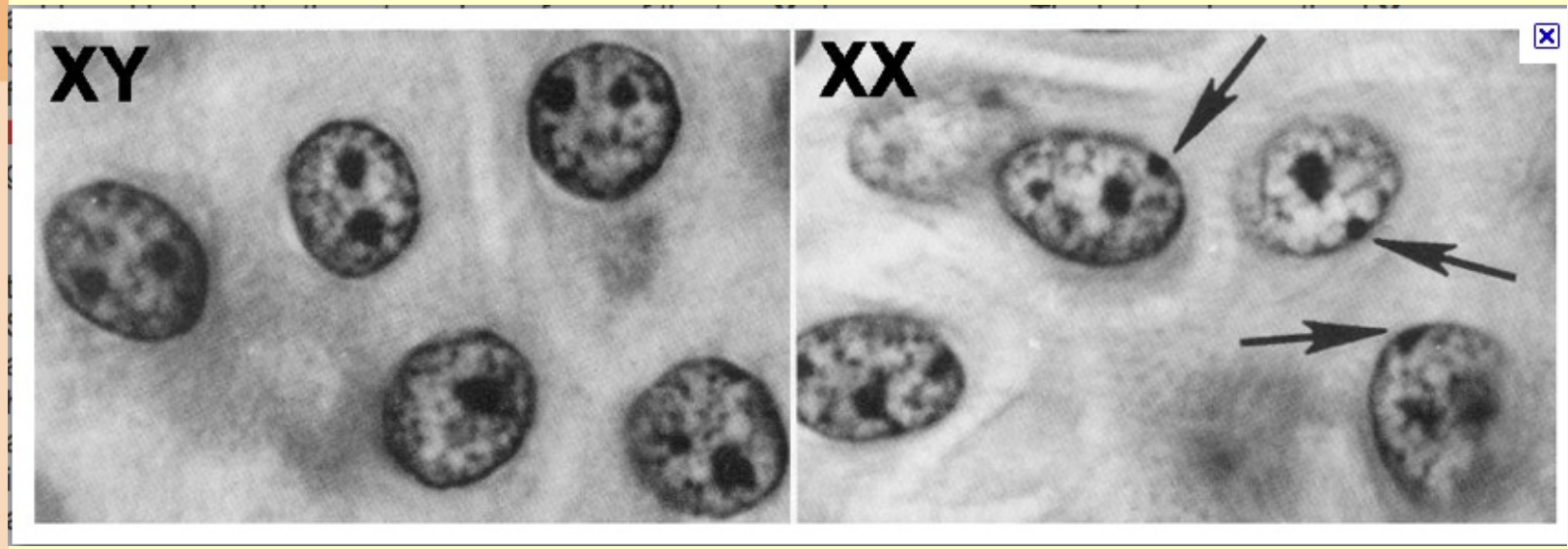


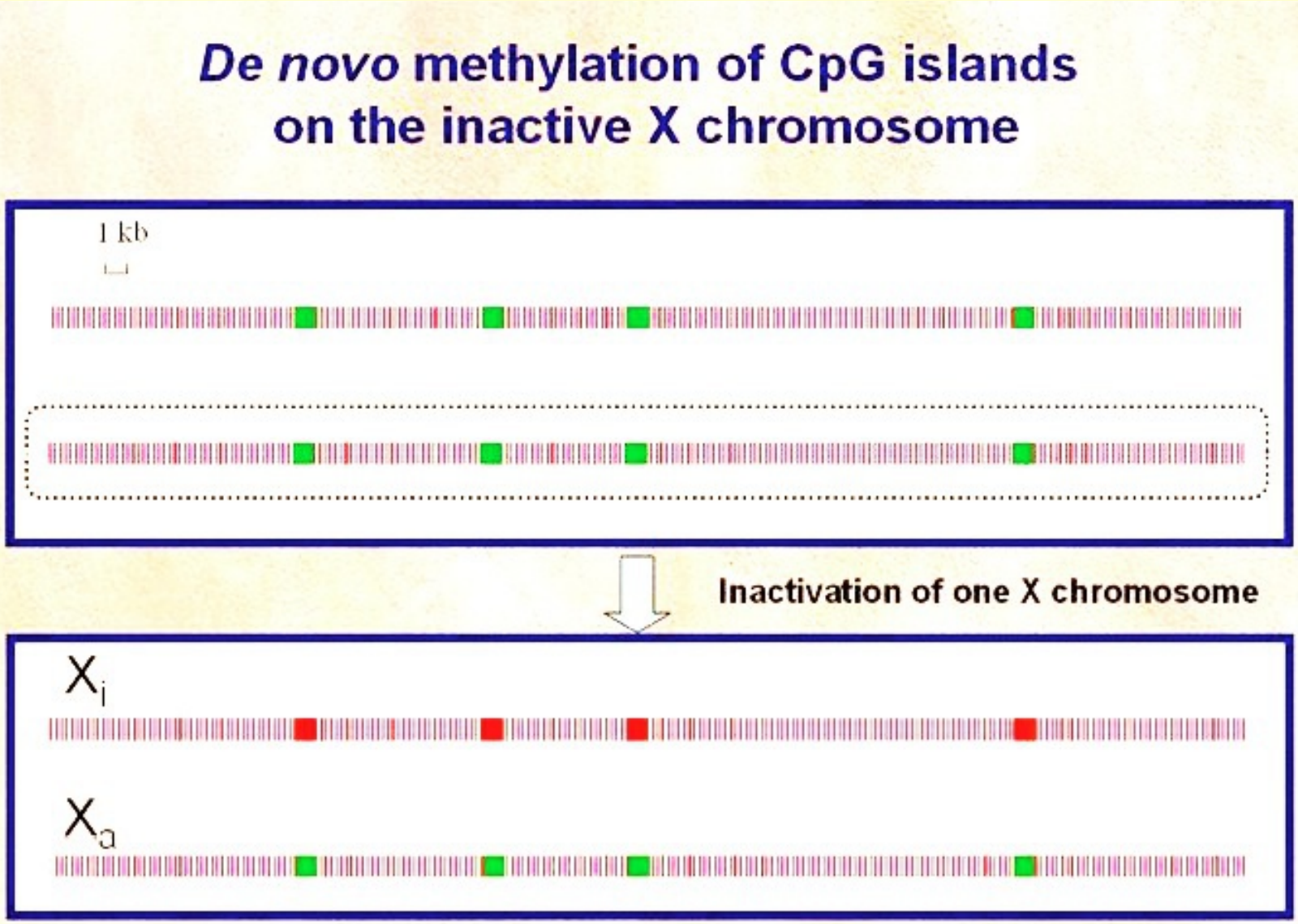
X Chromosome Inactivation: Barr Bodies



Barr, M. L., Bertram, E. G., (1949), A Morphological Distinction between Neurones of the Male and Female, and the Behaviour of the Nucleolar Satellite. *Nature.* ***163*** *(4148): 676-7.*

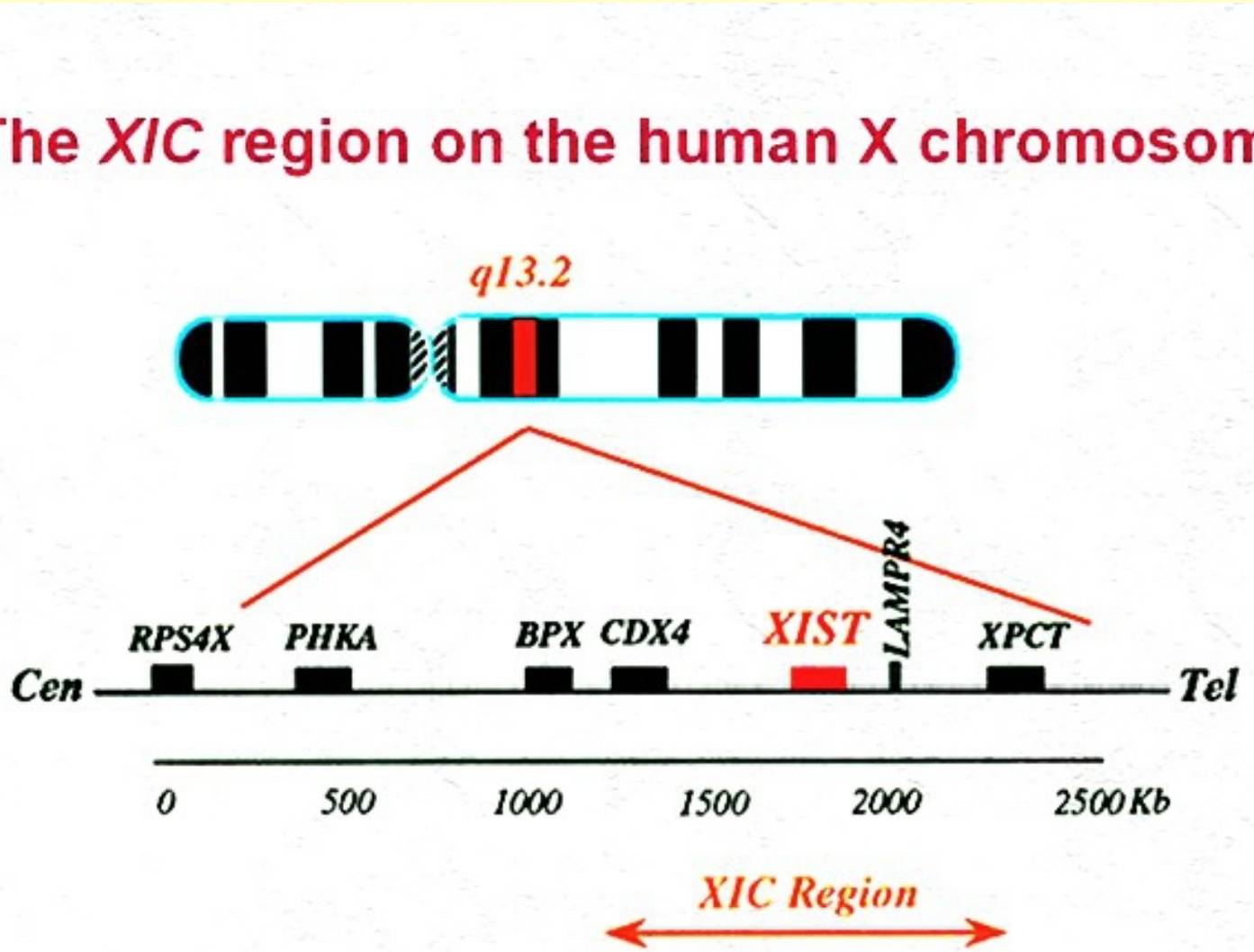
Lyon, M. F., (2003), The Lyon and the LINE hypothesis. j.semcdb 14, 313-318. (Abstract)

X Chromosome Inactivation: CG Island Methylation

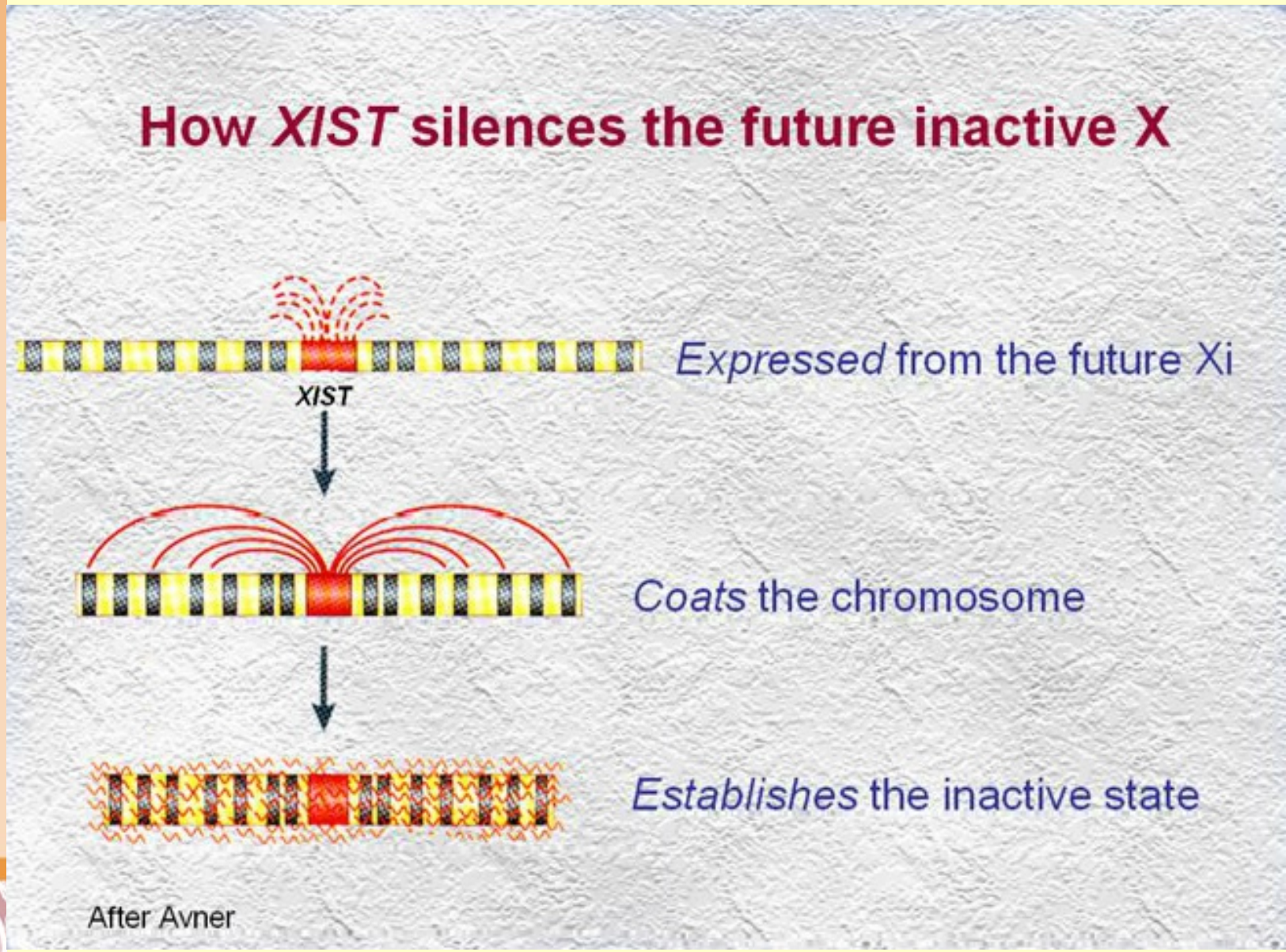


Adrien Bird, Henry Stewart Talks

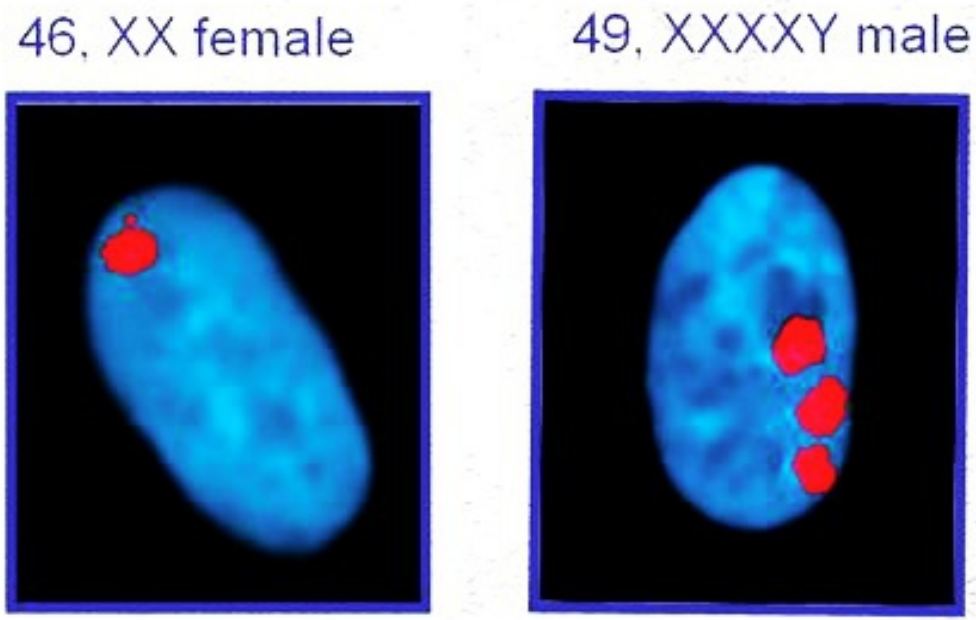
XIC Region



Xist Works in Cis

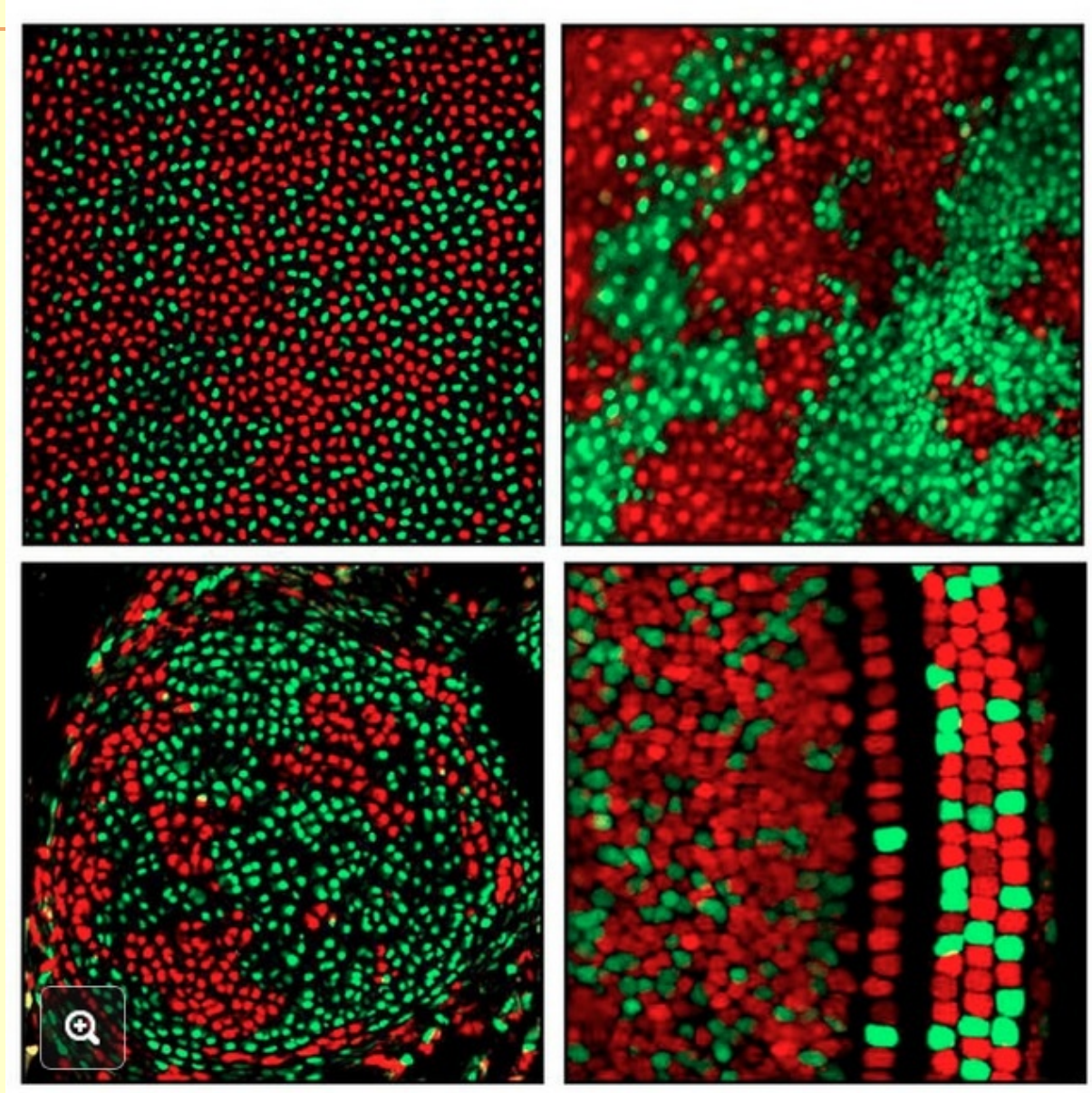


Only one X is active

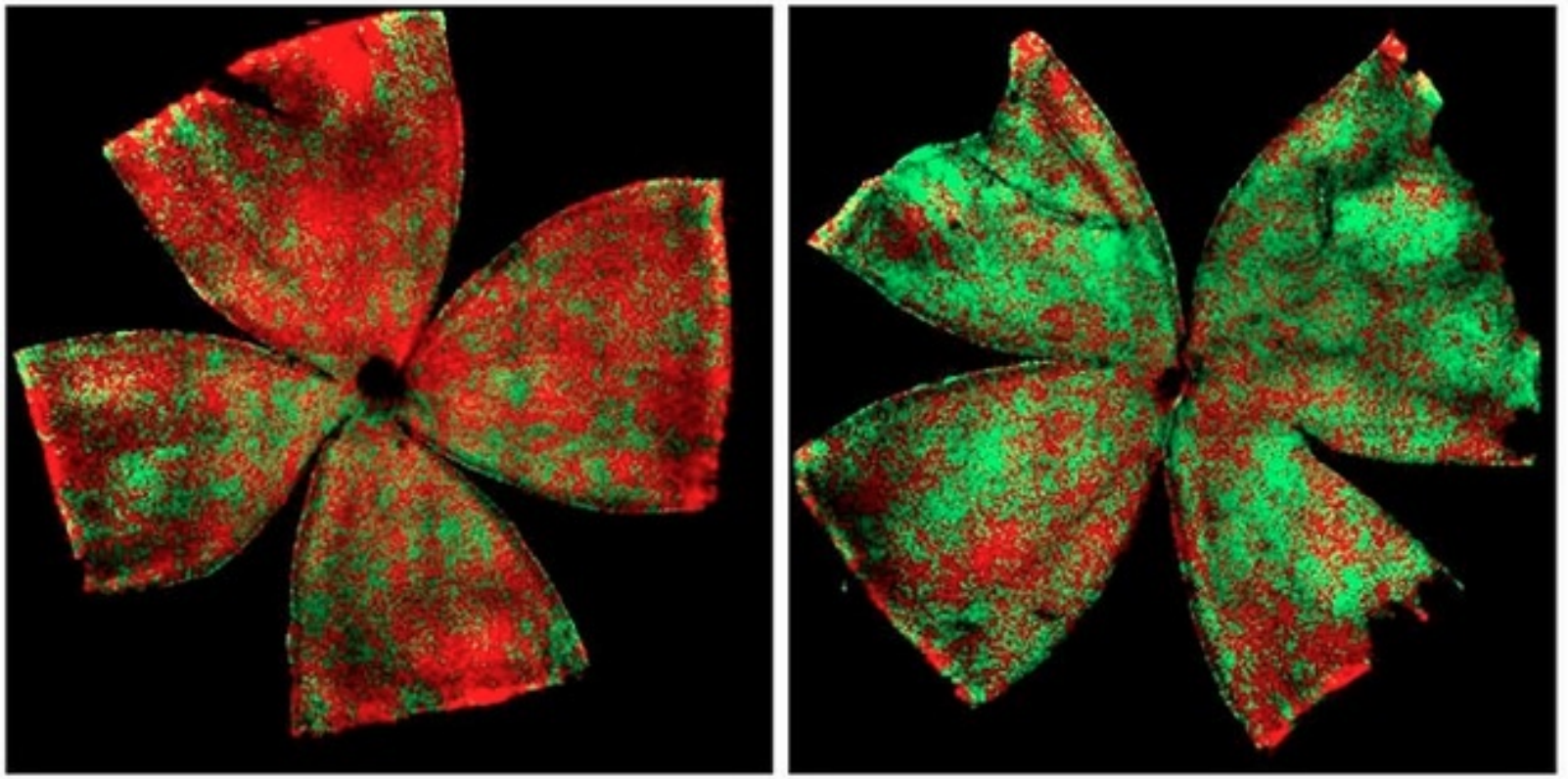


Barr bodies visualized by XIST RNA FISH

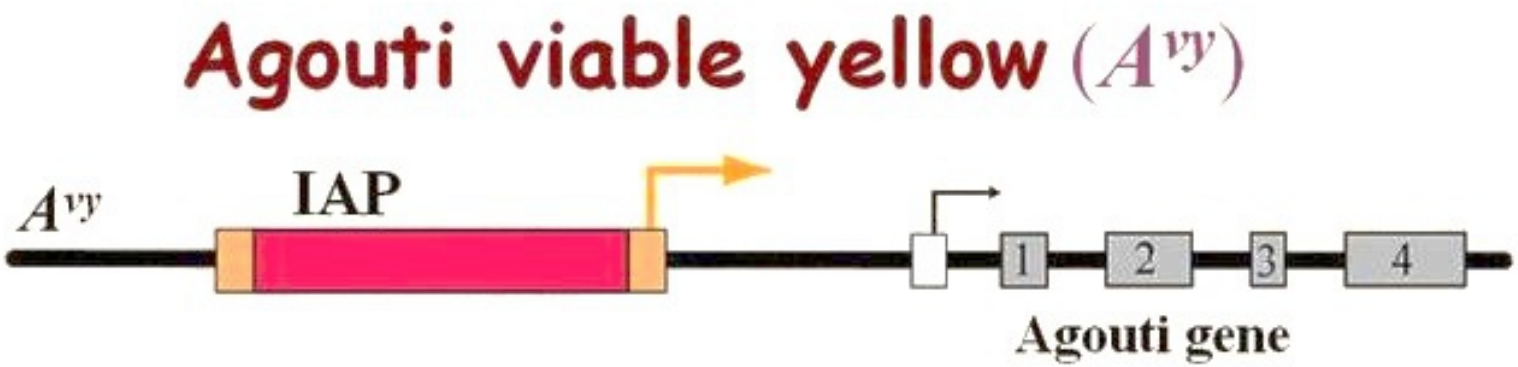
Female X chromosome Mosaicism (cornea, skin, cartilage & inner ear)



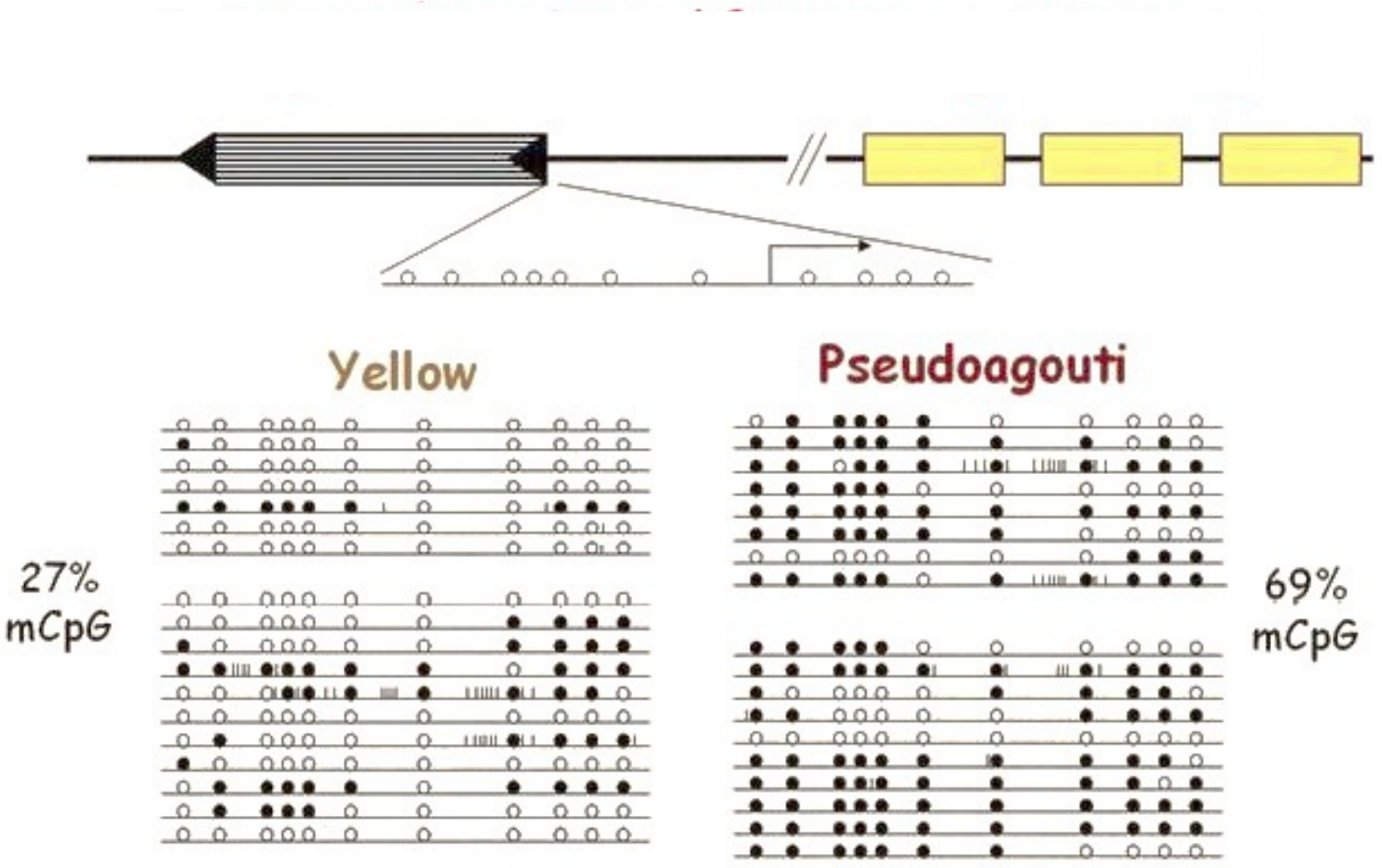
Female X chromosome Mosaicism Left and Right Retina



Agouti Genes in Mice



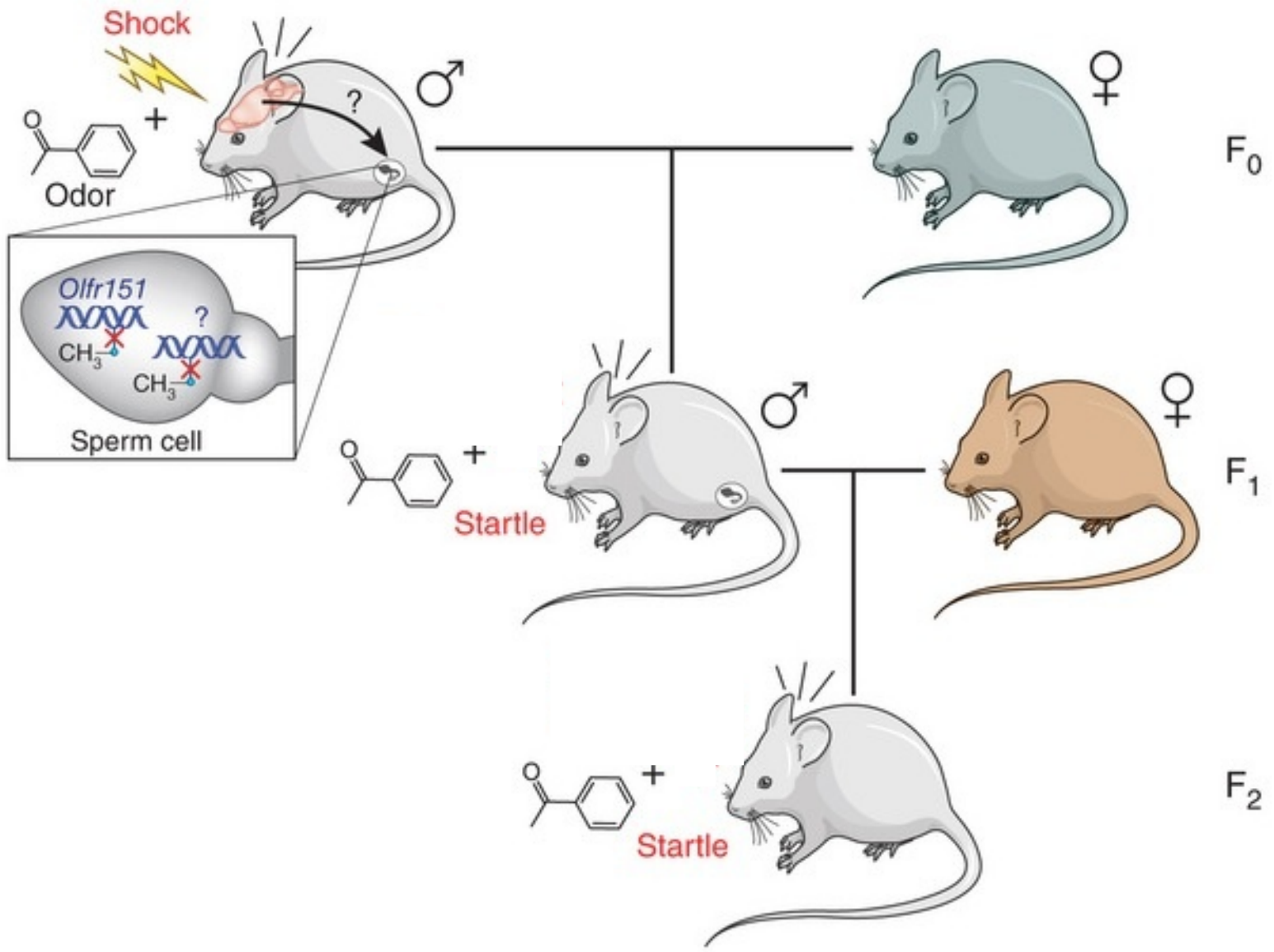
Methylation of Agouti Genes in Mice



Hongerwinter 1944

- German's blocked food to the Dutch in the winter of 1944.
- Calorie consumption dropped from 2,000 to 500 per day for 4.5 million.
- Children born or raised in this time were small, short in stature and had many diseases including, edema, anemia, diabetes and depression.
- The Dutch Famine Birth Cohort study showed that women living during this time had children 20-30 years later with the same problems despite being conceived and born during a normal dietary state.

Epigenetic Inheritance of Fear



Dias & Ressler 2014 Nature Neuroscience 17, 89-96.

Summary of Epigenetic Gene Regulation

- Patterns of DNA methylation in adult cells parallels cell fate, chromatin structure and gene activation.
- Most DNA methylation is removed at fertilization and re-established during embryogenesis.
- Imprinted genes keep their parental pattern of methylation giving rise to parental patterns of expression.
- Patterns of histone modifications parallel DNA methylation.
- Methylated gene regions are genetically inactive, highly condensed and special histone modifications.
- Active gene regions have little DNA methylation and distinctive histone modifications (acetyl groups and H3K4methyl).
- X chromosome inactivation in females is correlated with extensive CG island methylation on one chromosome, condensation, inactivation and Barr body formation.
- Alterations in gene and CG island methylation patterns are seen in aging and in cancer.
- Most CG islands are not methylated except for X chromosome inactivation and tumor suppressors in cancer.