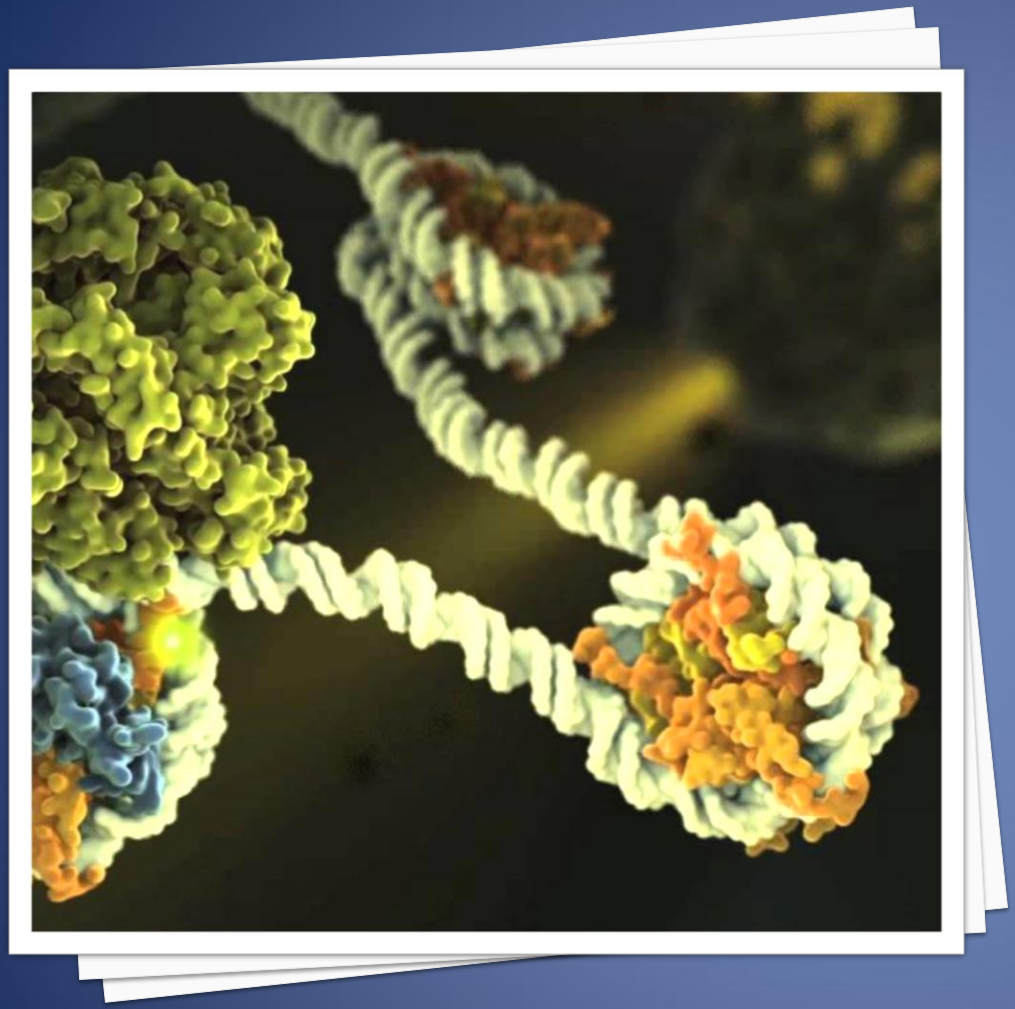
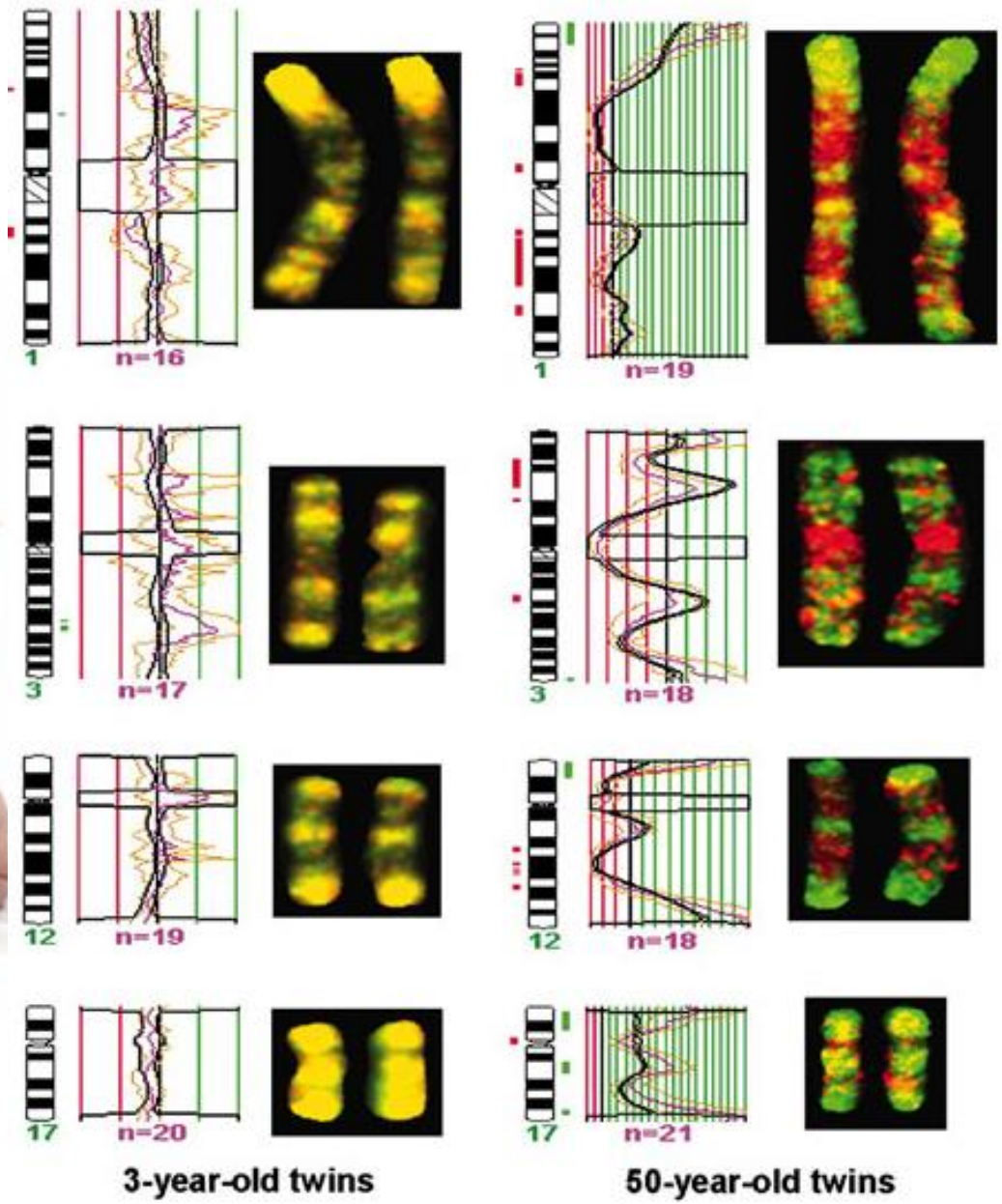


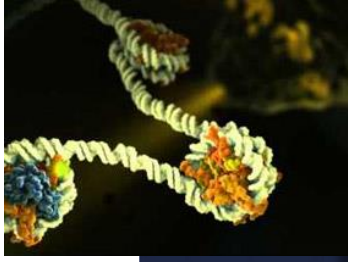
# BIOLOGIE GENERALA

# MECANISME EPIGENETICE

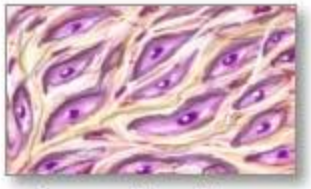
# GEMENI MONOZIGOTICI




ORGANISM



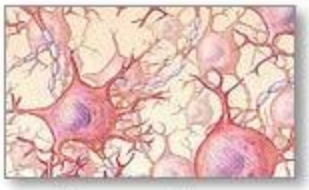
TESUTURI



Connective tissue

Epithelial tissue

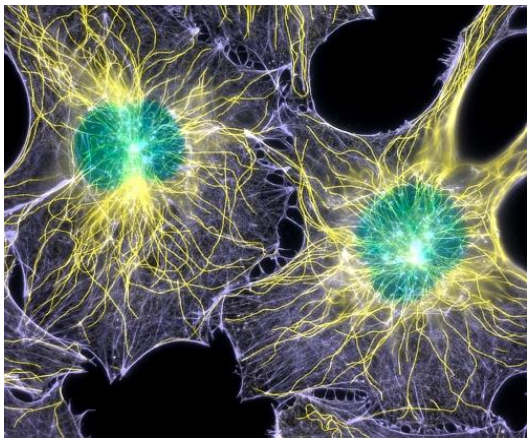
Muscle tissue



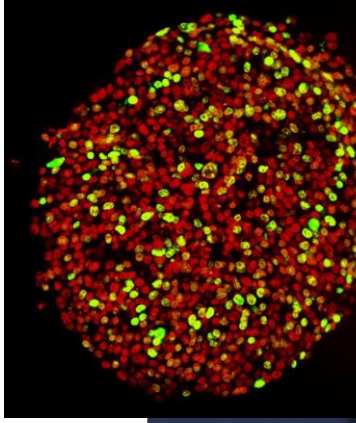
Nervous tissue

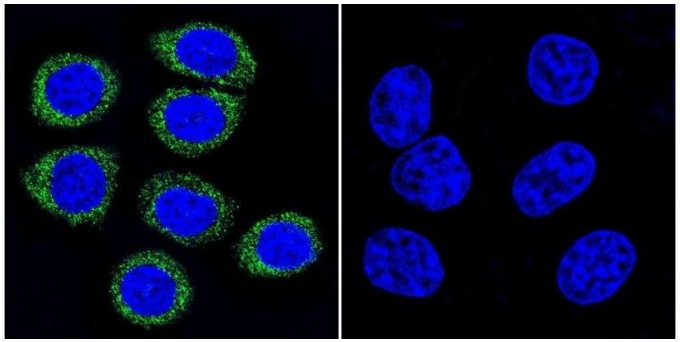
ADN

CELULE



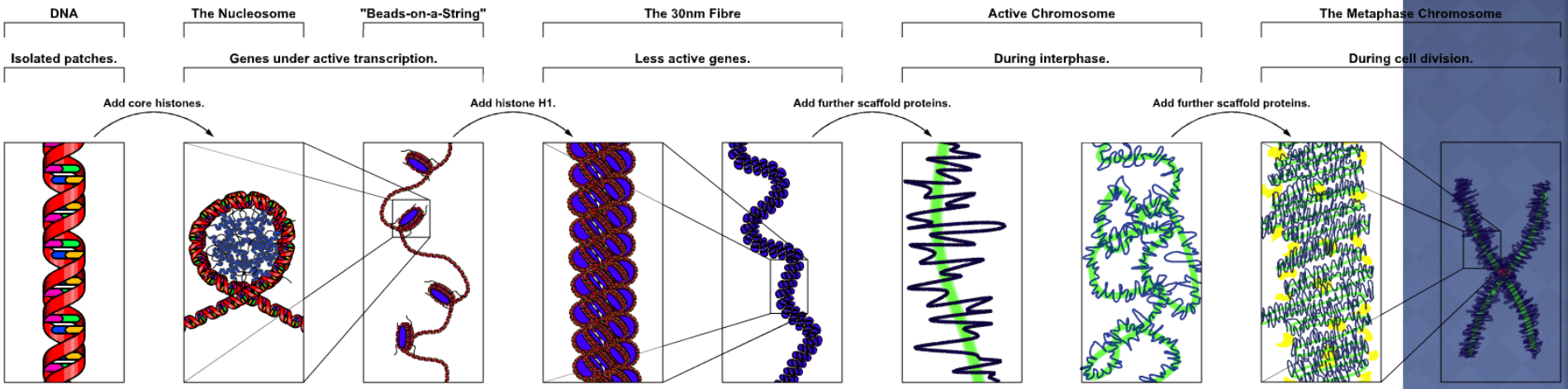
AND: 2 m



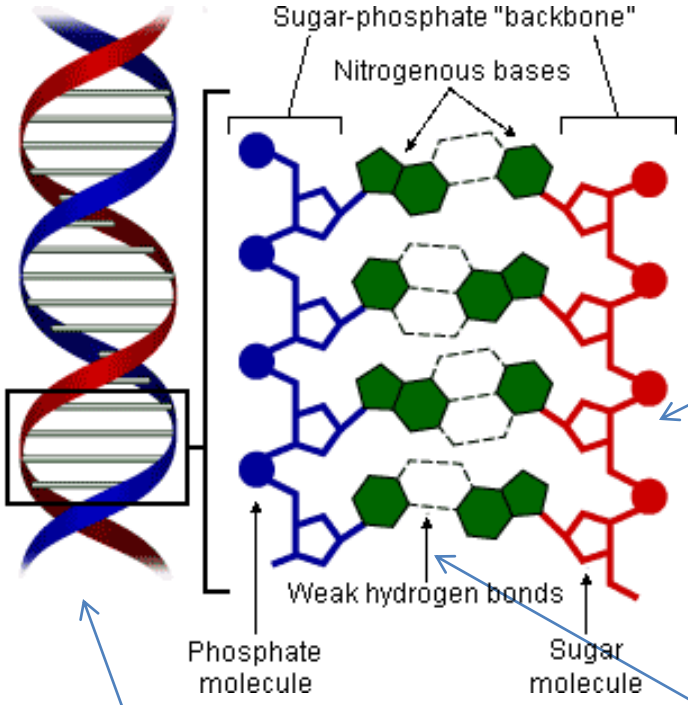


Nucleul unei celule: 10 µm

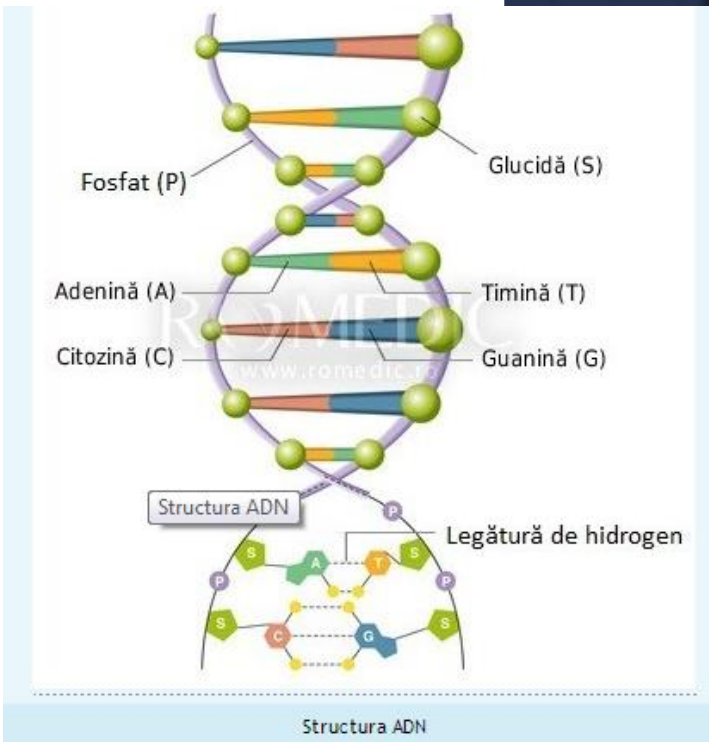
## Impachetarea si compactearea AND in nucleu



# STRUCTURA ȘI ORGANIZAREA ADN




**Structura primară**




**Structura terțiară,** dată de organizarea spațială tridimensională

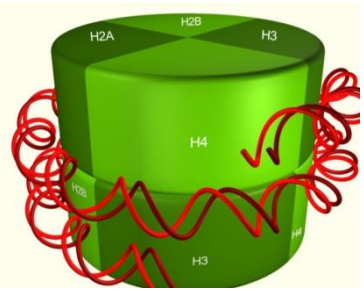
**Structura secundară** dată de interacțiunea dintre baze

# STRUCTURA ȘI ORGANIZAREA ADN

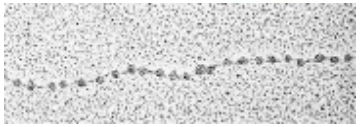
Cromozom

Fibra de cromatină

Solenoid




Nucleozom

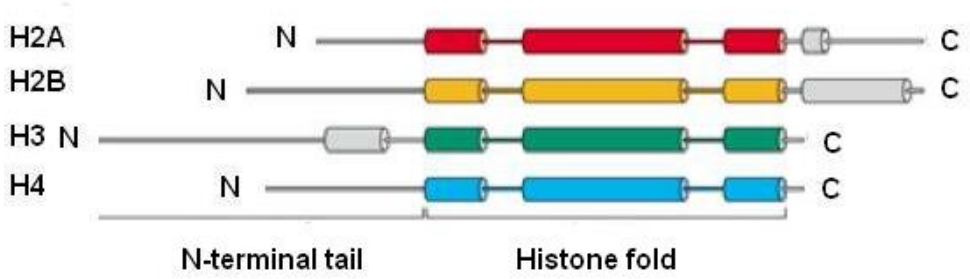




Miez **histonic (8 histone suprapuse)** În jurul căruia se înfășoară o **buclă de ADN-ul (146 perechi de baze)**

**Structura cuaternară** este dată de interacțiunea ADN cu alte molecule care intervin în plierea și împachetarea ADN În nucleu

# MIEZUL HISTONIC PREZINTA UN GRAD INALT DE CONSERVARE

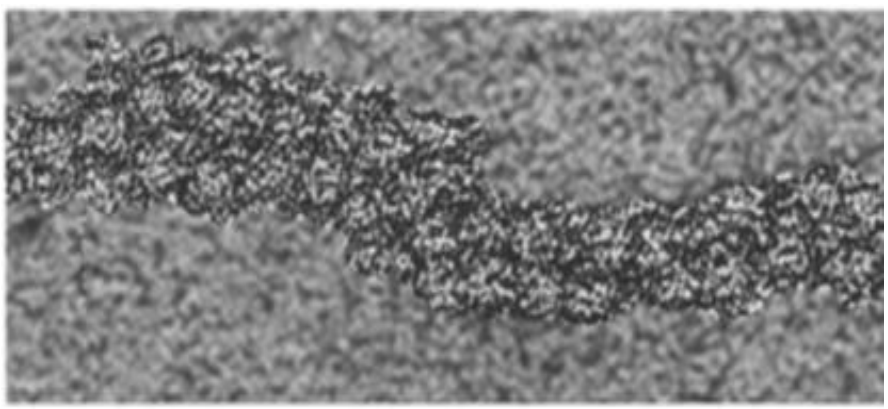


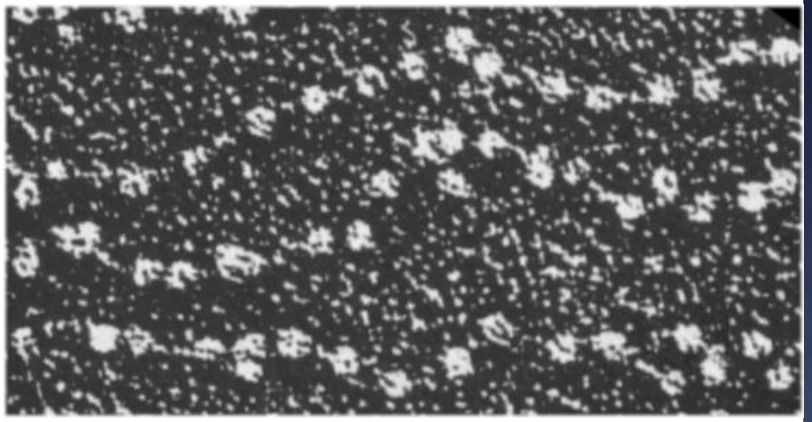

Histonele sunt proteine bazice cu o mare afinitate pt ADN prezente la toate eucariotele.

La eucariote se deosebesc 5 tipuri de histone : H1,H2A, H2B, H3, H4. Cu exceptia lui H1, celelalte tipuri (in special H3,H4) au o structura stabila, din punct de vedere evolutiv.

| Histone Type | Molecular Weight | Number of Amino Acids | Approx. Content of Basic Amino Acids |
|---|---|---|---|
| H1 | 17,000–28,000 | 200–265 | 27% lysine, 2% arginine |
| H2A | 13,900 | 129–155 | 11% lysine, 9% arginine |
| H2B | 13,800 | 121–148 | 16% lysine, 6% arginine |
| H3 | 15,300 | 135 | 10% lysine, 15% arginine |
| H4 | 11,300 | 102 | 11% lysine, 4% arginine |

# FIBRELE DE CROMATINA

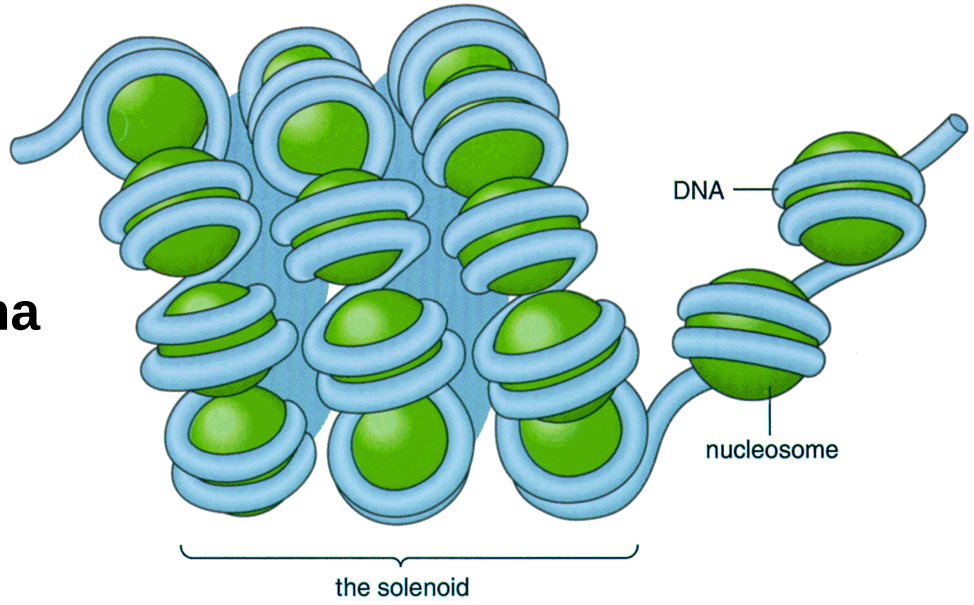




Cromatina vazuta in microscopie electronica.

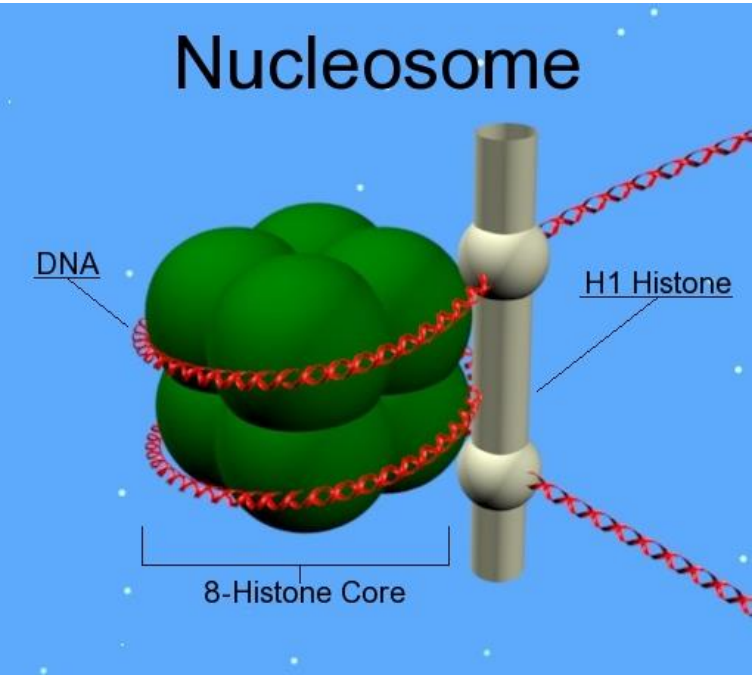
(**source: Alberts et al., Molecular Biology of The Cell, 3rd Edition)**

**30 nm**
**fibre de cromatina**




**11 nm**

# FIBRELE DE CROMATINA SI IMPACHETAREA ADN



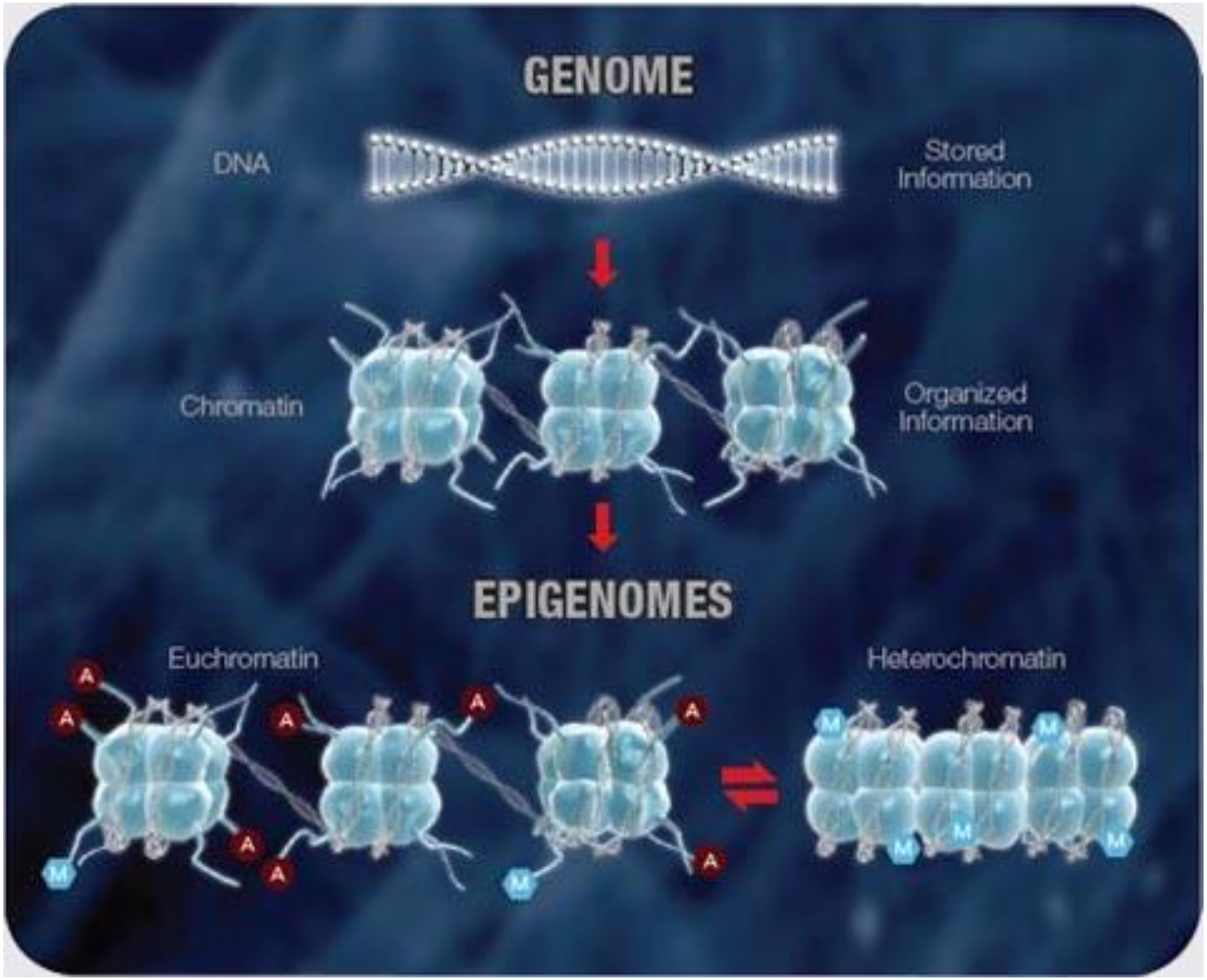

**Histonele** pot suferi o serie de **modificarii de genul acetilare, fosforilare, metilare** care determina la randul lor condesarea si decondensarea cromatinei, facand astfel accesibila **citirea informatiei genetice (decondensare)** sau **incriptarea informatiei genetice (condensare).**

Directionarea modificarilor suferite de histone sunt datorate cel putin intr-o anumita masura de modificarile survenite la nivelul ADN. Astfe, **metilarea ADN determina deacetilarea histonelor si condensarea cromatinei.**

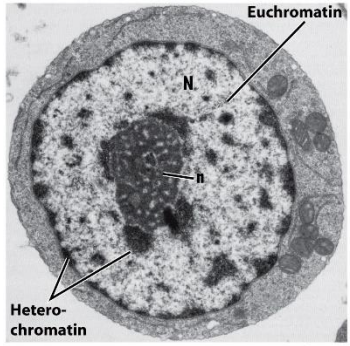
**AND-ul → histone → nucleosomi**

↓

**unitatea repetitiva a cromatine**

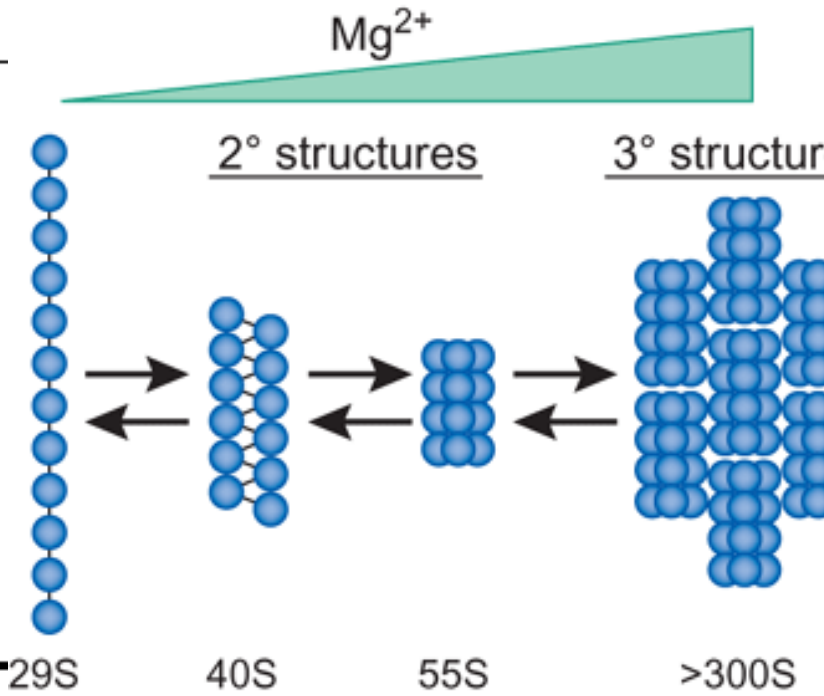

GENOME
DNA
Stored Information
Chromatin
Organized Information
EPIGENOMES
Euchromatin
Heterochromatin
A
M

# ORGANIZAREA CROMATINEI




**Proposed hierarchical classification scheme for chromatin structures.**

| Level of chromatin structure |
| --- |
| **Primary** – The linear arrangement of features such as nucleosomes on DNA. |
| **Secondary** – Structures formed by interactions of nucleosomes. |
| **Tertiary** – Structures formed by interactions between secondary structures. |

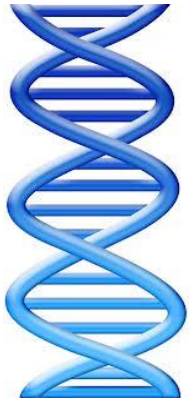



Woodcock and Dimitrov, COGD, 2001

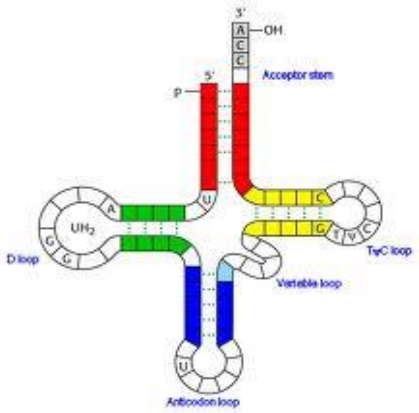
Caterino and Hayes, Nature Structural and Molecular Biology, 2

# DOGMA CENTRALĂ A BIOLOGIE MOLECULARE, F. CRICK 1958

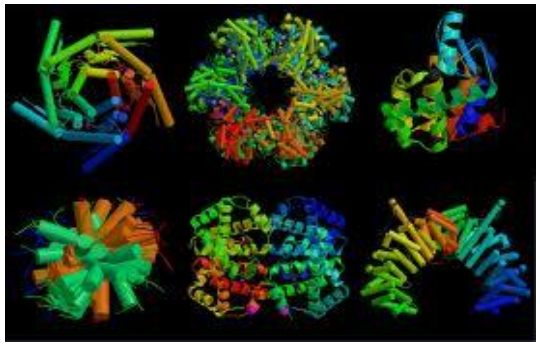

ADN

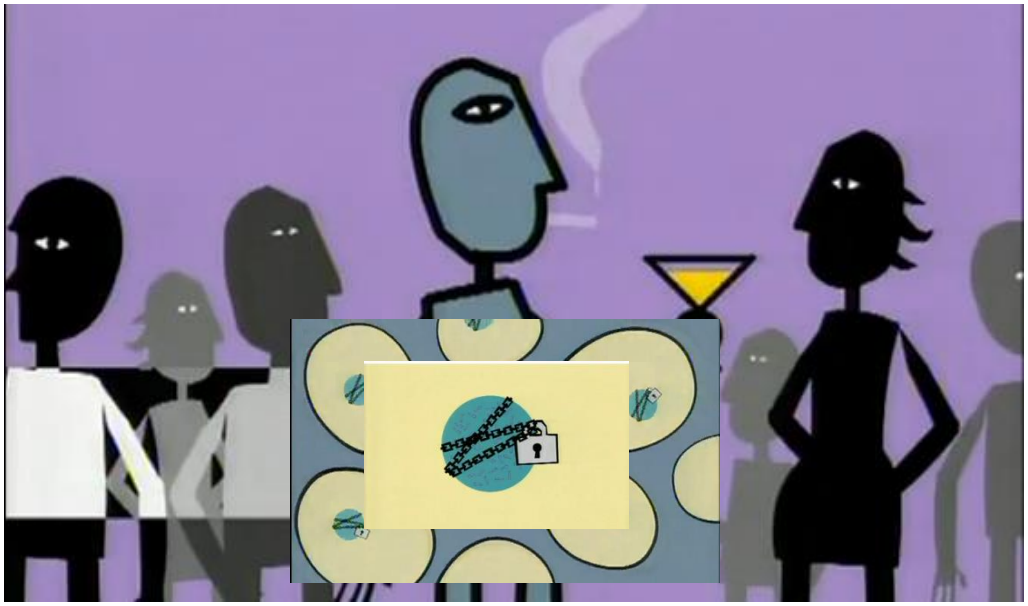


ARN




Proteine





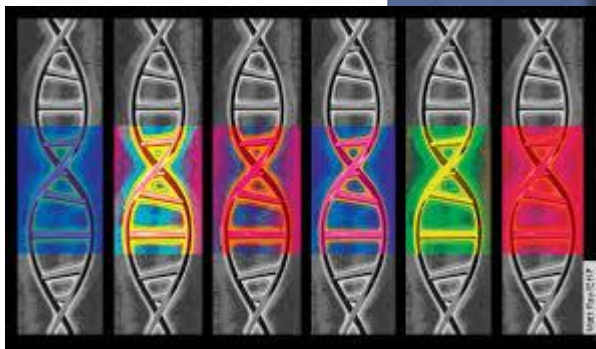
# CE ESTE EPIGENETICA?

•**Epigenetica** reprezinta o ramura a geneticii care se ocupa cu studiul modificarilor ereditare, manifestate fenotipic si din punct de vedere al expresiei genice, dar care se datoreaza unor mecanisme care nu implica modificari ale secventei AND.

•Aceste modificari se pot transmite de-a lungul generatiilor.

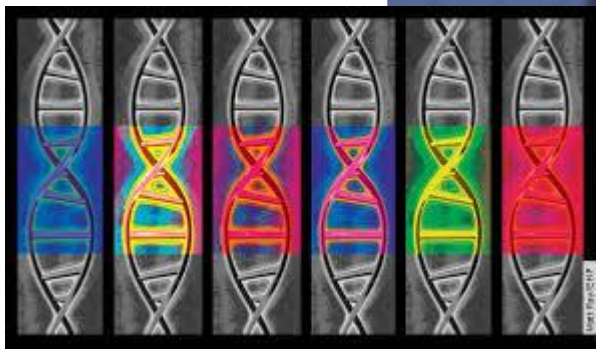
•Termenul **“epigenetică”** (prefixul **„epi-”** înseamnând **„deasupra”**) introdus de Prof. **Conrad Waddington**, în **1942**, **pentru a explica relaţiile dintre mediu şi genom.**

•**Epigenetica**, explică legătura dintre gene şi mediul înconjurător. Aşadar, **controlul epigenetic** se referă la **controlul de dincolo de gene**, acesta determinand o adevărată revoluţie în ştiinţă.



# FOAMETEA DIN IARNA 1944

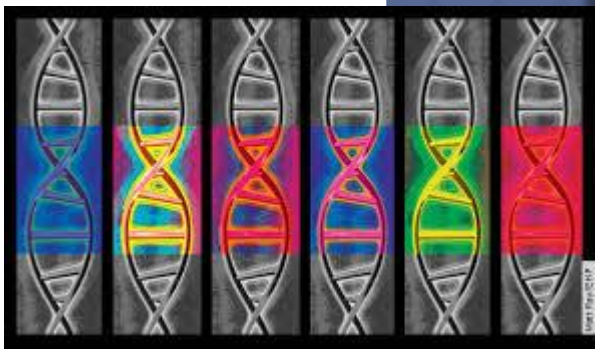
- Armata germana a blocat aprovizionarea cu hrana a Olandei.
- **Consumul caloric** a scazut de **la 2000 la 500 calorii pe zi**.
- Copii nascuti in acea perioada erau **mici de inaltime, slabi**, si au prezentat multe afectiuni inclusiv **diabet, obezitate si boli cardiovasculare**.
- Studiul realizat pe **grupul de indivizi afectati** de marea foamete din iarna 1944 a aratat ca **urmasii persoanelor** nascuti in acea perioada si care au avut la randul lor urmasi 20-30 de ani, dupa aceea **au prezentat aceleasi probleme** in ciuda faptului ca au fost conceputi si nascuti intr-o perioada de normalitate.



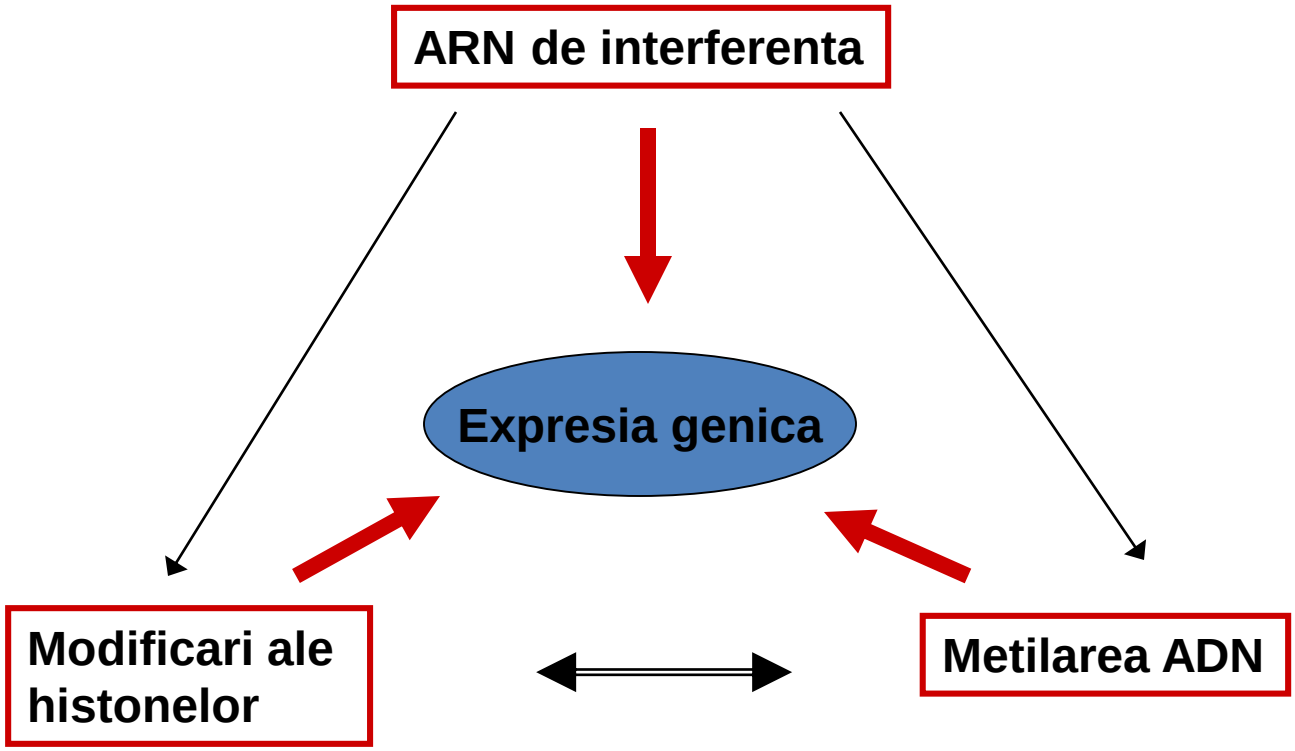
# FOAMETEA DIN IARNA 1944

**Analizele epigenetice efectuate pe indivizi la aproape 60 de ani de la acel incident au aratat diferente privind profilul de metilare la nivelul catorva gene implicate in crestere si control metabolic.**

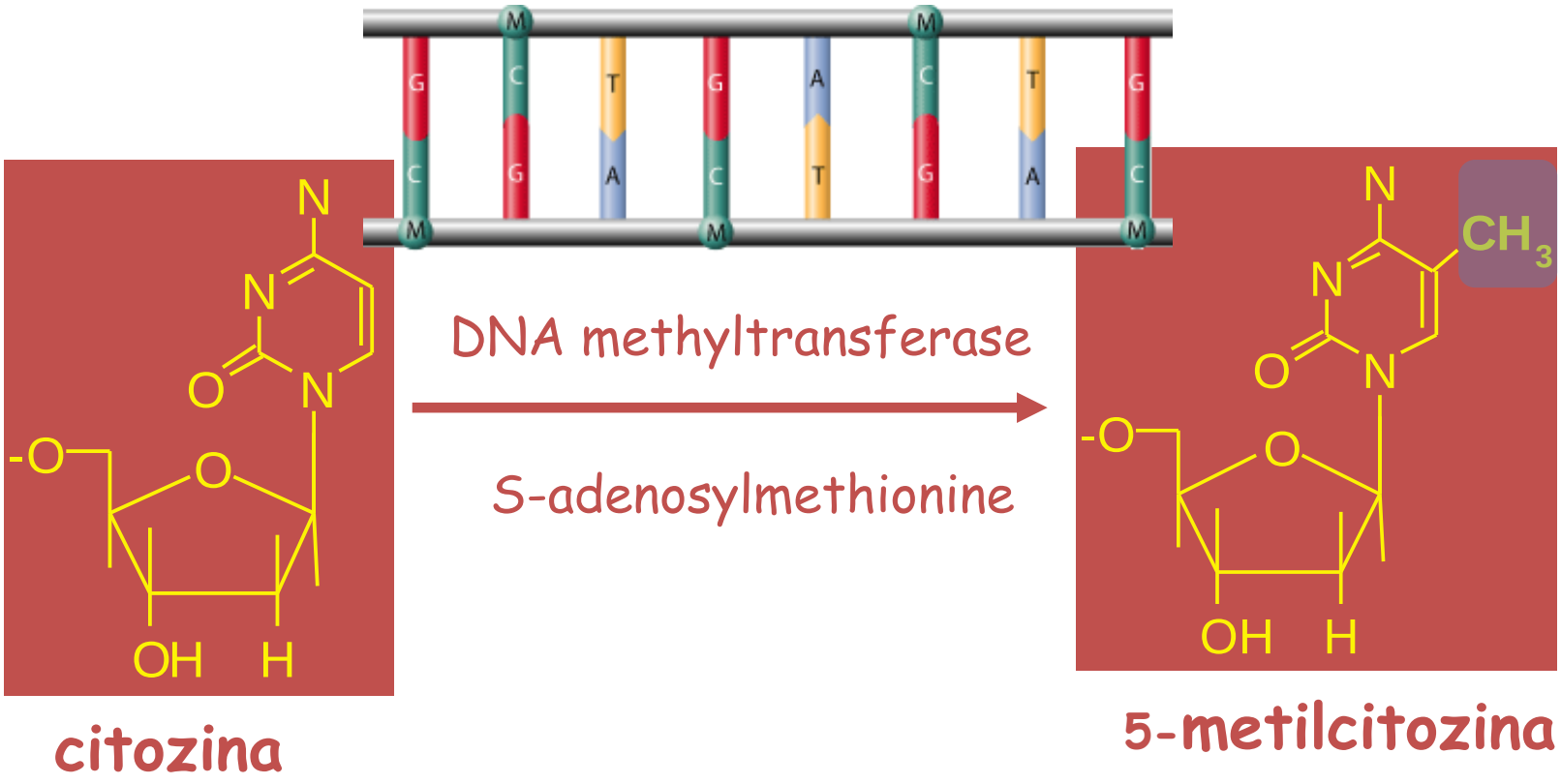
**Hipometilarea diferentiata la nivelul promotorului IGF2 o gene imprintata pe cale materna implicata in controlul cresterii si al dezvoltarii, a fost observata intre urmasii expusi la acest fenomen si cei neexpusi.**



# MECANISME EPIGENETICE

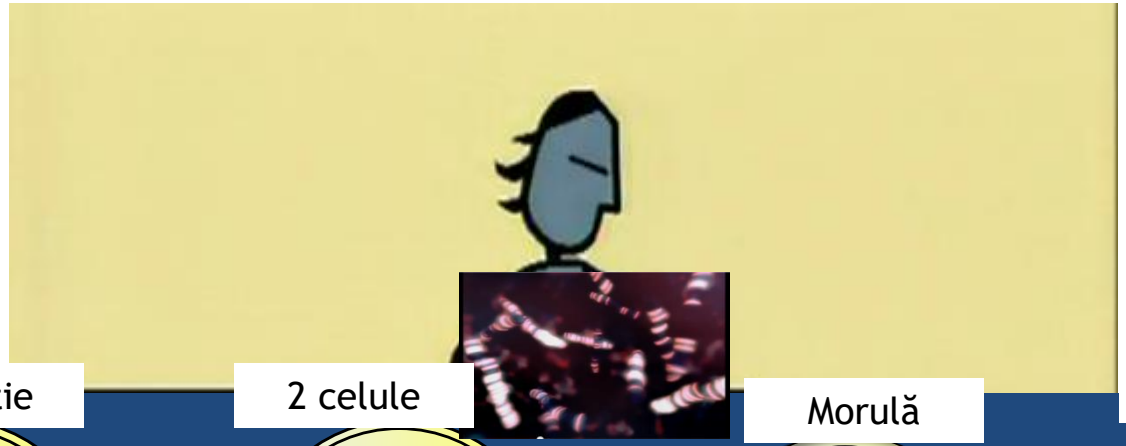


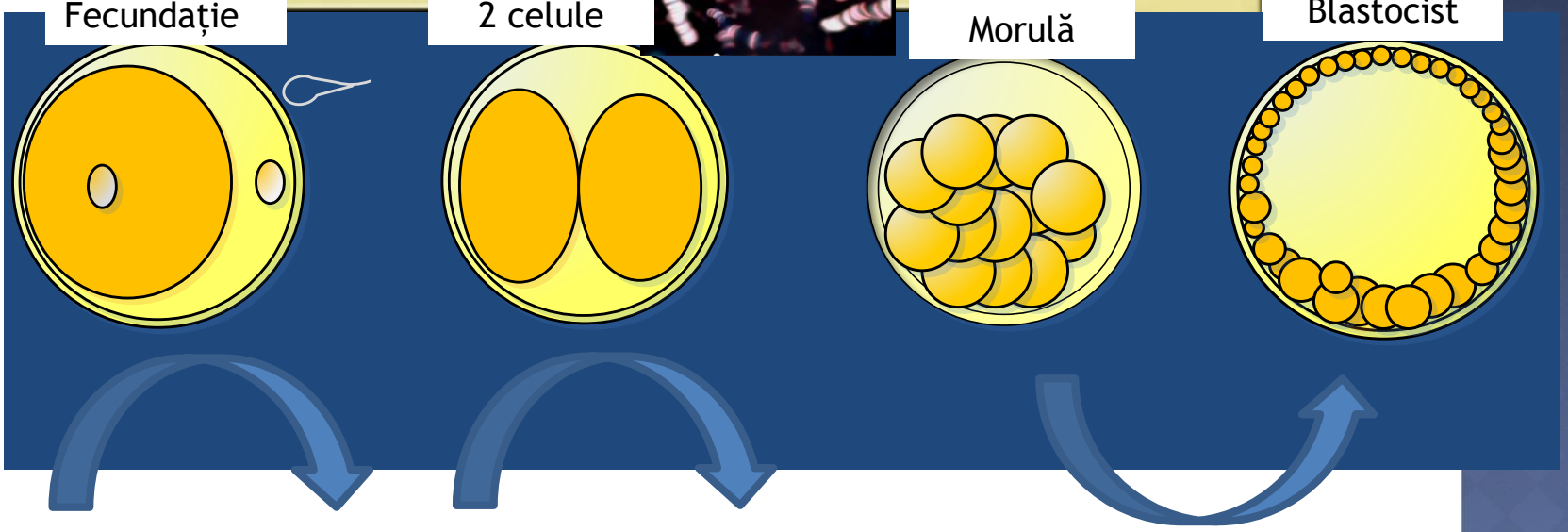
# METILAREA AND-LUI

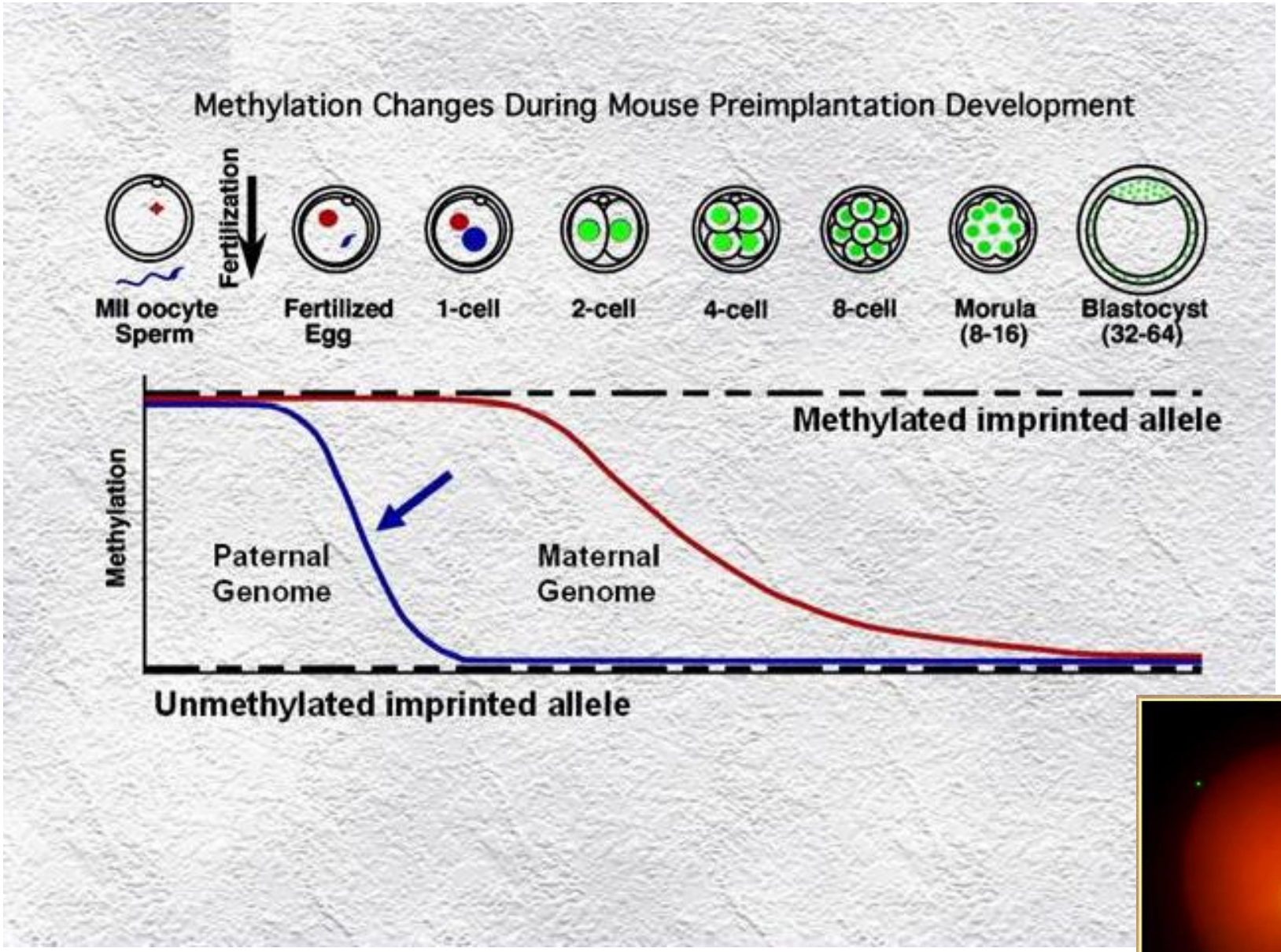


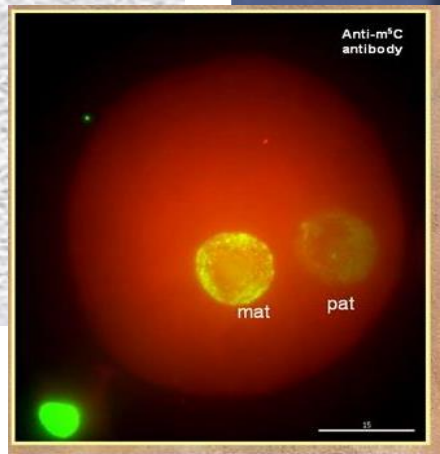

Unul dintre mecanismele epigenetice cel mai bine inteles, metilarea citozinei in pozitia C-5, are loc apropape exclusiv, la nivelul insulelor CpG

# Mecanisme epigenetice si Filtrarea infromatie genetice

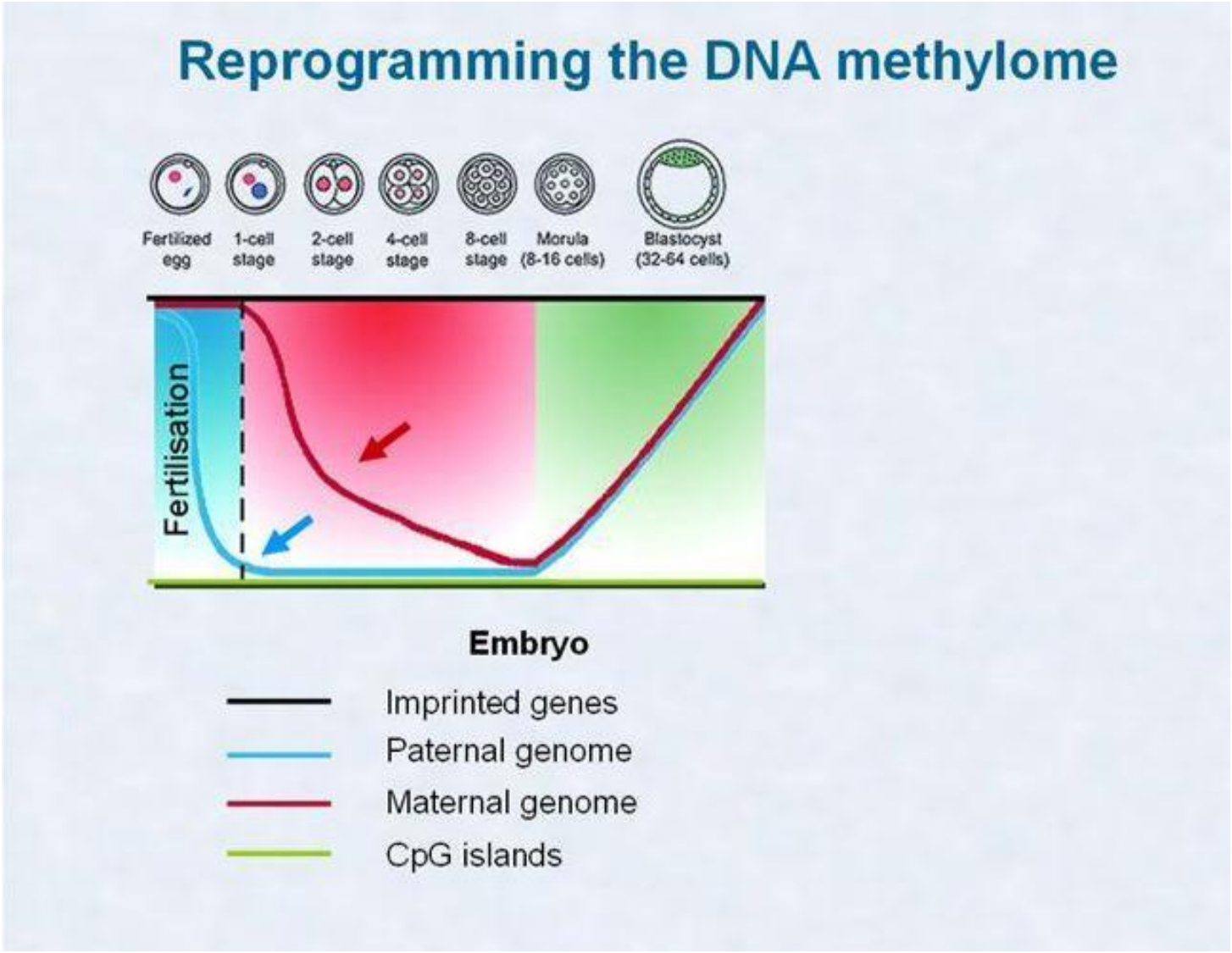





Methylation Changes During Mouse Preimplantation Development
Fertilization
MII oocyte
Sperm
Fertilized
Egg
1-cell
2-cell
4-cell
8-cell
Morula
(8-16)
Blastocyst
(32-64)
Methylated imprinted allele
Methylation
Paternal
Genome
Maternal
Genome
Unmethylated imprinted allele

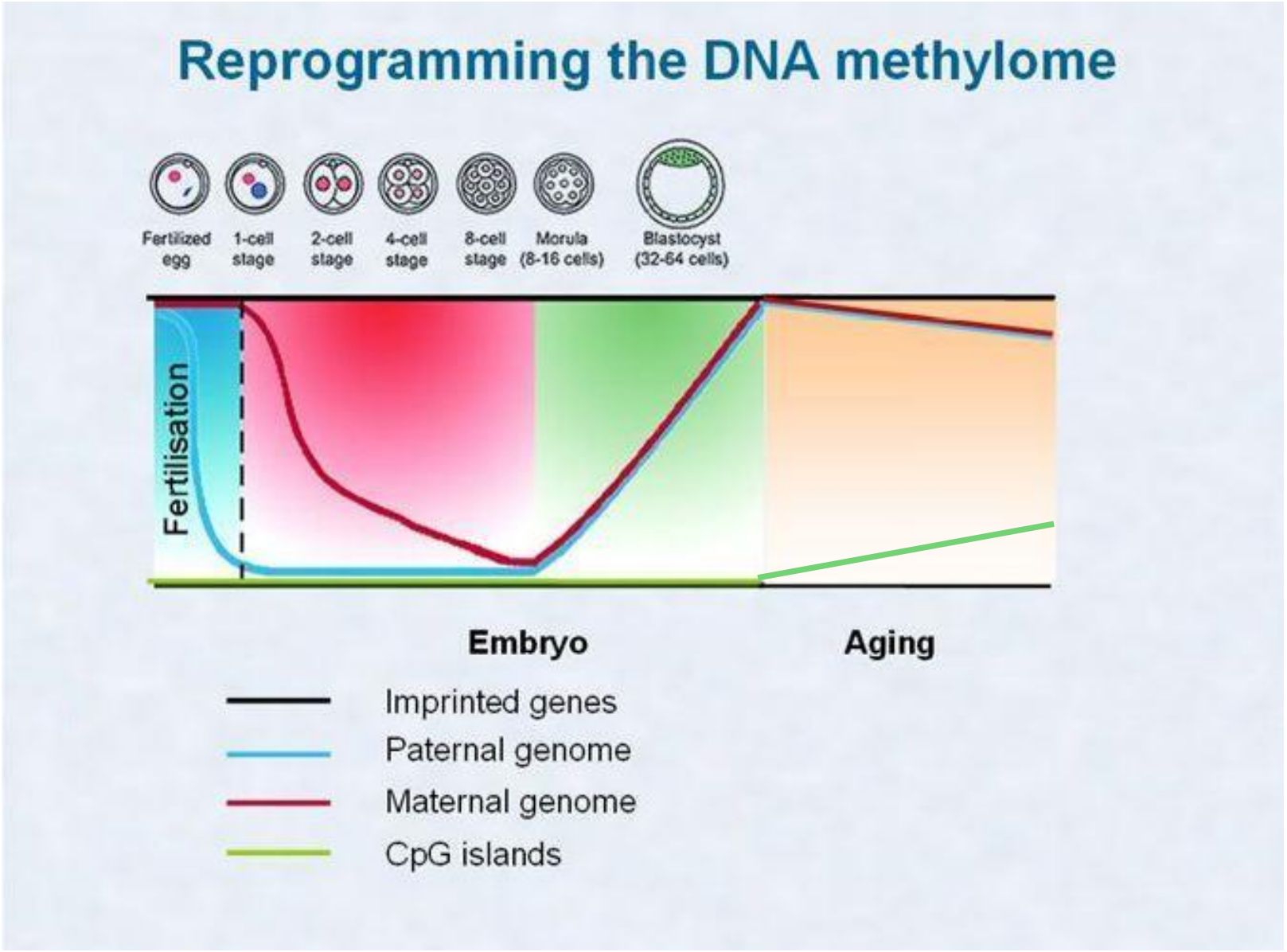

Anti-m5C
antibody
mat
pat

# MODIFICARI DE METILARE AND PE PARCURSUL DEZVOLTARII




Paula Vertino, Henry Stewart Talks

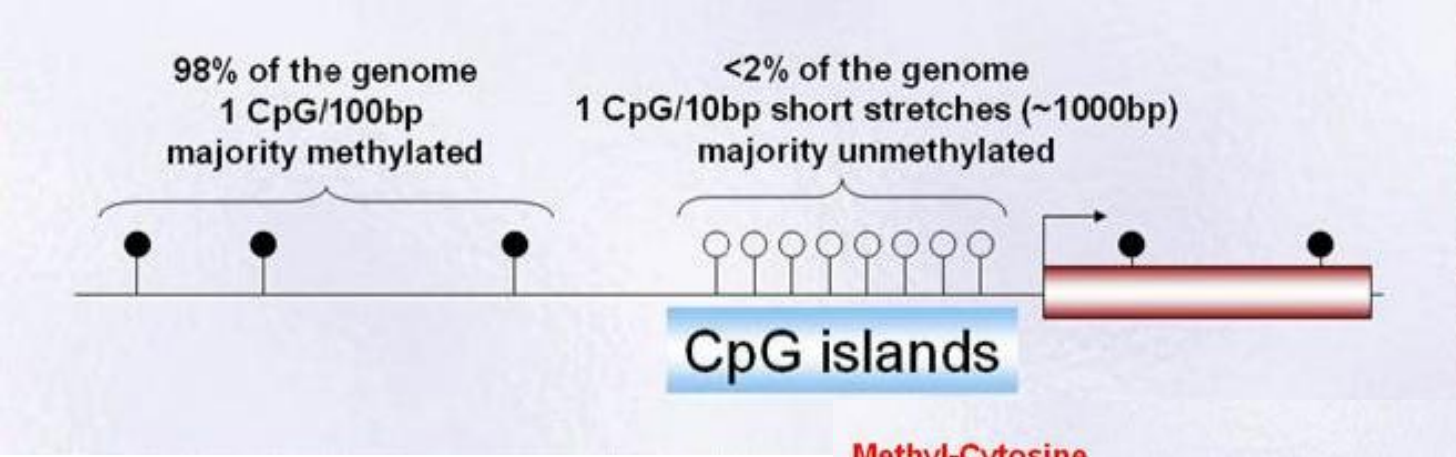
# MODIFICARI DE METILARE AND PE PARCURSUL DEZVOLTARII

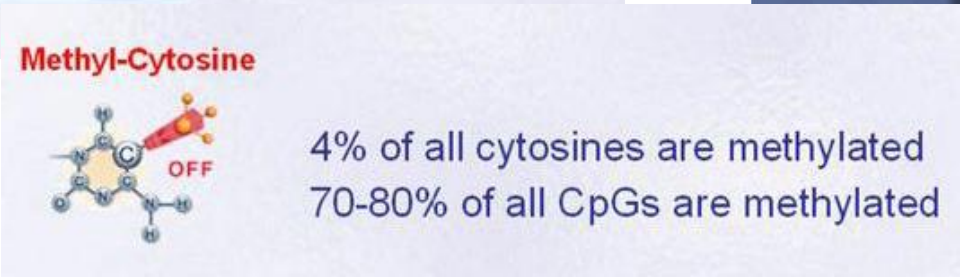


# INSULELE CG

- **Insulele CG (CpG): reprezinta un cluster de C si G adesea observate in jururl promotorului si cu un procent de GC mai mare de 50%).**

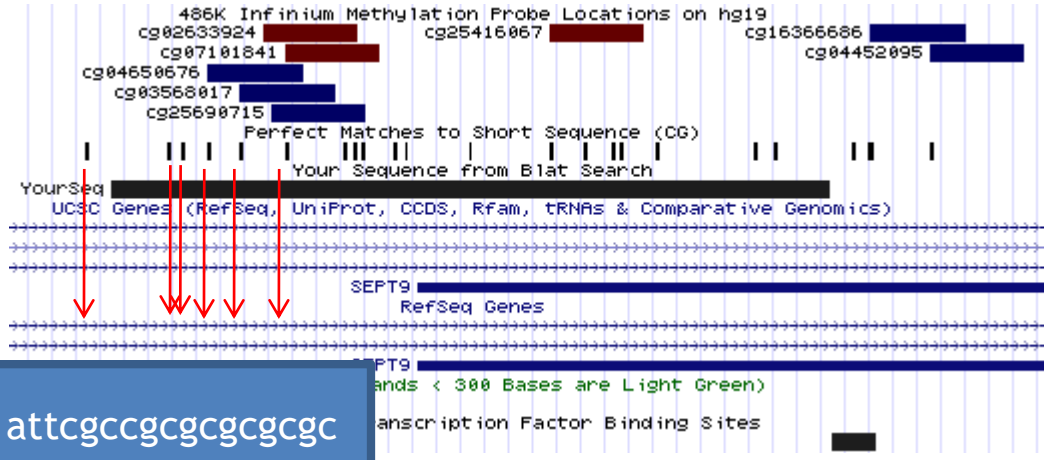
- **~29,000 CpG islands in human genome (~60% dintre toate genele sunt asociate cu insule CpG, dar in celulele normale majoritatea sunt nemetilate)**



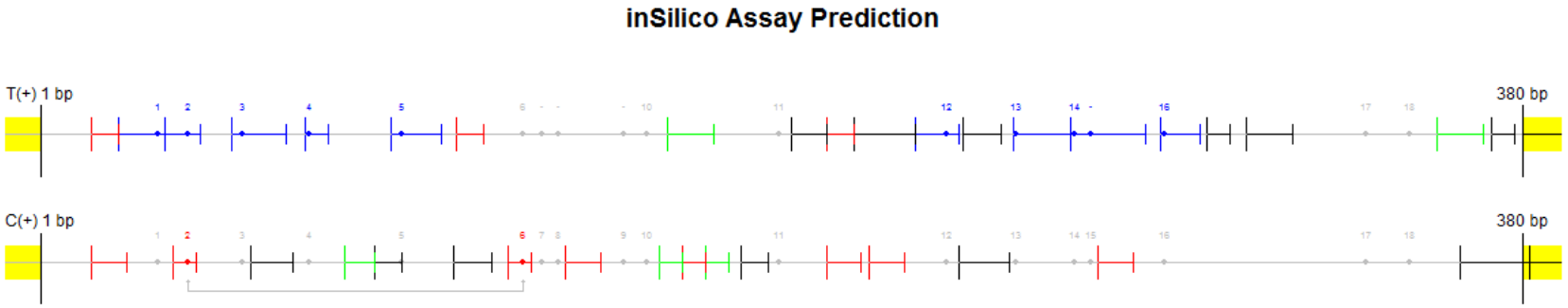
# INSULELE CPG

Insule CpG




Insule CpG

attcgccgcgcgcgcgc

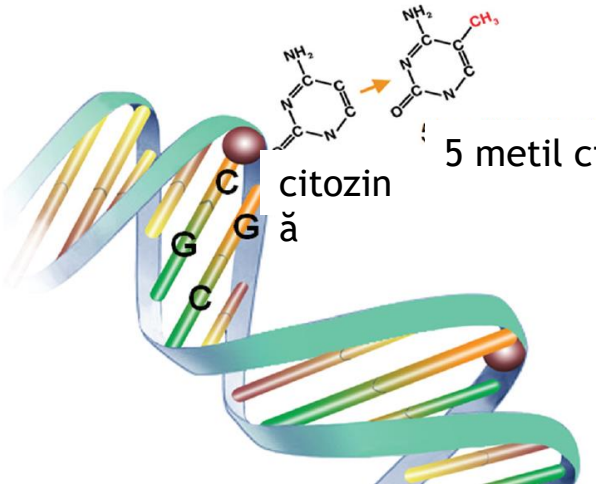


# METILAREA ADN

Metilarea ADN

DNMT1

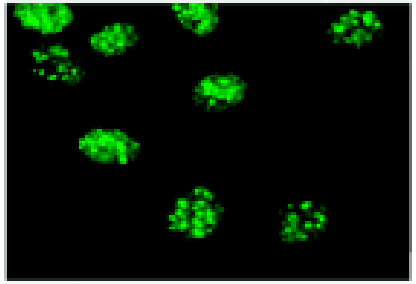
DNMT3a
DNMT3b
(de novo methylation of CpG)

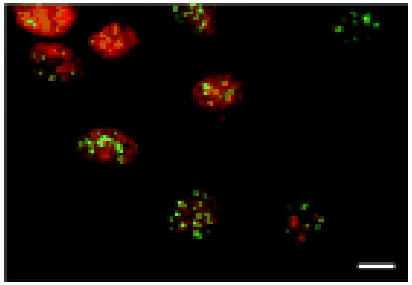



citozină

5 metil citozină

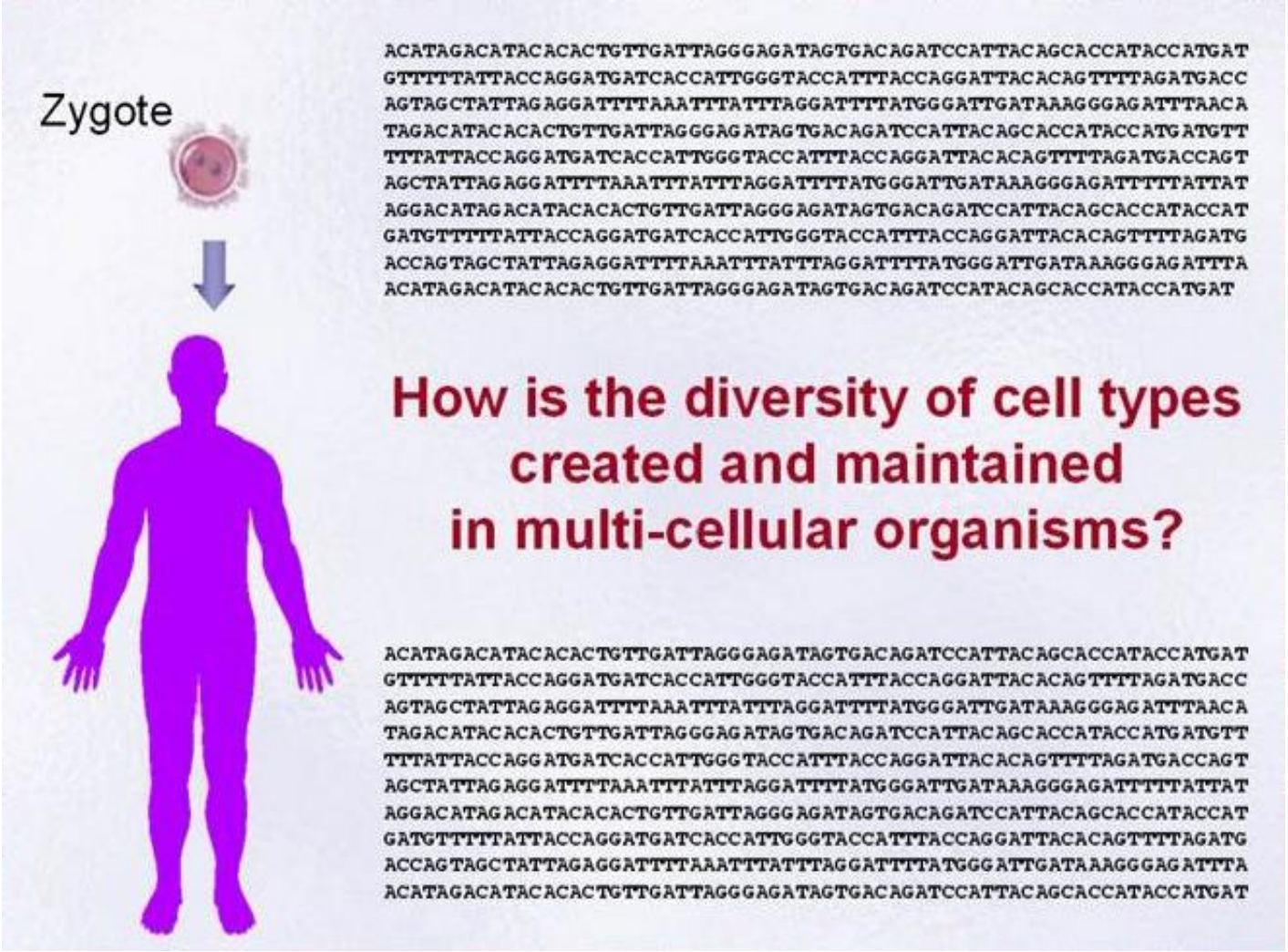
Aditia unei grupari CH3 la C5 a unei citozine din cadrul asa numitelor insule CpG





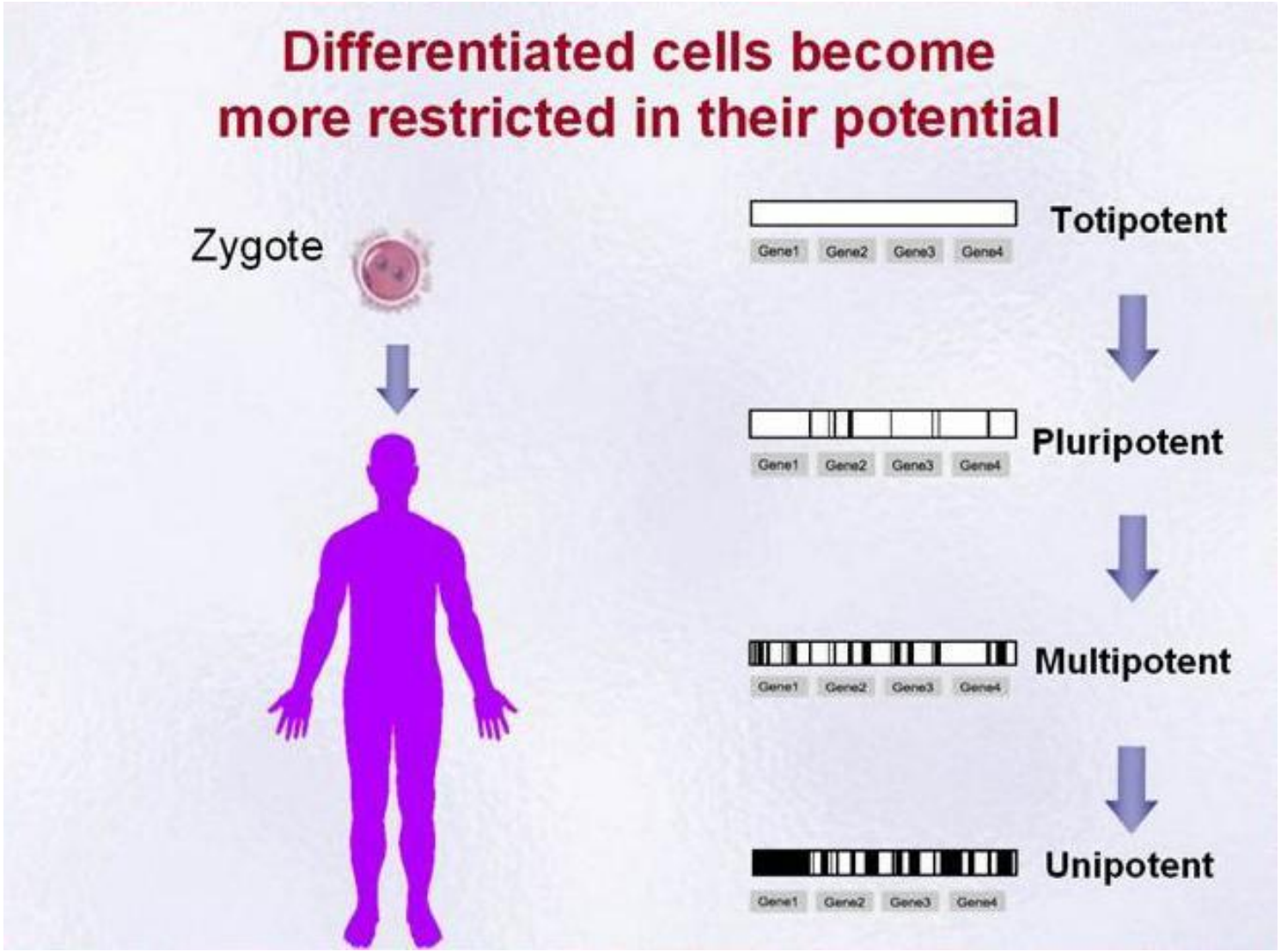
Metilarea ADN → De-acetilarea histonelor → Condensarea cromatinei

# METILAREA AND DE LA STADIUL DE ZIGOT LA STADIU DE ADULT



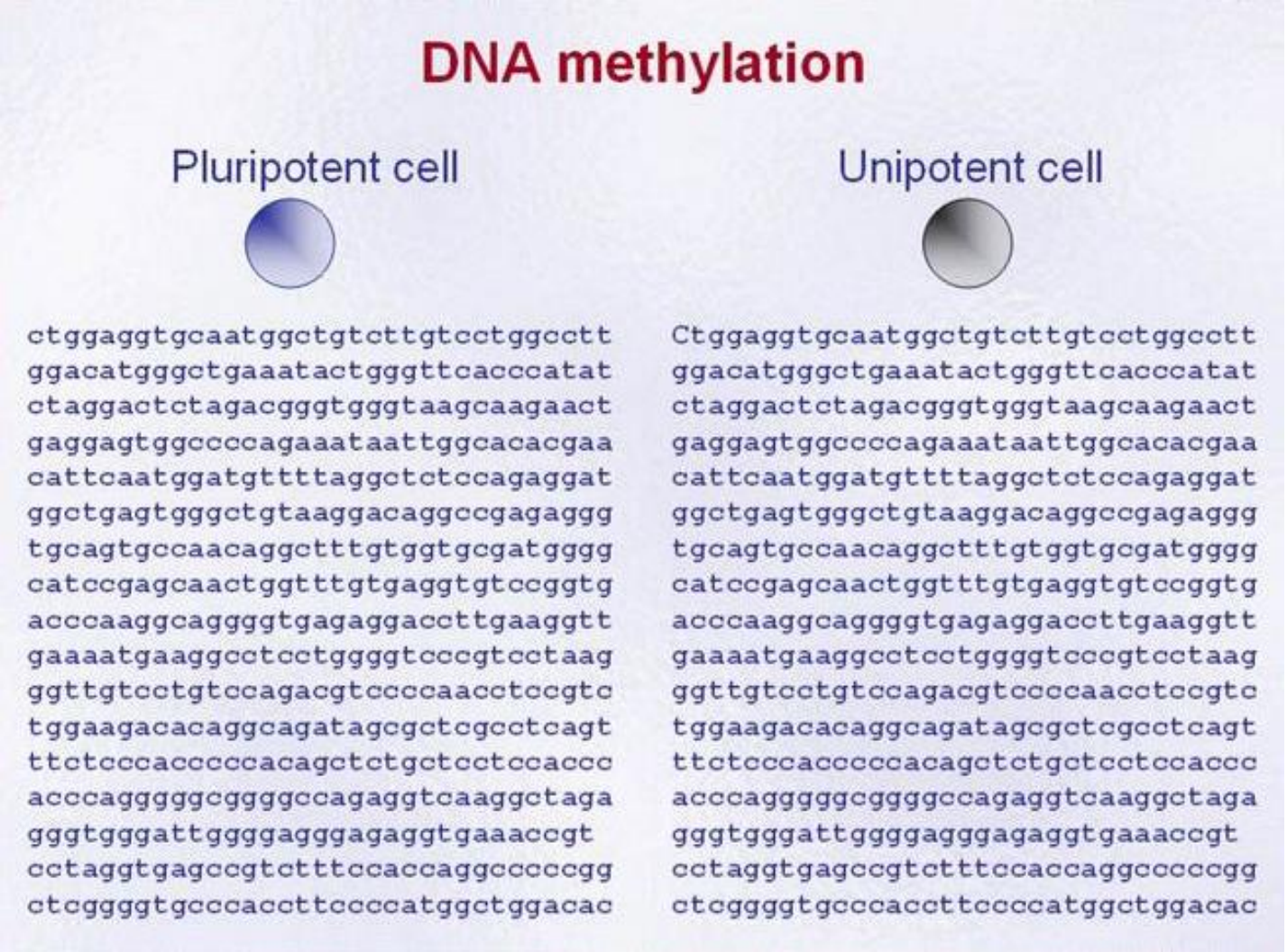

Alex Meissner, Henry Stewart Talks

# METILAREA AND DE LA STADIUL DE ZIGOT LA STADIU DE ADULT




Alex Meissner, Henry Stewart Talks

# METILAREA DIFERENTIALA A ADN LA CELULELE STEM TOTIPOTENTE FATA DE CELULELE STEM UNIPOTENTE

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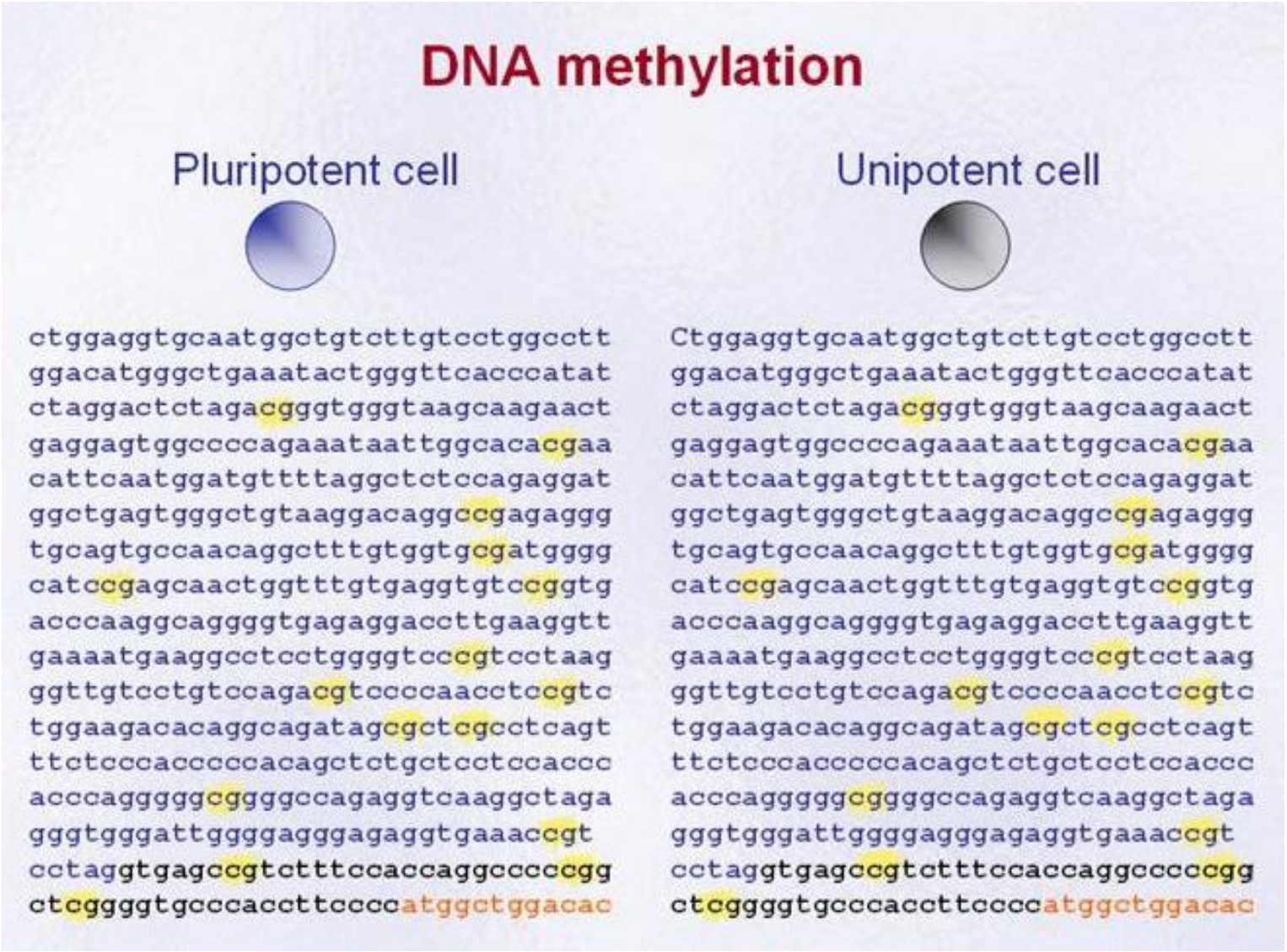


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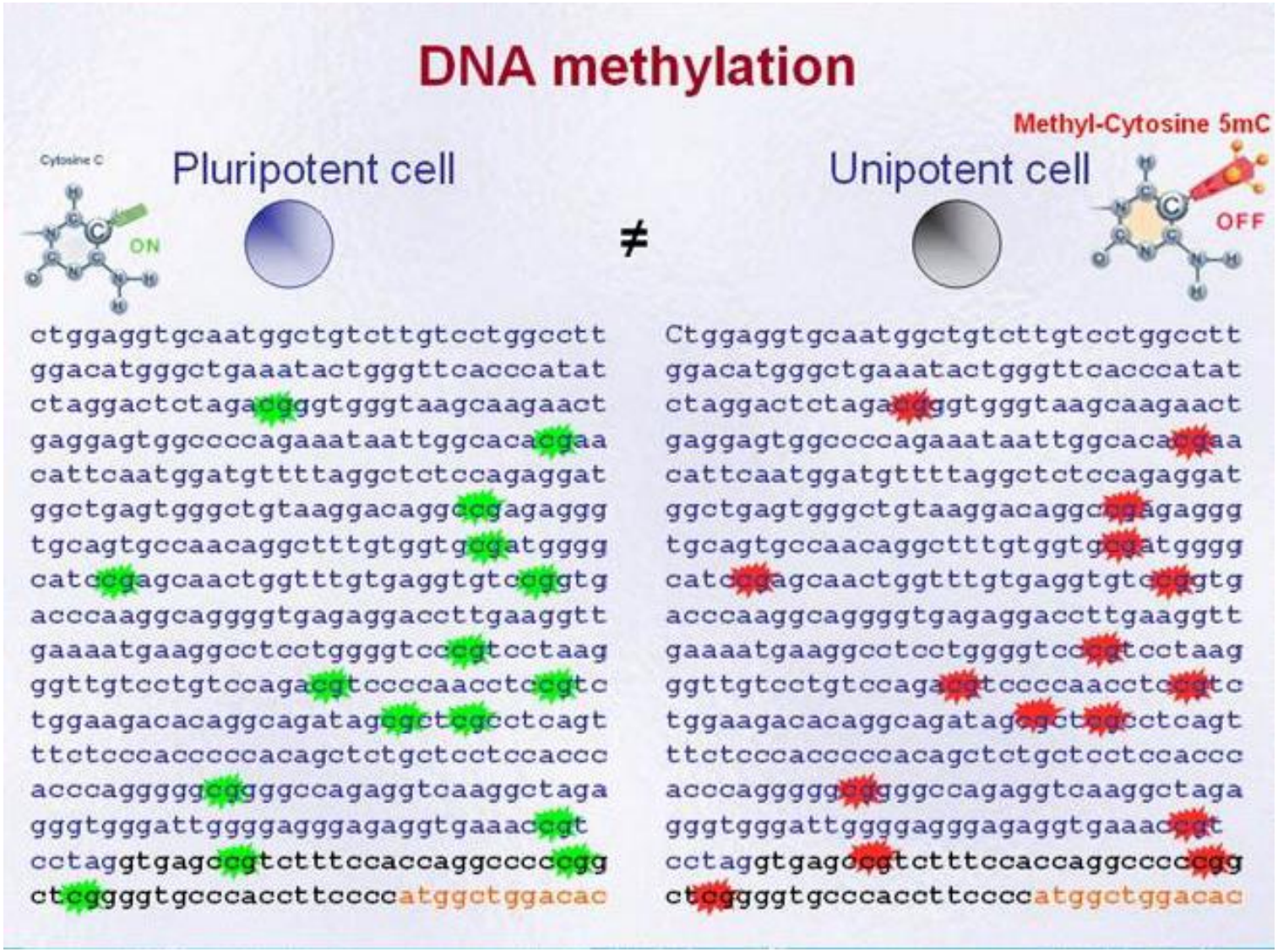
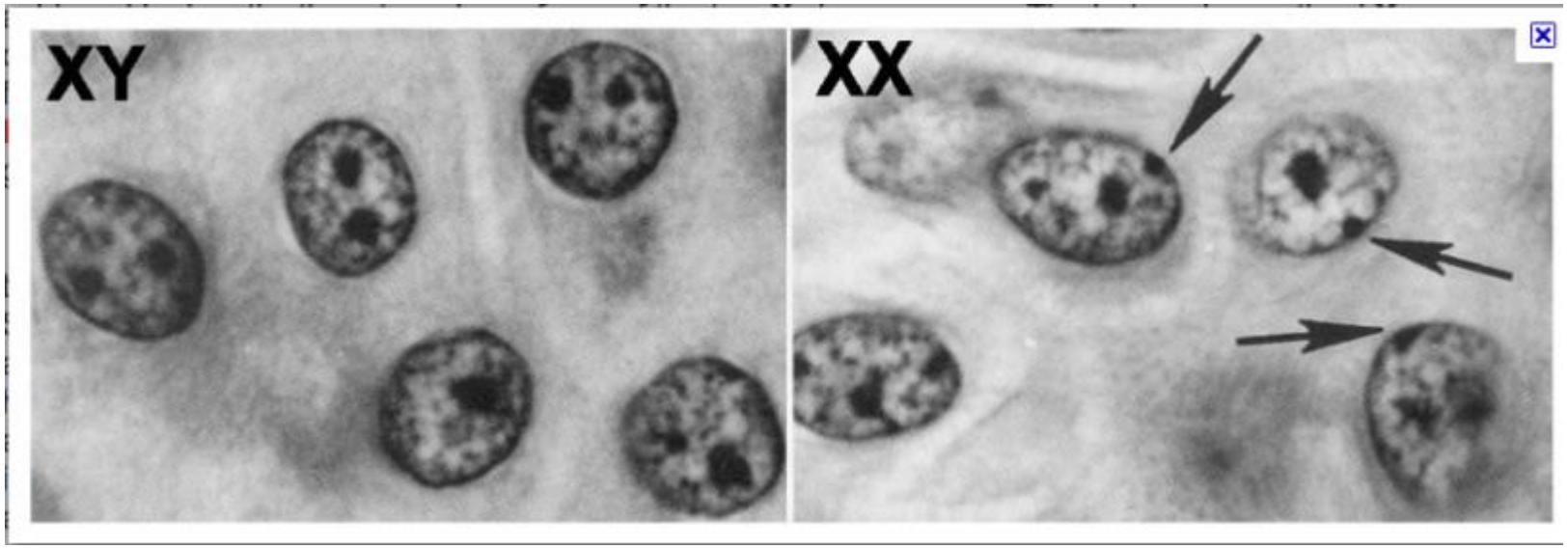



Alex Meissner, Henry Stewart Talks

# METILAREA AND INTERVINE IN INACTIVAREA CROMOZOMULUI X: CORPUSCULUL BAR

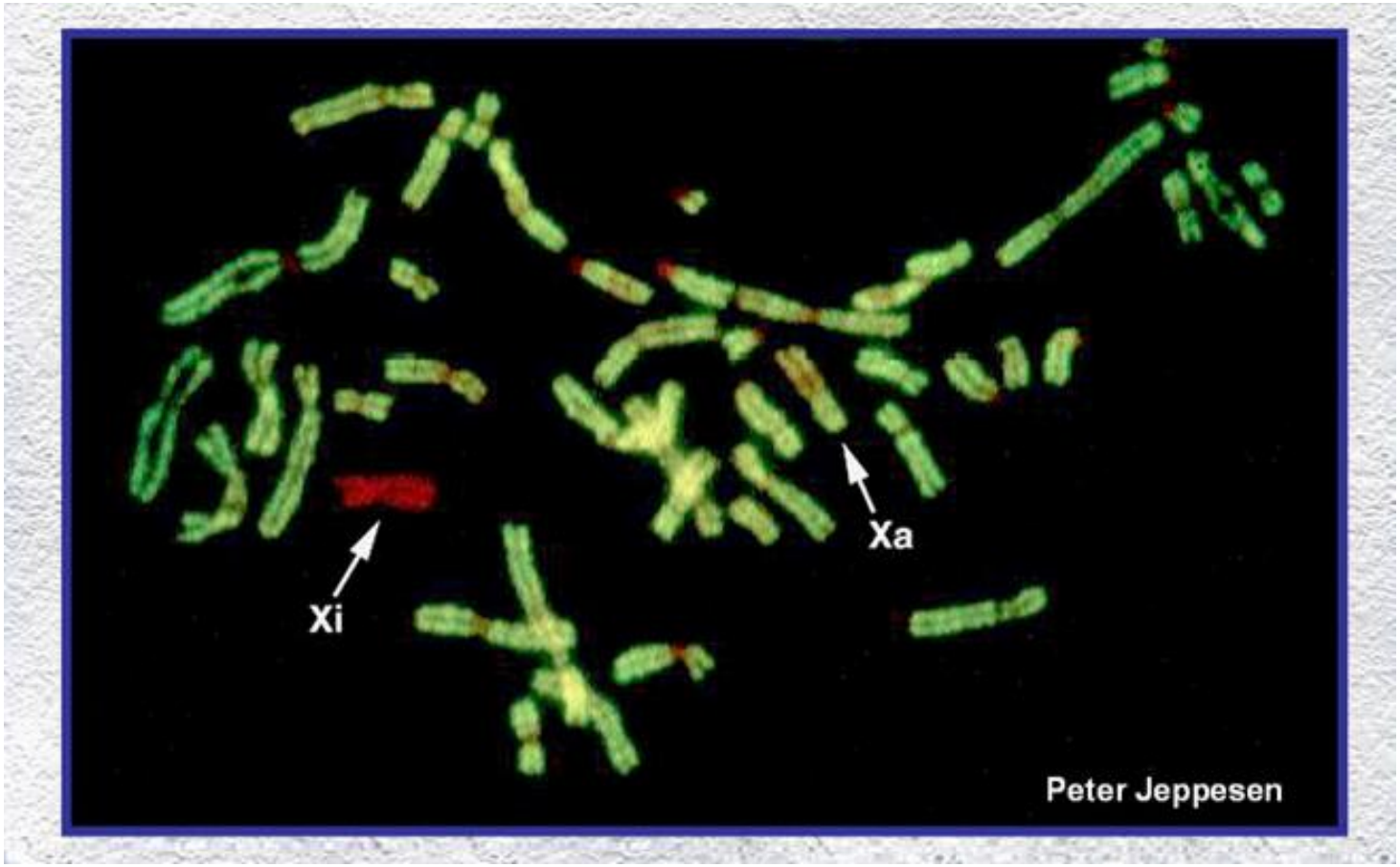



Barr, M. L., Bertram, E. G., (1949), A Morphological Distinction between Neurones of the Male and Female, and the Behaviour of the Nucleolar Satellite. *Nature.* ***163*** *(4148): 676-7.*

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

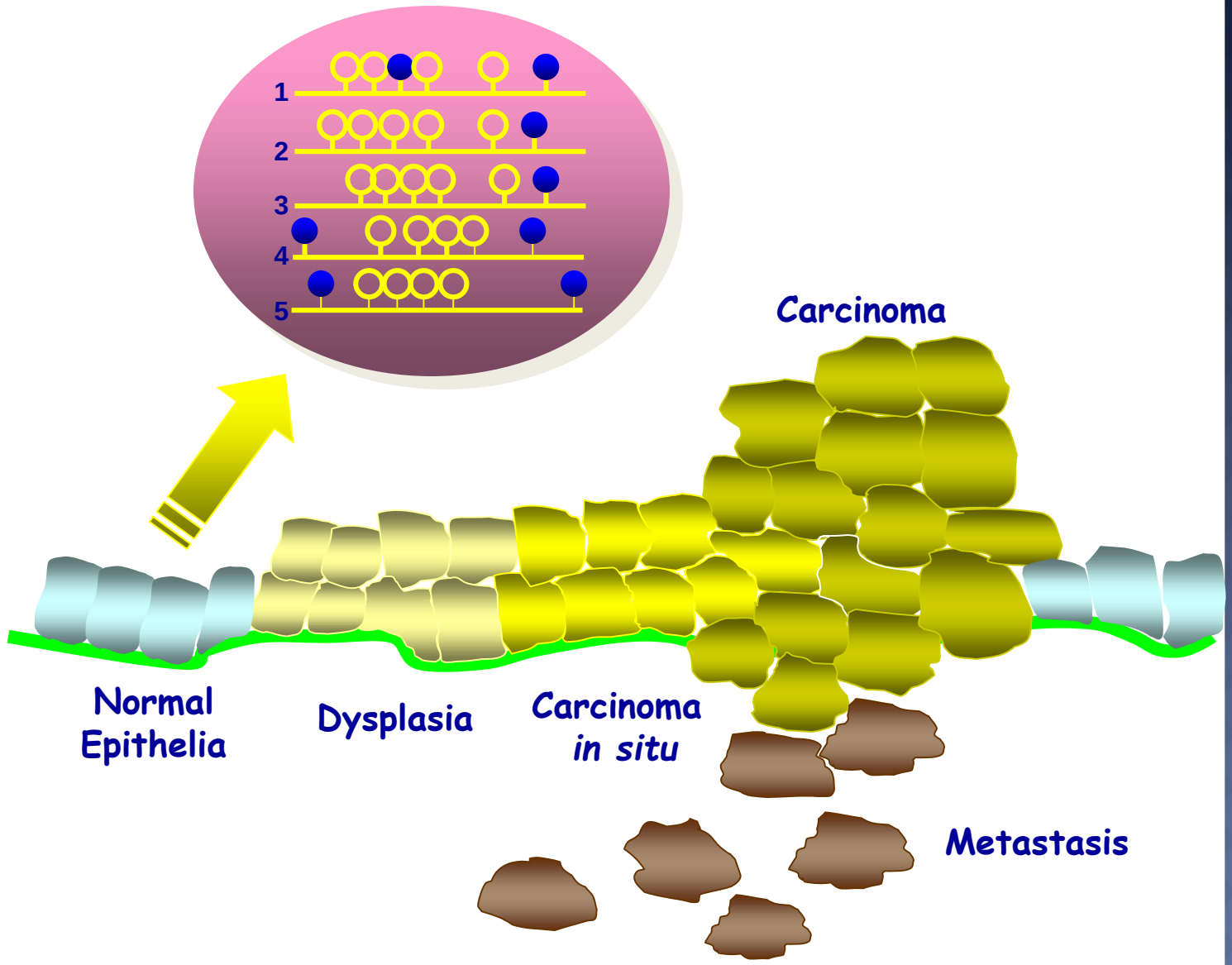
La mamifere mecanismul de compensare a dozei pentru genele situate pe cromozomul X, la sexul feminin, se realizează prin mecanismul epigenetic de inactivarea a unuia din cromozomii X sau heterocromatinizare. Acest mecanism a fost propus de Mary Lyon în 1961.

# CROMOZOMUL X INACTIVAT PREZINTA HISTONA H4 NEACTILATA




Barbara Migeon, Henry Stewart Talks

# Metilarea insulelor CpG : un semnal stabil, transmisibil si detectabil



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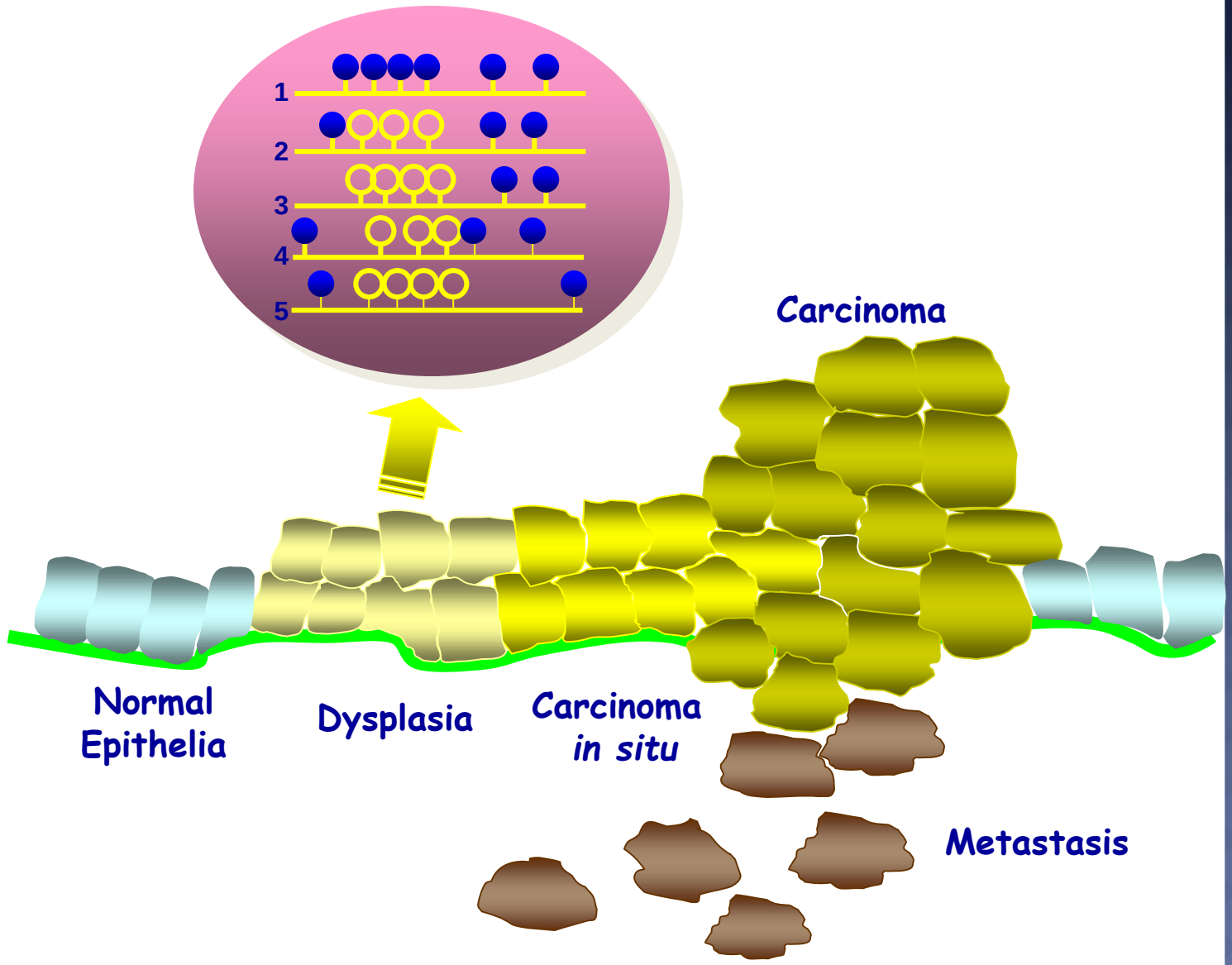

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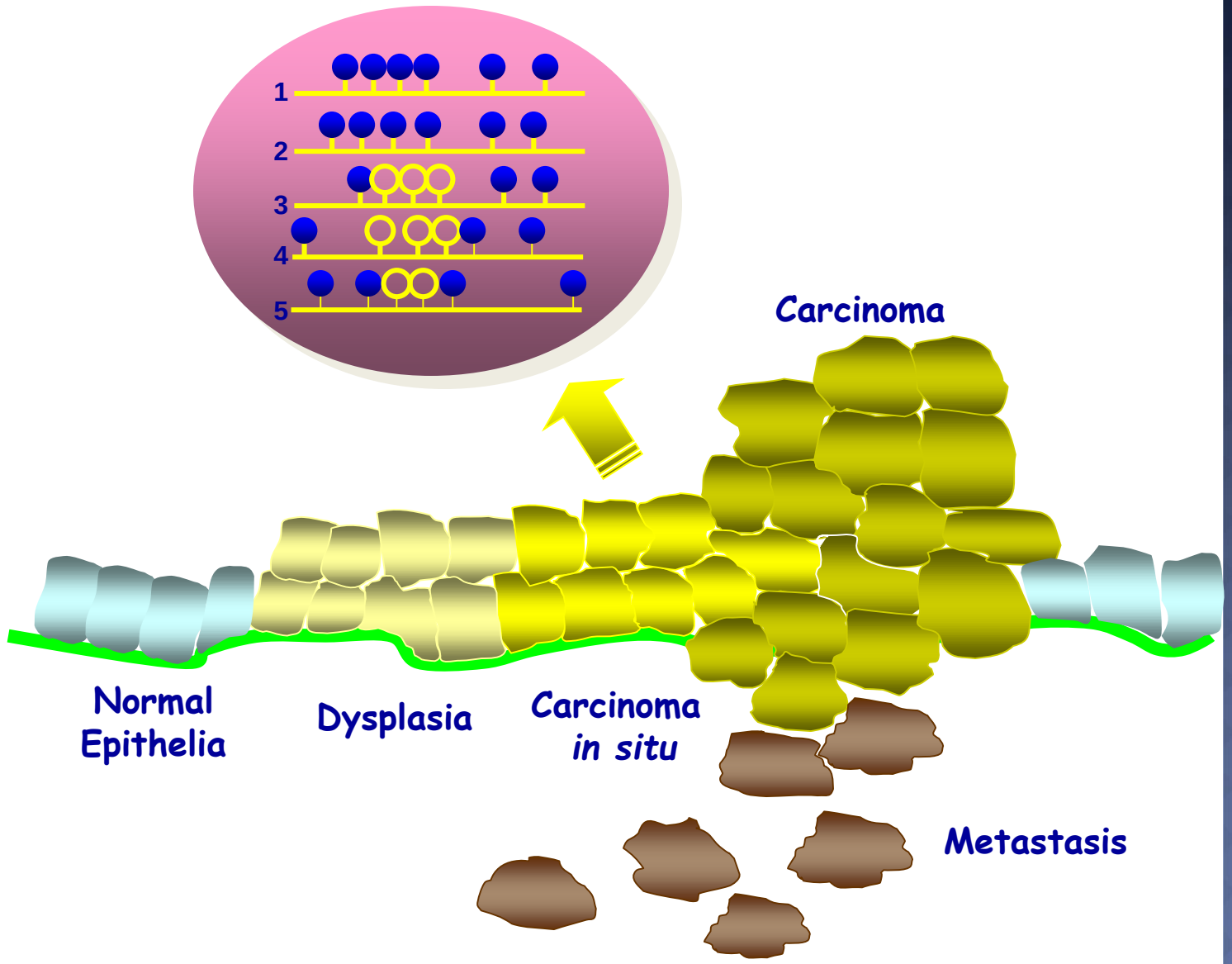

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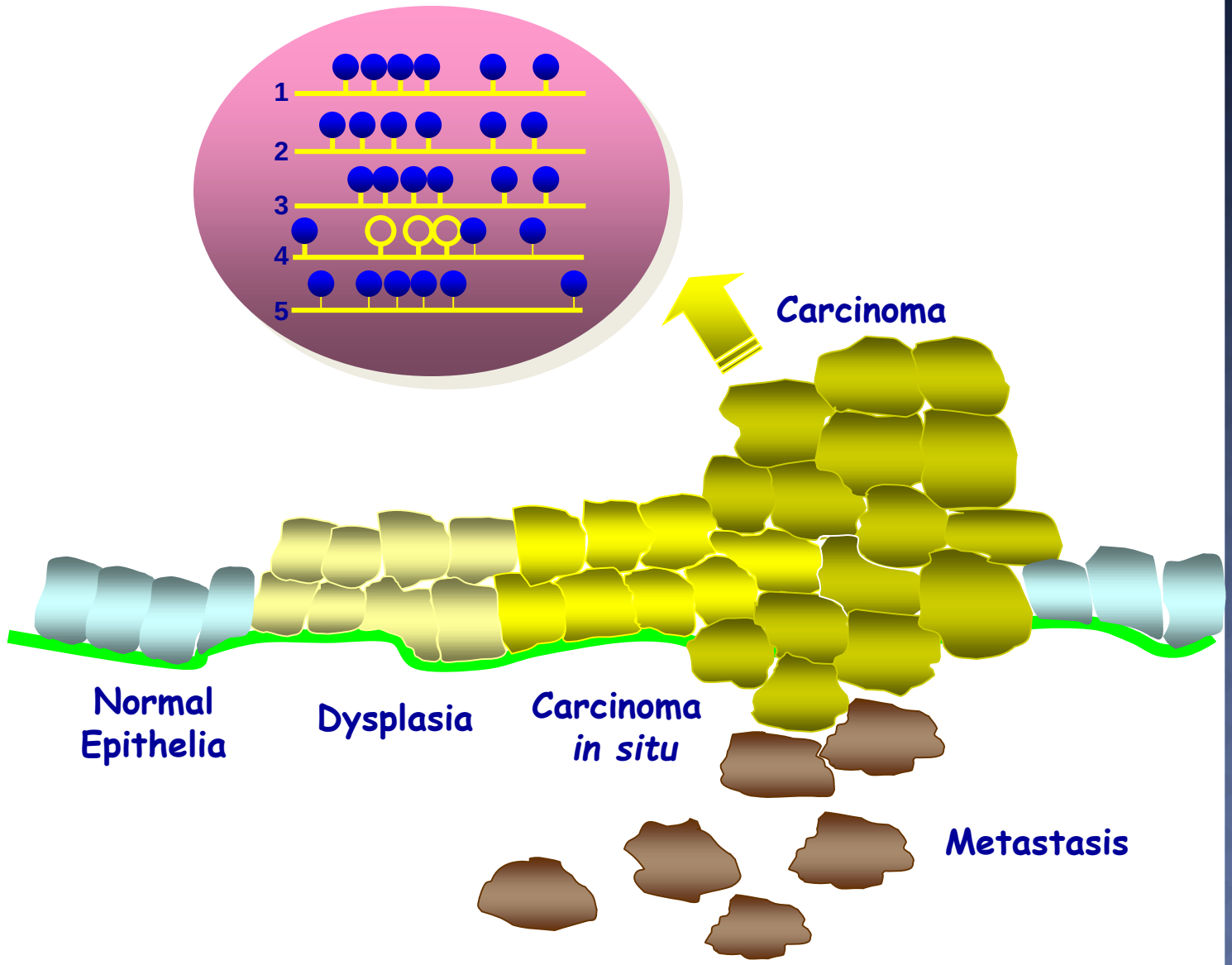


PNAS

2007

# Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development

Dana C. Dolinoy*†‡, Dale Huang*, and Randy L. Jirtle

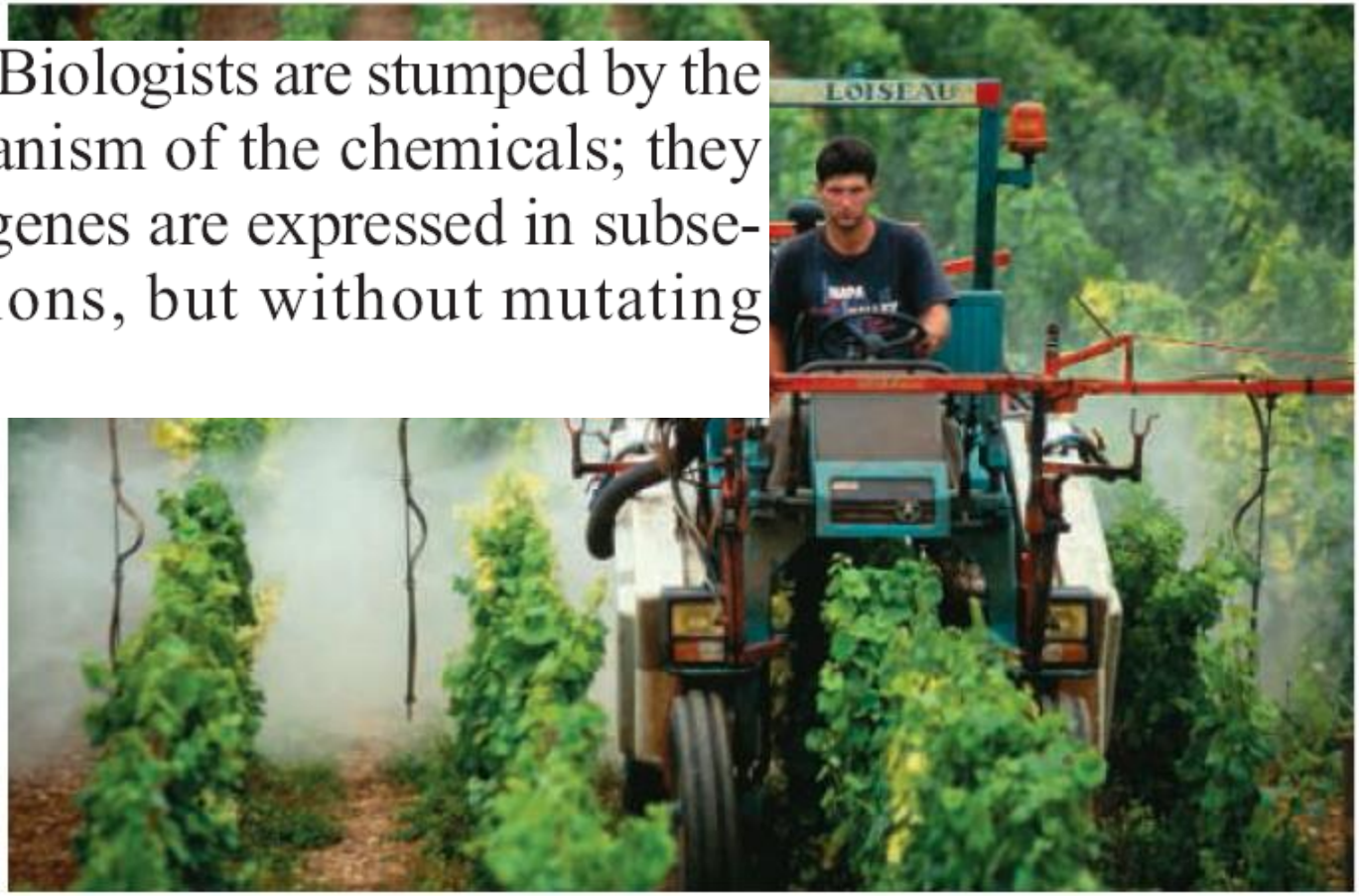
The hypothesis of fetal origins of adult disease posits that early developmental exposures involve epigenetic modifications, such as DNA methylation, that influence adult disease susceptibility. *In utero* or neonatal exposure to bisphenol A (BPA), a high-production-volume chemical used in the manufacture of polycarbonate plastic, is associated with higher body weight, increased breast and prostate cancer, and altered reproductive function.

evidence that epigenetic patterning during early stem cell development is sensitive to BPA exposure. Moreover, maternal dietary supplementation, with either methyl donors like folic acid or the phytoestrogen genistein, negated the DNA hypomethylating effect of BPA. Thus, we present compelling evidence that early developmental exposure to BPA can change offspring phenotype by stably altering the epigenome, an effect that can be counteracted by maternal dietary supplements.

DEVELOPMENTAL BIOLOGY

# Endocrine Disrupters Trigger Fertility Problems in Multiple Generations

Biologists are stumped by the apparent mechanism of the chemicals; they may alter how genes are expressed in subsequent generations, but without mutating DNA.




**Unfertile ground.** The fungicide vinclozolin, which is sprayed on vineyards like these, can cause fertility problems in male offspring of exposed rats.

# SUMMARY OF EPIGENETIC GENE REGULATION

- Metilarea AND in celulele adulte modifica structura cromatinei si controleaza expresia genica.
- Metilarea AND este indepartata la fertilizare si restabilita pe parcursul embriogenezei.
- Genele imprintate mentin expresia materna si paterna a informatiei genetice.
- Modificarile histonelor se realizeaza in paralel cu profilul de metilare al AND.
- Regiunile metilate sunt regiuni inactive, puternic condensate si cu modificari specifice ale histonelor.
- Regiunile active sunt putin metilate si prezinta modificari distincte ale histonelor.
- Inactivarea cromozomului X la femela este corelata cu zone extinse de insule CpG, metilate.
- Modificari ale profilului de metilare sunt observate o data cu imbatranirea organismului sau in cazul unor afectiuni cum ar fi cancerul.