EPIGENETICS

Mechanisms for nutrition determinants of later health outcomes

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- We inherit genes from both Mom & Dad, but yet for some of these genes we express only the gene from one parent
- *Epigenetics*: study of heritable changes in gene expression that occur without a change in DNA sequence

EPIGENETICS: WHO CARES?

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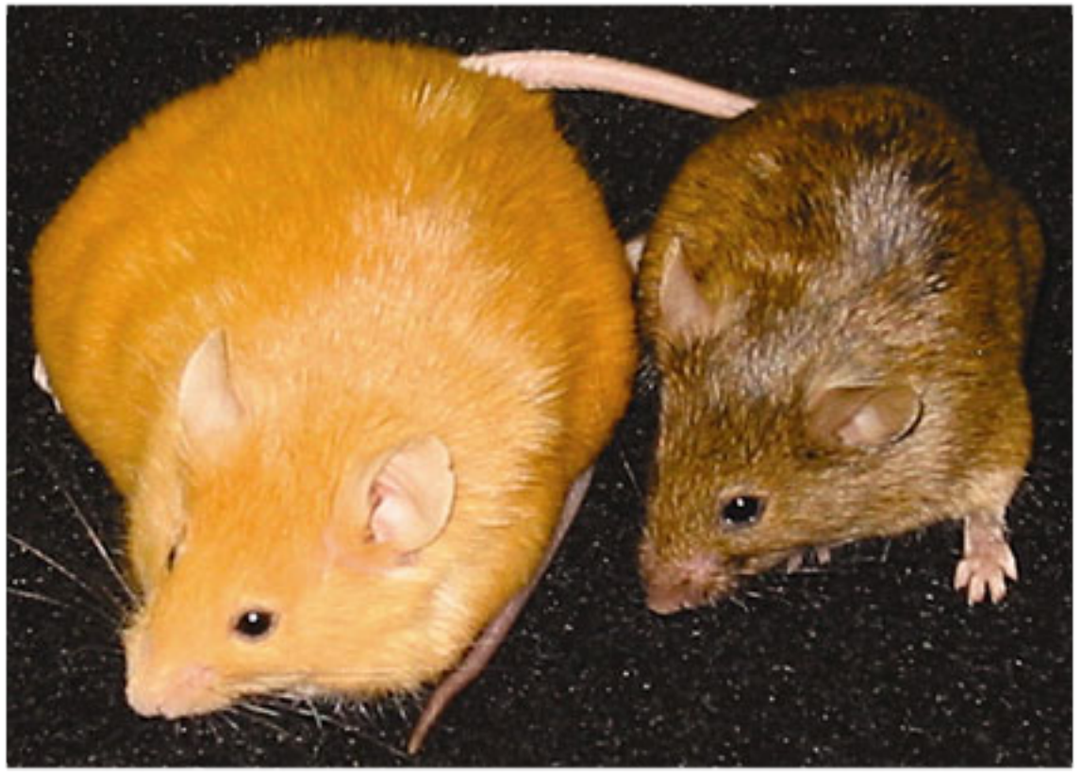
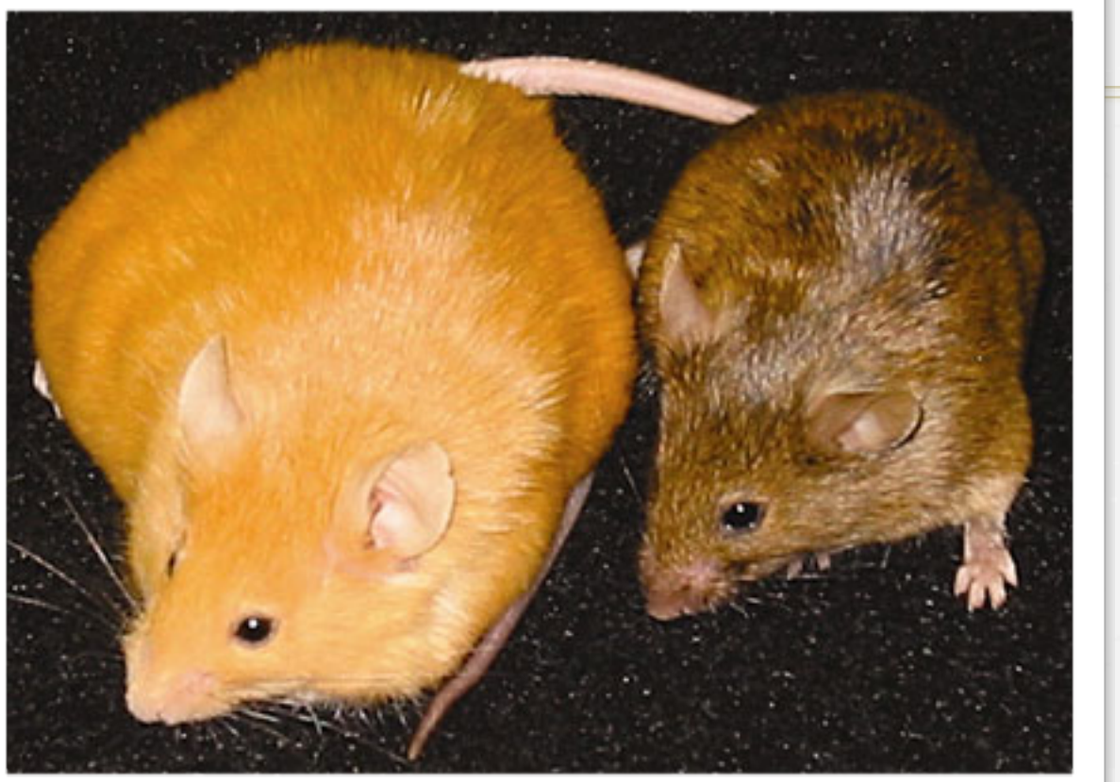
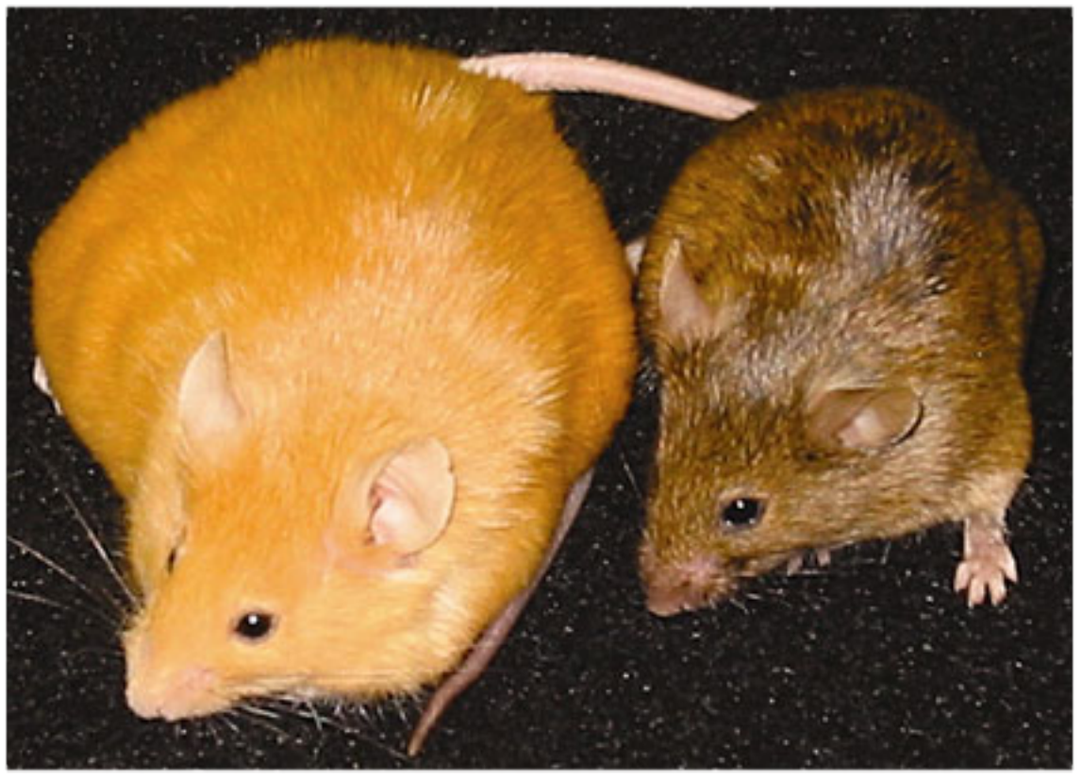


EPIGENETICS: WHO CARES?



- These mice are genetically identical (they're twins) and the same age

EPIGENETICS: WHO CARES?



- These mice are genetically identical (they're twins) and the same age
- How can they be so different?

WHO CARES?

Journal ADA – August 2006

Research and Professional Briefs

Continuing Education Needs of Registered Dietitians Regarding Nutrigenomics

RENEE ROSEN; CARRIE EARTHMAN, PhD, RD; LEN MARQUART, PhD, RD; MARLA REICKS, PhD, RD

ABSTRACT

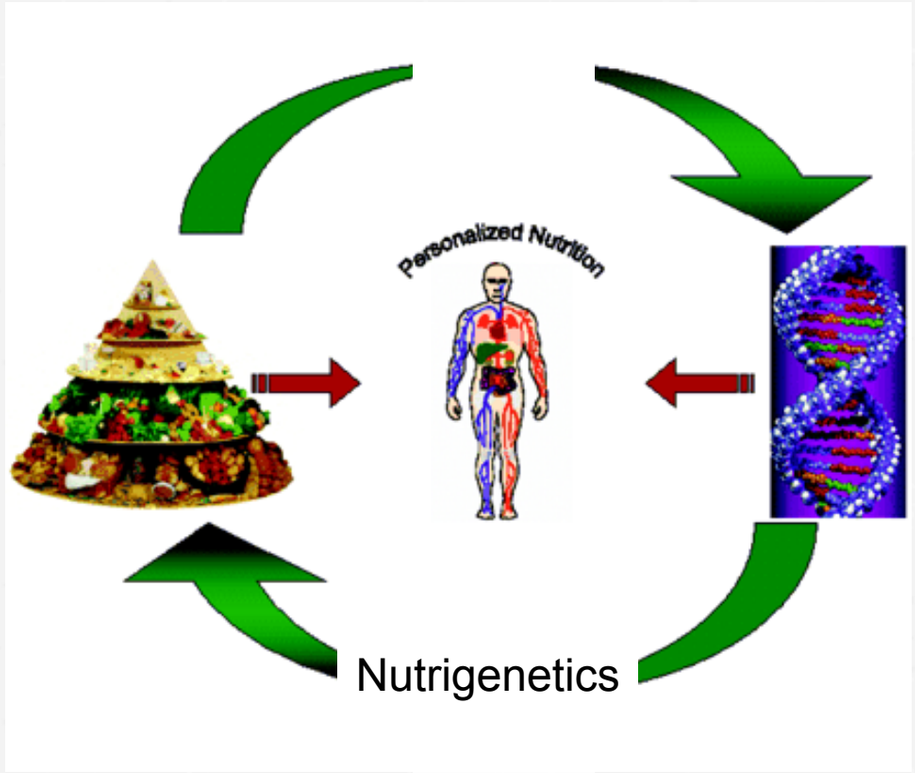
The purpose of this study was to assess continuing education needs for registered dietitians regarding application of the science of nutritional genomics in clinical settings. A cross-sectional survey was mailed to a random national sample of 2,500 registered dietitians with a 40% response rate (n=995). The survey assessed knowledge; attitudes related to benefits and barriers to application; perceptions of consumer motivators and barriers; attitudes regarding ethical, legal, and social issues; and preferences for continuing education. Differences were determined according to year of registration using non-

products. Consumer attitudes regarding efficacy or acceptance of advances in food technology and nutrition are affected by level of awareness (7,8). In the case of nutritional genomics, registered dietitians (RDs) will be asked to translate scientific knowledge of how diet affects individual humans into practice in both clinical and public health practice settings (9,10).

The most recent Commission on Accreditation for Dietetics Education list of foundation knowledge and skill requirements for didactic programs states that "graduates will have knowledge of genetics" (11). However, recent survey results from directors of Didactic Programs in Dietetics indicated that current curricula provided little

WHO CARES?

Influence of specific nutrients on gene expression

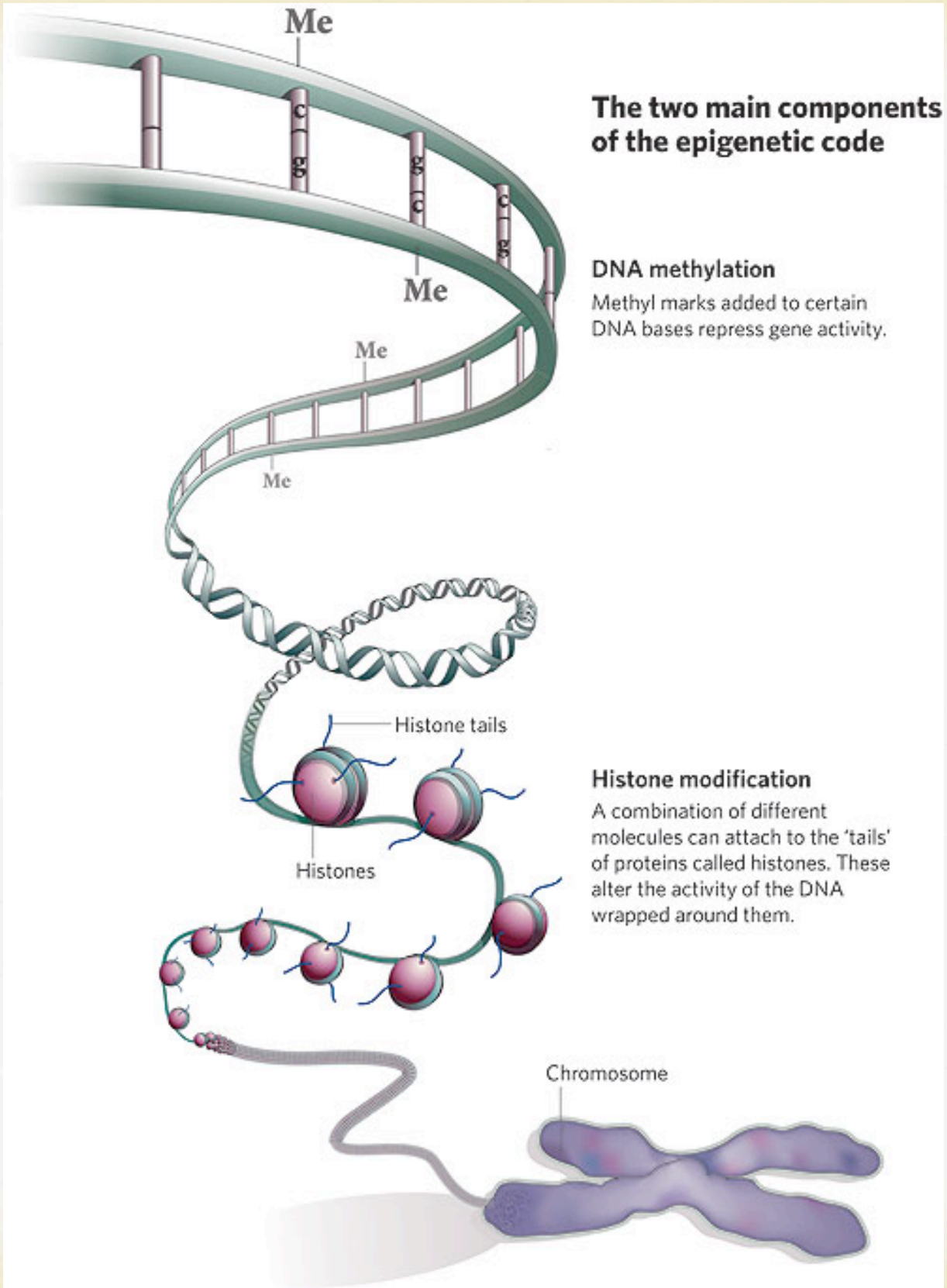


Effects of fixed genetic variation (e.g. SNP's) on responsiveness to diet

WHO CARES?

- Epigenetics:
  - mediate the size of an infant at birth
  - likely mediate how cigarette smoking in a grandmother can increase risk of asthma in her *grandchildren*
  - why malnutrition at the time of puberty in a male is associated with a **4-fold** lower risk in Type 2 Diabetes in his *grandson*

HOW DO WE ALTER THE EPIGENOME?



The two main components of 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.

ALTERING THE EPIGENOME

- DNA Methylation
- Methyl-CpG-binding proteins
- Histone Modifications
- Crosstalk
- Imprinting
- SNPs
- Nutrition & the Epigenome

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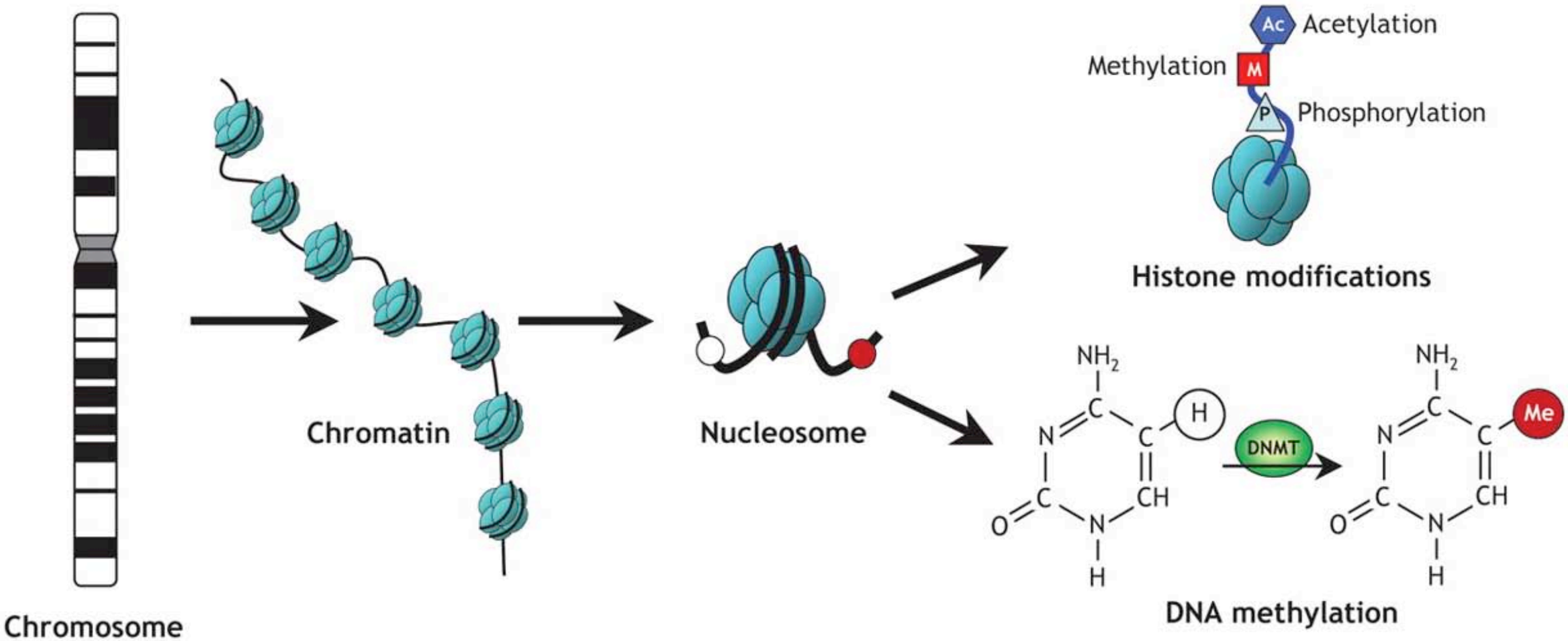
DNA METHYLATION



- Methylation occurs on Cytosine bases that are followed by a Guanosine (a "CpG")
- Most CpG sites in DNA are methylated (90-98%)
- But there are some CpG areas where most of the CpG's are <u>not</u> methylated- **"CpG islands"**

CpG Islands

- CpG islands span the 5’ end of the regulatory region of genes
- When the islands are methylated, gene expression is suppressed or silenced

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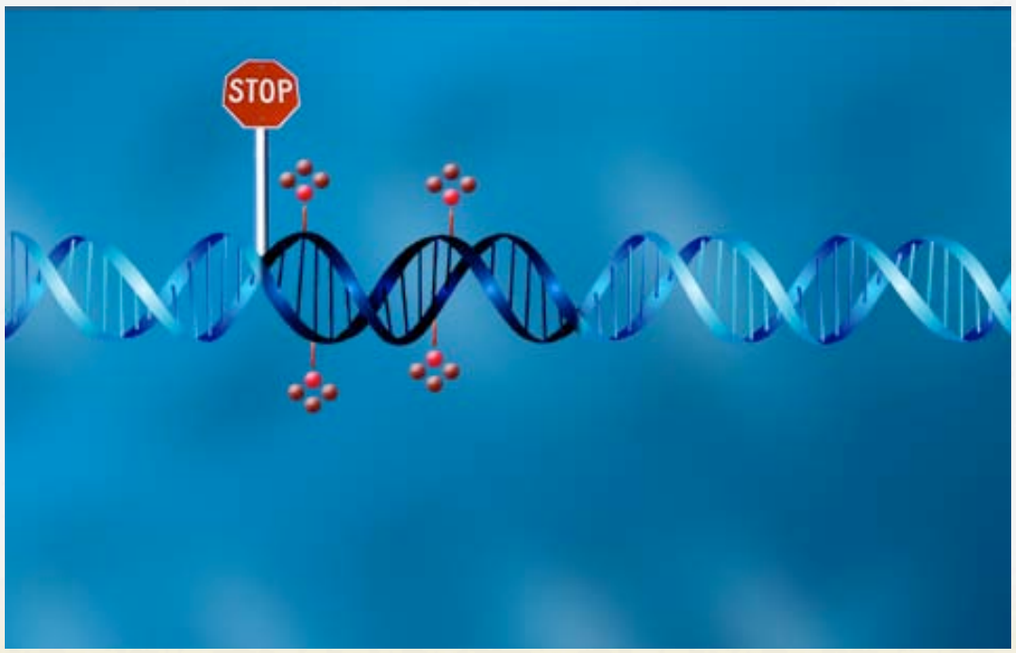

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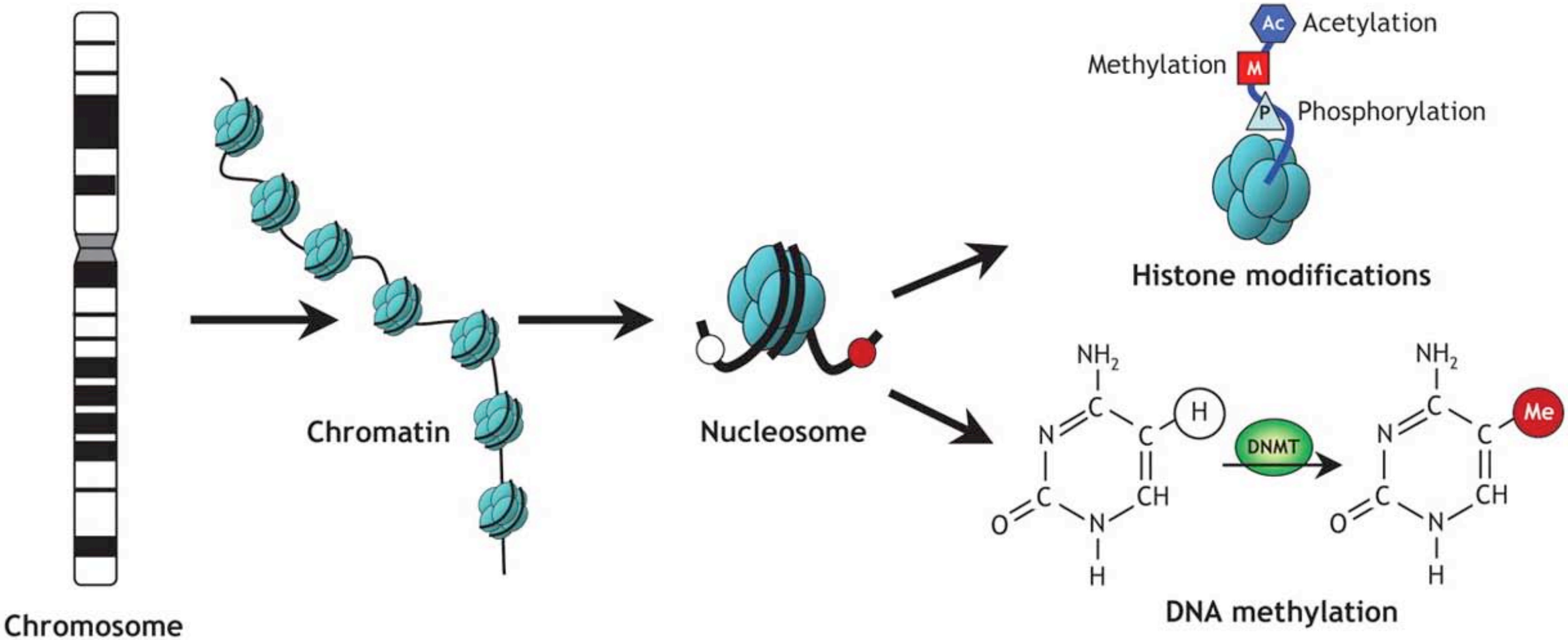
CpG Islands

- CpG islands span the 5’ end of the regulatory region of genes
- When the islands are methylated, gene expression is suppressed or silenced
- CpG islands in the gene promoter region function as the critical switch that regulate gene expression

DNA Methylation: How does it happen?



- DNA methyltransferases:
  - DNMT1, DNMT3a, & DMNT3b

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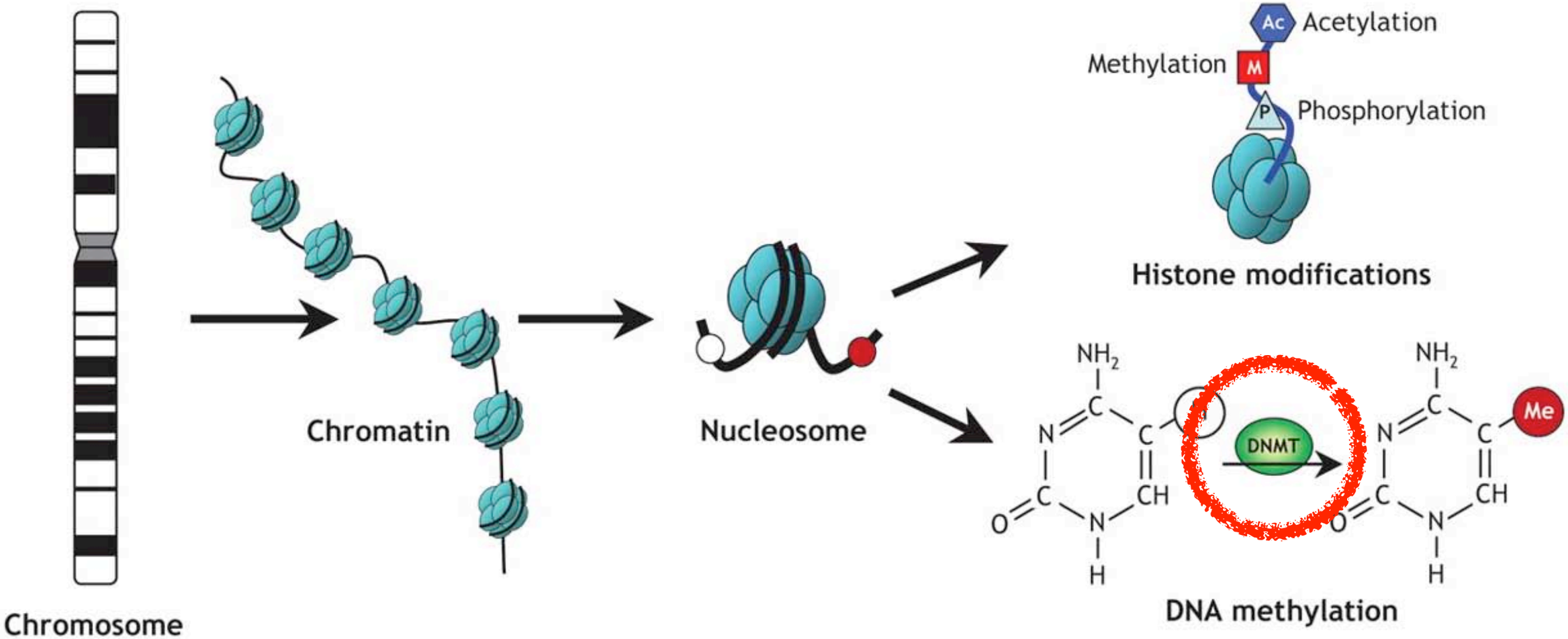

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SIGNAL AMPLIFICATION DOWNSTREAM

- Methylated cytosines serve as docking sites for proteins that prevent transcription factors from accessing their binding sites on the gene promoter
- These proteins are methyl-CpG binding proteins
  - 1. MECP2
  - 2. Kaiso family of proteins

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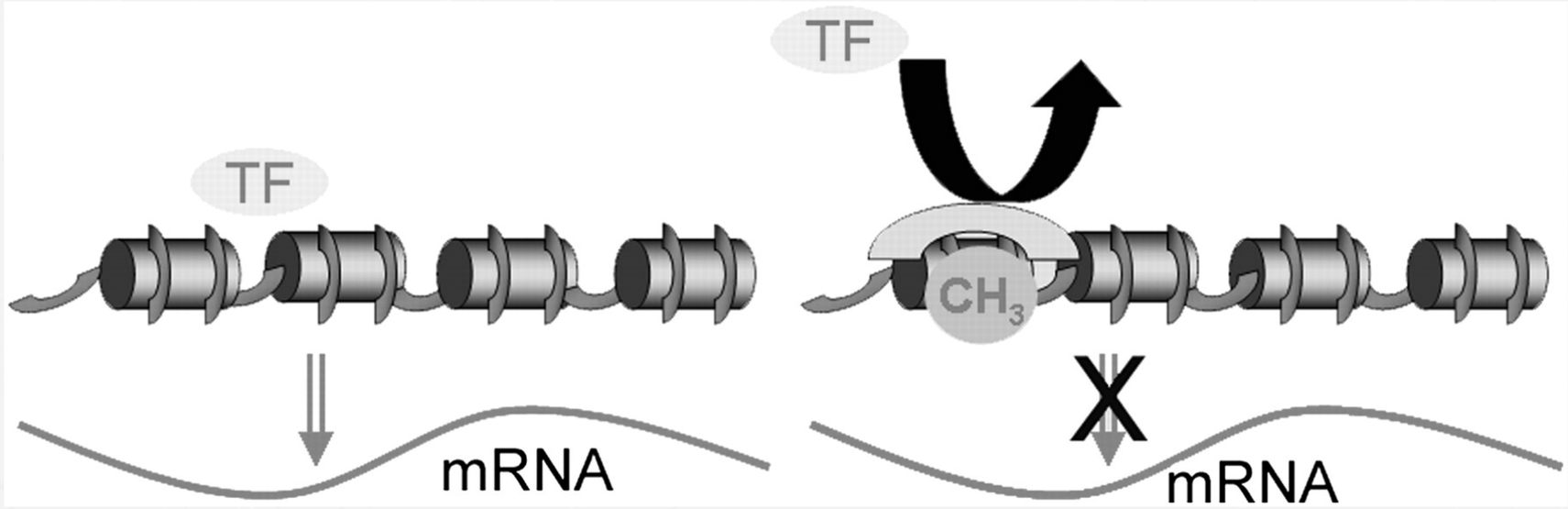
FIGURE 1 Epigenetic marks alter gene expression



Zeisel, S. H Am J Clin Nutr 2009;89:1488S-1493S

The American Journal of Clinical Nutrition

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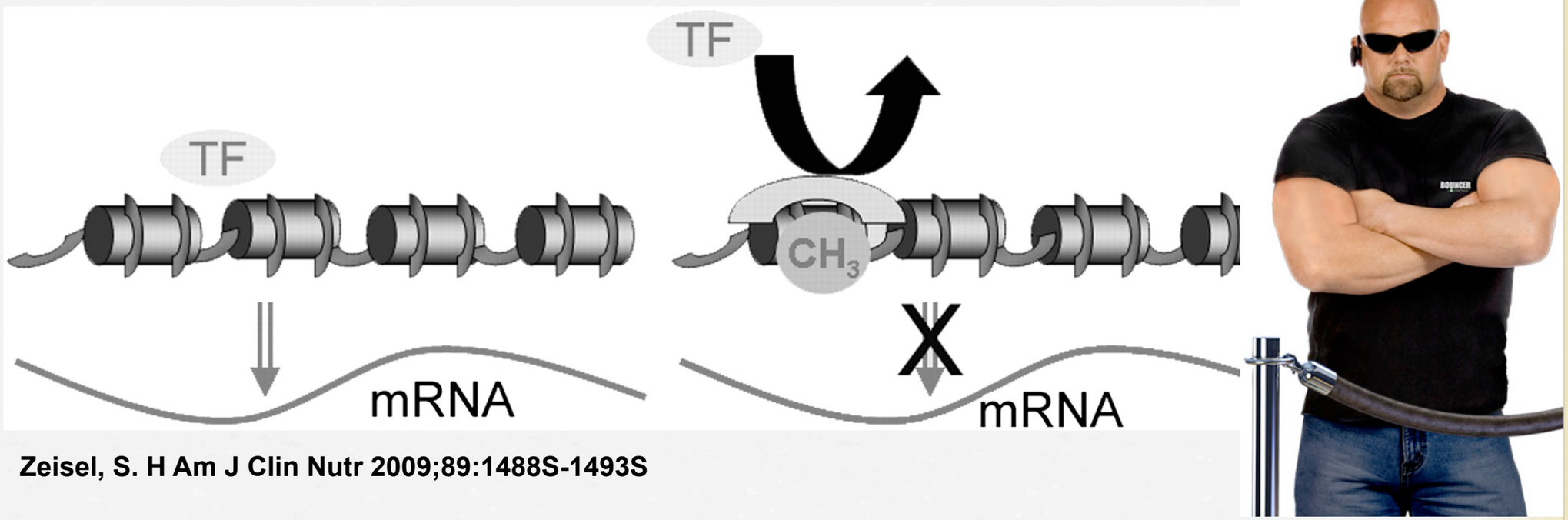

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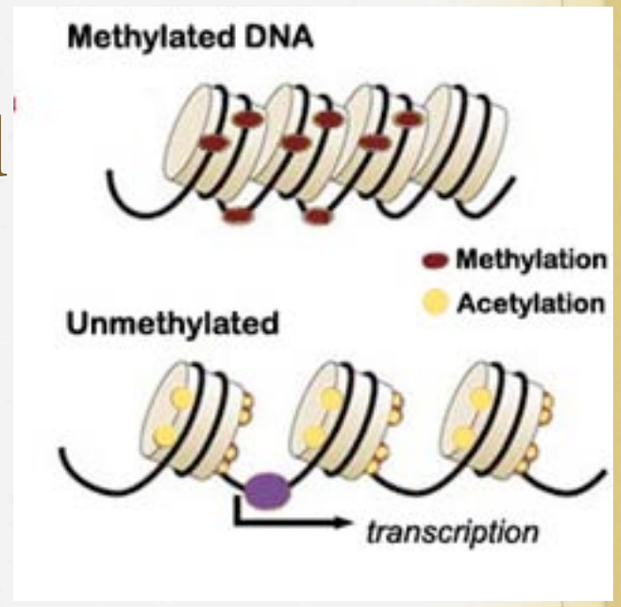
HISTONE MODIFICATIONS

- Functional interactions between histones and DNA are modulated by their methylation and acetylation status

- DNA is tightly wound around histones and prevents access to transcription factors (TFs)

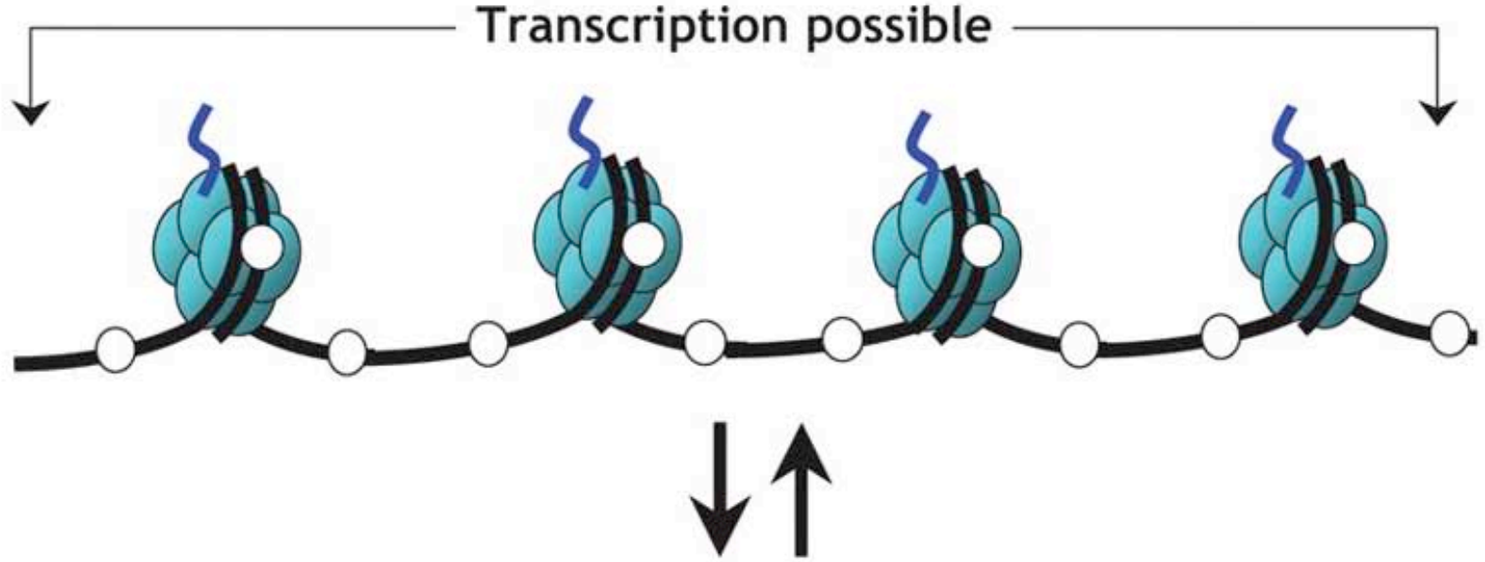
- When modified by methylation or acetylation, these proteins loosen up and create gaps through which TFs can come in



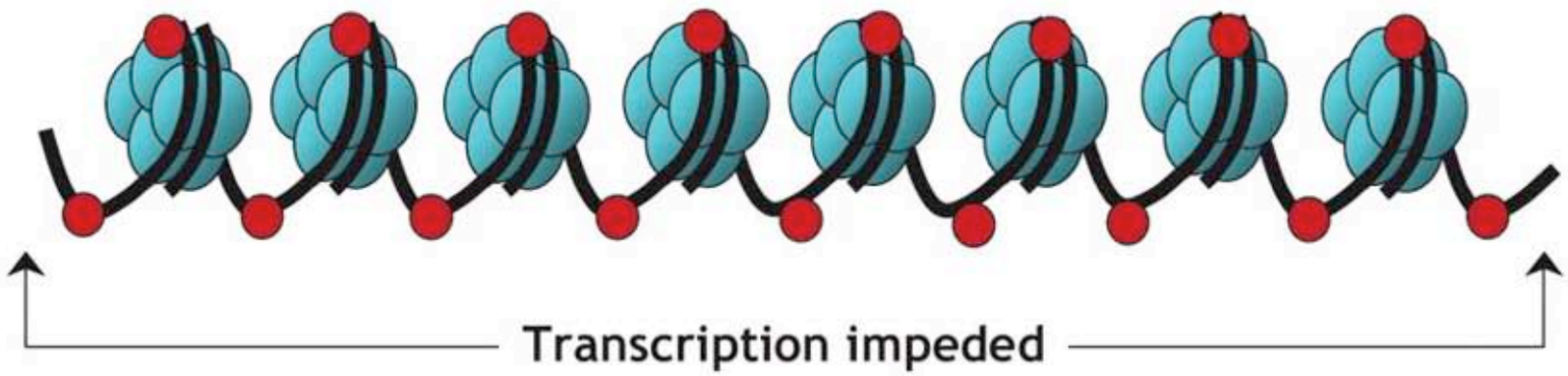
HISTONE MODIFICATIONS

D

Gene "switched on"
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones



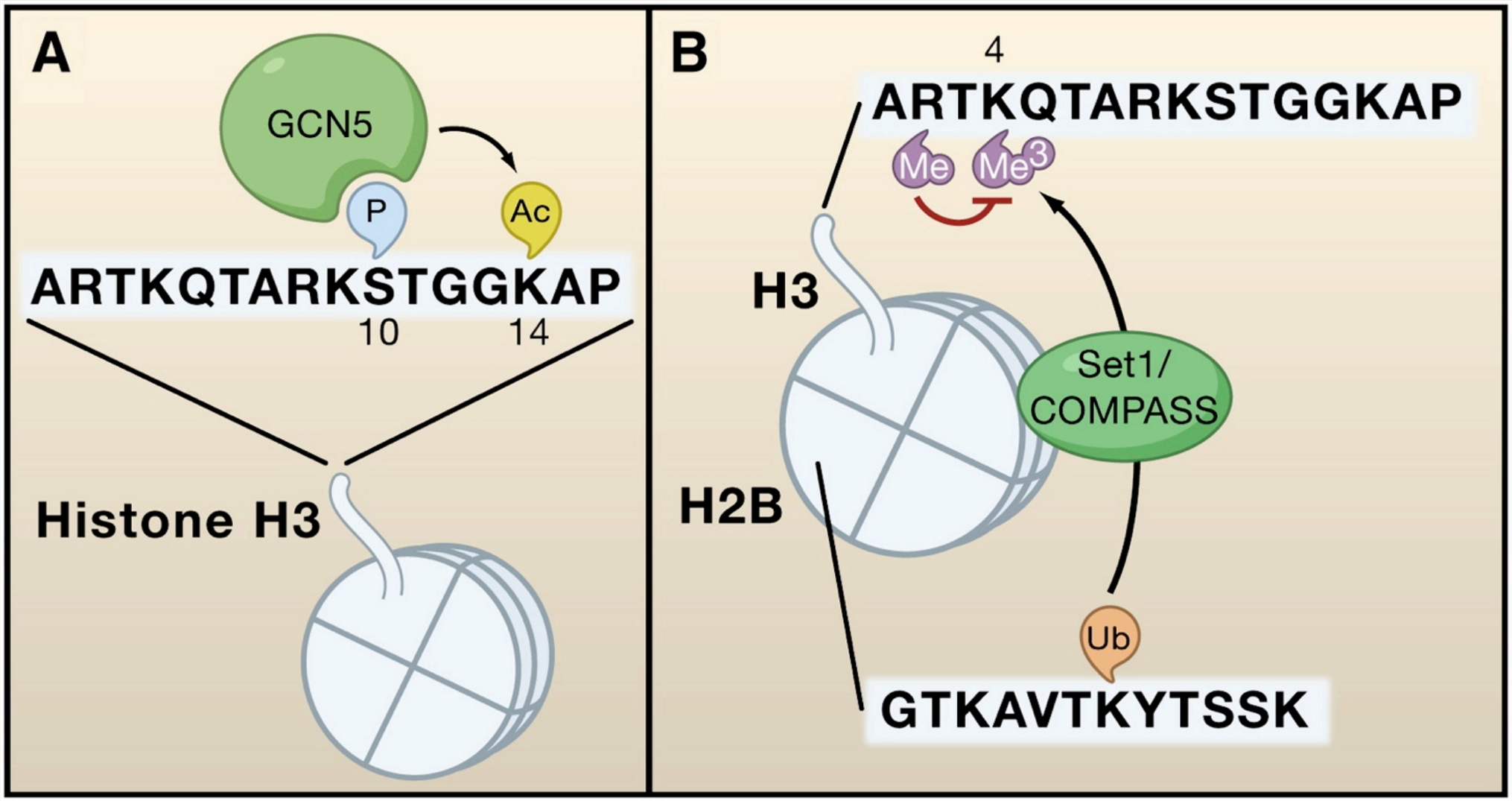
Gene "switched off"
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones



CROSSTALK

Histone *DNA*

CROSSTALK



Prior Phosphorylation

Histone to Histone

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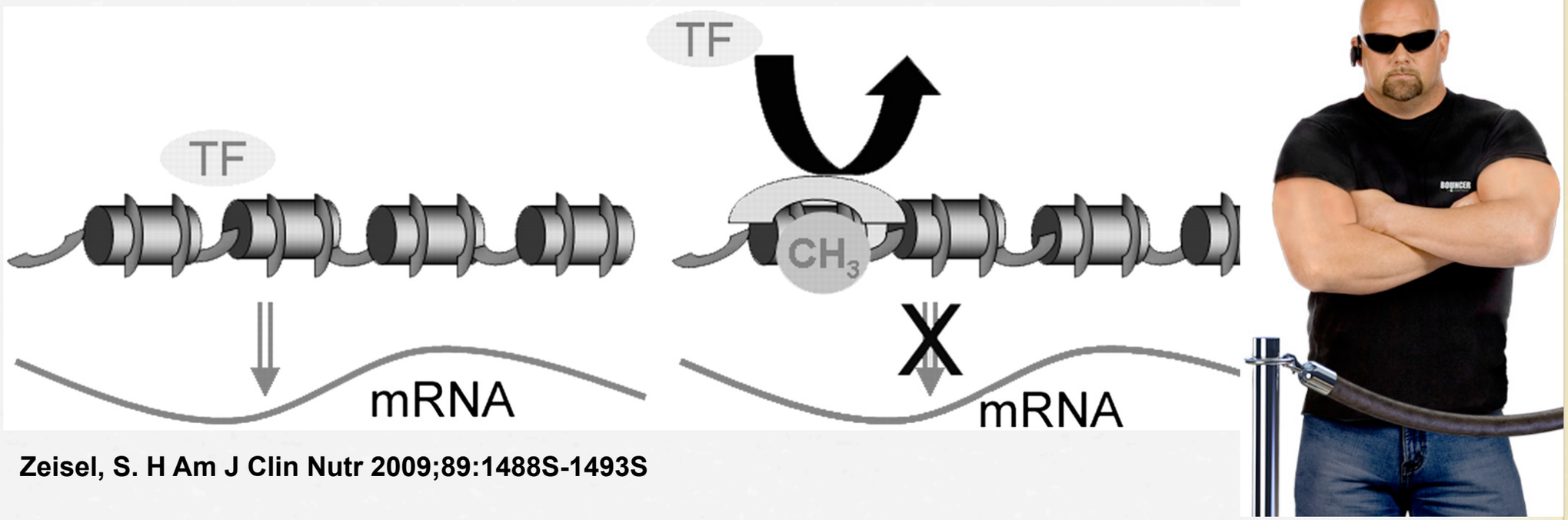
FIGURE 1 Epigenetic marks alter gene expression



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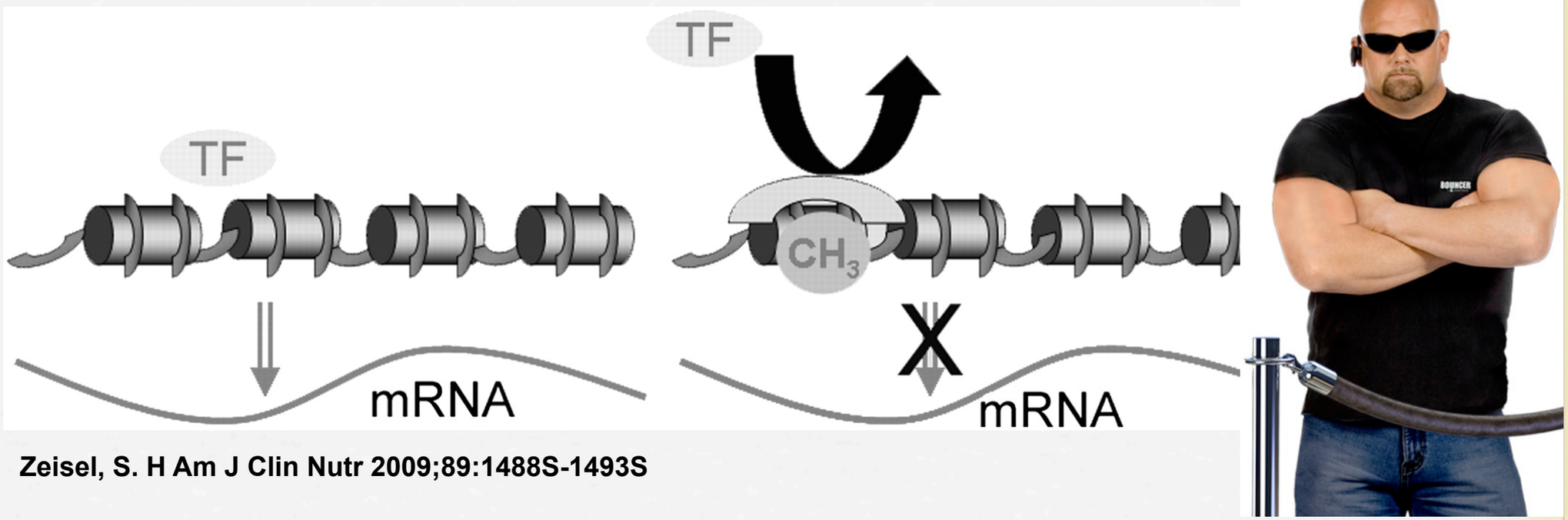

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The methyl-CpG-binding proteins can now attract a variety of other proteins some of which have enzymatic activity that can further modify neighboring histones

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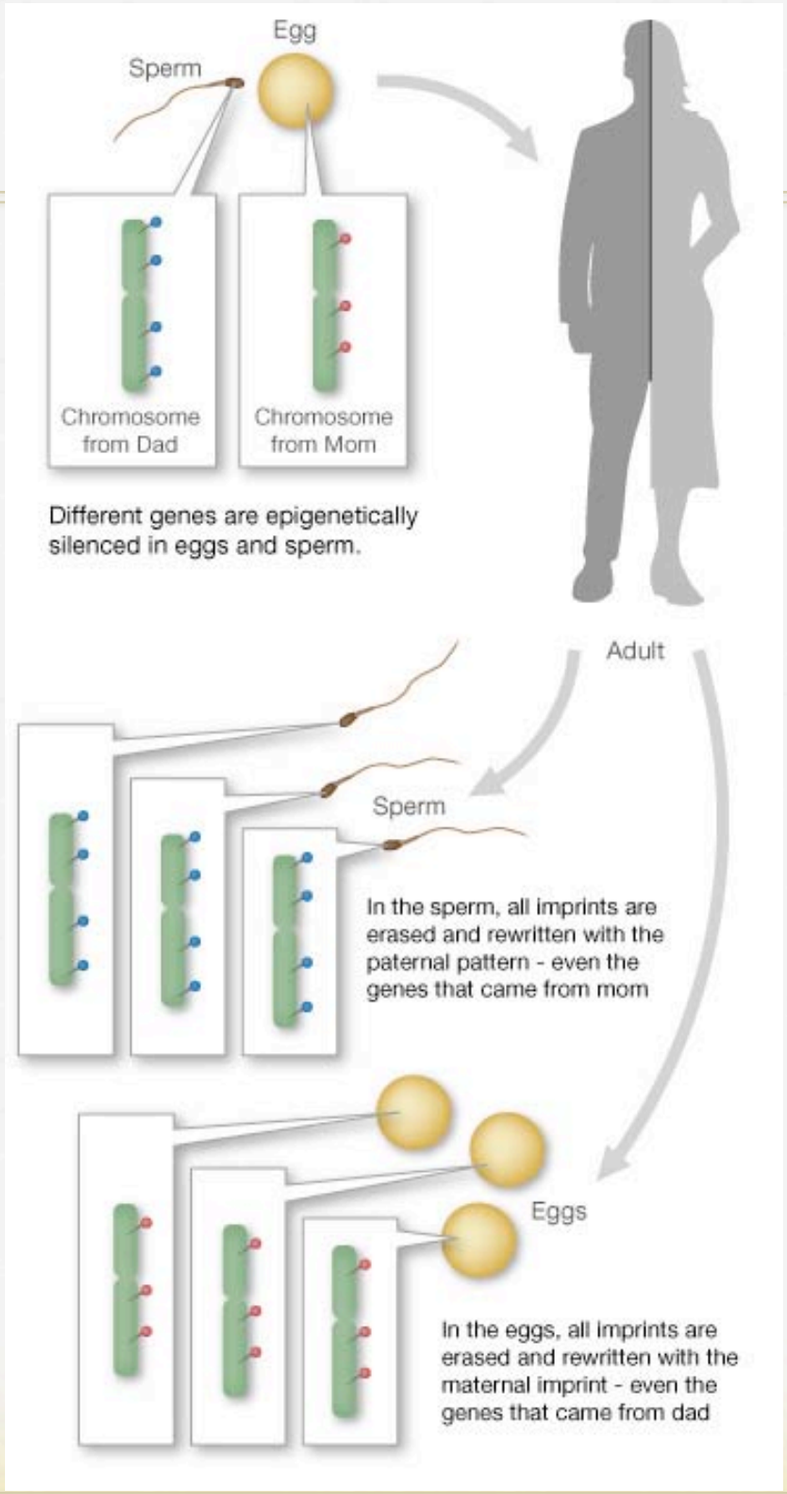
IMPRINTING

- Parental influence on the genome
  - For most genes we inherit two working copies
  - But on imprinted genes we inherit only one working copy
  - Imprinting is unique to mammals and flowering plants. In mammals, about 1% of genes are imprinted

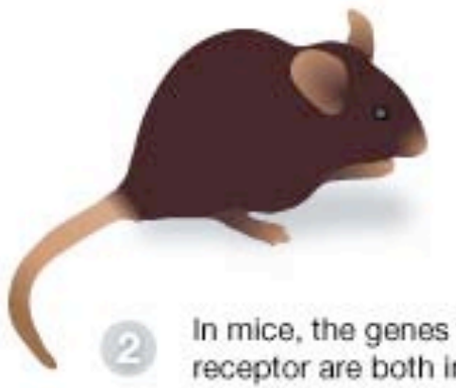
IMPRINTING


Egg
Sperm
Chromosome from Dad
Chromosome from Mom
Different genes are epigenetically silenced in eggs and sperm.
Adult
Sperm
In the sperm, all imprints are erased and rewritten with the paternal pattern - even the genes that came from mom
Eggs
In the eggs, all imprints are erased and rewritten with the maternal imprint - even the genes that came from dad

IMPRINTING

AN EXAMPLE OF IMPRINTING

1. In mammals, the growth factor Igf2 interacts with the Igf2 receptor.



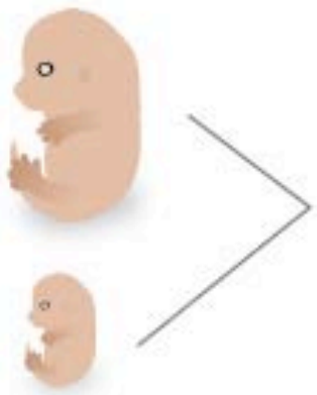
Genes from mom:
Igf2 receptor - ON
Igf2 - OFF

Genes from dad:
Igf2 receptor - OFF
Igf2 - ON

2. In mice, the genes for Igf2 and the Igf2 receptor are both imprinted.

Deleting the mother's Igf2 receptor gene produces overly large offspring.

Deleting the father's Igf2 gene produces dwarf offspring.



Deleting the mother's Igf2 receptor gene AND the father's Igf2 gene produces normally sized offspring.

3. The imprints on the Igf2 and Igf2 receptor genes normally cancel each other out. Changing the imprint on one copy of the gene has a dramatic effect on the size of the offspring. This result supports the genetic conflict hypothesis

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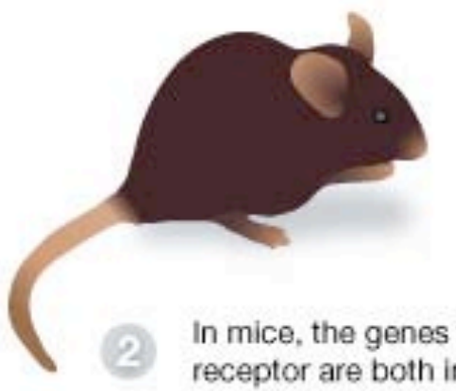

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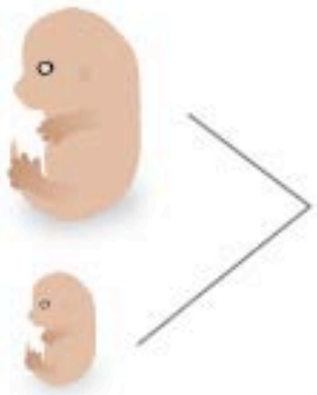

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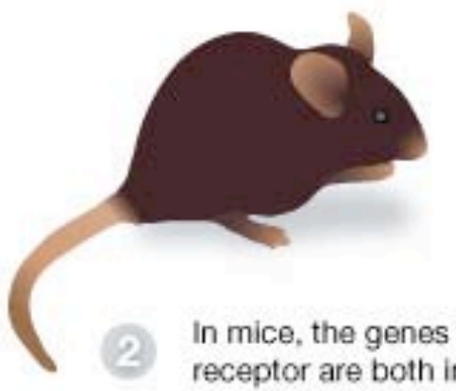

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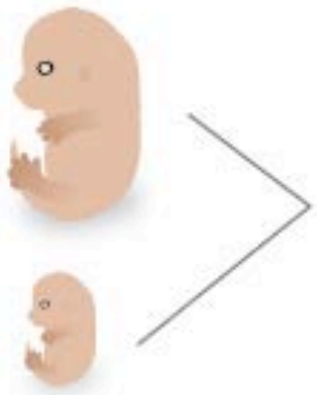

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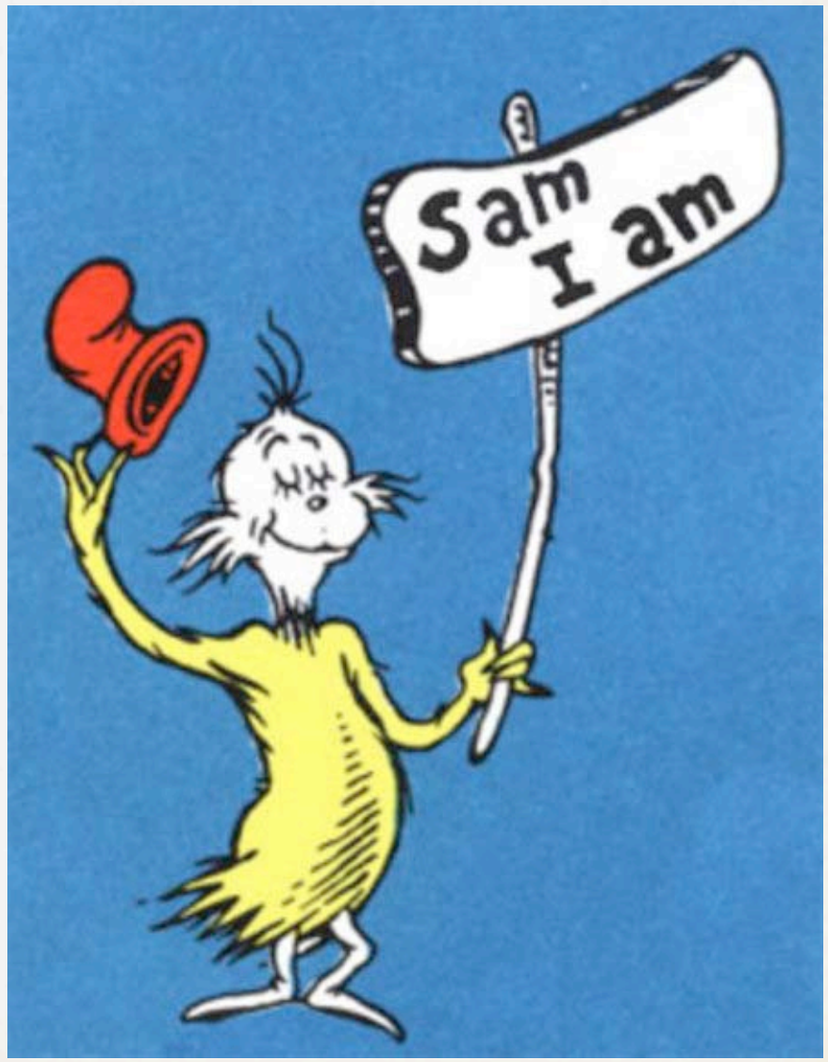
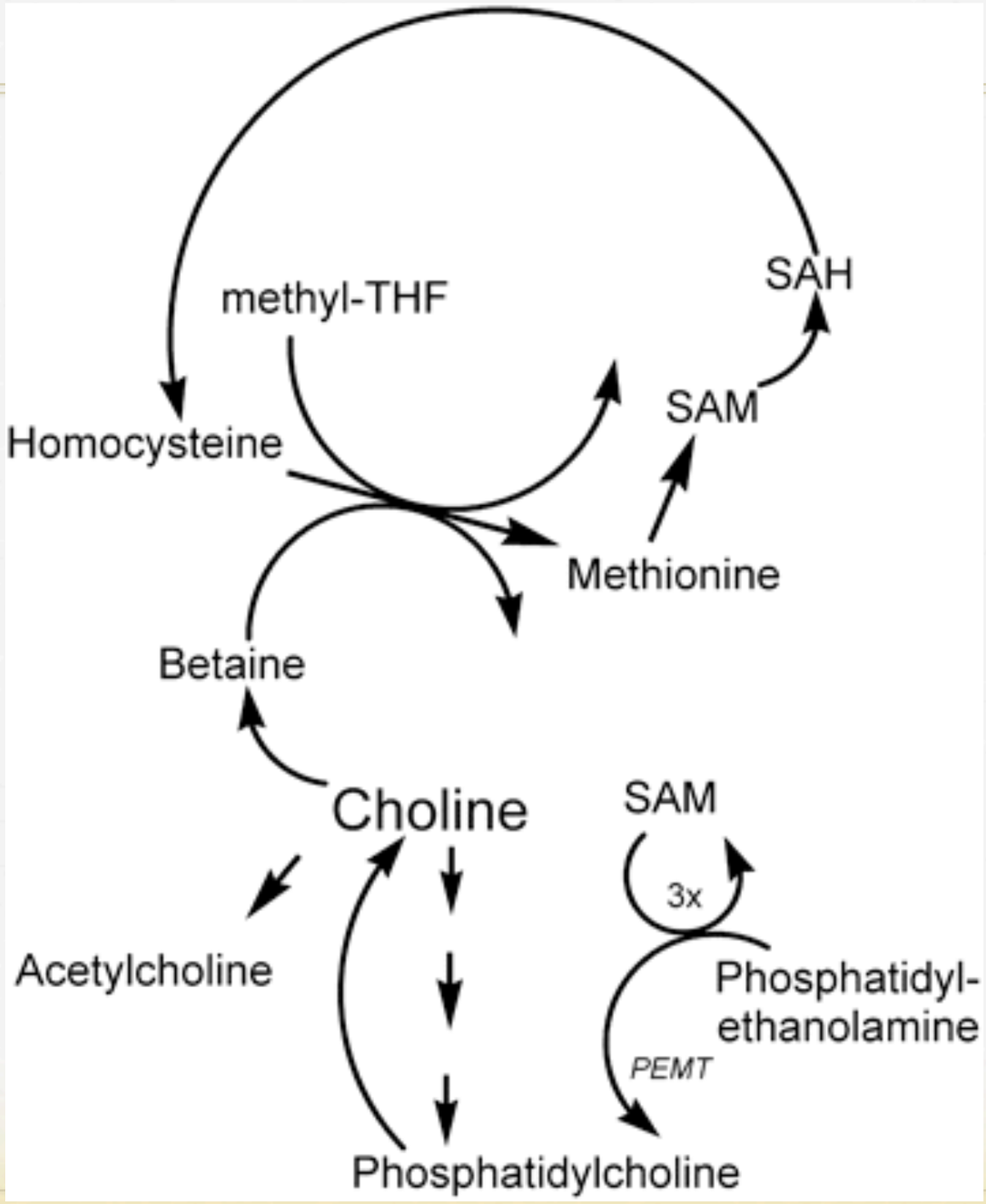
Ligers & Tigons!

NUTRITION AND EPIGENETIC MARKS

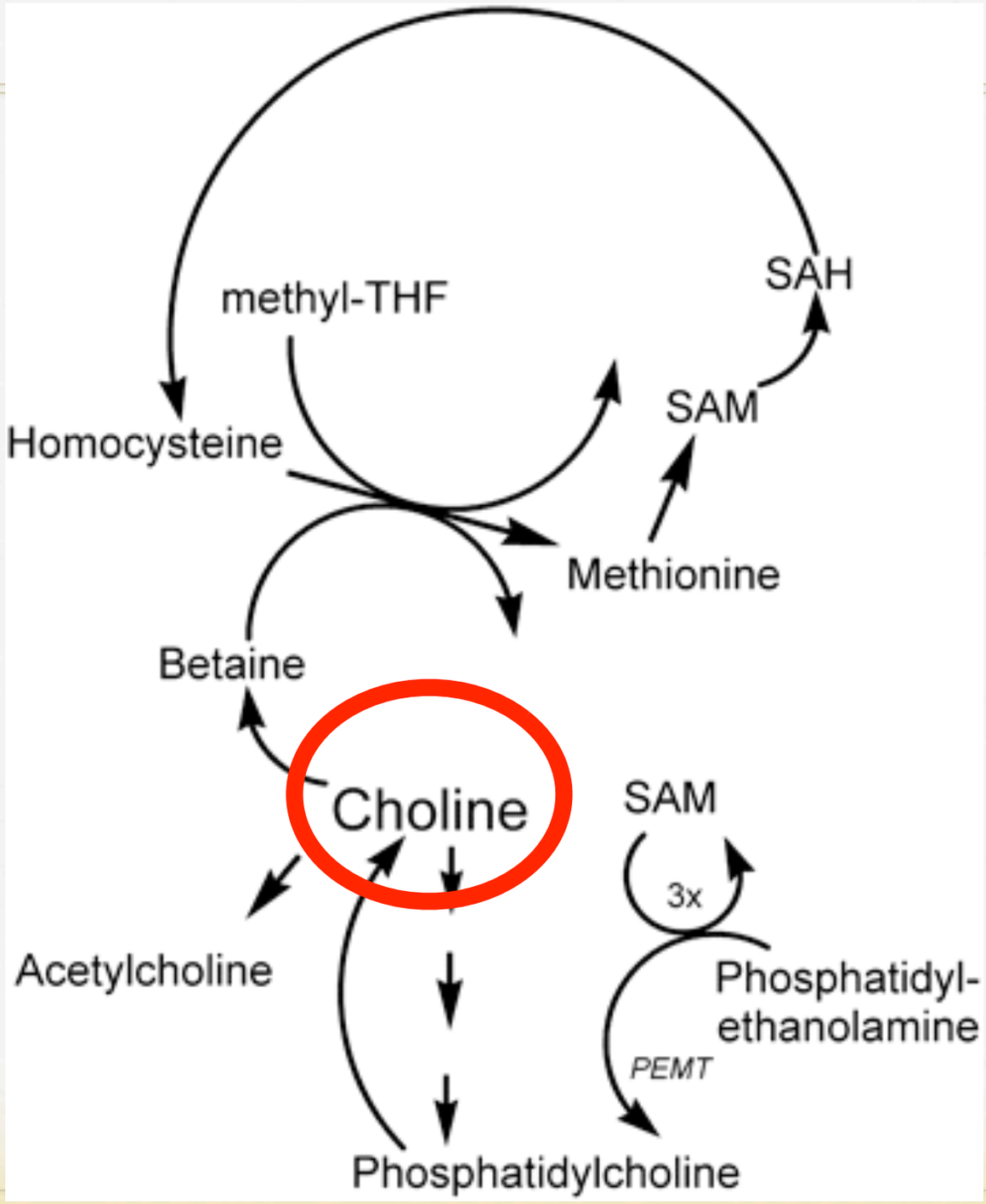
- DNA and histone methyltransferases all use S-adenosylmethionine (SAM) as the methyl donor
- SAM is formed from methyl groups derived from choline, methionine, or methyl-tetrahydrofolate



SAM


methyl-THF
SAH
SAM
Homocysteine
Methionine
Betaine
Choline
SAM
3x
Acetylcholine
Phosphatidyl-
ethanolamine
PEMT
Phosphatidylcholine

SAM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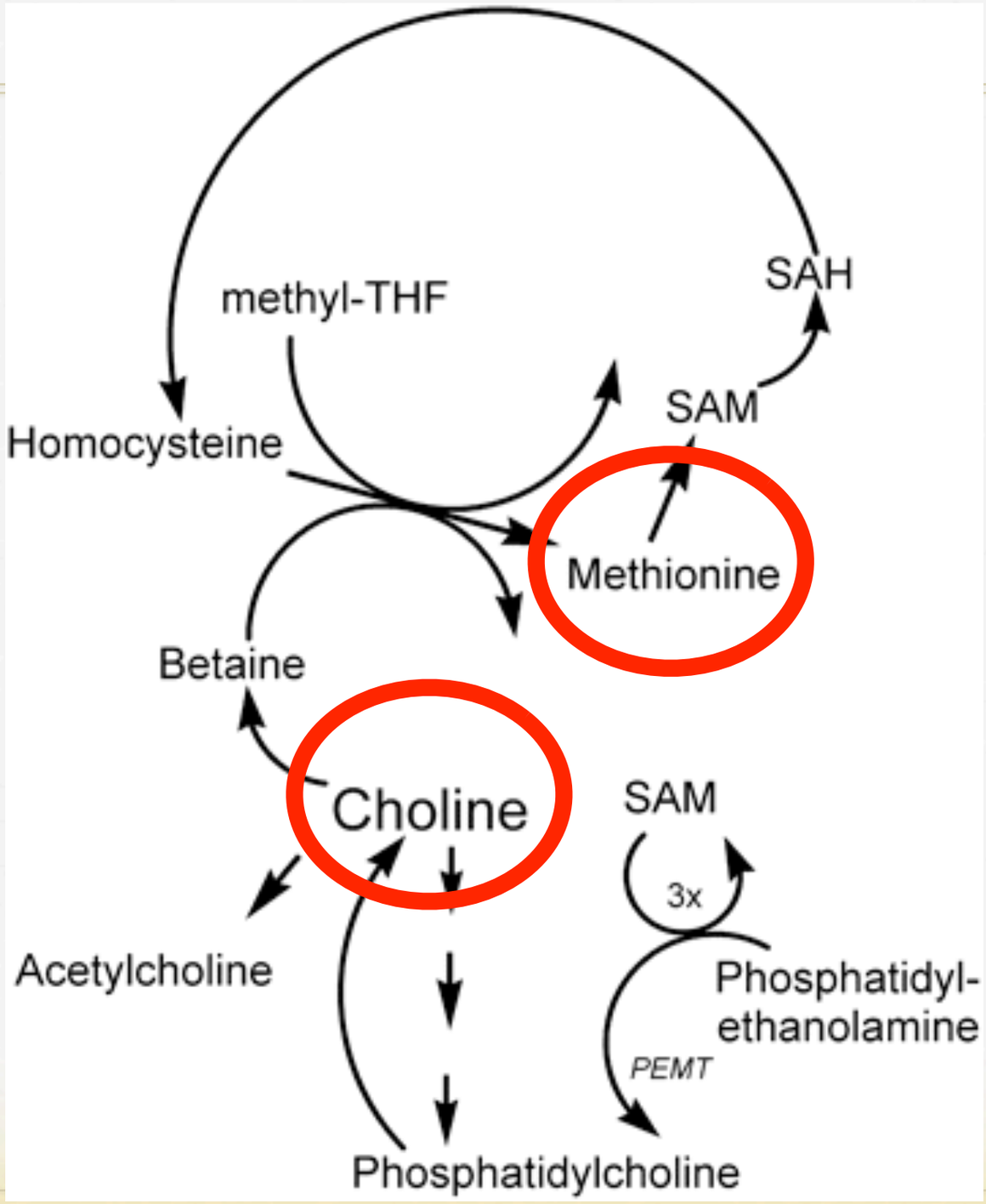
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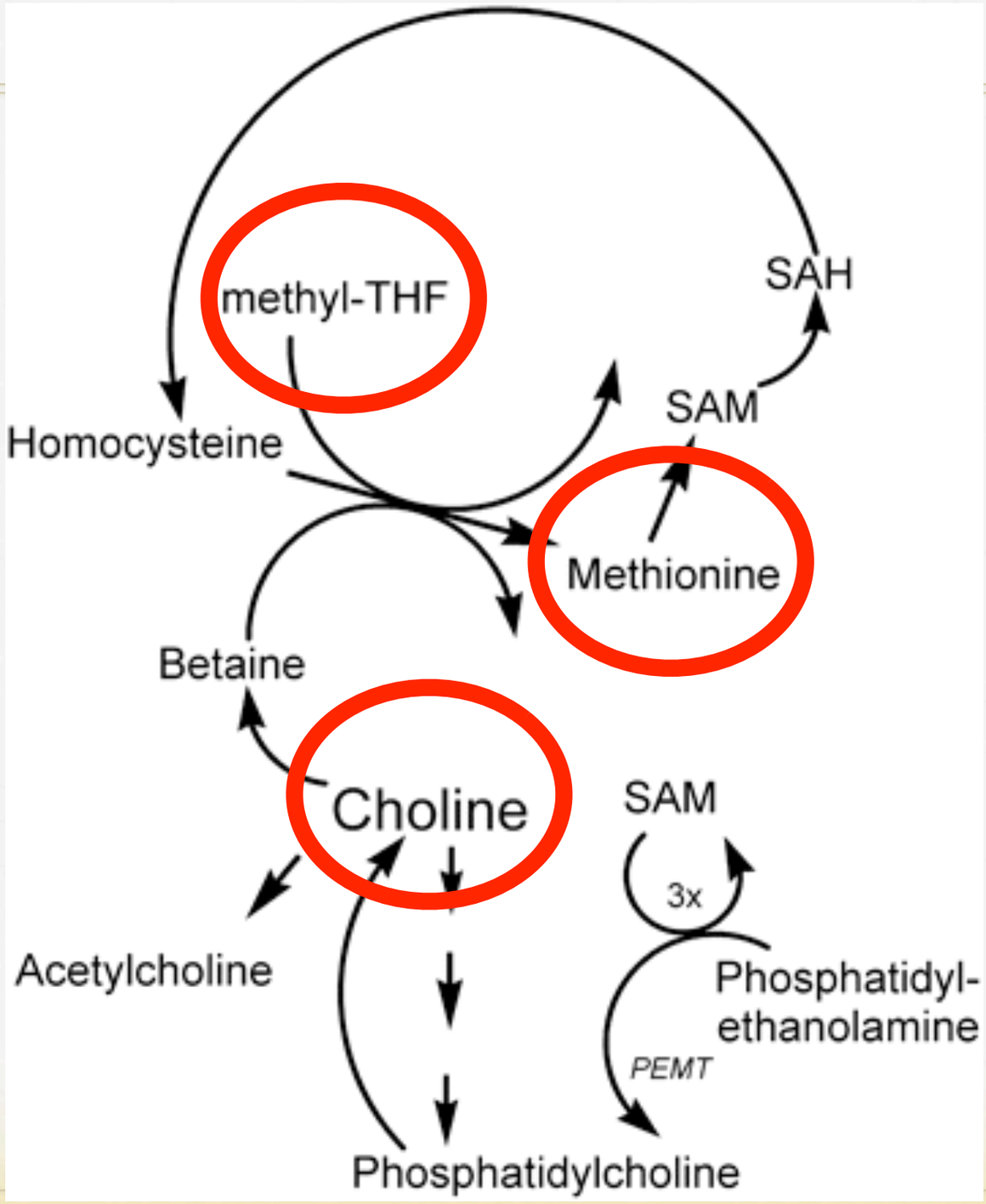
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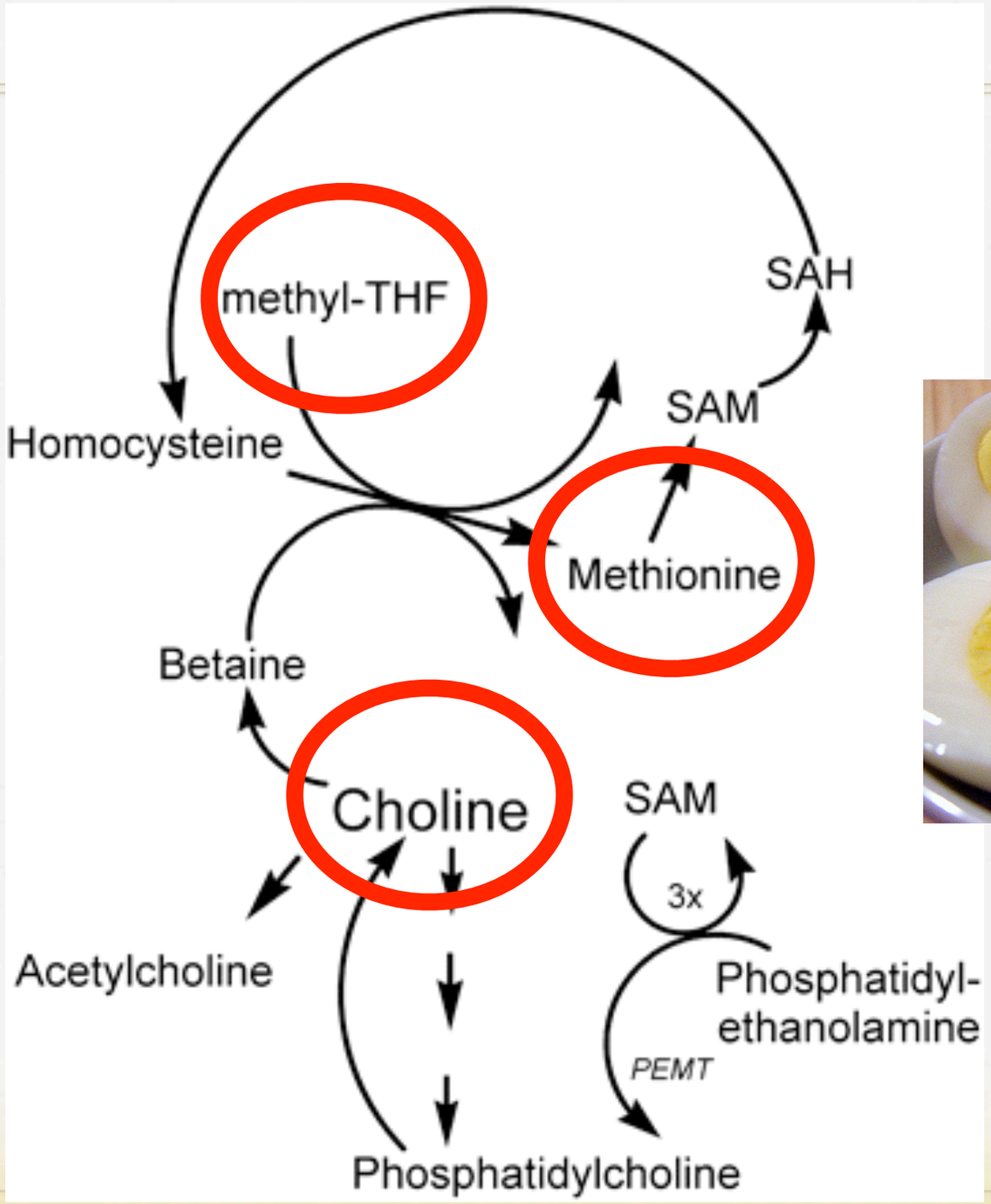
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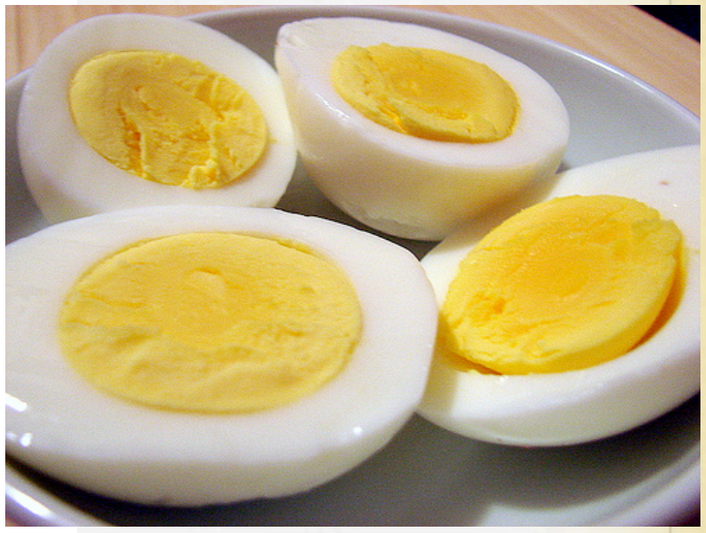
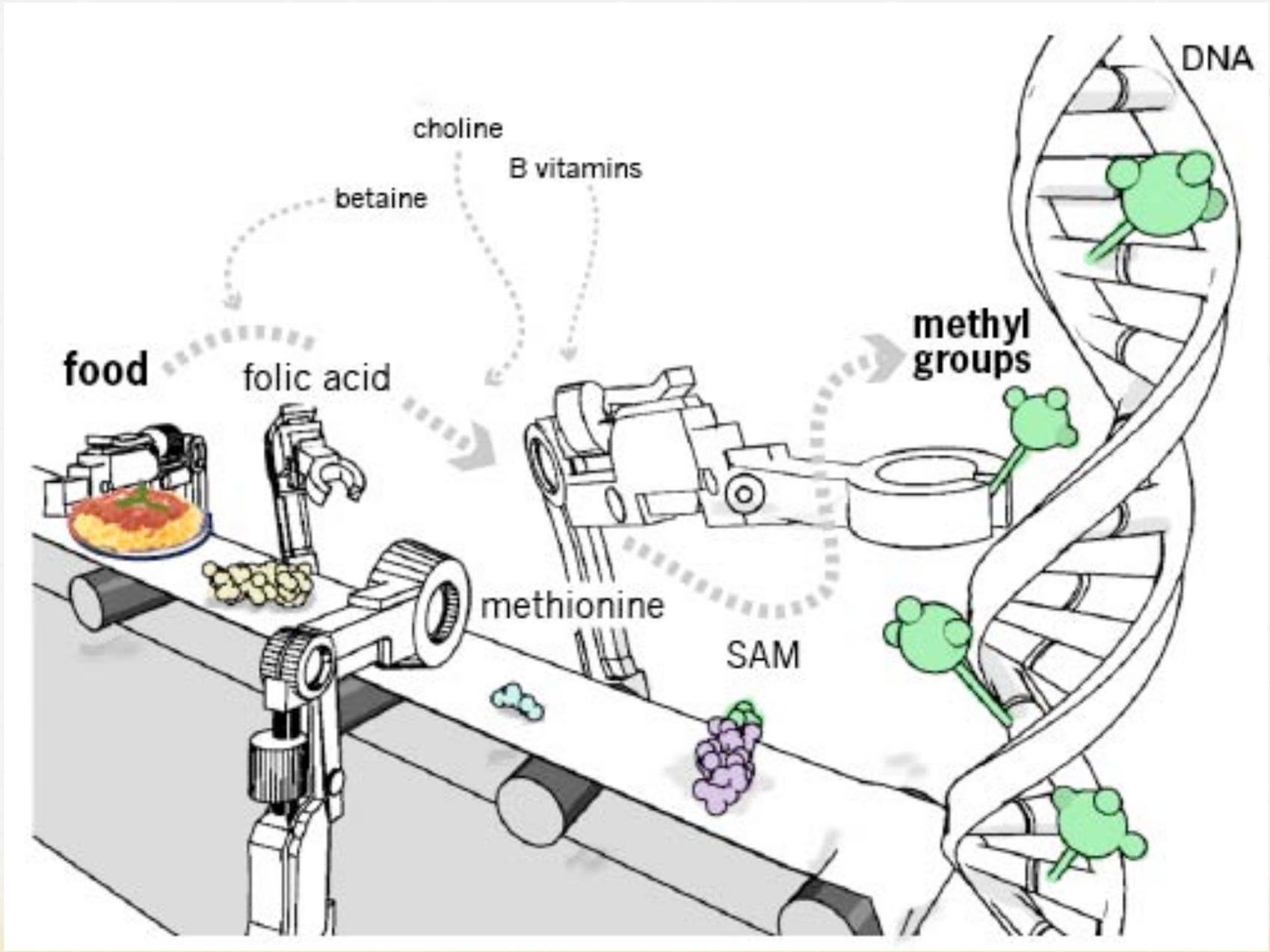
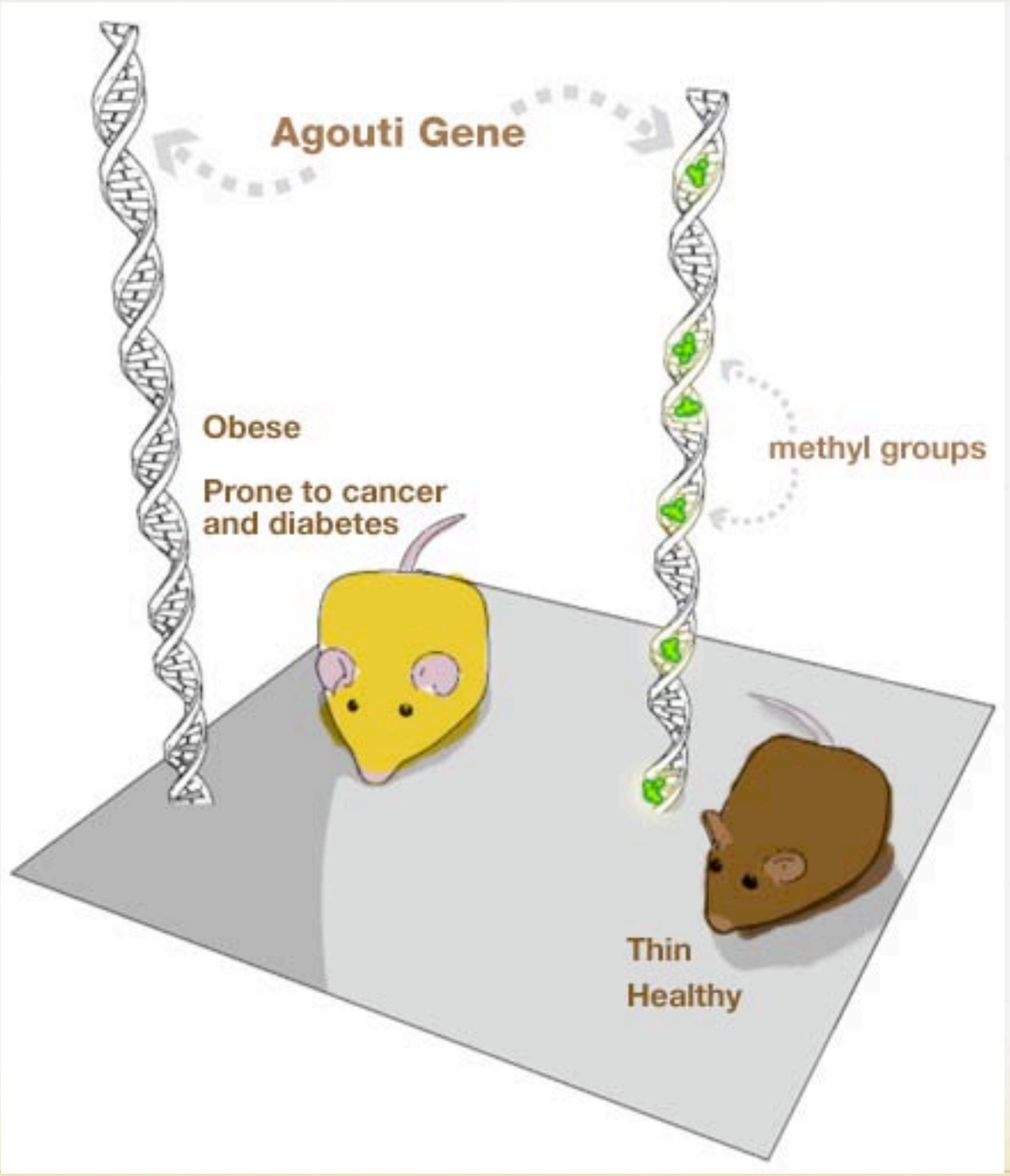


FOLIC ACID, SAM AND METHYLATION



GENE EXPRESSION



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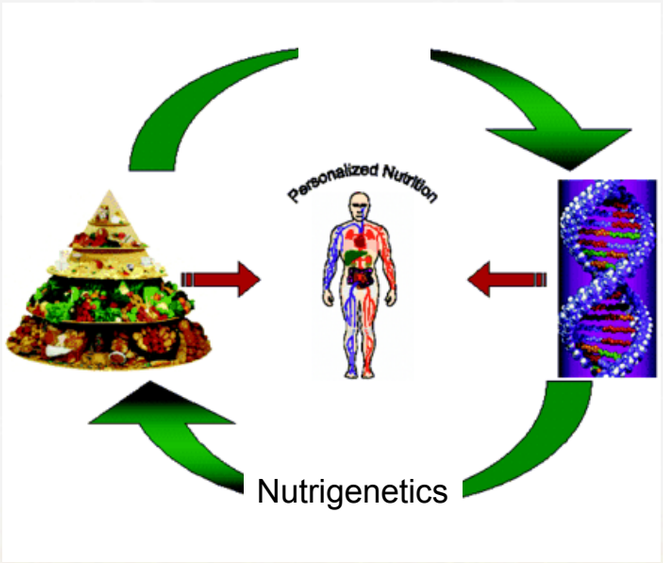
SNPs

- Genetic variations in genes of methyl metabolism can change epigenetic marks on DNA
- There are multiple SNPs in genes of methyl-group metabolism that change human dietary requirements for methyl donors

Influence of specific nutrients on gene expression



Effects of fixed genetic variation (e.g. SNP's) on responsiveness to diet

Nutrition related SNPs

- MTHFR C677T SNP- a common variant increases folate requirement
- PEMT
  - Choline is either derived from diet or by *de novo* biosynthesis catalyzed by an enzyme coded by the PEMT gene
  - Estrogen upregulates PEMT gene activity
    - However even in non-menopausal women where there's adequate estrogen to induce PEMT, studies have shown that even these women have organ dysfunction when deprived of choline
  - SNP variant in PEMT promoter region- choline deficiency in diet resulted inorgan dysfunction

LATER OUTCOMES OF EPIGENETICS?

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Moose Offer Trail of Clues on Arthritis

George Desort

LONG-RUNNING A study that began in 1958 has found poor nutrition as the cause of arthritis.

LATER EFFECTS?

- Grandfathers who lived their preteen years during times of plenty were more likely to have grandsons with diabetes

- Equally notable was that the effects were sex specific.

  - A grandfather's access to a plentiful food supply affected the mortality rates of his grandsons only, not those of his granddaughters, and a paternal grandmother's experience of feast affected the mortality rates of her granddaughters, not her grandsons.