Methylation & environmental toxins

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Your Genes & Nutrition

For Optimal Health & Wellness

Speaker Disclosure

- I am an advisor for Pure Encapsulations.
- I have no other conflicts of interest to disclose.
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Learning objectives

- To gain an understanding of methylation
- Learn about methyltransferases in detoxification
- Demonstrate the variety environmental toxins that impact on methylation
- Review epigenetics and foetal programming
- Ways to support methylation and minimize the potential effects of chemicals and toxins

What is methylation

- A "methyl" group is one carbon connected to three hydrogen atoms
- Methylation refers to the adding of methyl groups to a compound, such as DNA, proteins, hormones, heavy metals

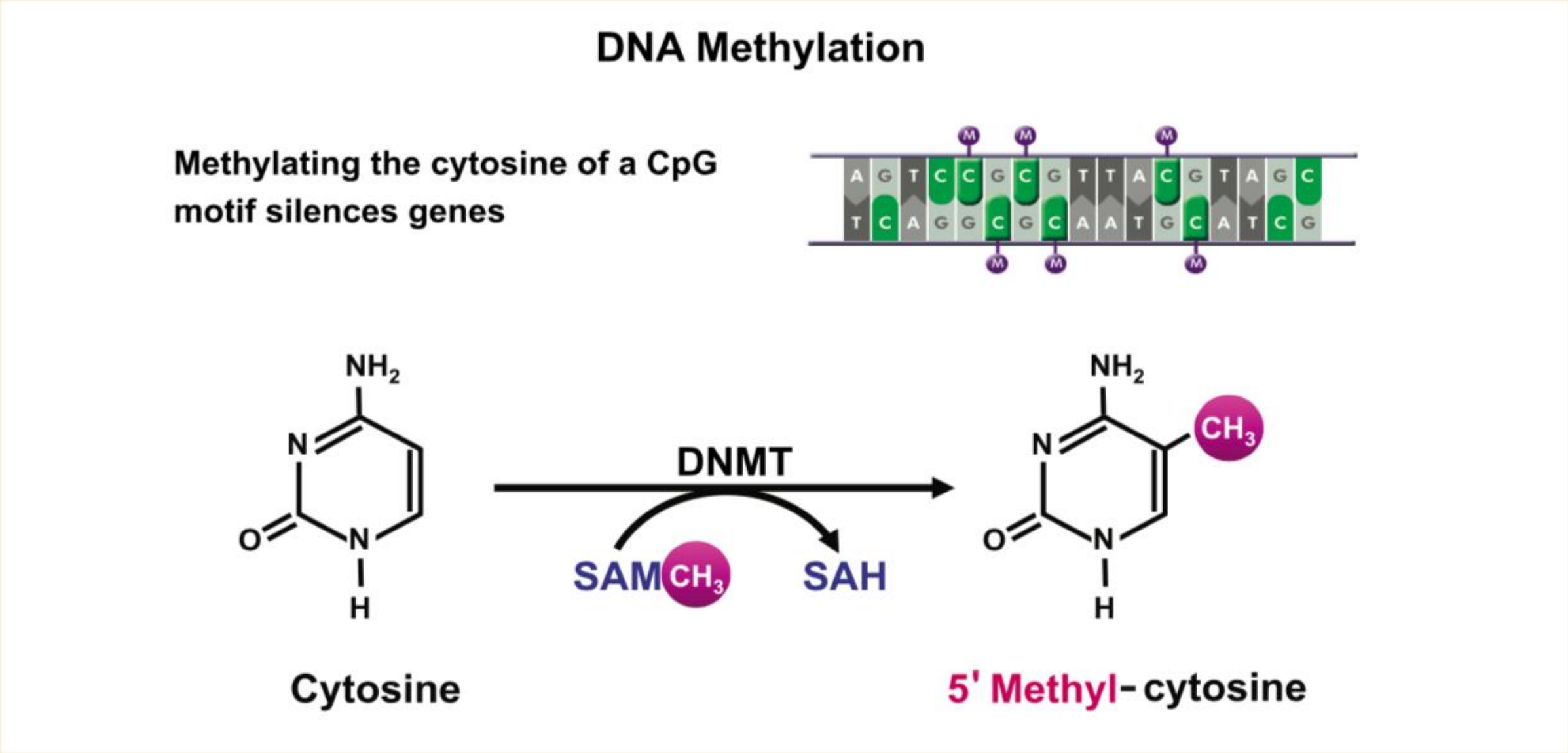


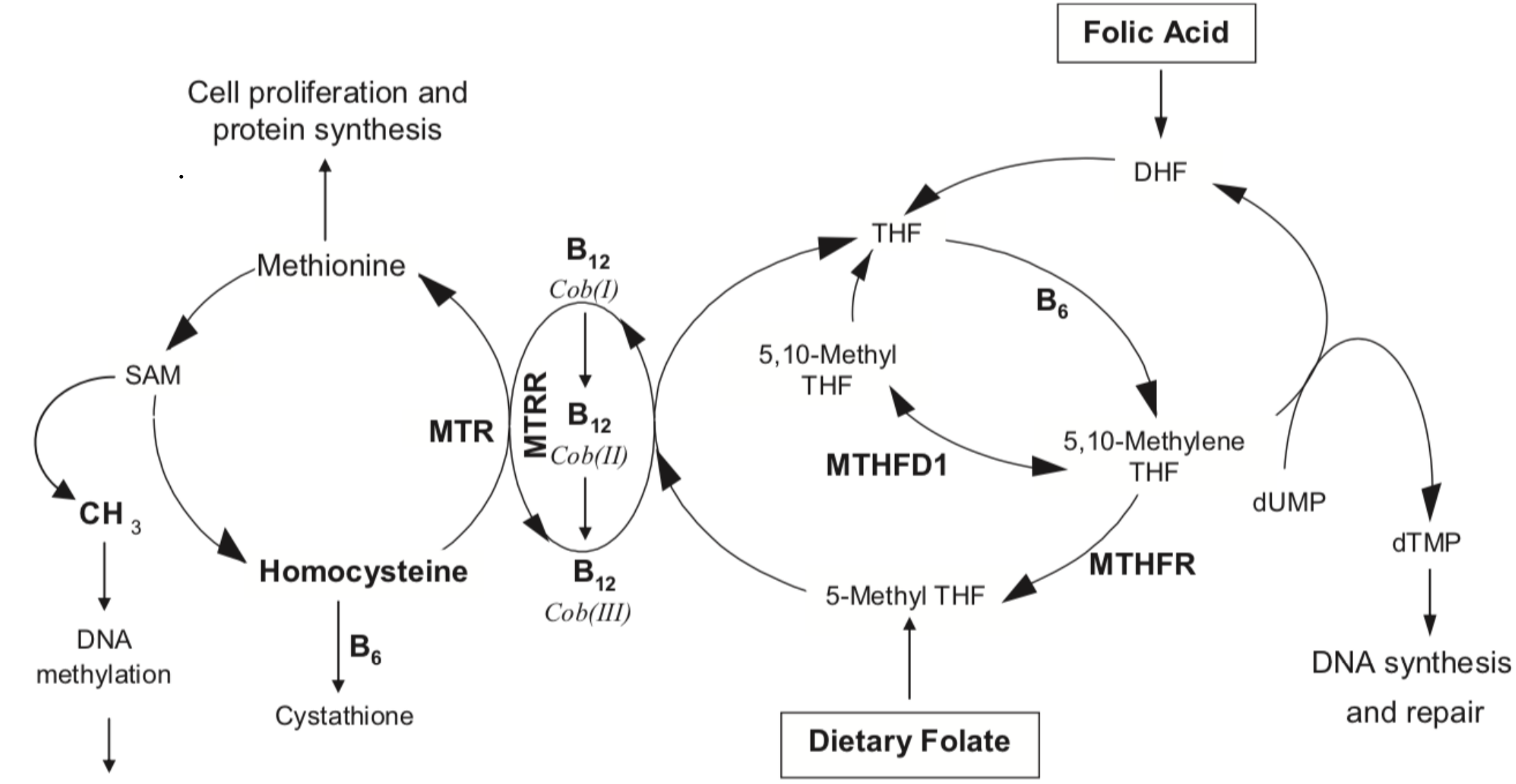
Figure 1 Schematic representation of DNA methylation, which converts cytosine to 5'methyl-cytosine via the actions of DNA methyltransferase (DNMT). DNA methylation typically occurs at cytosines that are followed by a guanine (i.e., CpG motifs).

NOTES: SAM = S-adenosylmethionine; SAH = S-adenosylhomocysteine.

Samir Zakhari, Alcohol Metabolism and Epigenetics Changes, 2013

FIGURE 1

A simplified scheme of one-carbon metabolism. Key intermediates and enzymes are given



Furness. One-carbon metabolism enzyme polymorphisms and UPI. Am J Obstet Gynecol 2008.

Methylation and detoxification

- Methyl transferase enzymes (MTs)
- Catechol O-methyltransferase (COMT)
  - Catechol oestrogens
  - Catecholamines
  - Catechol drugs and other substances
- Support for methylation consists of nutrient cofactors and methyl donors
- Conversely, a high sucrose diet may inhibit methylation enzymes such as COMT
  - Busserolles J.et al.,Rats fed a high sucrose diet have altered heart antioxidant enzyme activity and gene expression. *Life Sciences*. 2002

Arsenite methyltransferase (AS3MT)

- Arsenic is converted to methylarsonic acid (MMA) and dimethylarsinic acid (DMA) by Arsenic methyltransferase (AS3MT) enzymes
- MMA most toxic
- Some populations have been exposed to arsenic for many generations
- Genetic variations within genes required to metabolise arsenic may have enabled these people to thrive despite the toxic load in their environment.
  - Eichstaedt CA. et al., Positive selection of AS3MT to arsenic water in Andean populations. Mutat Res. 2015.

Genetic susceptibility to Arsenic

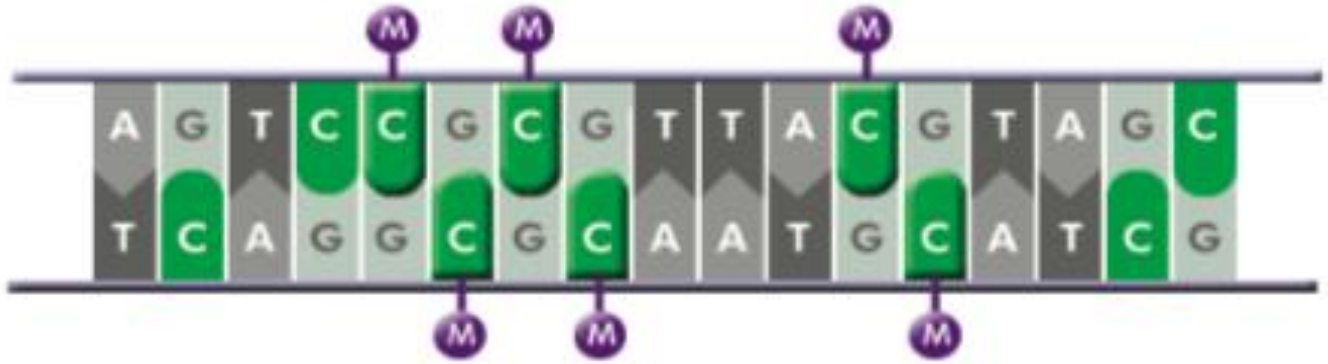
- AS3MT rs1046778 C > T
  - C allele associated with decreased expression and lower excreted MMA levels.
  - TT genotype associated with 175% increase of *AS3MT* expression in compared to CC
- AS3MT rs7085104 G > A
  - G allele decreased expression and lower excreted MMA levels.
    - PMID: 21247820
    - PMID: 26366667

Arsenic

- Arsenic is considered toxic and carcinogenic
  - Chronic exposure at high levels associated with cancers neurological and metabolic disorders
- Arsenic (As) is found in the air, soil and water
  - Commonly found in rice, fruit juice and vegetables
- Anthropogenic actions like mining and pesticide use contribute to elevated levels of arsenic
  - Nordstrom DK. Public health. Worldwide occurrences of arsenic in ground water. Science. 2002

Epigenetics

- Epigenetics investigates heritable changes in gene expression occurring without changes in DNA sequence
- There are several epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA (miRNA) expression



Epigenetics and environmental toxins

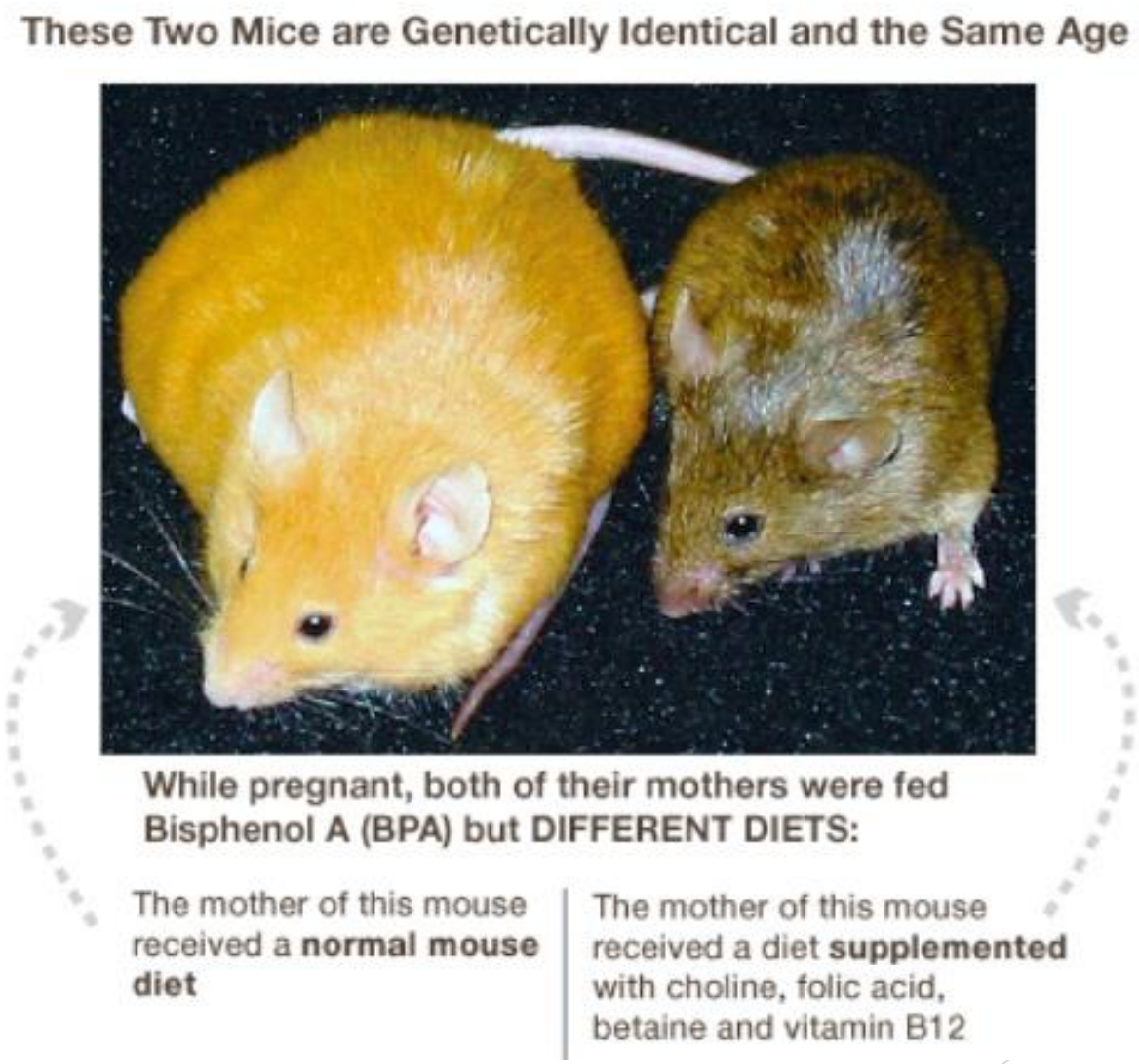
- In-vitro, animal, and human investigations have identified several classes of environmental chemicals that alter epigenetic marks, including
  - Metals (cadmium, arsenic, nickel, chromium, methylmercury)
  - Air pollutants (particulate matter, black carbon, benzene)
  - Endocrine-disrupting/reproductive toxicants (diethylstilbestrol, bisphenol A, persistent organic pollutants, dioxin).
  - Peroxisome proliferators (trichloroethylene, dichloroacetic acid, trichloroacetic acid)
    - Baccarelli, A and Bollati, V "Epigenetics and environmental chemicals." *Current opinion in pediatrics* vol. 21,2 (2009)

Benzene

- High benzene exposure is linked with increased risk of leukemia
- Studies in gas station attendants and traffic police show airborne benzene exposure was associated with a significant reduction in global methylation (measured in LINE-1 and Alu) and hypermethylation in p15 and hypomethylation of MAGE-1 cancer-antigen gene
- This findings show that low-level benzene exposure may induce altered DNA methylation reproducing the aberrant epigenetic patterns found in malignant cells

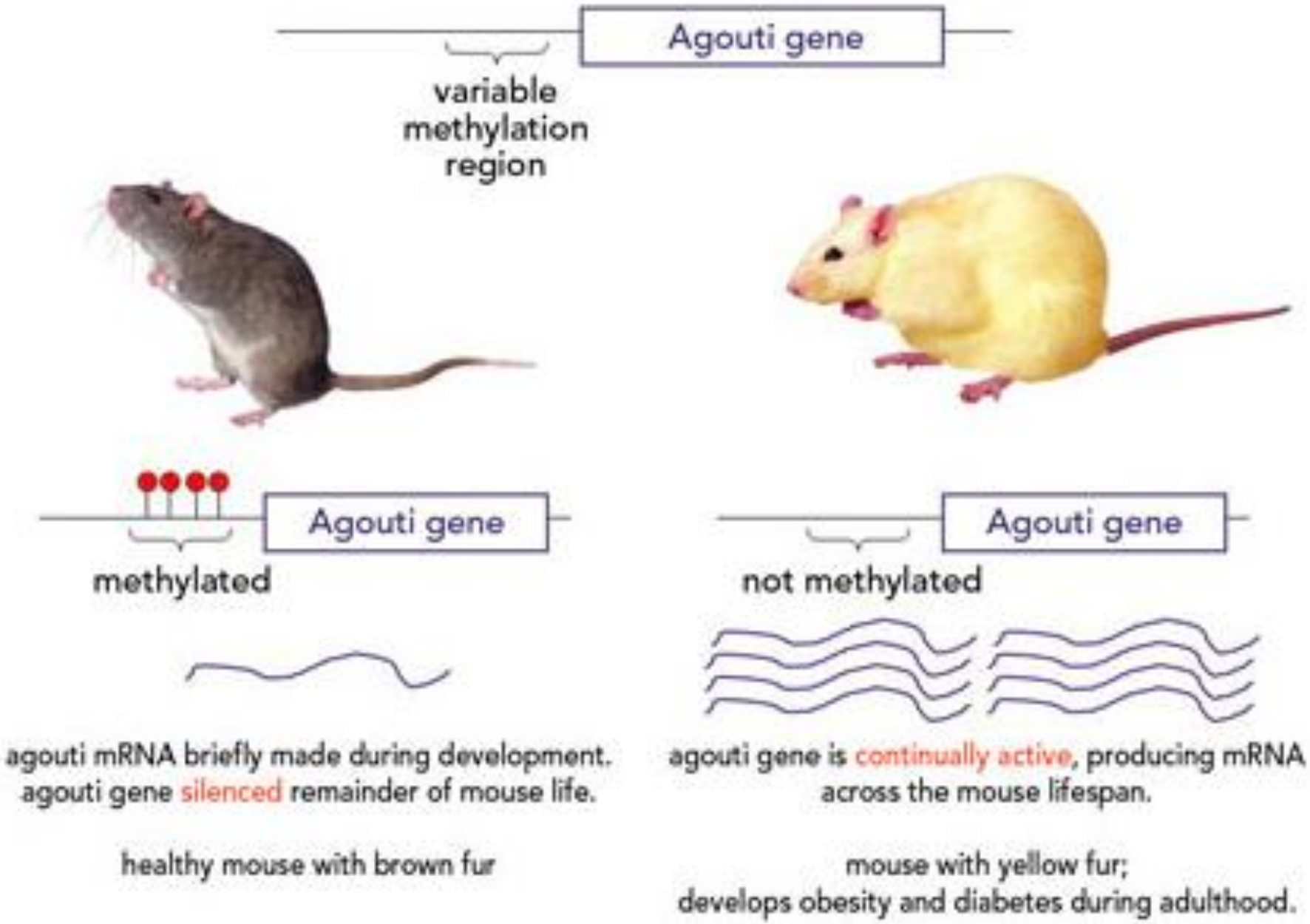
- Proceedings of the International Symposium on Recent Advances in Benzene Toxicity, Munich, Germany, 9-12 October 2004. Chem Biol Interact. 2005
- Bollati V, et al. Changes in DNA methylation patterns in subjects exposed to low-dose benzene. Cancer Res. 2007
- Baccarelli, A and Bollati, V. Epigenetics and environmental chemicals. Current opinion in pediatrics vol. 2. 2009

Endocrine disruptors



Hanna C, Hum Reprod. 2012.

Methylation: Impact on Phenotype ar Disease Risk



Waterland RA, Jirtle RL, Mol Cell Biol. 2003

1 Zygote → Implantation

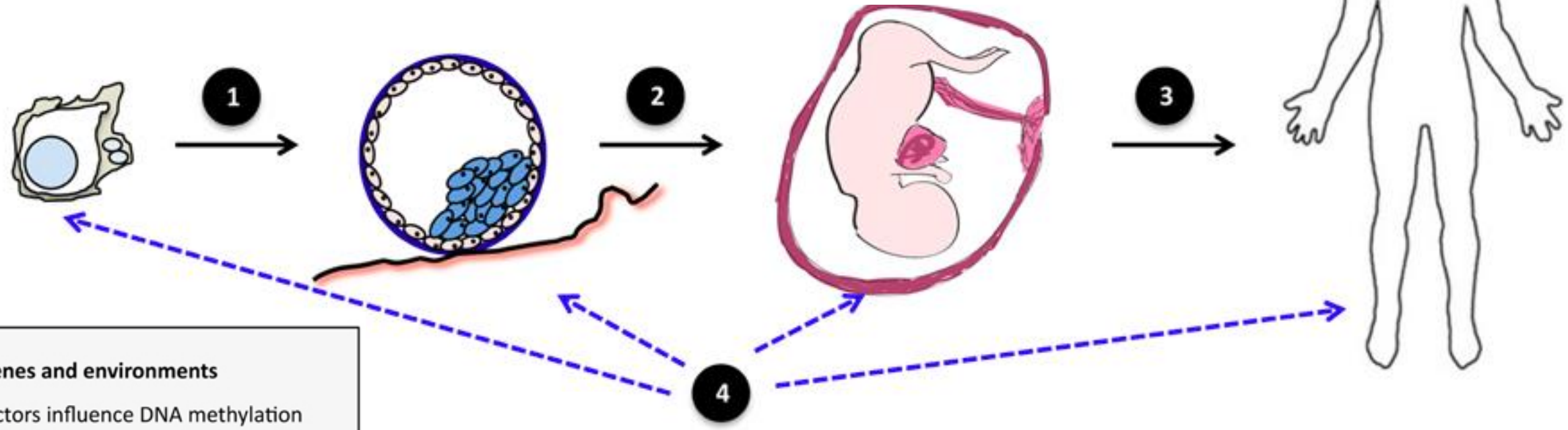
- Global DNA de-methylation occurs
- Passively during cell division and actively by cytosine deamination
- DNA de-methylation allows embryonic stem cells to become pluripotent
- Mono-allelic DNA methylation within imprinted genes is not erased

2 Implantation → Fetal development

- Global re-methylation occurs
- Critical role of *de novo* DNMTs (3a, 3b, and 3L)
- Cell-specific DNA-methylation patterns develop to aid in cell differentiation
- Primordial germ cells undergo second round of DNA-methylation reprogramming: genomic imprints are reestablished to reflect the sex of the embryo

3 Fetal development → Adulthood

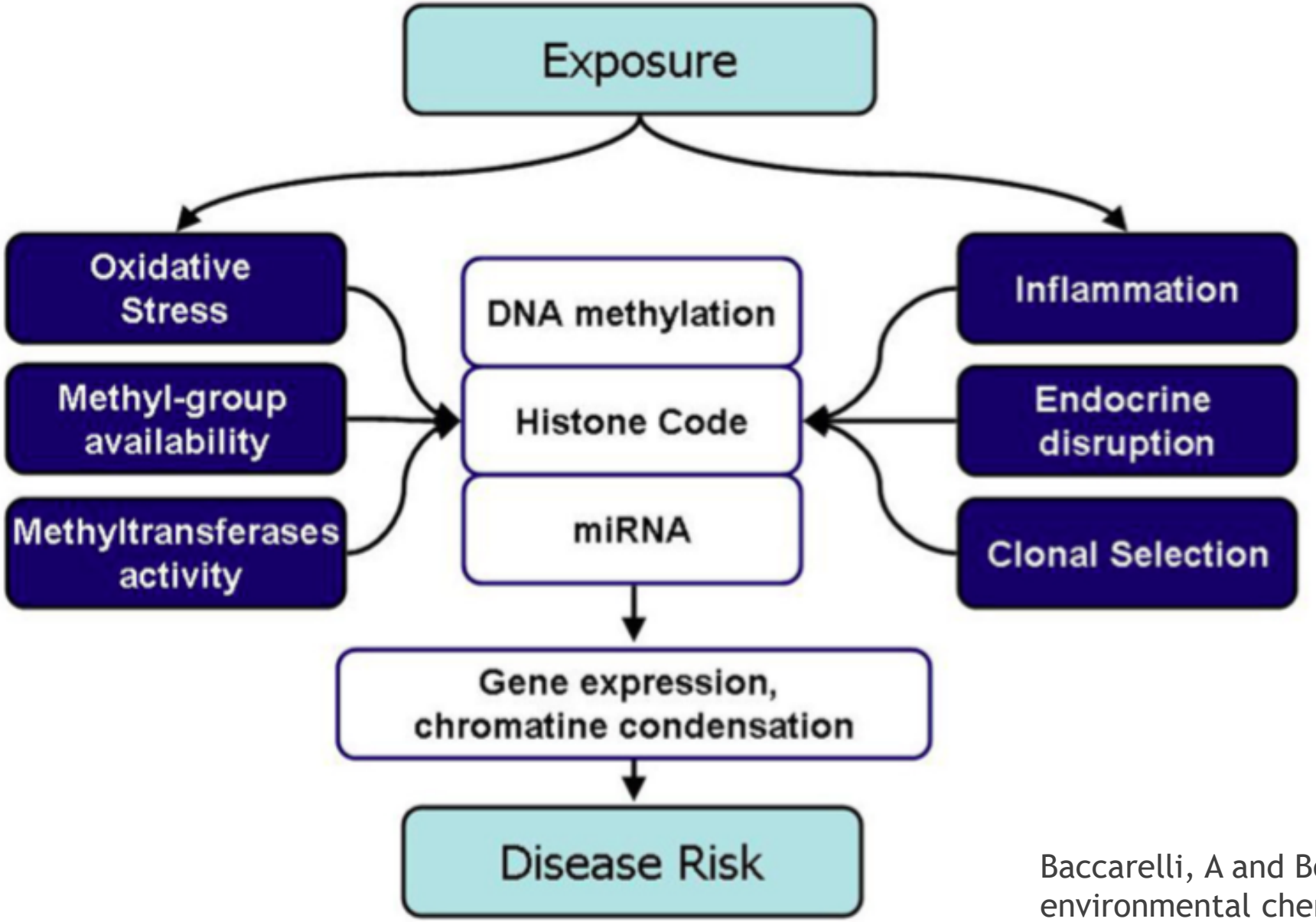
- Established DNA methylome is maintained trough consecutive cell divisions
- Critical role of DNMT1 in maintenance of DNA-methylation patterns during DNA replication
- Aging can modify DNA methylation through *epigenetic drift* (accumulation of small defects in transmitting and maintaining DNA methylation)



4 Genes and environments

- Genetic factors influence DNA methylation
- Environmental exposures, such as **cigarette smoke**, can alter DNA methylation at all stages of human development: early exposure may lead to soma-wide changes, while exposure during adulthood may lead to more tissue-specific changes

Environmental Epigenetics



Baccarelli, A and Bollati, V. Epigenetics and environmental chemicals. 2009

How to support methylation and reduce risk of toxicity

- Reduce chemical and toxic load
- Optimise diet and nutrient intake
- Improve sleep
- Reduce stress
- Be active and aim for a healthy weight

Table 9

Selected dietary sources of nutrients for methylation support (adapted from [111]).

Methionine	Meats, poultry, fish, shellfish, egg, nuts (especially Brazil nuts), seeds (especially sesame seeds and pumpkin seeds), spirulina, teff, soybeans Lower amounts found in other legumes and whole grains (especially teff and oats)
Vitamin B12	Meats and meat products (especially liver and kidney), poultry, fish, shellfish, and eggs
Vitamin B6	Meats, nuts (especially pistachio), garlic, whole grains, seeds (especially sesame and sunflower seeds), legumes (especially chickpeas and lentils), and prunes
Betaine	Quinoa, beets, spinach, whole grains (especially rye, kamut, bulgur, amaranth, barley, and oats) sweet potato, meats, and poultry
Folate	Beans and legumes (especially mung beans, adzuki beans, chickpeas, and lentils), liver, nuts (especially peanuts), seeds (especially sunflower seeds), spinach, asparagus, mustard greens, and avocado
Magnesium	Seeds (especially pumpkin seeds and sesame seeds), beans (especially soybeans), nuts (especially Brazil nuts and almonds), and whole grains (especially amaranth)

Hodges, R and Minich, D. "Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application." *Journal of nutrition and metabolism* vol. 2015

Supplements to support methylation

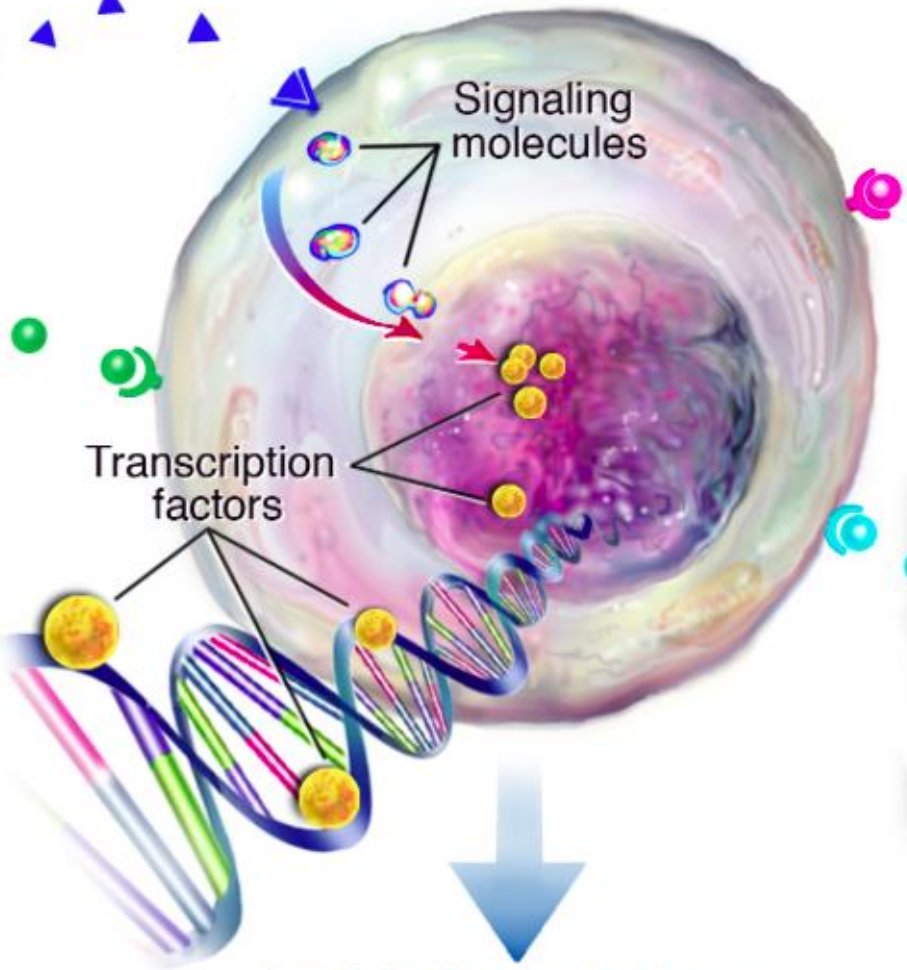
- Folate: Folic acid, Folinic acid and 5-methylTHF
  - 200µg - 400µg folic acid saturation (effects DHFR) – Lucock
  - Dosage - Generally max of 1 mg
    - NTDs, BMI > 30, overall/holistic approach
- Must have adequate B12, B6, B3, B2 before considering folate supplementation
- Magnesium, zinc, vit C
- Those with folate related SNPs that slow enzyme activity may benefit from active forms of folate
- Quality supplements (Nrf2 upregulators, glutathione etc)

Epigenetics and Gene Activation
for Improved Health and Longevity

Excercise
- BDNF

Environment
- Clean air, water and soil
- No smoking

Nutritional Factors
- Calorie Restriction
- Mediterranean Diet
- Polyphenols



Emotional Health
- Religion
- Meditation
- Spirituality

Anti-Inflammatory
Anti-oxidant, Anti-mutation

Summary

- Methylation is associated with various functions in the body and can impact on detoxification, hormone levels, mood, fertility and overall health
- Methylation abnormalities may increase susceptibility to various environmental toxins
- Environmental toxins can alter methylation status
- Diet, nutrient intake and lifestyle changes can be implemented to support methylation
- Methylation support can help the body tolerate various environmental toxins and reduce risk of disease

Thank you

What form of vitamin B12 and what dose?

- Article in EJCN outlined how to treat B12 deficiency
- Recommends methylcobalamin and adenosylcobalamin
  - Methylcobalamin - methylation and DNA synthesis
  - Adenosylcobalamin - energy production
  - Addresses both functions of B12 deficiency
  - 500–750 µg of each
- Recommends hydroxocobalamin
  - Particularly for smokers
  - If you suspect toxins this may be a better choice
- Paper concludes that oral route is comparable to the intramuscular route for rectifying vitamin B12 deficiency
- Thakkar, K and Billa, G. EJCN, 2015.