
# Impact of Environment on the Epigenome

Lode Godderis (Md, Phd)[1,2]

[1] KULeuven, Center for Environment and Health, Belgium;
[2] Idewe, Heverlee, Belgium

# Outline

- Introduction
- Objective
- Impact environment on health through epigenetics
- Impact environment on development through epigenetics
- Conclusion

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# Introduction

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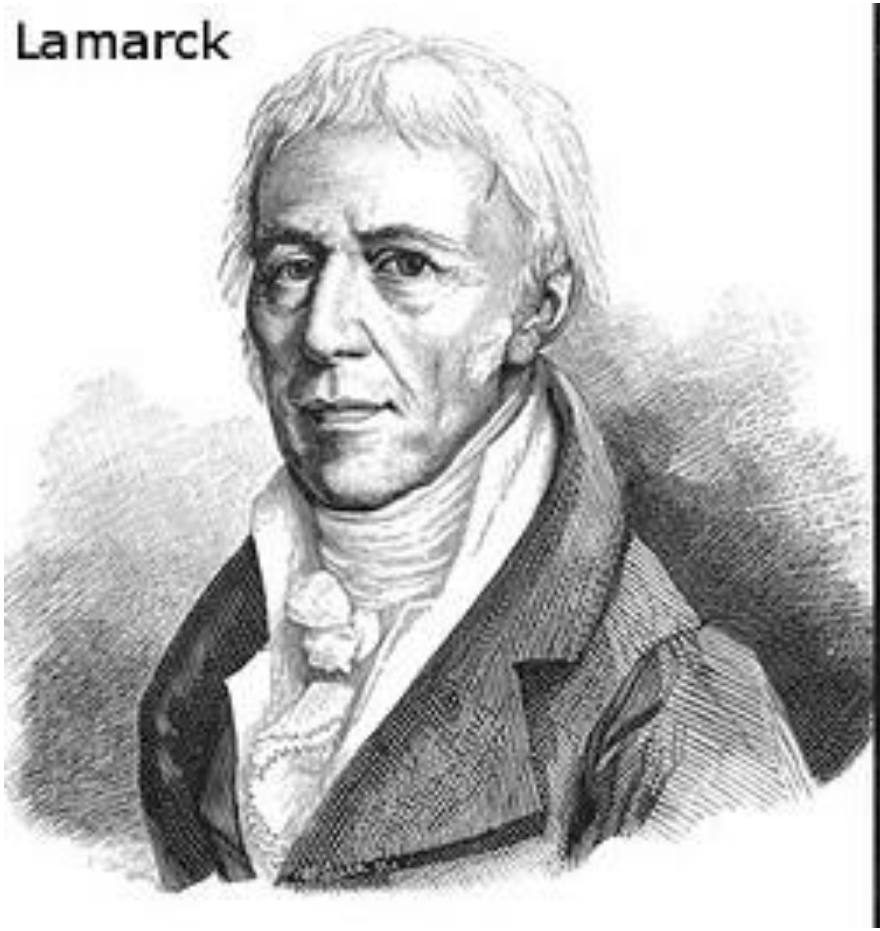
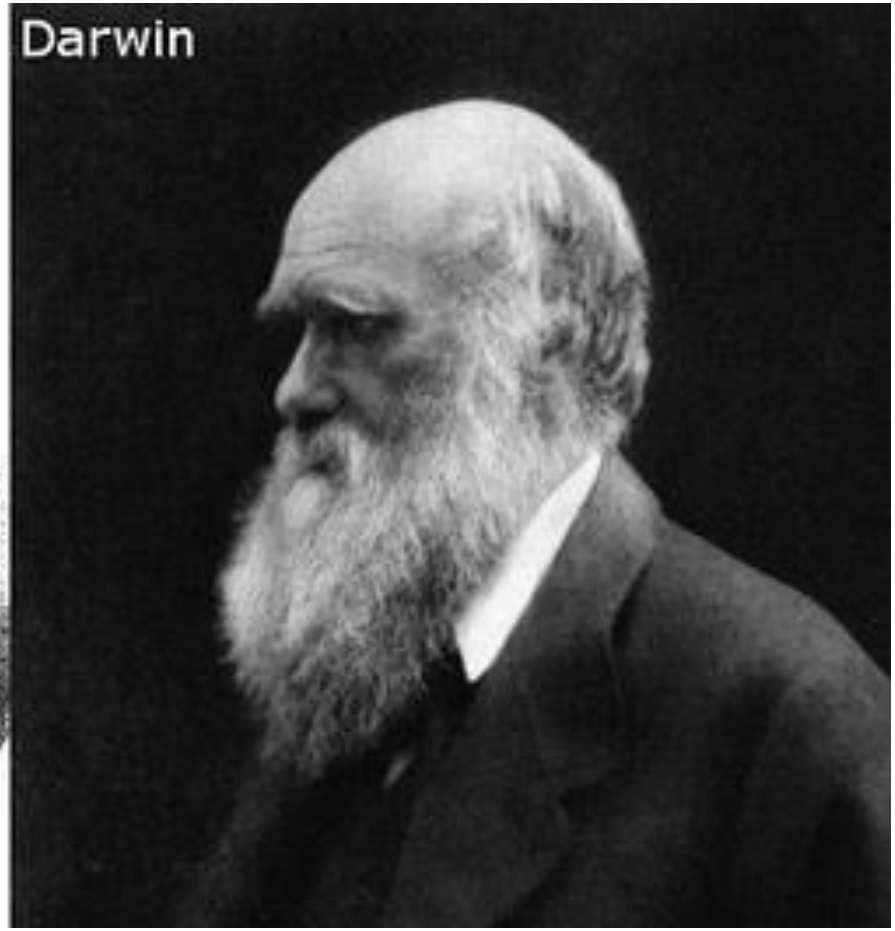
# Introduction

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# Introduction

"Heritable changes that regulate gene expression that occur without change in nucleotide sequence"



Bird (Nature, 2007)

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# Objective

## Impact environment on health through epigenetics


## Impact environment on development through epigenetics


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# Impact environment on health through epigenetics


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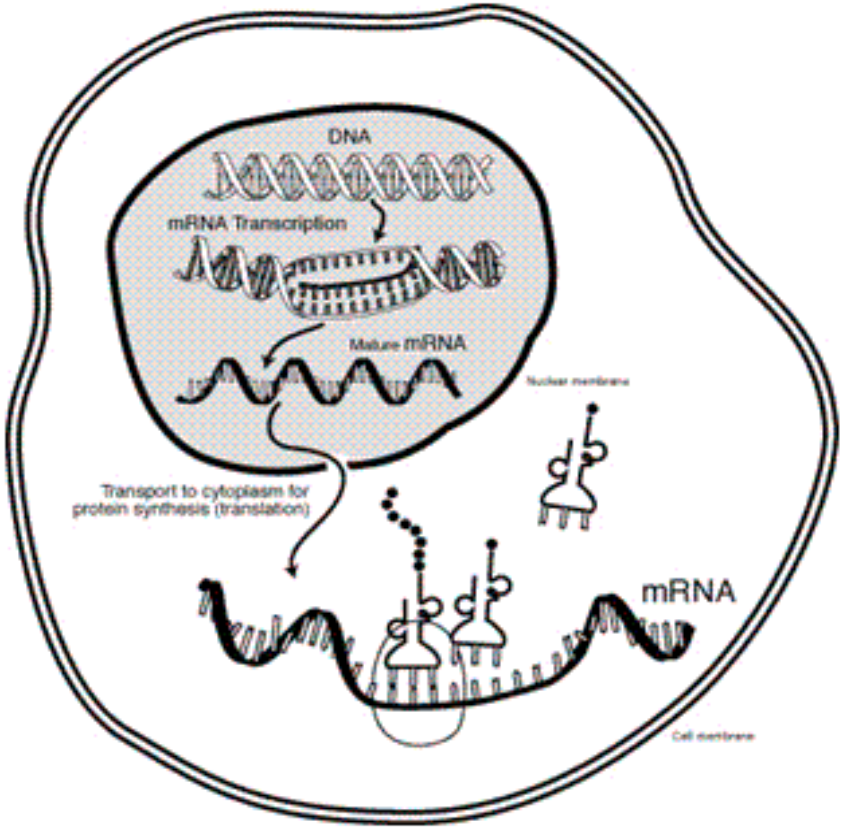
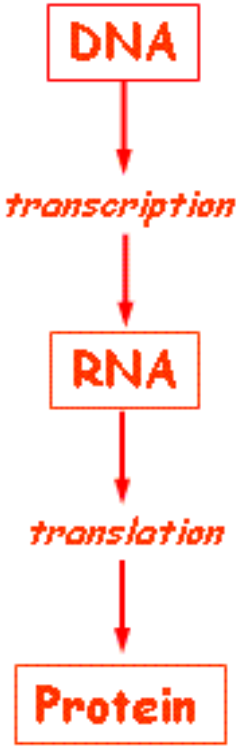
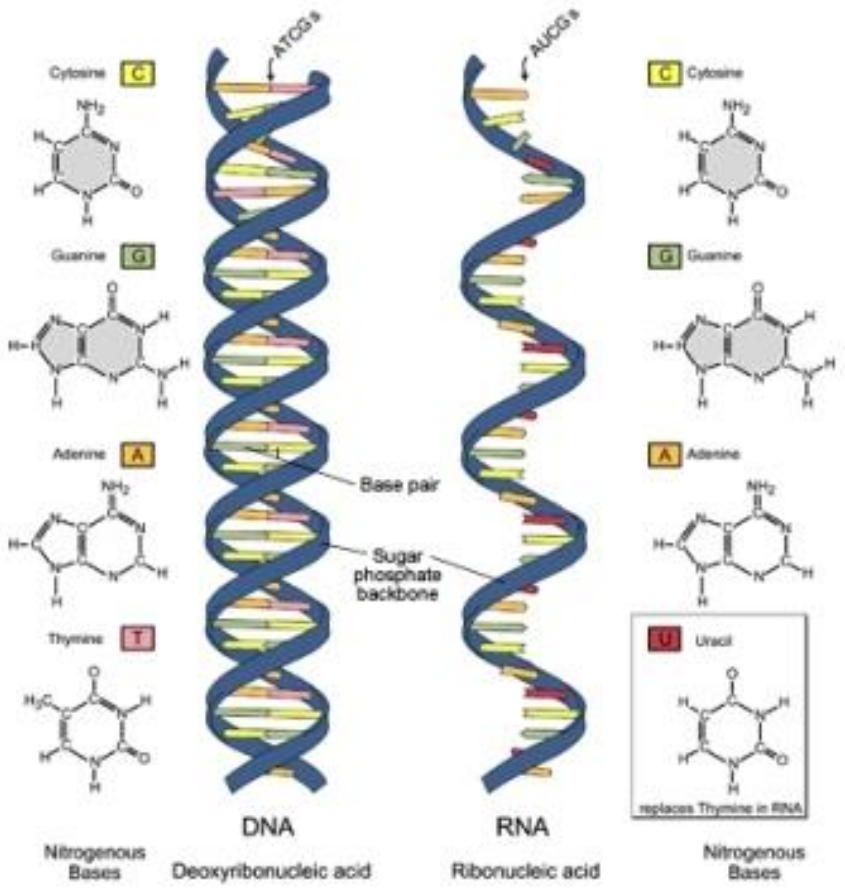
# Genetic mechanisms



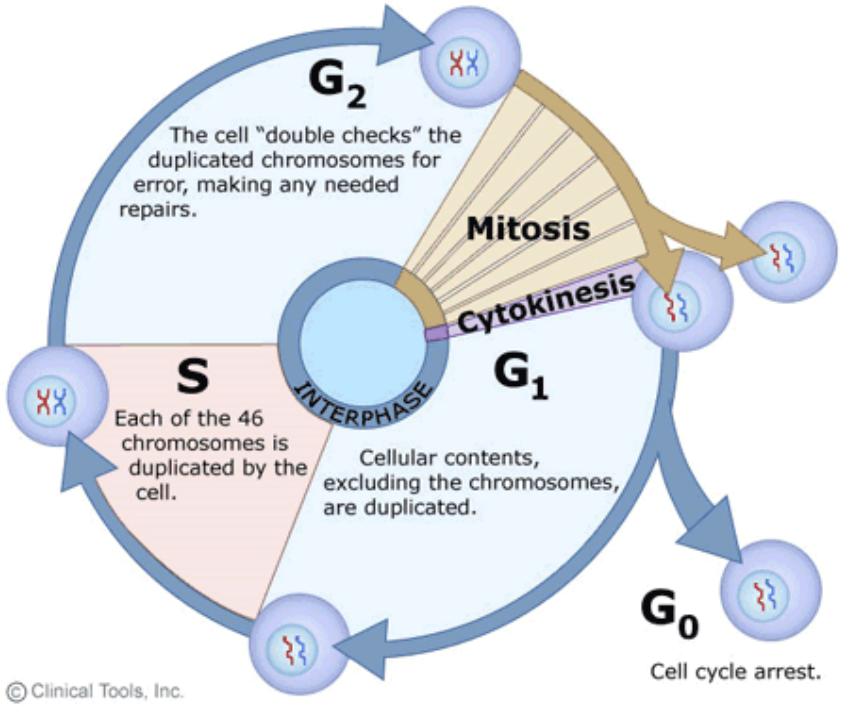
# Genetic mechanisms

- Mutagens
- Intercalating agents and cross-linkers
- Clastogens
- Aneugens

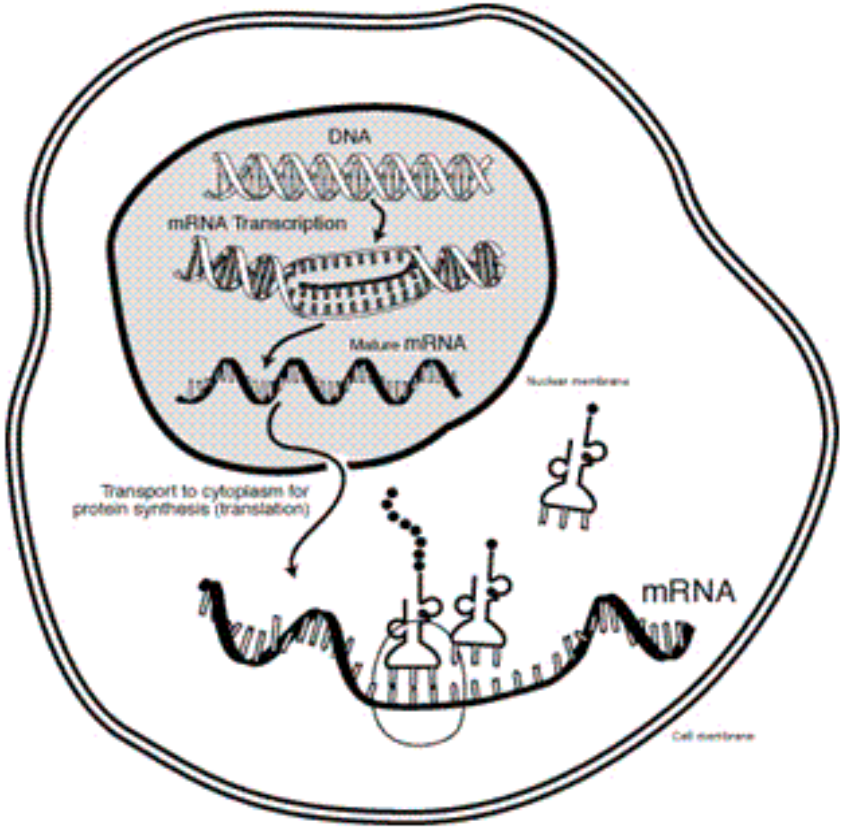


# Genetic mechanisms

- Proto-oncogene ➔ Oncogene
  - Gain of function
  - RAS, MYC
- Tumor suppressor gene
  - Loss of function
  - P53, APC



# Response of cells





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# Response of cells

| Agents | IARC | Category | Concentration (μM) | | |
|---|---|---|---|---|---|
| | | | High | Medium | Low |
| Formaldehyde*,1,2 | 1 | Aldehyde | 100 | 10 | 1 |
| Styrene**,1 | 2B | Aromatic hydrocarbon | 5000 | 500 | 50 |
| Styrene 7,8-oxide*,1 | 2A | Aromatic hydrocarbon | 500 | 50 | 5 |
| Benzene**,1 | 1 | Aromatic hydrocarbon | 100 | 10 | 1 |
| Hydroquinone*,1 | 3 | Aromatic hydrocarbon | 0.5 | 0.05 | 0.005 |
| Mitomycin C*,2 | 2B | Cytostaticum | 0.5 | 0.05 | 0.005 |
| Ethylenedibromide**,1,2 | 2A | Organobromide | 1000 | 100 | 10 |
| Epichlorohydrin*,1 | 2A | Organochloride | 500 | 50 | 5 |
| Acrylamide**,1 | 2A | Amide | 500 | 50 | 5 |
| Trichloroethylene**,1 | 2A | Chlorinated hydrocarbon | 5000 | 500 | 50 |
| Carbontetrachloride**,1 | 2B | Chlorinated hydrocarbon | 1000 | 100 | 10 |
| Cyclophosphamide**,1 | 1 | Cytostaticum | 50 | 5 | 0.5 |
| Benzo[a]fluoranthene**,1 | 2B | Poly aromatic hydrocarbon | 500 | 50 | 5 |
| Benzo[a]pyrene**,1 | 1 | Poly aromatic hydrocarbon | 500 | 50 | 5 |
| Benz[a]anthracene**,1 | 2B | Poly aromatic hydrocarbon | 500 | 50 | 5 |

*Direct acting agent; **Indirect acting agent,
1: DNA adduct forming agent; 2: DNA Cross linking agent.
doi:10.1371/journal.pone.0039205.t001

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Godderis et al. (Plos One 2012)

# Response of cells

| GO ID | GO Processes | Carcinogens* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | AA | BA | BP | CCL | CP | FA | HQ | MMC | ST | TCE |
| GO:0009440 | Cyanate catabolic process | ✓ | ✓ | × | × | × | × | × | ✓ | ✓ | × |
| GO:0019885 | Antigen processing and presentation of endogenous peptide antigen via MHC class I | ✓ | × | × | ✓ | × | ✓ | ✓ | × | ✓ | ✓ |
| GO:0000085 | G2 phase of mitotic cell cycle | × | ✓ | × | ✓ | ✓ | ✓ | ✓ | ✓ | × | ✓ |
| GO:0006977 | DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest | × | ✓ | × | ✓ | ✓ | × | × | × | × | ✓ |
| GO:0050823 | Peptide antigen stabilization | × | × | ✓ | ✓ | × | ✓ | ✓ | × | ✓ | ✓ |
| GO:0001833 | Inner cell mass cell proliferation | × | × | × | × | ✓ | ✓ | ✓ | × | ✓ | × |

* Carcinogens [AA:Acrylamide; BA:Benz[a]anthracene; BP:Benzo[a]pyrene; CCL:Carbontetrachloride; CP:Cyclophosphamide; FA:Formaldehyde; HQ:Hydroquinone; MMC:Mitomycin C; ST;Styrene; TCE:Trichloroethylene]

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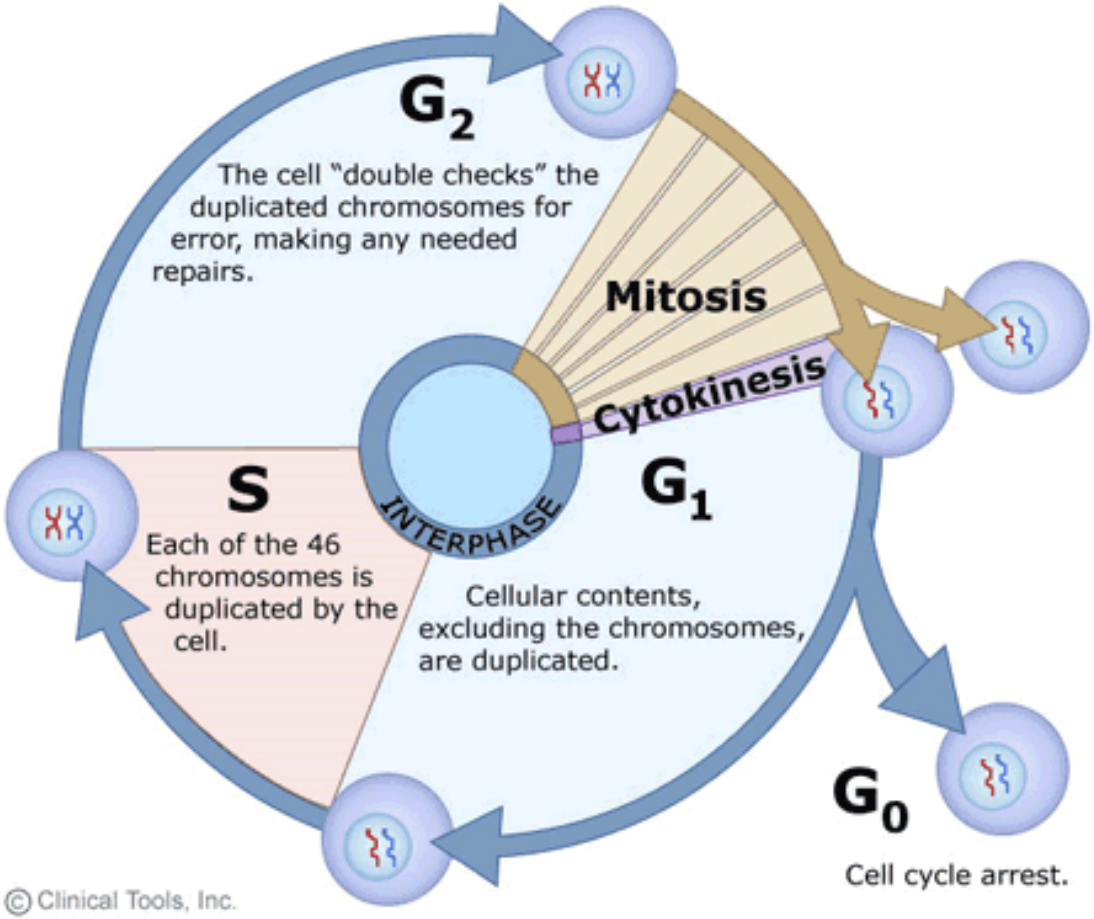
Godderis et al. (Plos One 2012)

# Response of cells



# Response of cells

| GO ID | GO Processes | Carcinogens* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | AA | BA | BZ | EDB | EPI | HQ | SO | ST | TCE |
| GO:0030503 | Regulation of cell redox homeostasis | ✓ | ✓ | × | ✓ | × | × | × | ✓ | × |
| GO:0042789 | mRNA transcription from RNA polymerase I | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | × | × |
| GO:0007050 | Cell cycle arrest | ✓ | × | ✓ | × | ✓ | ✓ | × | ✓ | × |
| GO:0032792 | Inhibition of CREB transcription factor | ✓ | × | × | ✓ | × | ✓ | × | ✓ | × |
| GO:0043065 | Positive regulation of apoptosis | ✓ | × | ✓ | × | ✓ | × | × | ✓ | × |
| GO:0001975 | Response to amphetamine | ✓ | × | ✓ | × | × | ✓ | × | ✓ | × |
| GO:0001711 | Endodermal cell fate commitment | × | ✓ | × | × | ✓ | ✓ | × | × | ✓ |
| GO:0006450 | Regulation of translational fidelity | × | ✓ | × | × | ✓ | ✓ | × | × | ✓ |
| GO:0015855 | Pyrimidine transport | × | ✓ | × | × | ✓ | × | ✓ | × | ✓ |
| GO:0030858 | Positive regulation of epithelial cell differentiation | × | ✓ | × | × | ✓ | ✓ | × | × | ✓ |

* Carcinogens [AA:Acrylamide; BA:Benz[a]anthracene; BZ:Benzene; EDB:Ethylenedibromide; EPI:Epichlorohydrin; HQ:Hydroquinone; SO:Styrene 7,8-oxide; ST:Styrene; TCE:Trichloroethylene]

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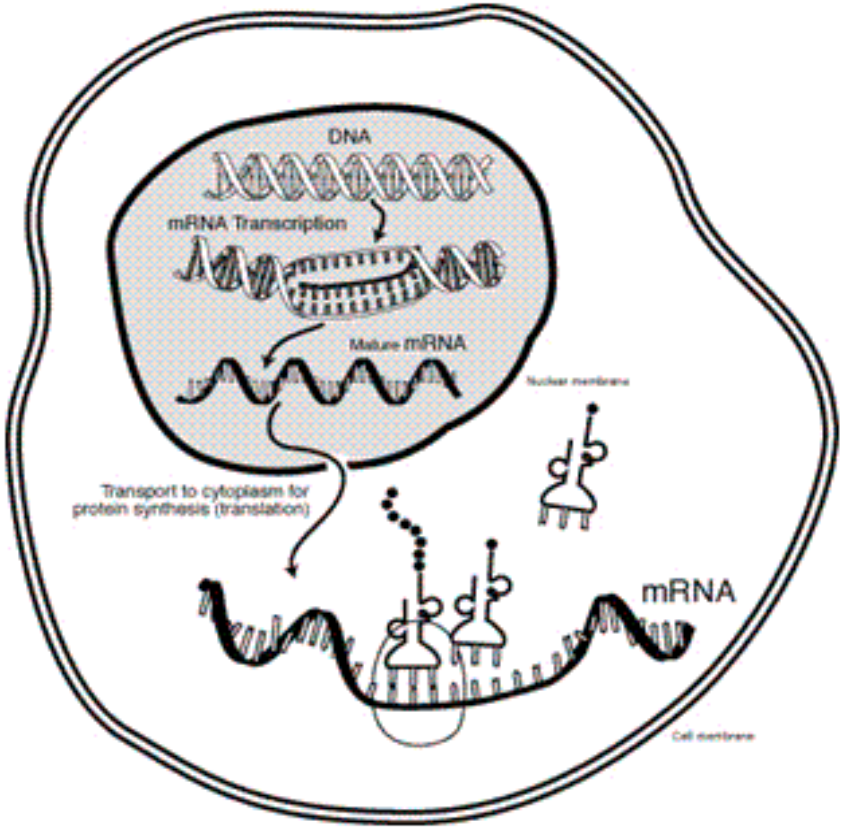
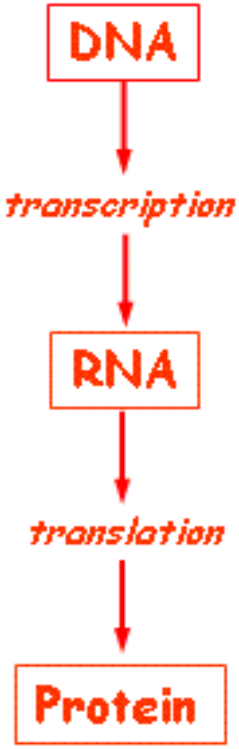
Godderis et al. (Plos One 2012)

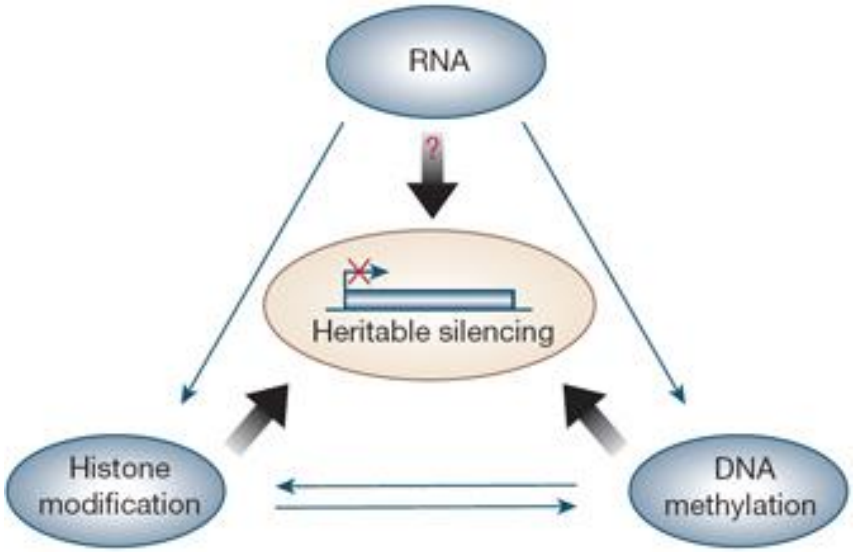
# Epigenetic mechanisms



# Epigenetic mechanisms

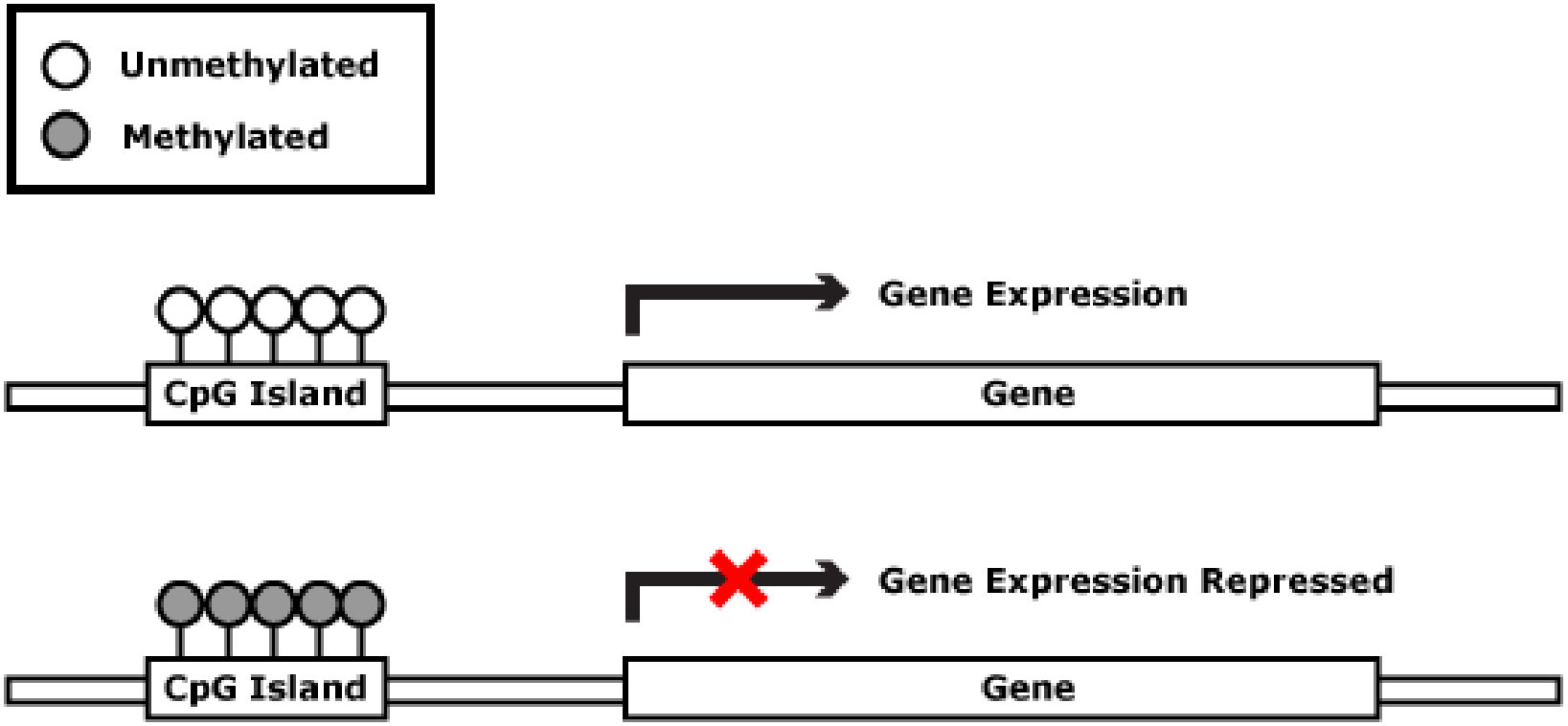
- DNA methylation
- Histone modification
- Non-coding RNA



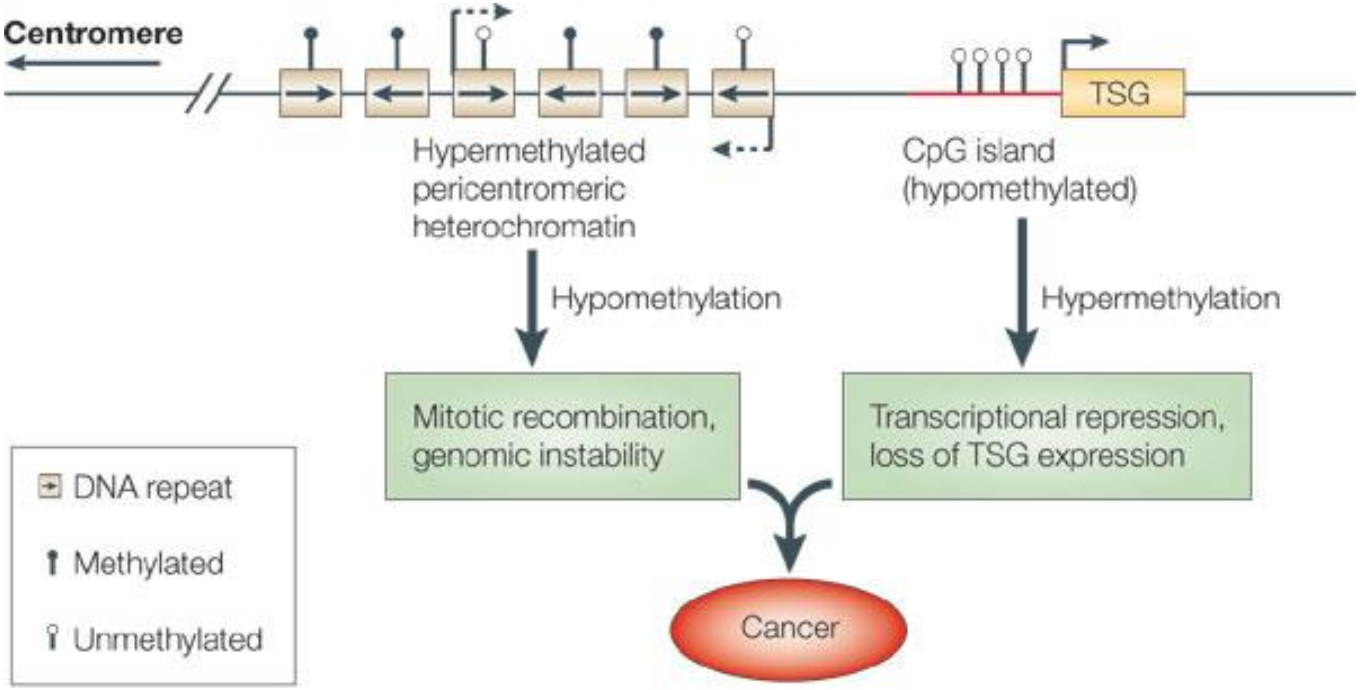
# Epigenetic mechanisms

- **DNA methylation**
- Histone modification
- Non-coding RNA

# Epigenetic mechanisms: gene-specific DNA methylation

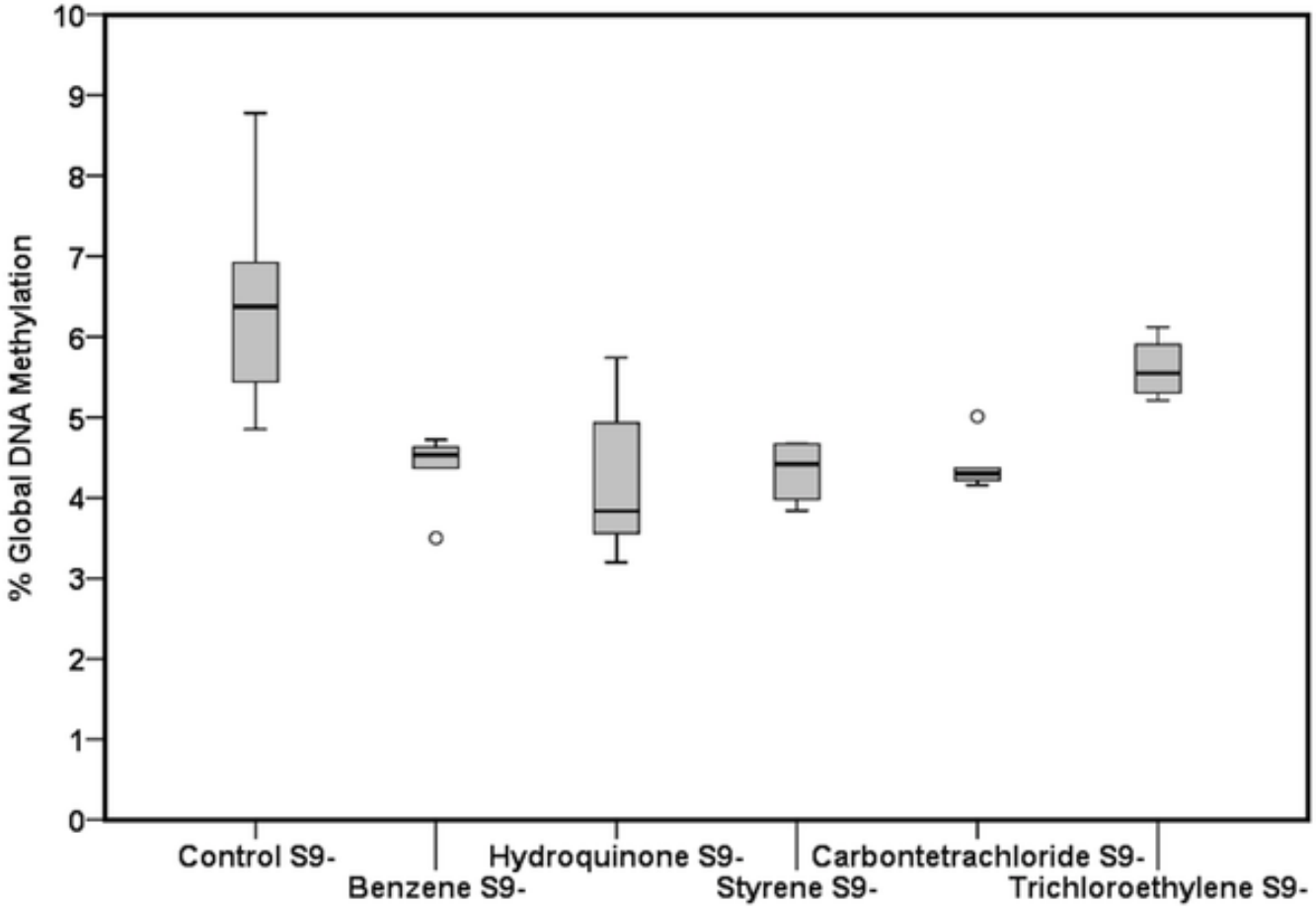


# Epigenetic mechanisms: global DNA methylation




Robertson (Nat Rev Genet, 2005 )

# Epigenetic mechanisms: global DNA methylation

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Tabish et al. (Plos One, 2012)

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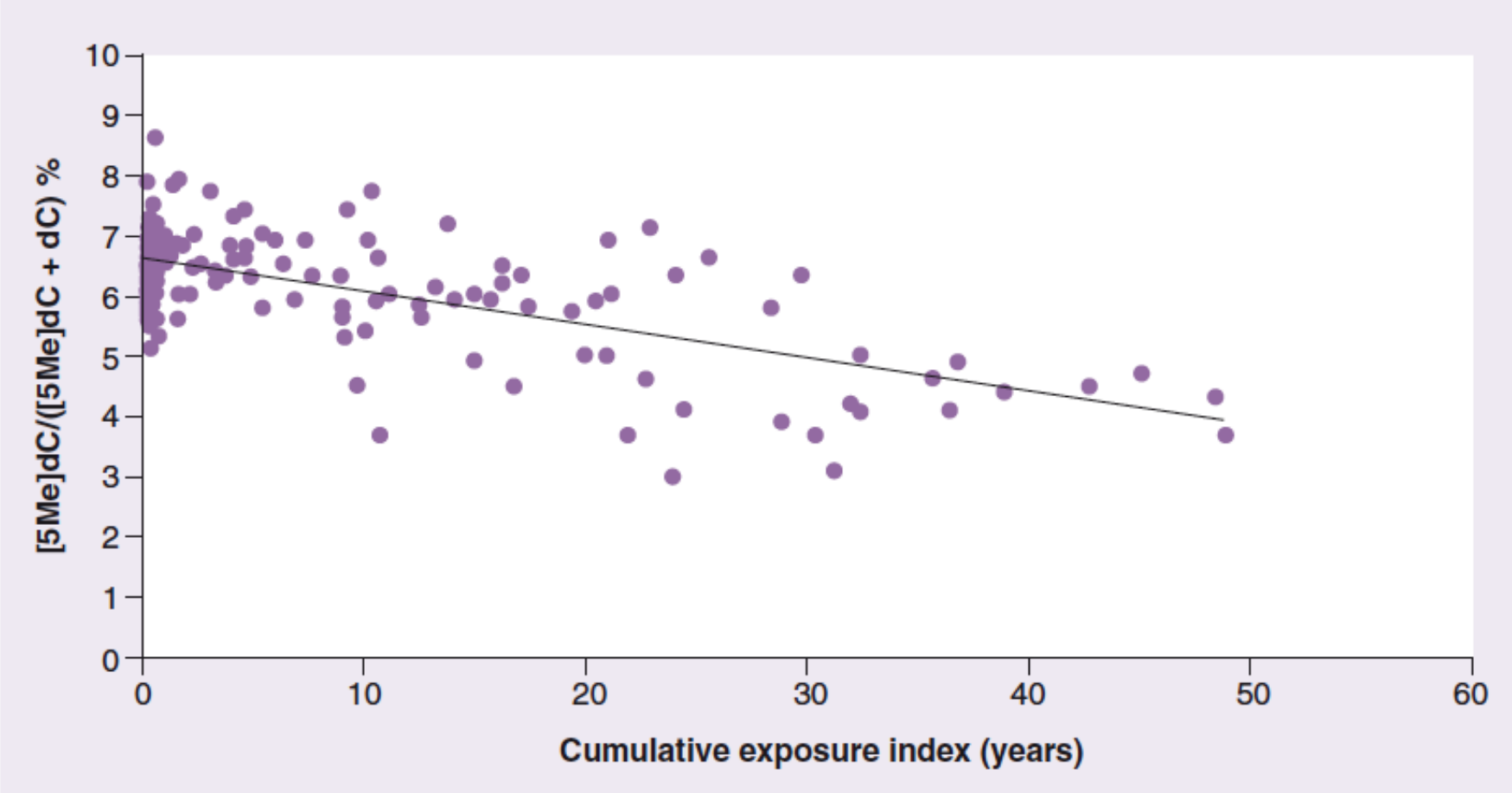


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Godderis et al. (Epigenomics, 2012)

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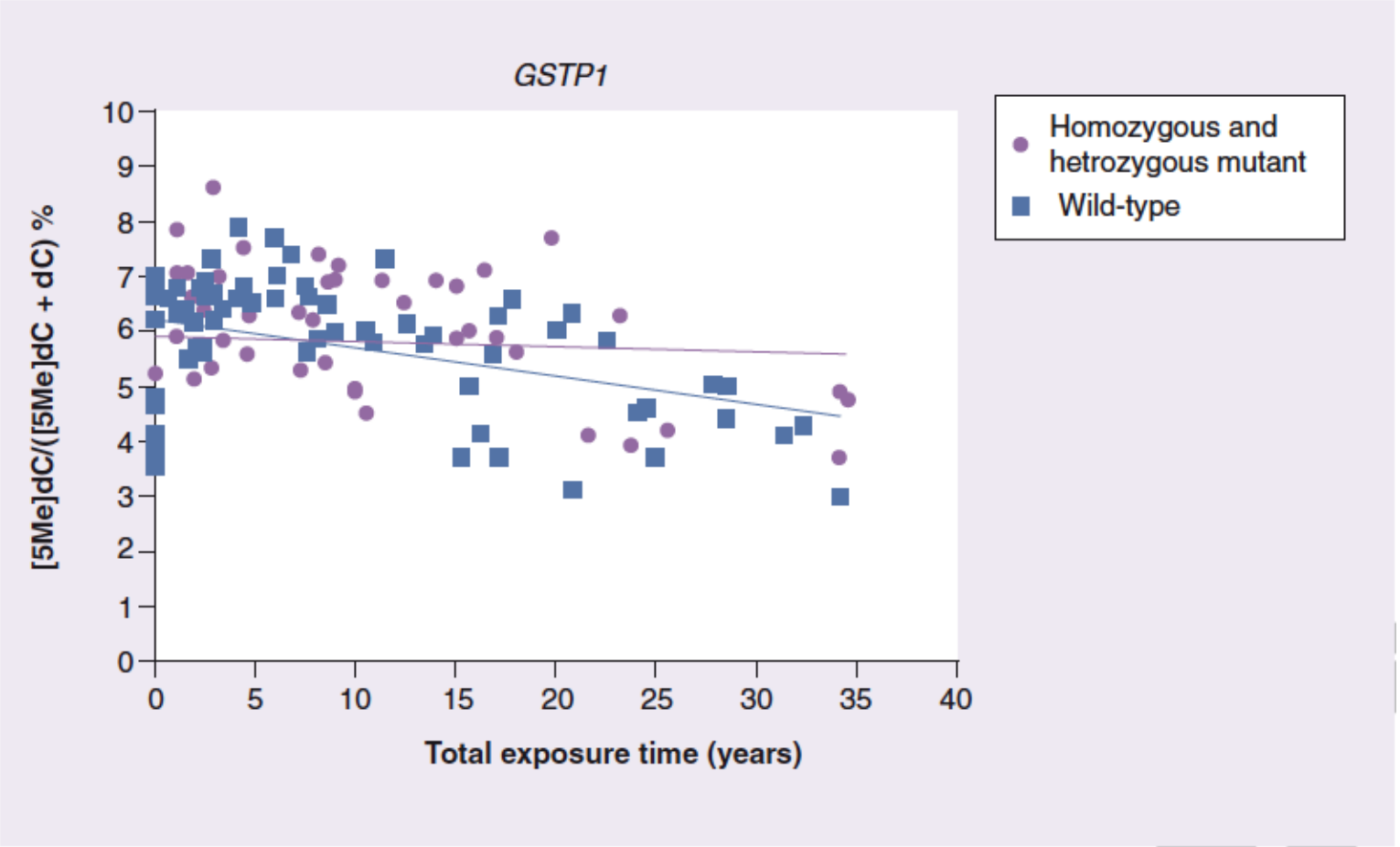


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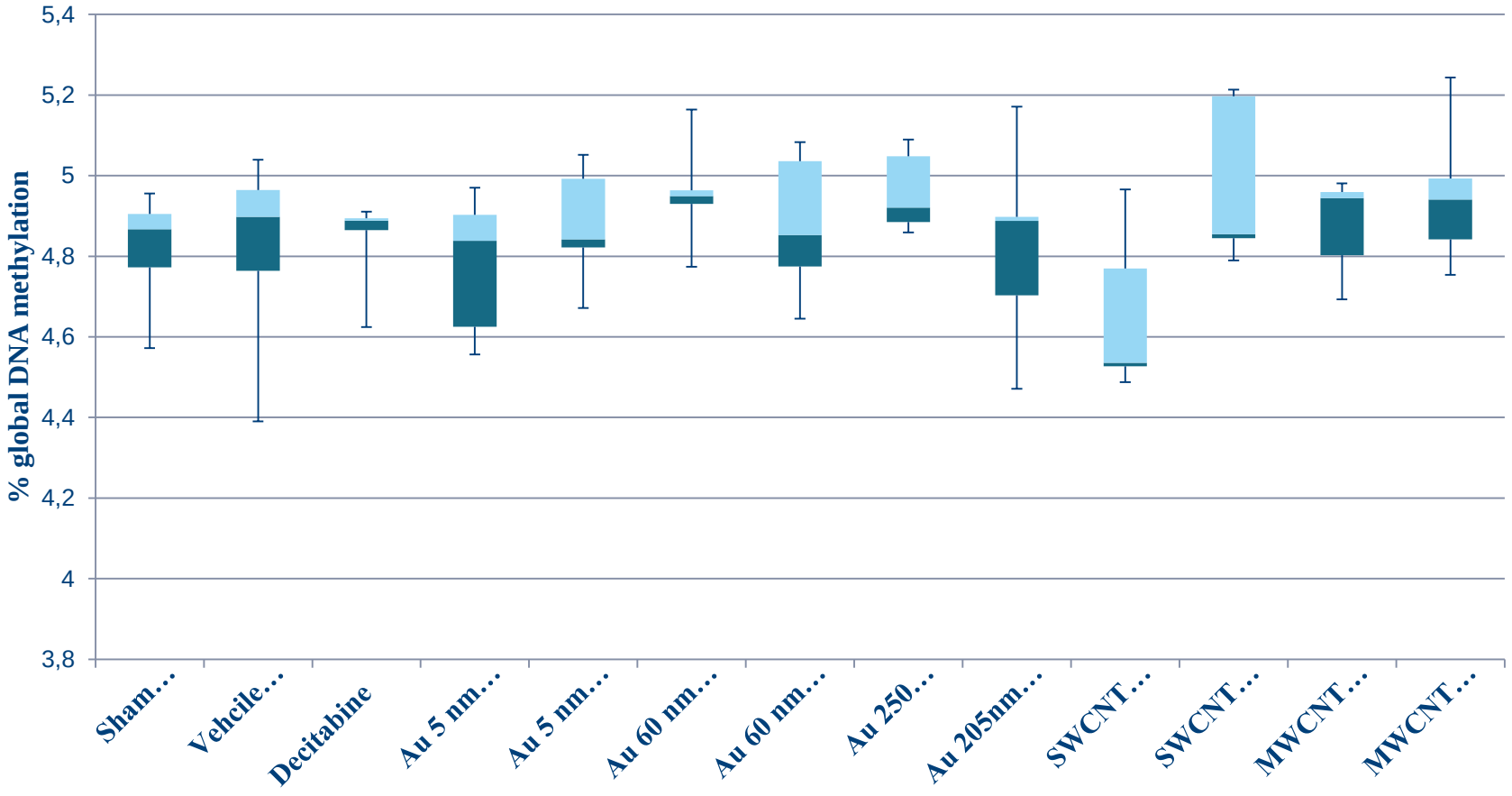


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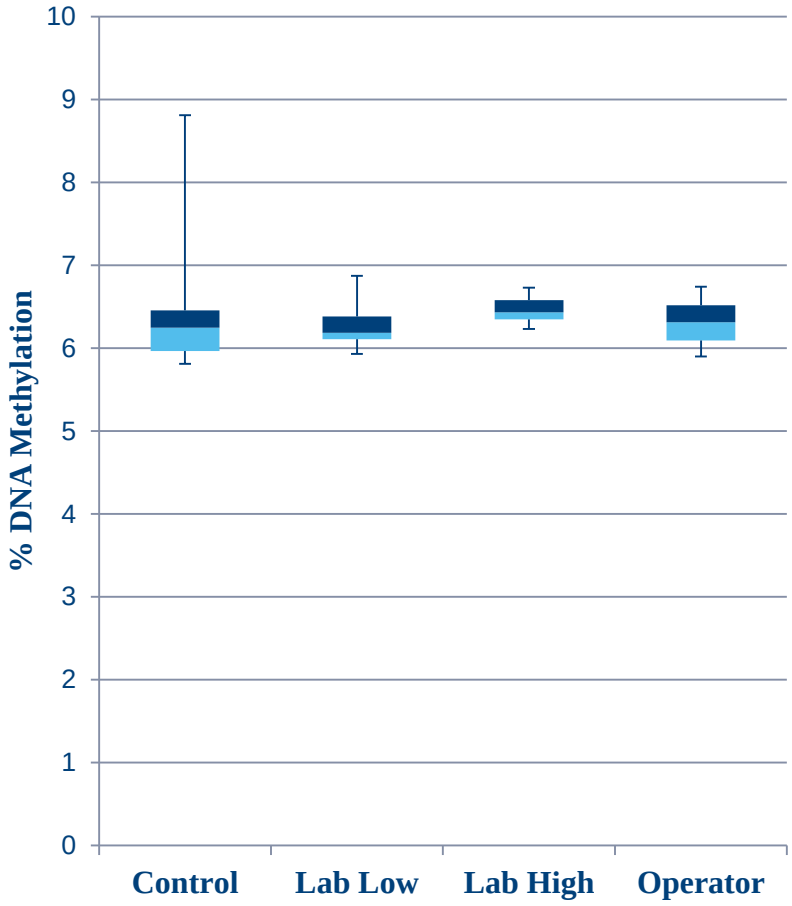


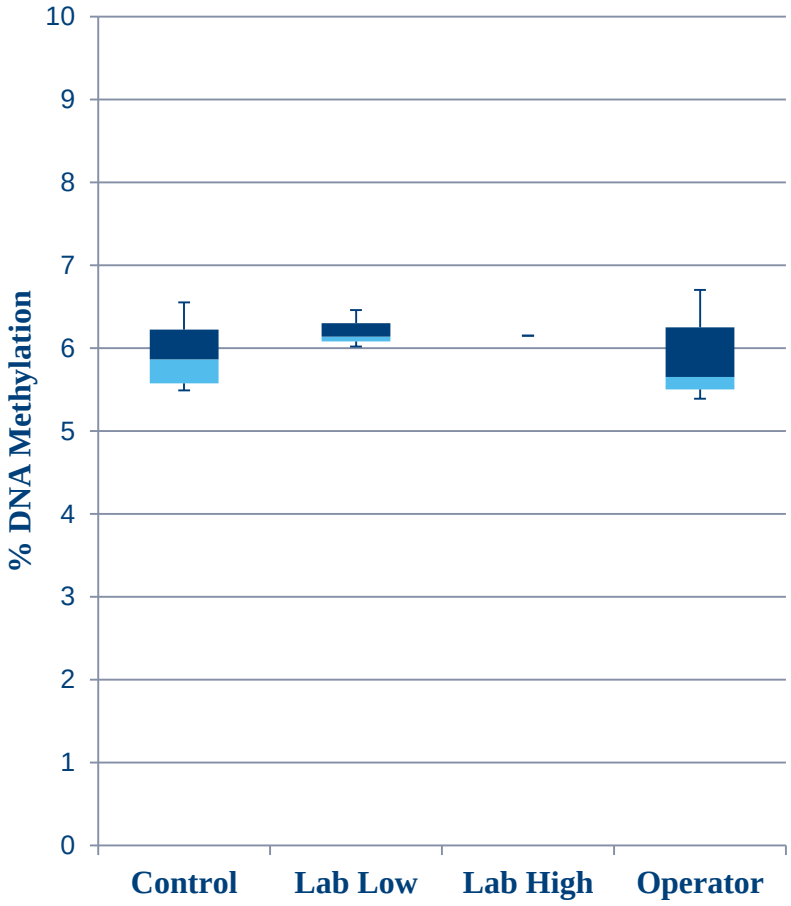


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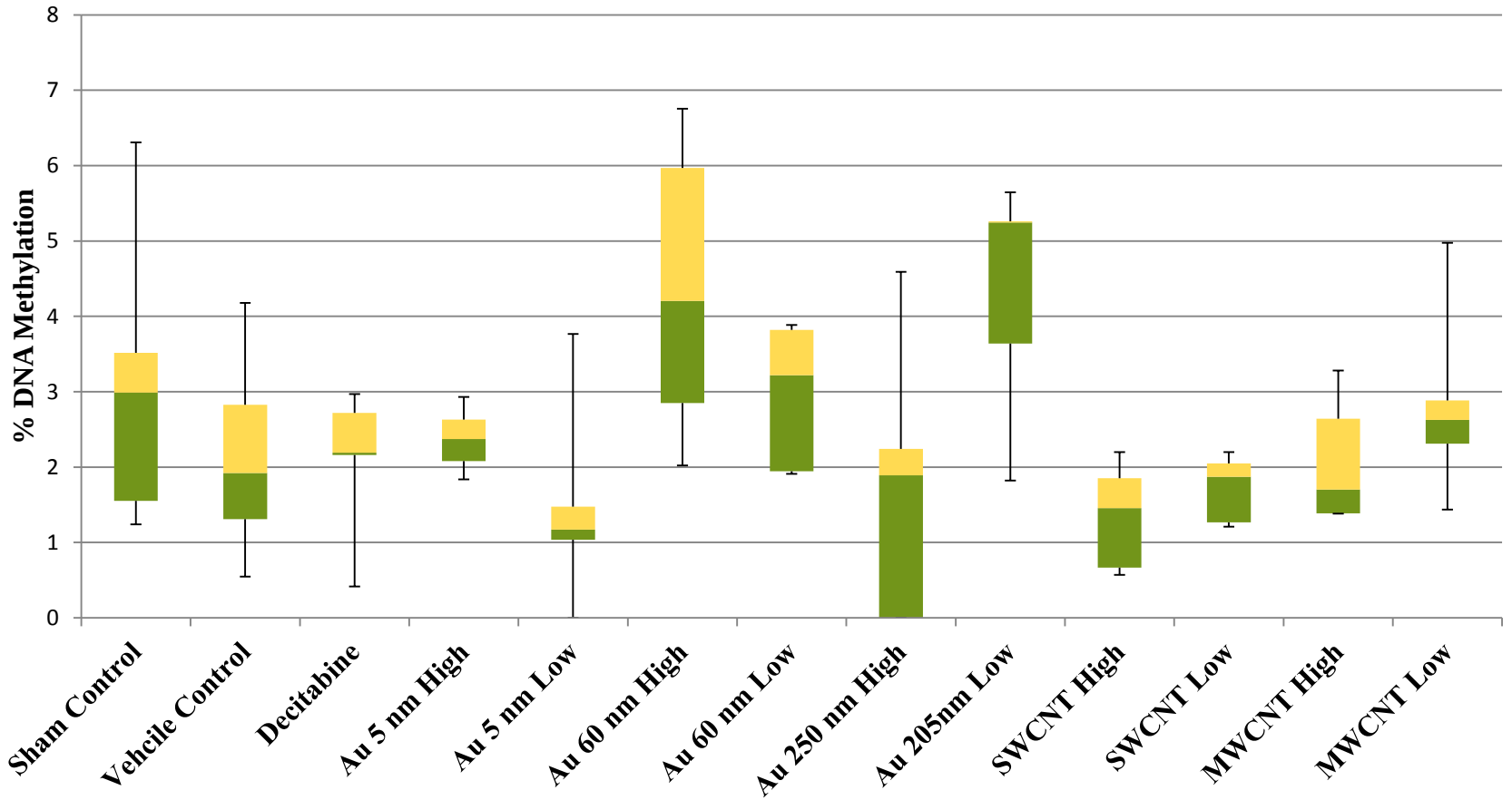
# Epigenetic mechanisms: gene-specific DNA methylation

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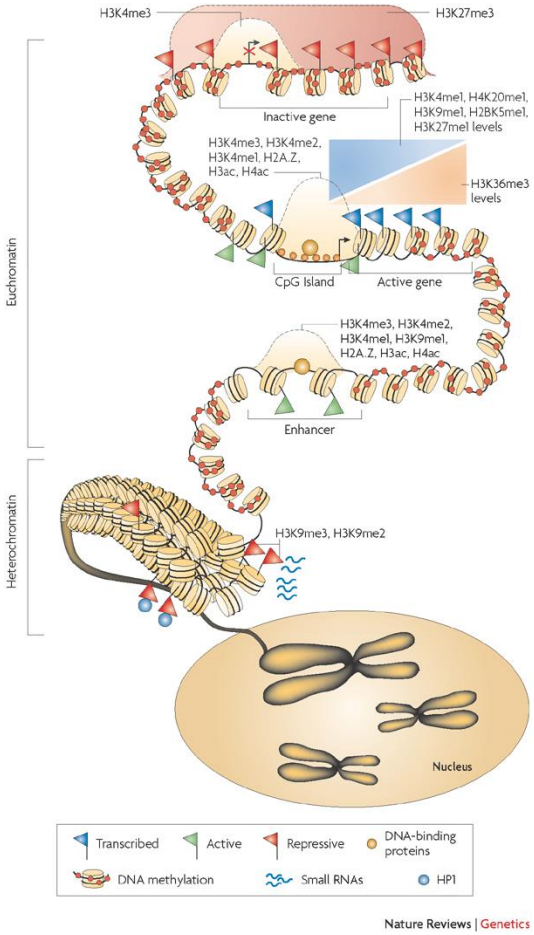
# Epigenetic mechanisms

- DNA methylation
- **Histone modification**
- Non-coding RNA

# Epigenetic mechanisms: histone modification

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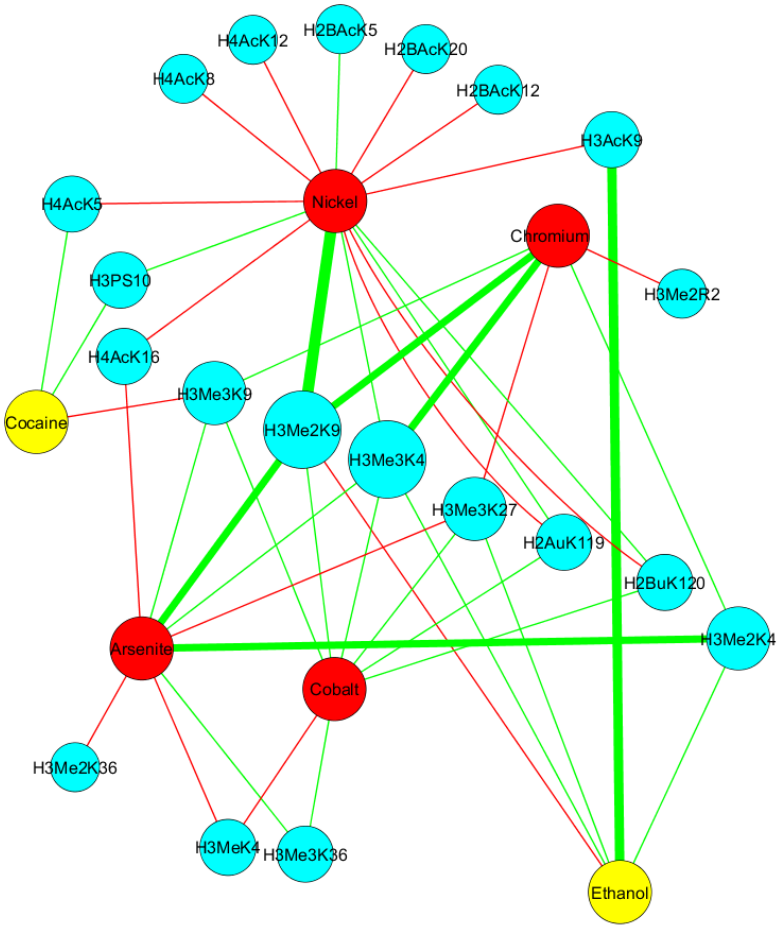
Schones and Zhao (Nature Revi Gen, 2008)

# Epigenetic mechanisms: histone modification

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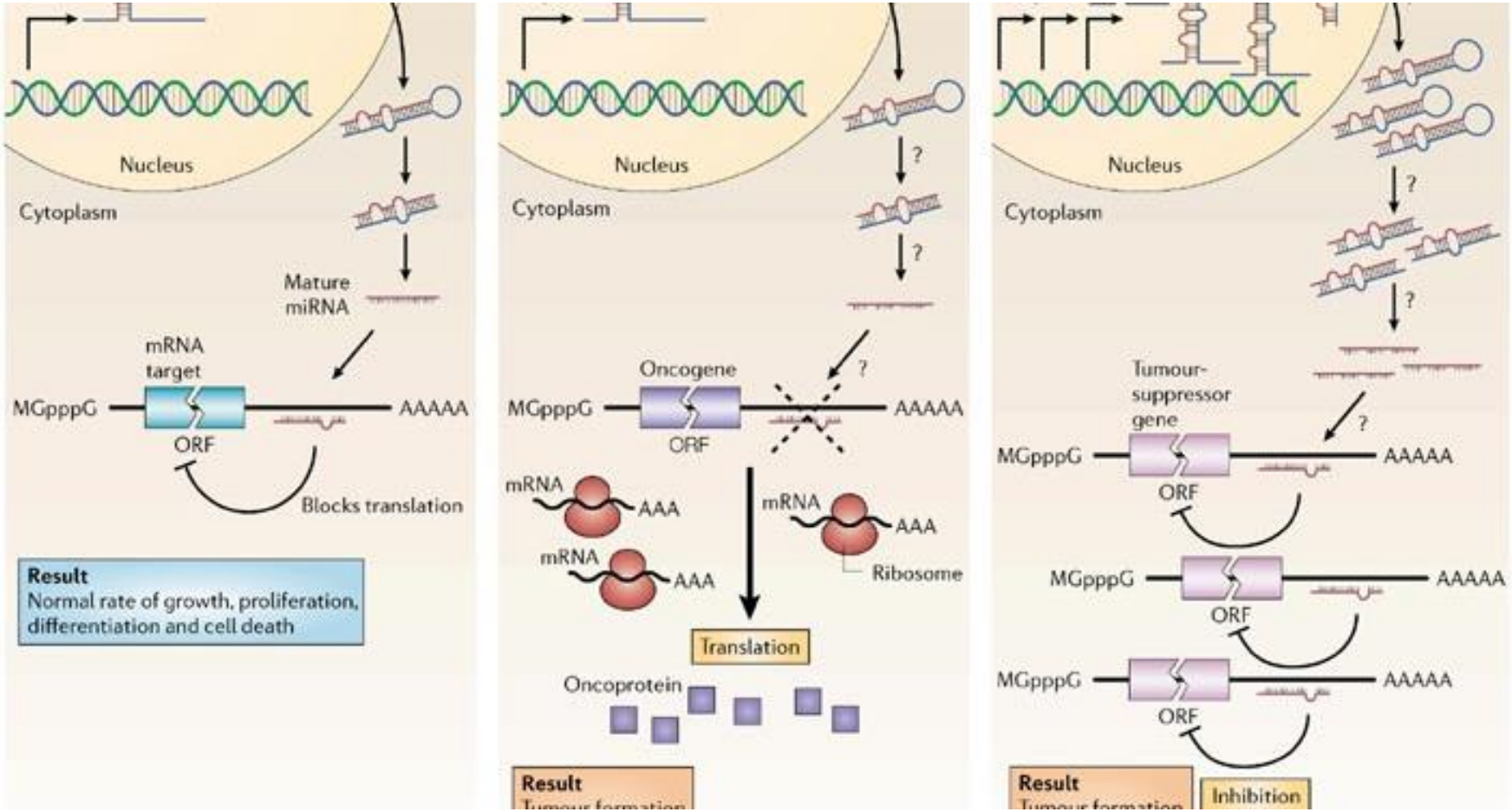
Dik et al. (Crit Rev in Tox, 2012)

# Epigenetic mechanisms

- DNA methylation
- Histone modification
- **Non-coding RNA**

# Epigenetic mechanisms: non coding RNA

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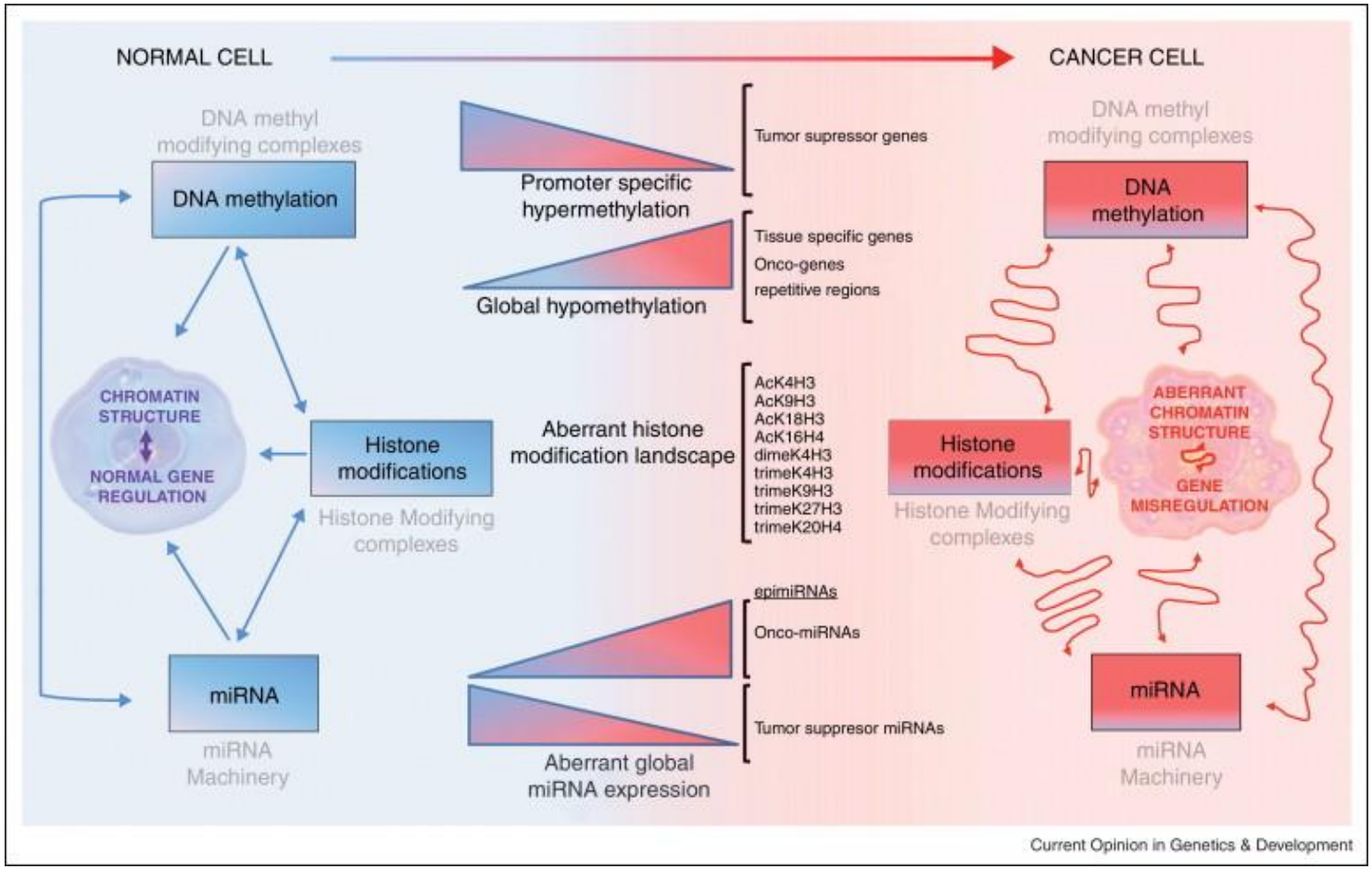
Esquela-Kerscher and Slack (Nature Reviews Cancer, 2006)

# Epigenetic mechanisms and cancer




Sandoval and Esteller (Cur Opin in Gen and Dev, 2012)

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- **Impact environment on development through epigenetics**
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# Impact environment on development through epigenetics


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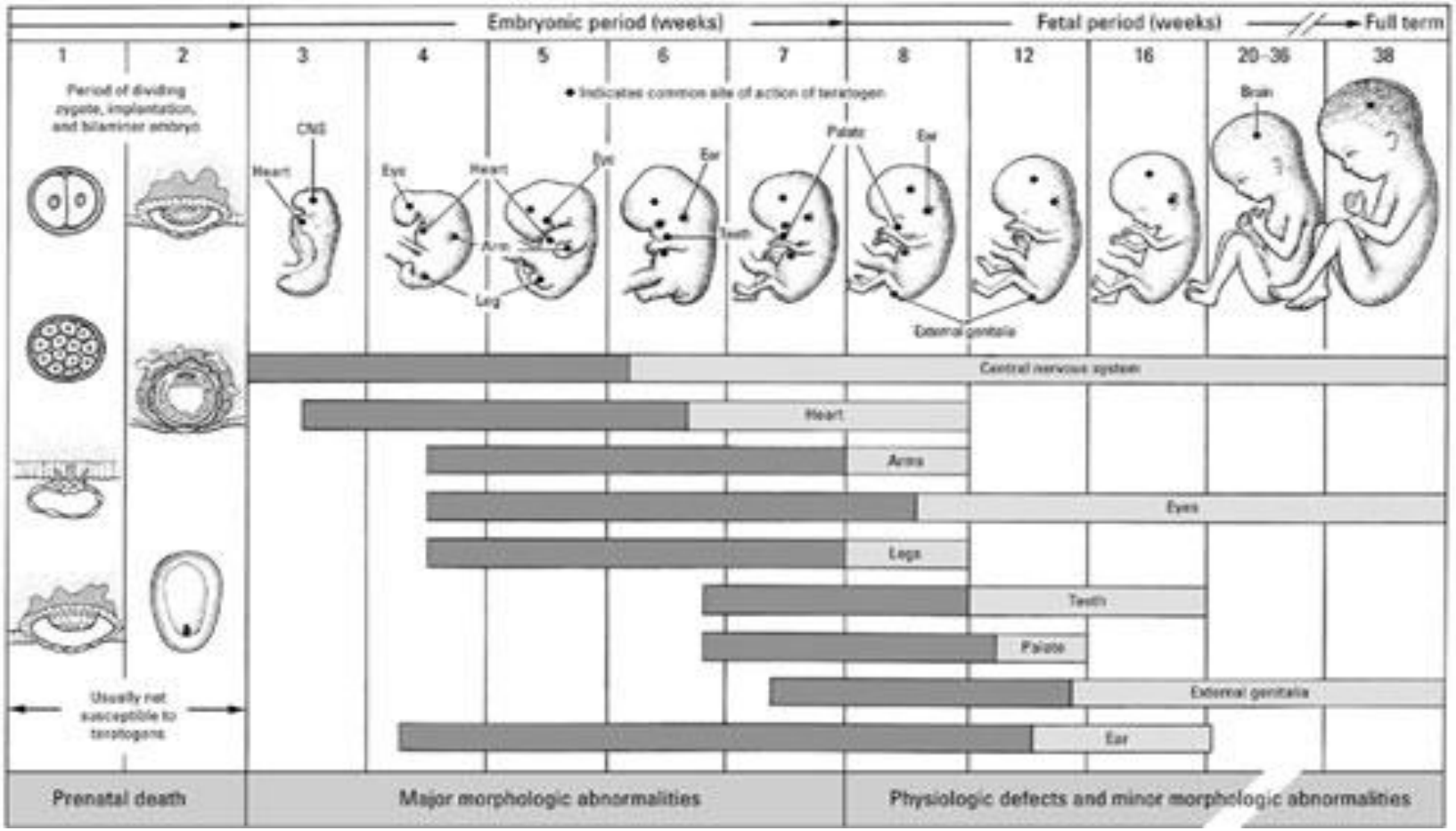
# Impact environment on development through epigenetics

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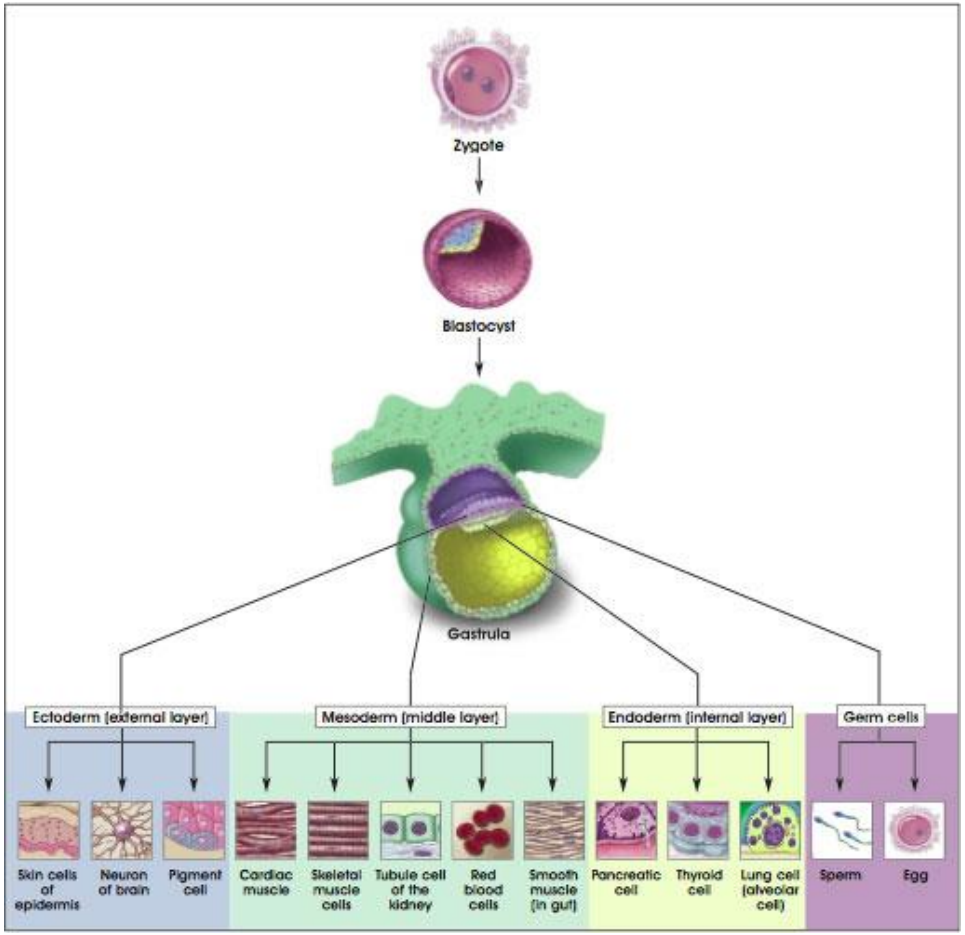
# Epigenetics, a natural mechanism

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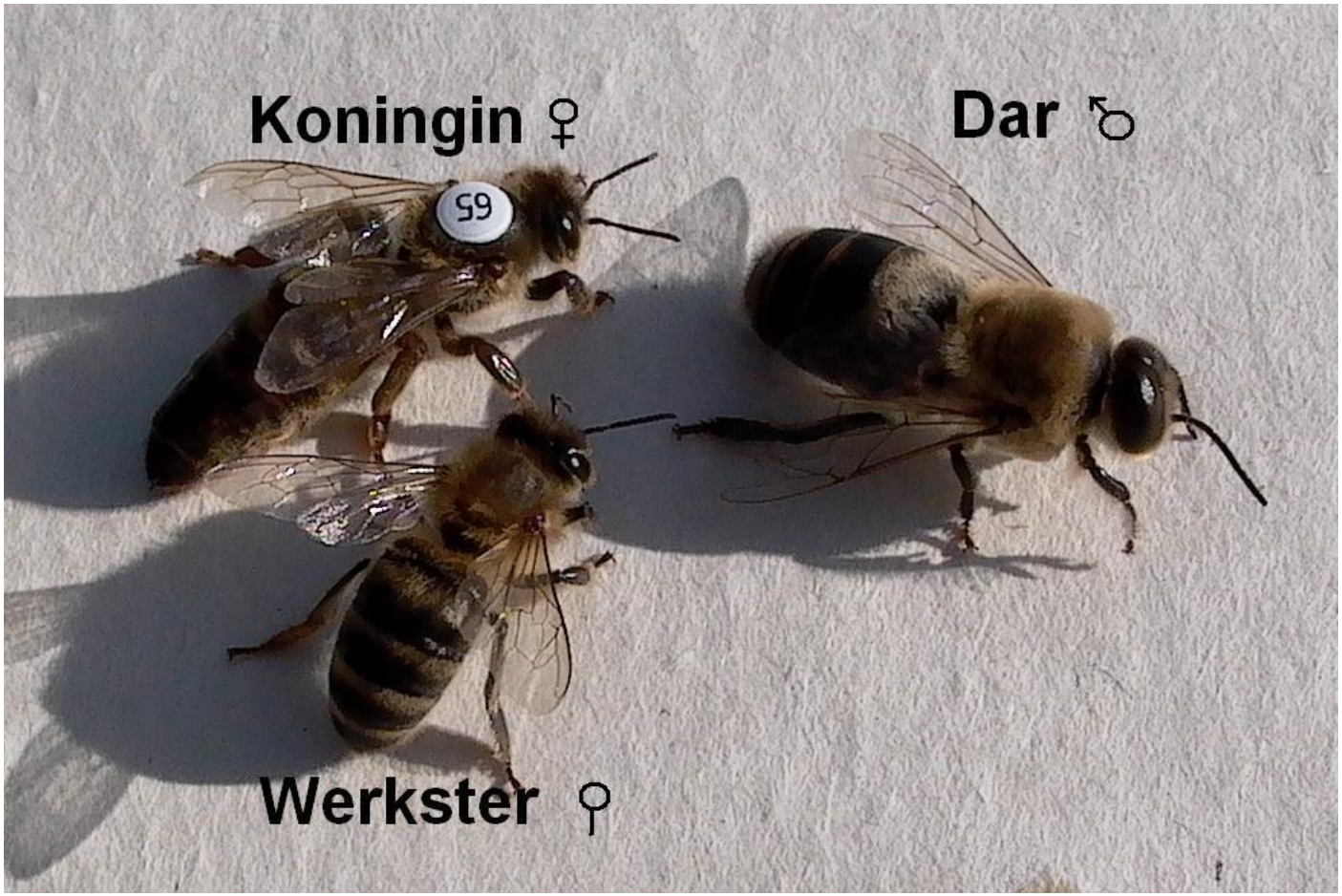
# Cradle and environment do matter

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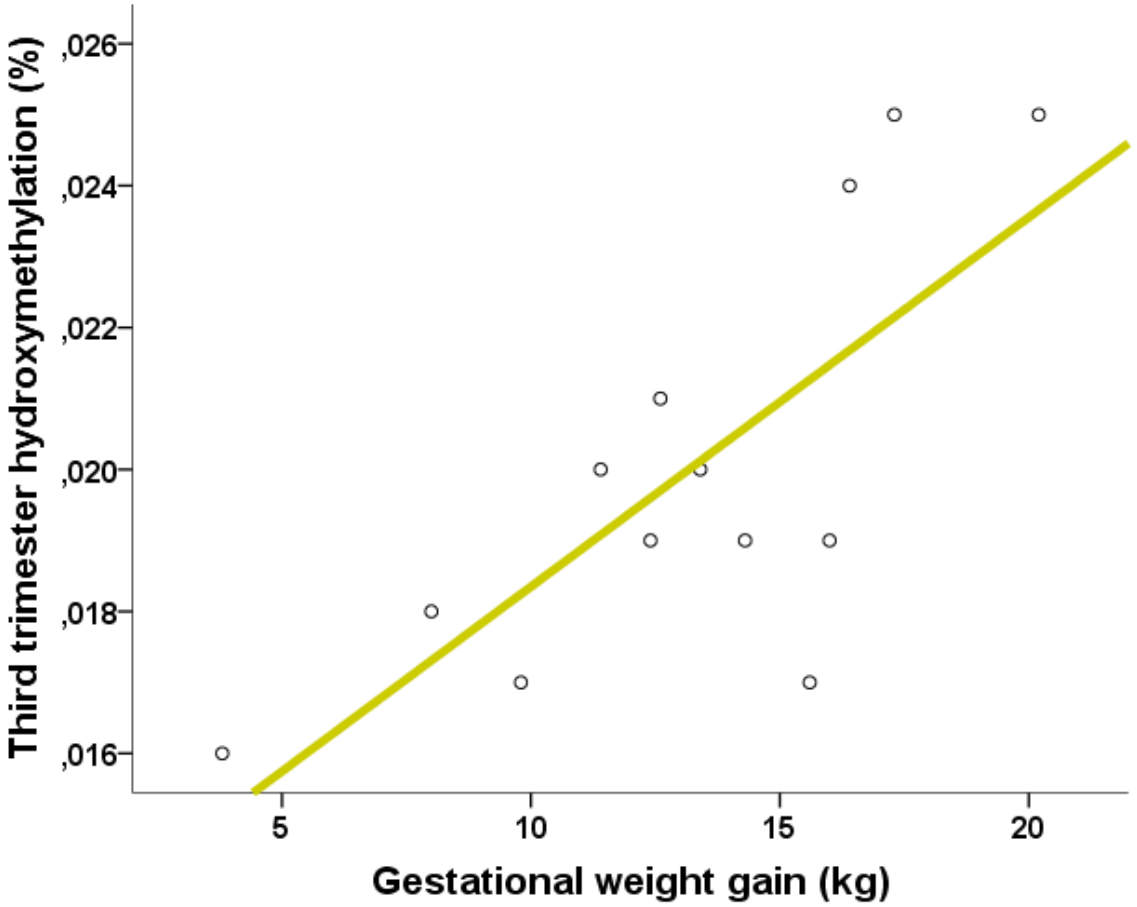
# Cradle and environment do matter

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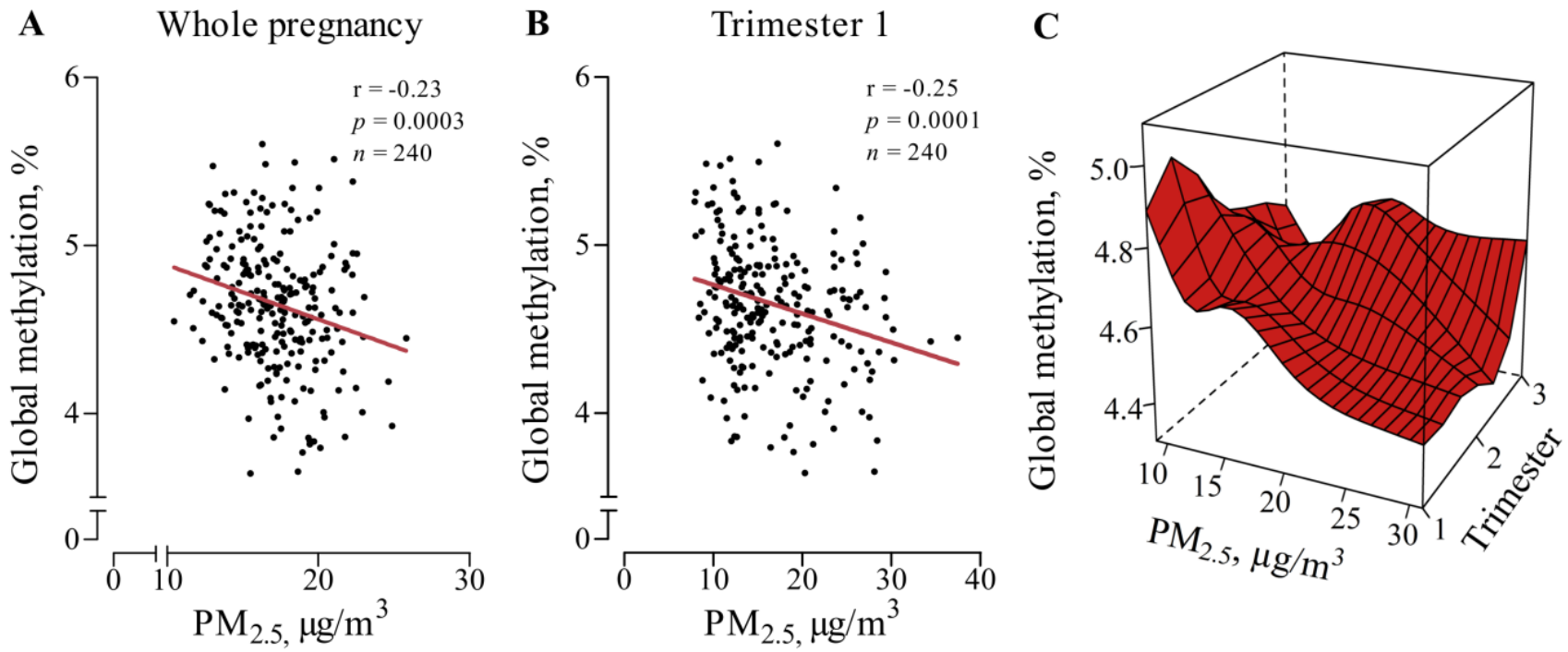
# Cradle and environment do matter

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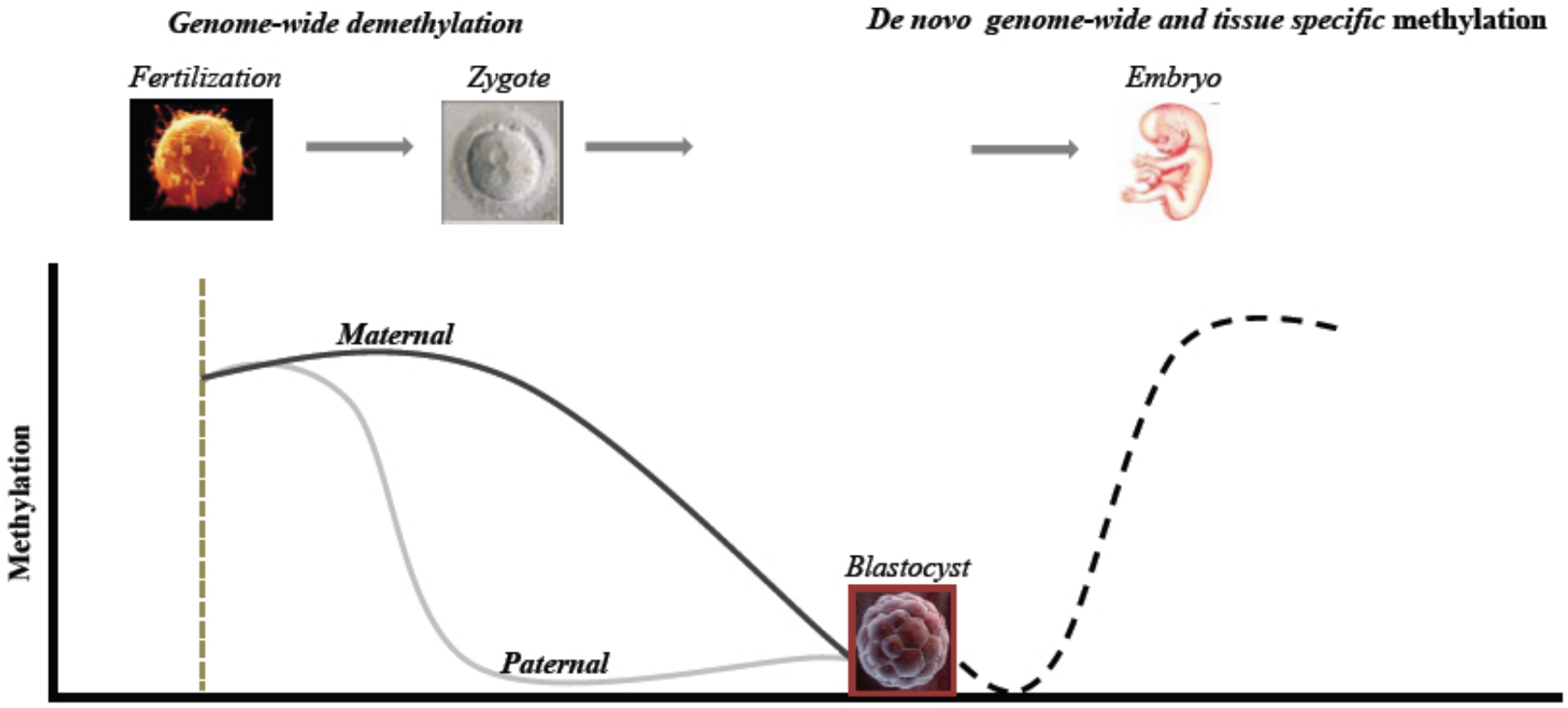
Janssen et al. (Part Fibre Toxicol. 2013)

# Cradle and environment do matter

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Rodríguez-Rodero et al. (Discov Med 2010)

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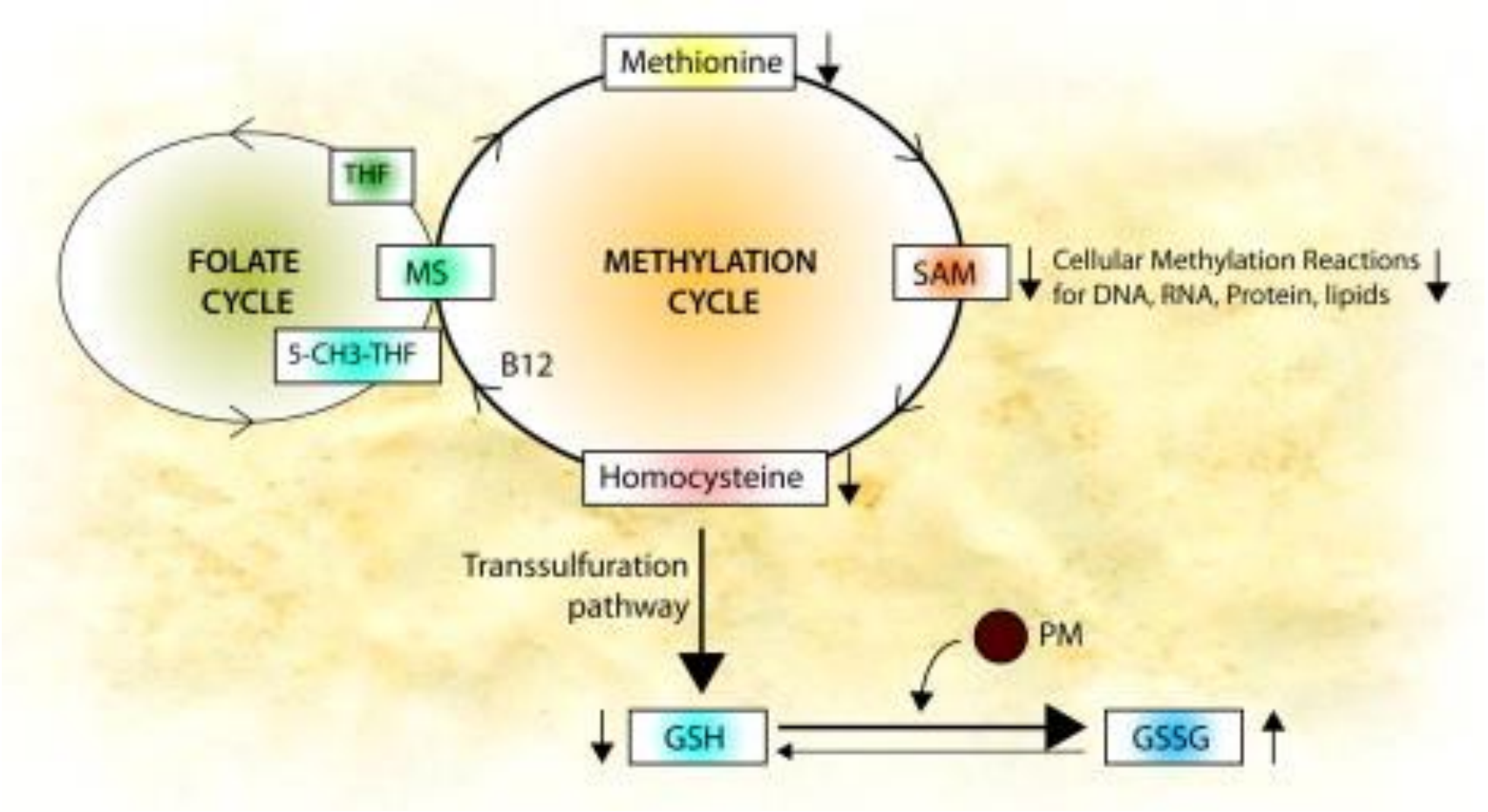
# Conclusion

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Ji et al. (Journal of Allergy and Clinical Immunology, 2012)

# Conclusion

## Nasal cell DNA methylation, inflammation, lung function and wheezing in children with asthma

**Aims:** DNA methylation is increasingly proposed as a mechanism for underlying asthma-related inflammation. However, epigenetic studies are constrained by uncertainties on whether samples that can be easily collected in human individuals can provide informative results. **Methods:** Two nasal cell DNA samples were collected on different days by nasal brushings from 35 asthmatic children aged between 8 and 11 years old. We correlated DNA methylation of *IL-6*, *iNOS*, Alu and LINE-1 with fractional exhaled nitric oxide, forced expiratory volume in 1 s and wheezing. **Results:** Fractional exhaled nitric oxide increased in association with lower promoter methylation of both *IL-6* (+29.0%; p = 0.004) and *iNOS* (+41.0%; p = 0.002). Lower *IL-6* methylation was nonsignificantly associated with wheezing during the week of the study (odds ratio = 2.3; p = 0.063). **Conclusion:** Our findings support the use of nasal cell DNA for human epigenetic studies of asthma.

**KEYWORDS:** airway obstruction · asthma · children · DNA methylation · epigenetics · inflammation

Andrea Baccarelli*[1,2], Franca Rusconi[3], Valentina Bollati[2], Dolores Catelan[4], Gabriele Accetta[4], Lifang Hou[5], Fabio Barbone[6], Pier Alberto Bertazzi[2] & Annibale Biggeri[4]

Asthma is the most common chronic disease of childhood in developed countries, affecting nearly 6.5 million children in the USA [1], and 234.9 million individuals worldwide [2]. Airway inflammation is a key feature in the pathogenesis of childhood asthma [3], and is characterized by the presence of inflammatory including allergic asthma, and have been shown to induce the expression of other genes that might contribute to the asthma phenotype [14].

Although inflammation-related processes have been associated with changes in DNA methylation of promoters in specific genes, including *IL-6* and *iNOS*, the bulk of DNA methylation

## Epigenetic Modifications: Basic Mechanisms and Role in Cardiovascular Disease

Diane E. Handy, Rita Castro and Joseph Loscalzo

*Circulation* 2011;123;2145-2156
DOI: 10.1161/CIRCULATIONAHA.110.956839
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

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## Variable DNA Methylation Is Associated with Chronic Obstructive Pulmonary Disease and Lung Function

Weiliang Qiu[1], Andrea Baccarelli[2], Vincent J. Carey[1], Nadia Boutaoui[3], Helene Bacherman[1], Barbara Klanderman[1], Stephen Rennard[4], Alvar Agusti[5], Wayne Anderson[6], David A. Lomas[7], and Dawn L. DeMeo[1,8]

Review

## Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases

Lucia Migliore[a,*], Fabio Coppedè[b]

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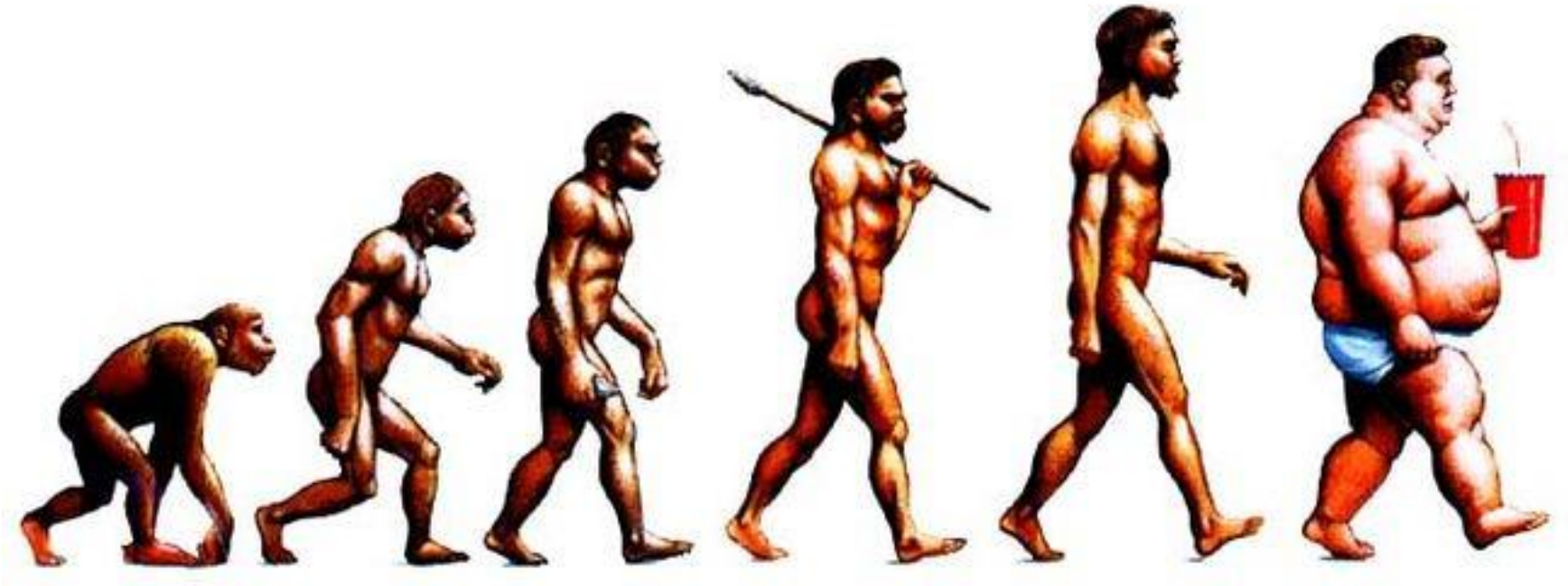
# Conclusion



Thanks to: Prof dr P. Hoet, dr Katrien Poels, A.Tabish, S Pauwels

idewe
Externe Dienst voor Preventie en Bescherming op het Werk vzw

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