



What is epigenetics?

Lode Godderis (Md, Phd)^{1,2}

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² Idewe, Heverlee, Belgium



Outline

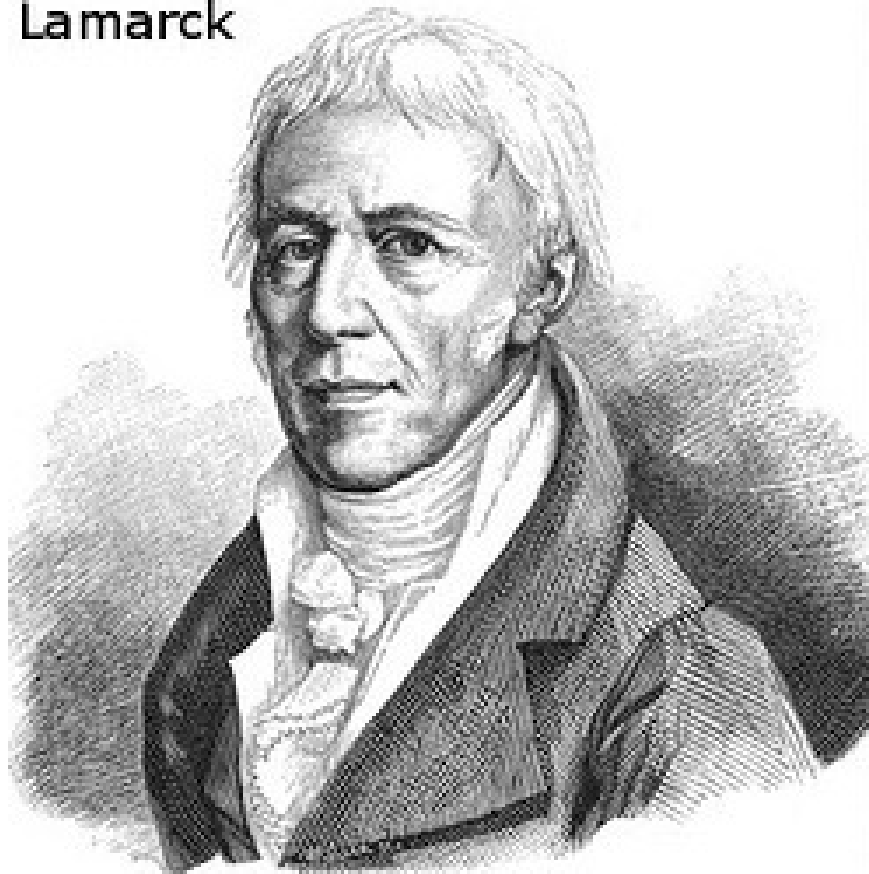
- **Introduction**
- Objective
- Impact environment on health through epigenetics
- Impact environment on development through epigenetics
- Conclusion

Introduction

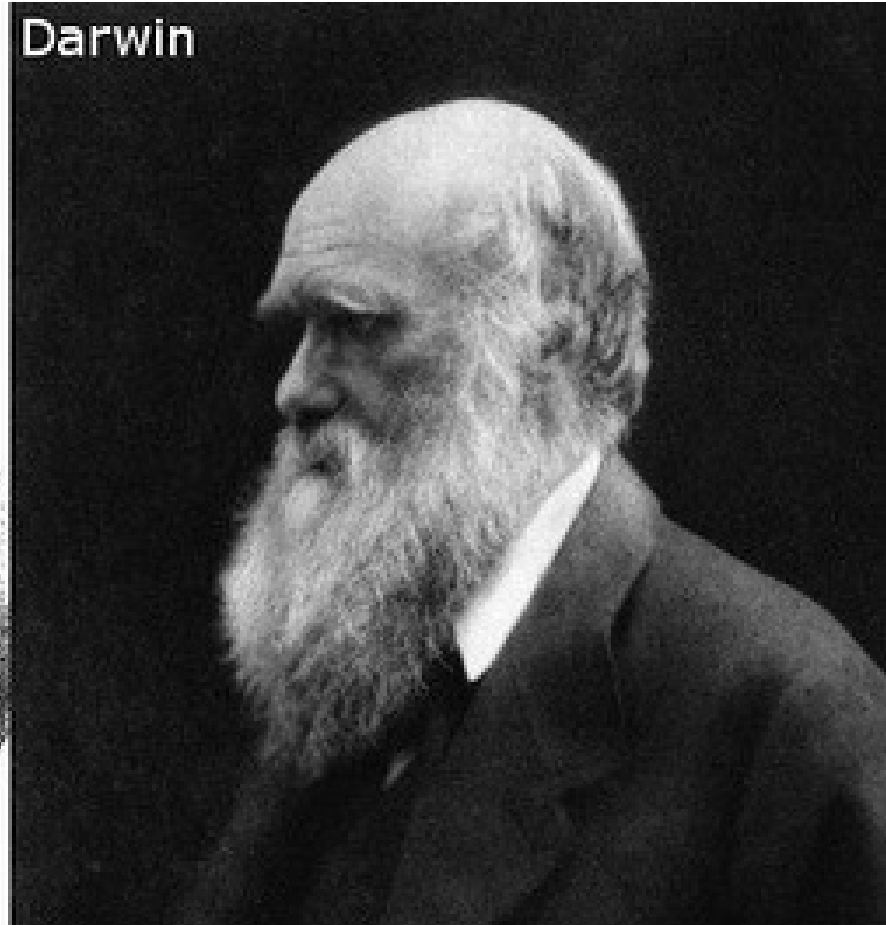


Introduction

Lamarck



Darwin



Introduction

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

Outline

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

Objective

Impact environment on health through epigenetics



Impact environment on development through epigenetics



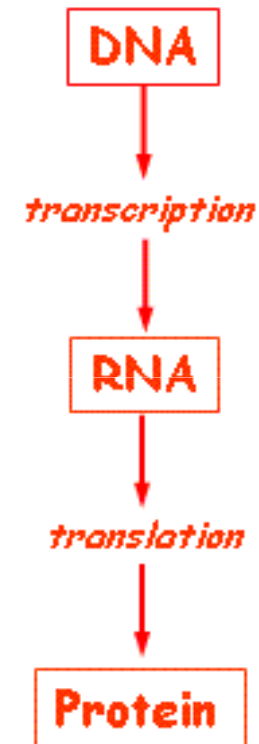
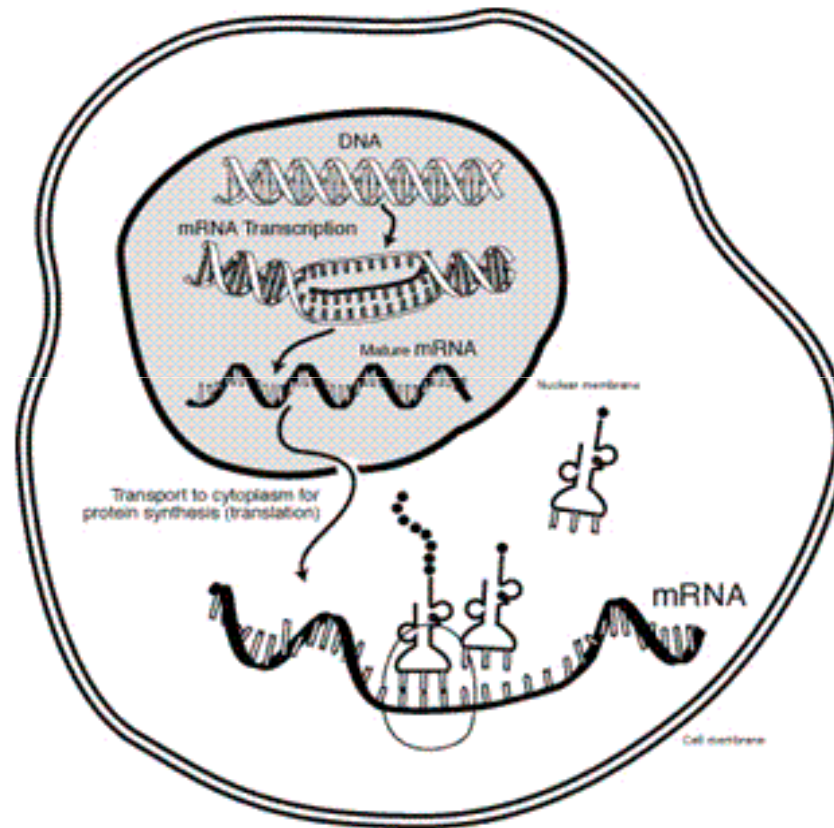
Outline

- Introduction
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- **Impact environment on health through epigenetics**
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Impact environment on health through epigenetics

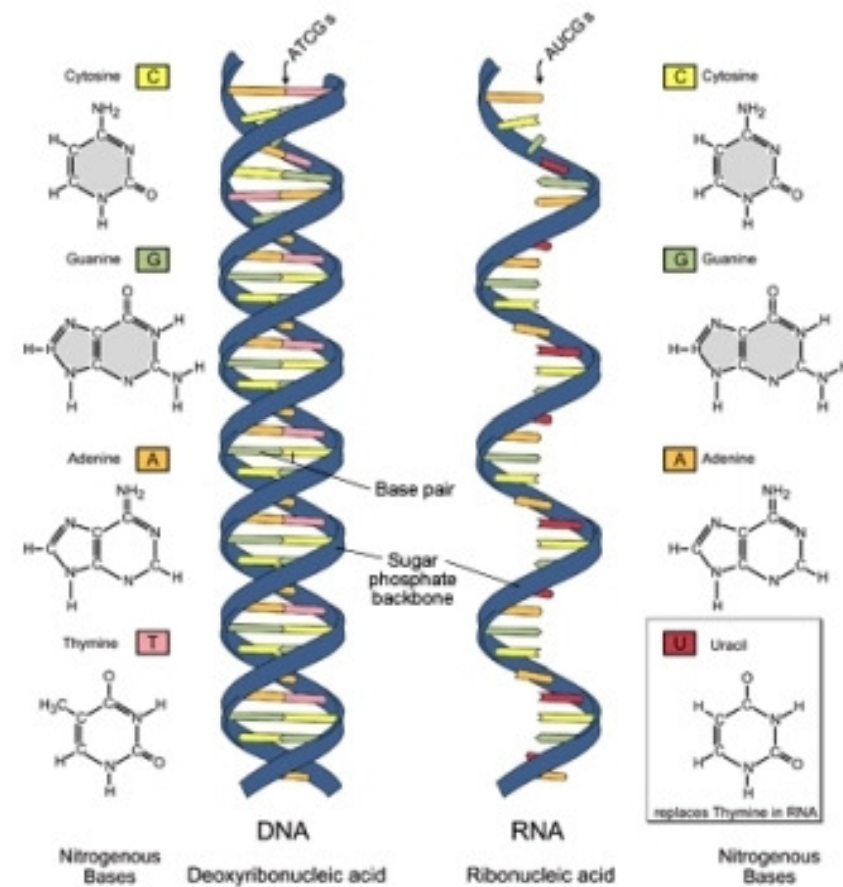


Genetic mechanisms



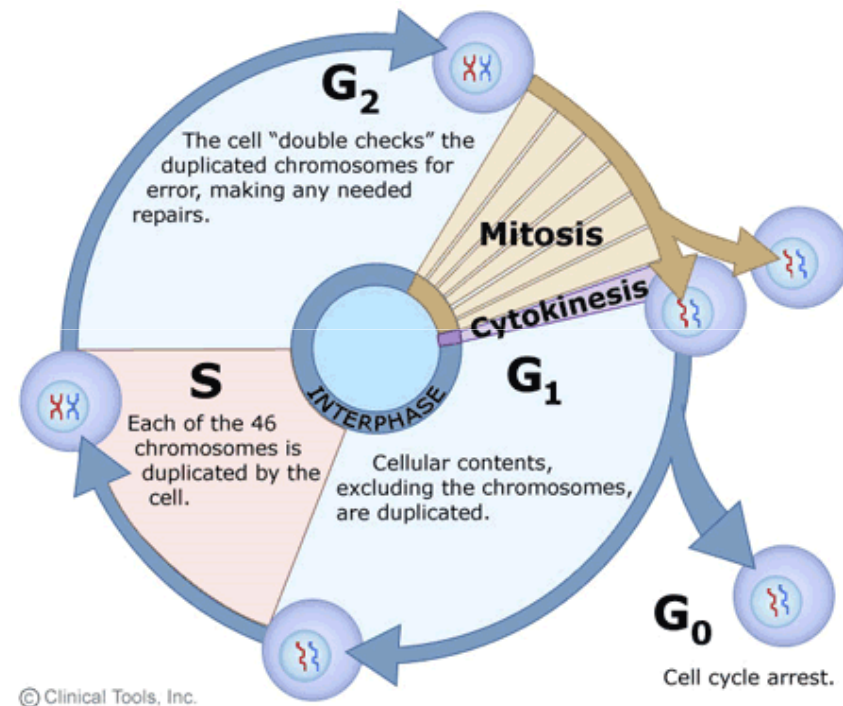
Genetic mechanisms

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

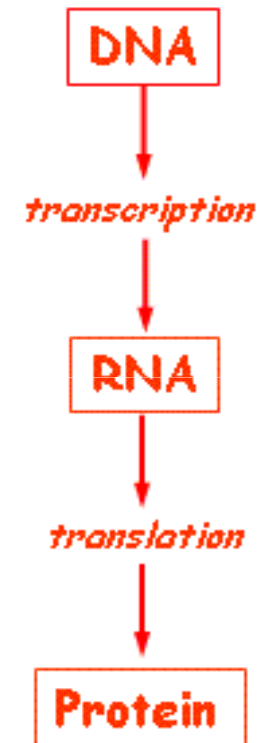
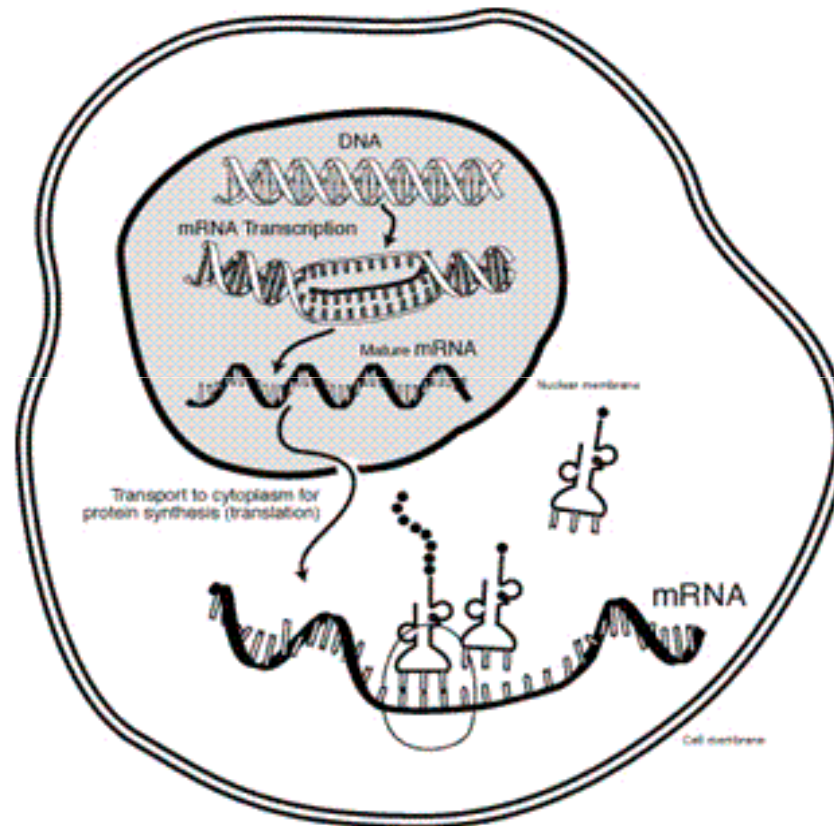


Genetic mechanisms

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



Response of cells



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
Benzo[a]anthracene ^{**,1}	2B	Poly aromatic hydrocarbon	500	50	5

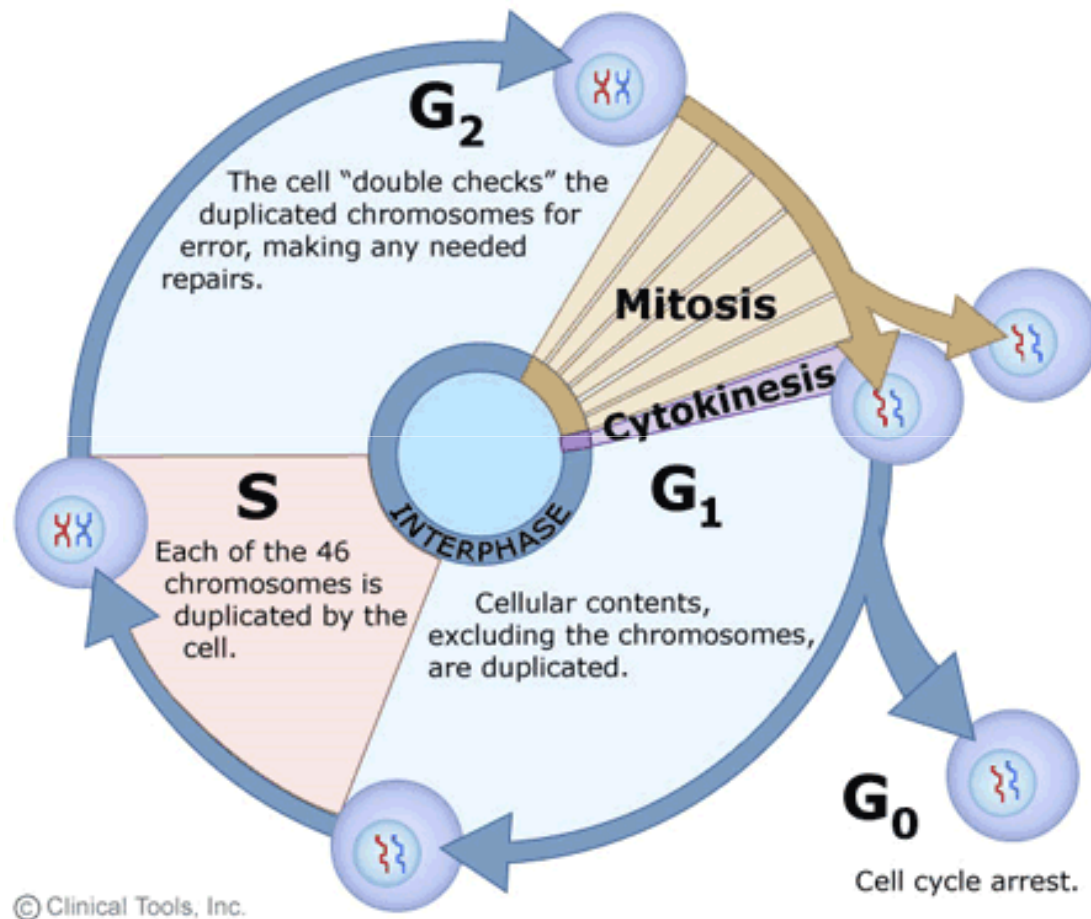
*Direct acting agent; **Indirect acting agent,
 1: DNA adduct forming agent; 2: DNA Cross linking agent.
 doi:10.1371/journal.pone.0039205.t001

Response of cells

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

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

Response of cells

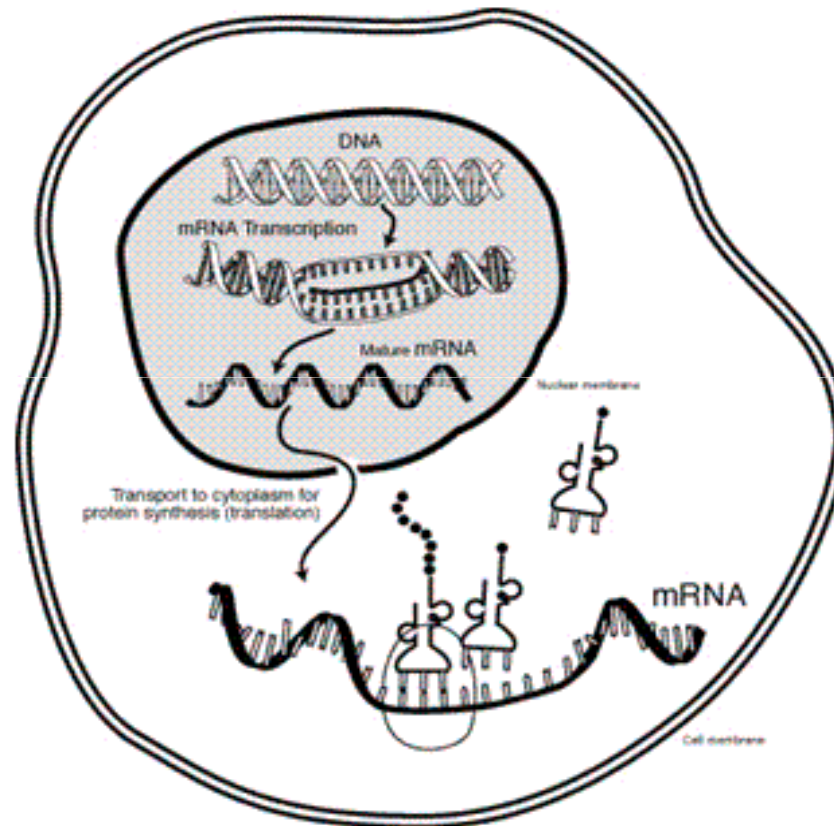


Response of cells

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

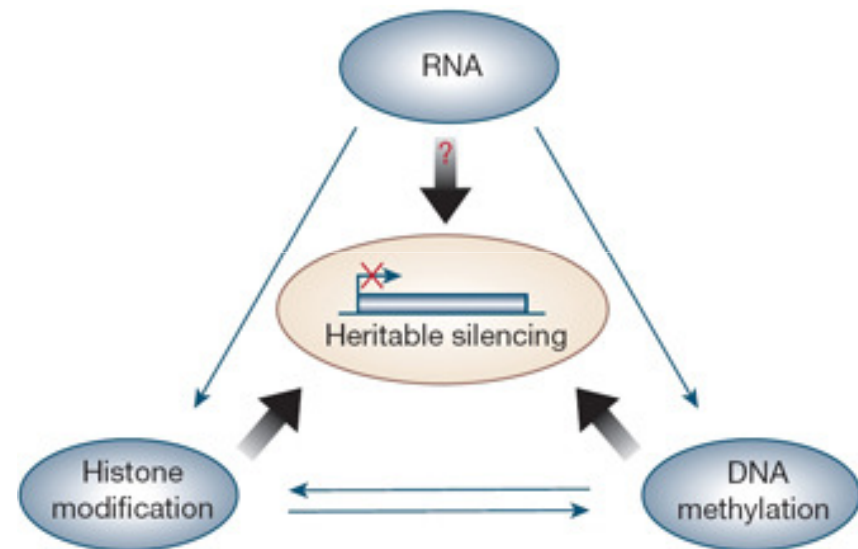
* Carcinogens [AA:Acrylamide; BA:Benzo[a]anthracene; BZ:Benzene; EDB:Ethylenedibromide; EPI:Epichlorohydrin; HQ:Hydroquinone; SO:Styrene 7,8-oxide; ST:Styrene; TCE:Trichloroethylene]

Epigenetic mechanisms



Epigenetic mechanisms

- DNA methylation
- Histone modification
- Non-coding RNA

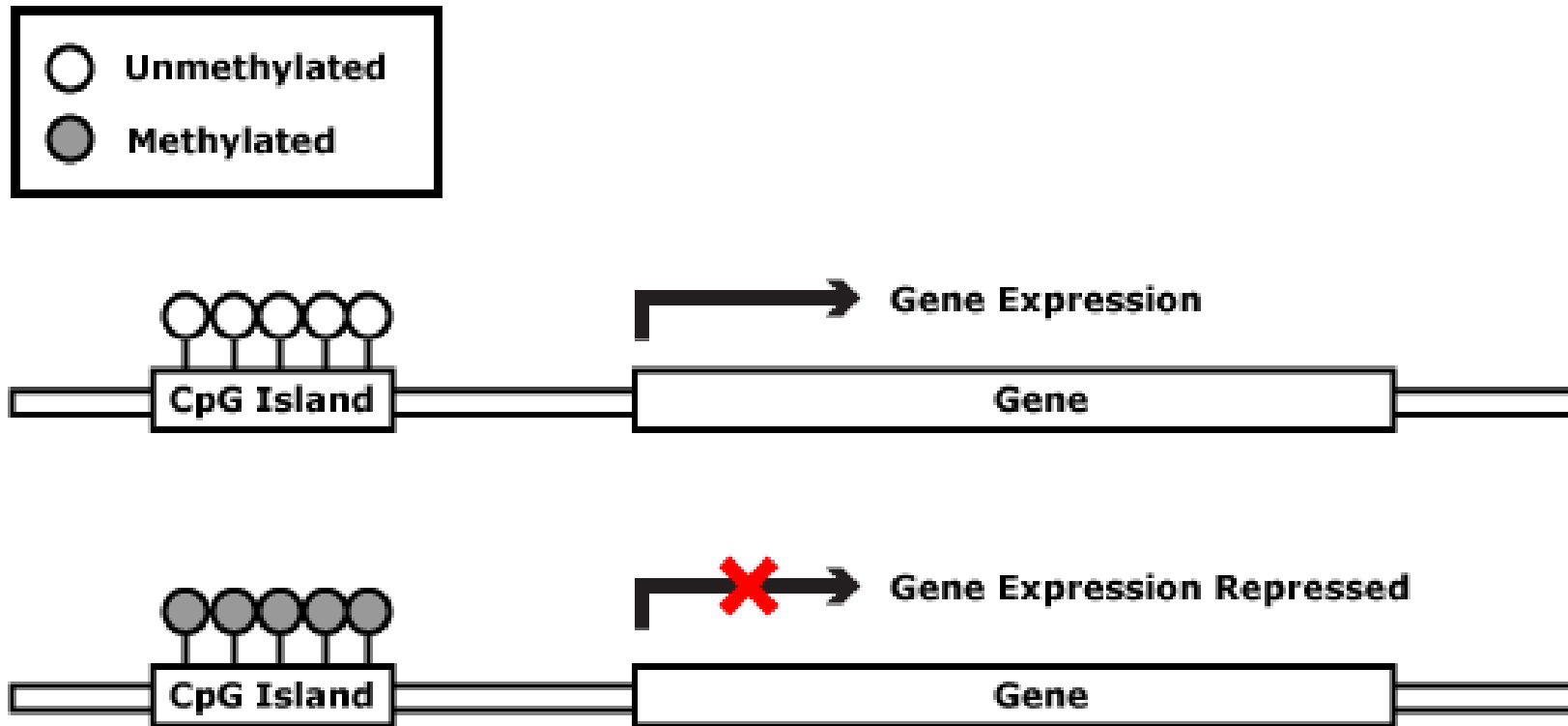


Epigenetic mechanisms

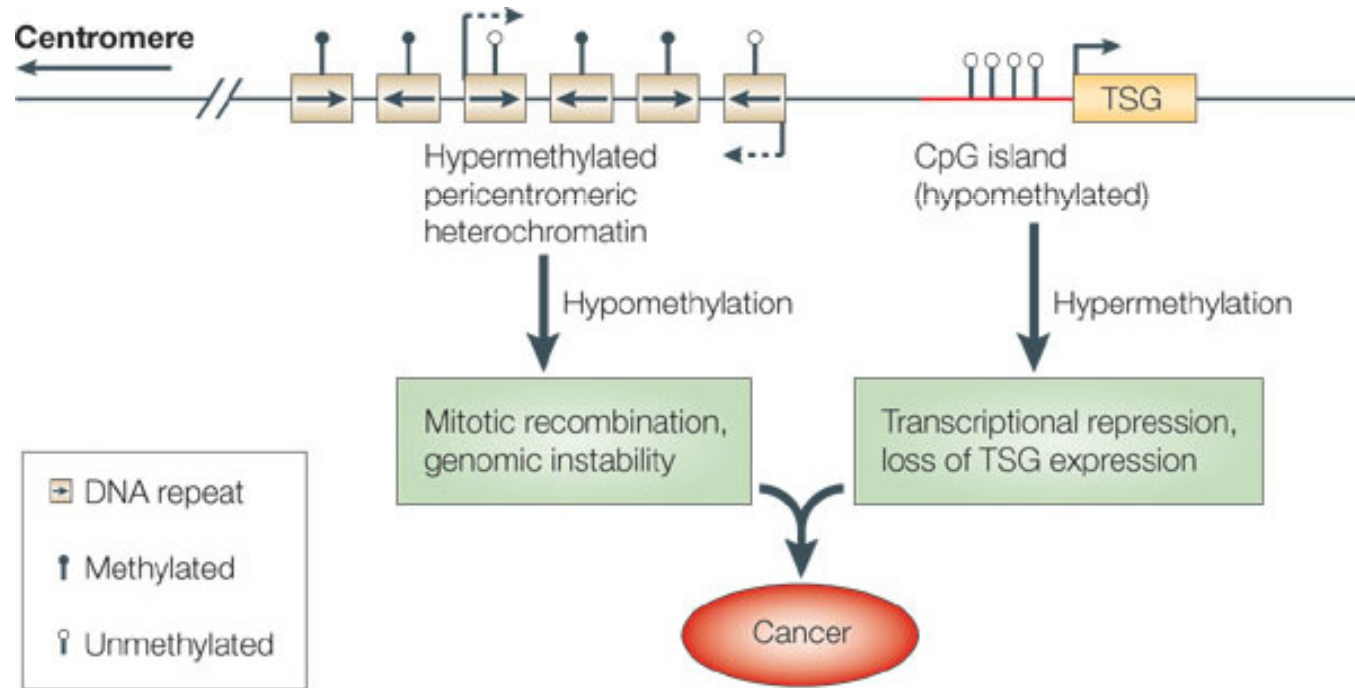
- **DNA methylation**
- Histone modification
- Non-coding RNA



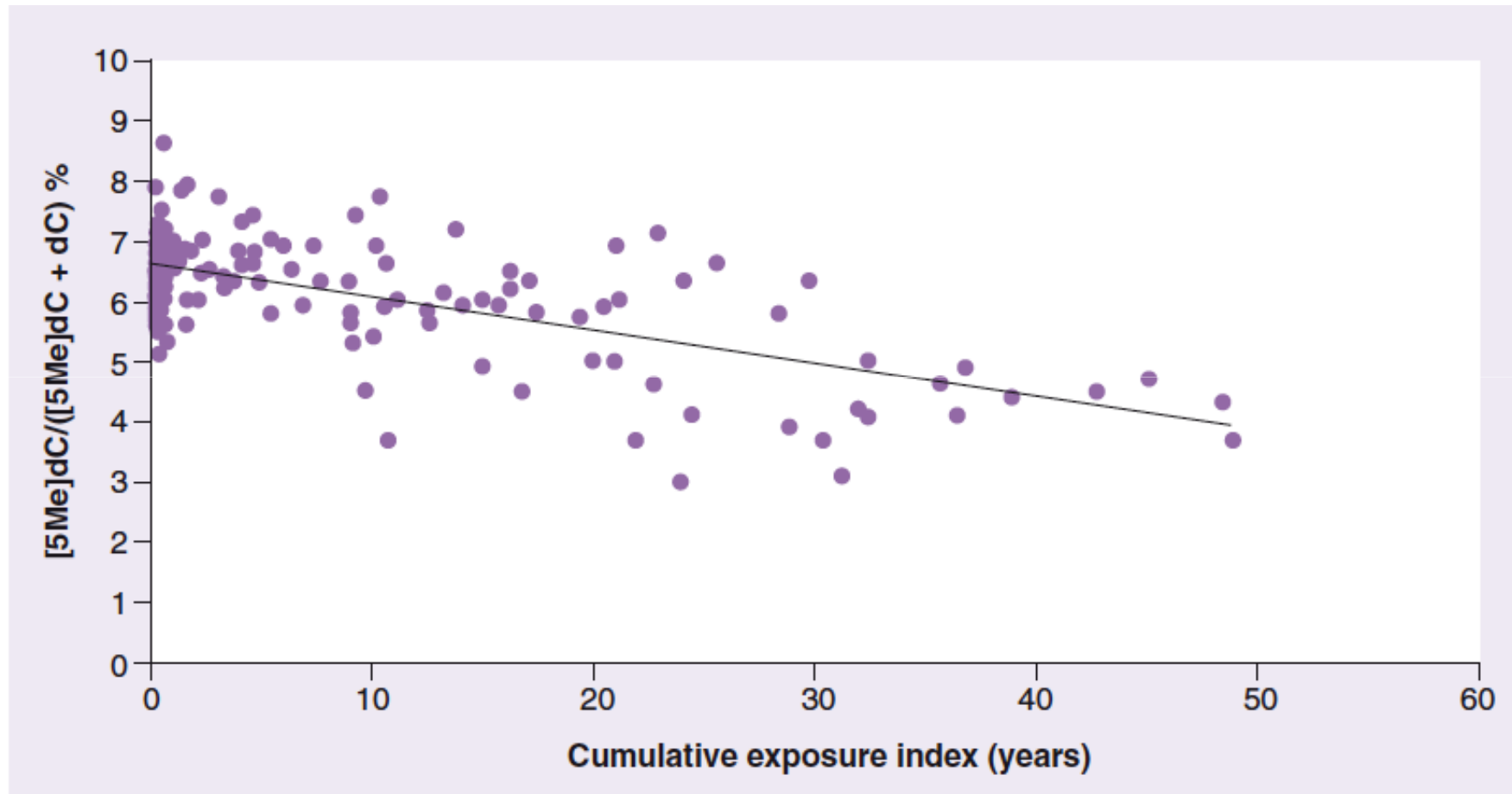
Epigenetic mechanisms: gene-specific DNA methylation



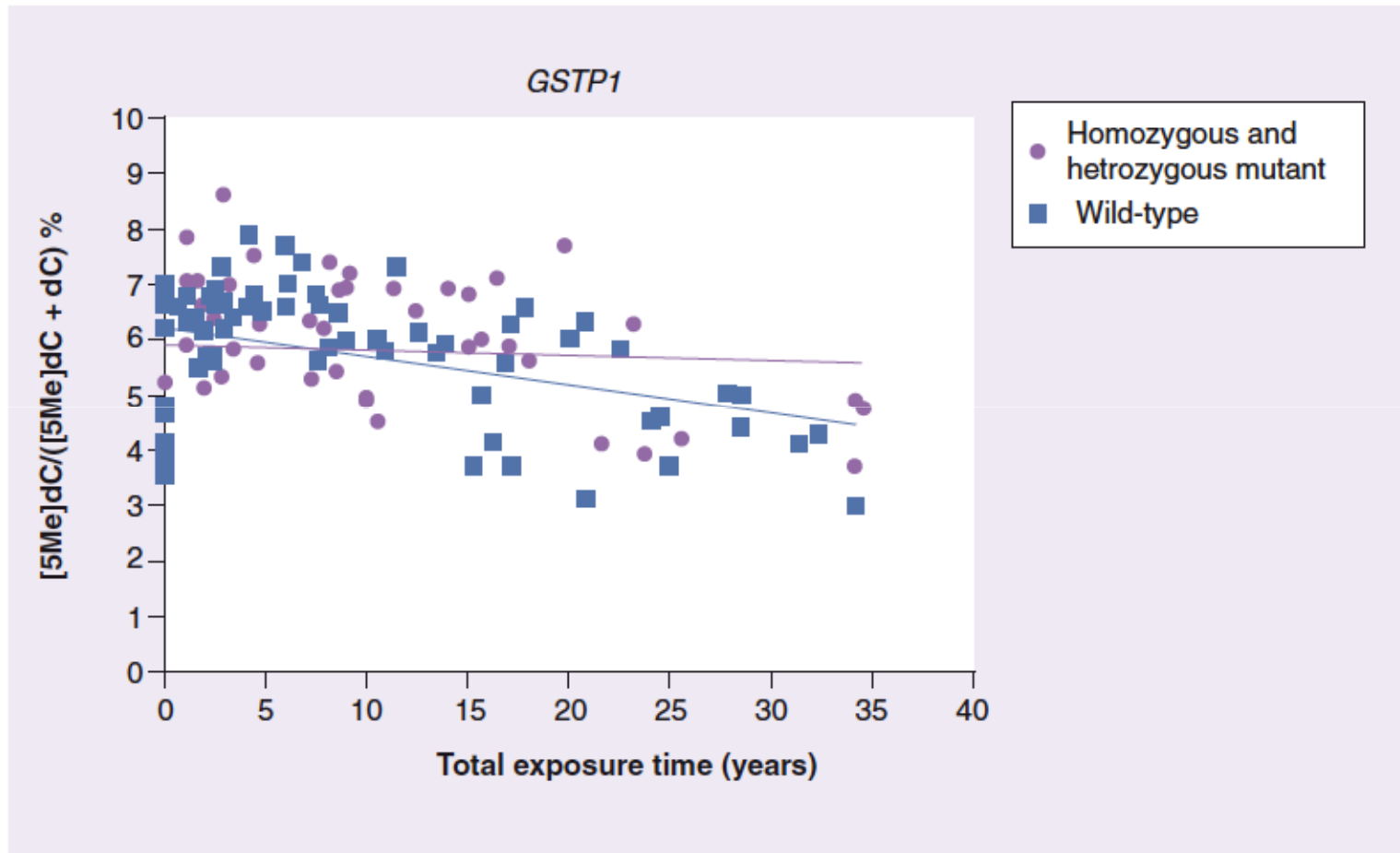
Epigenetic mechanisms: global DNA methylation



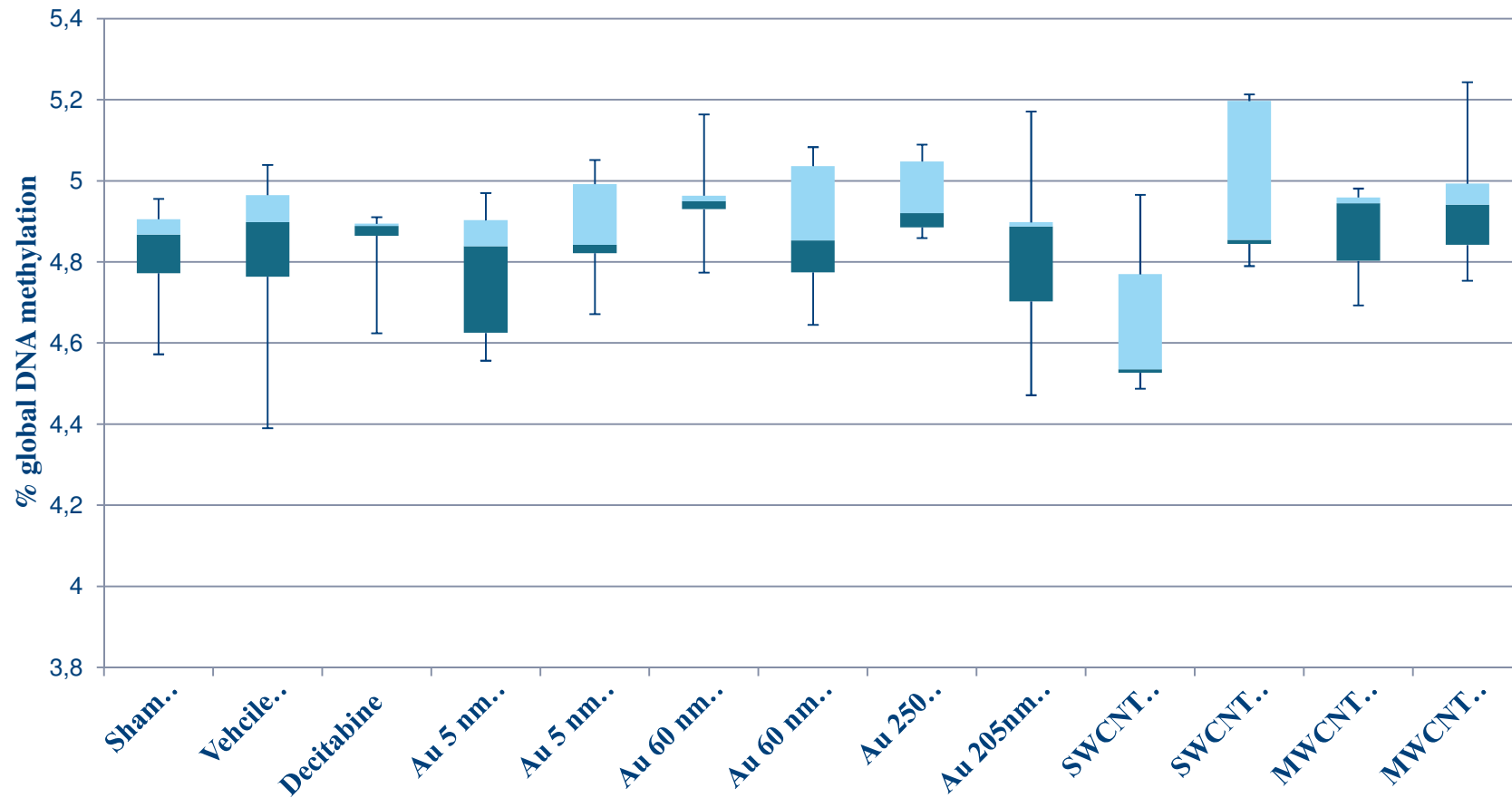
Epigenetic mechanisms: global DNA methylation



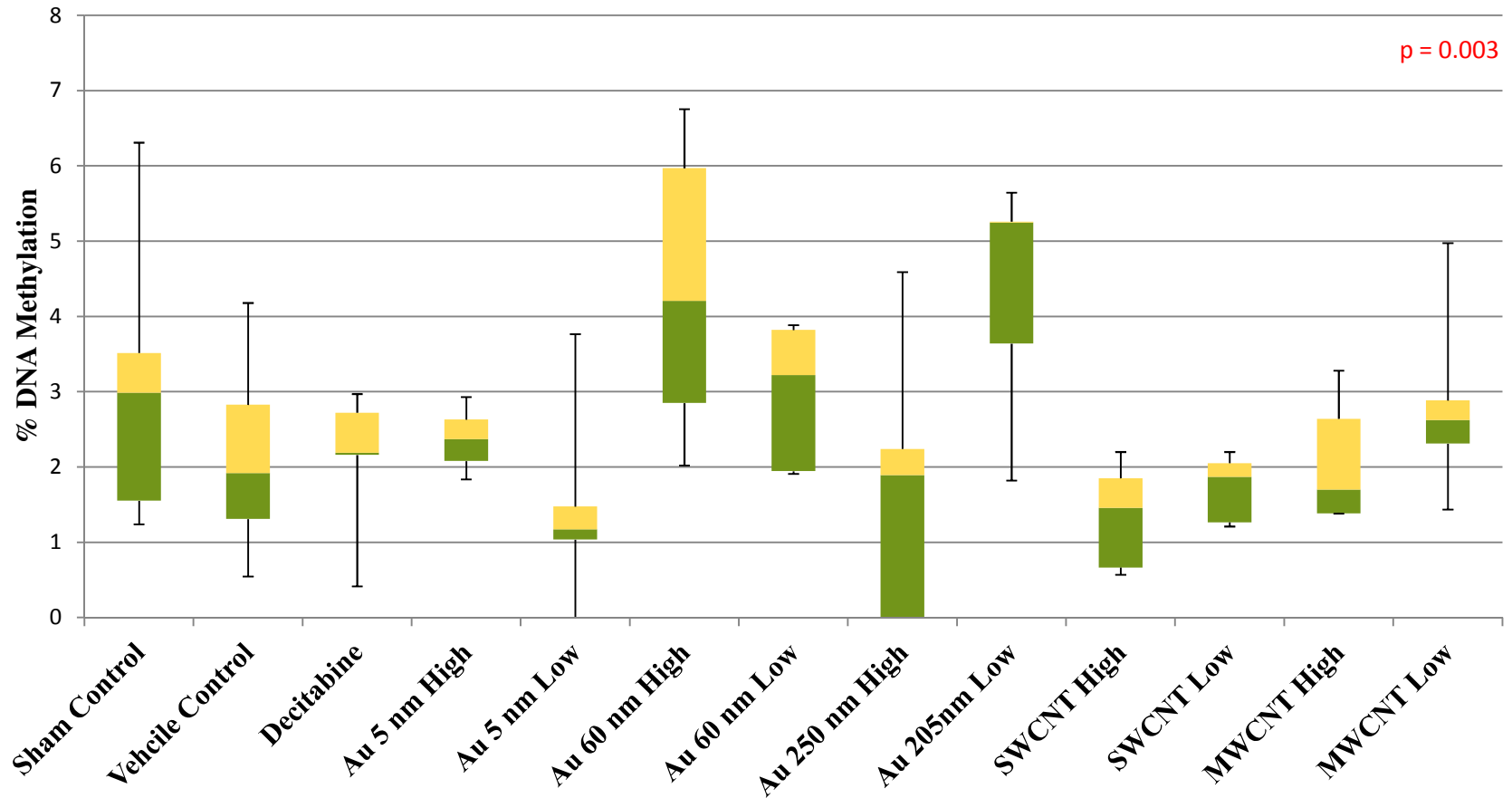
Epigenetic mechanisms: global DNA methylation



Epigenetic mechanisms: global DNA methylation

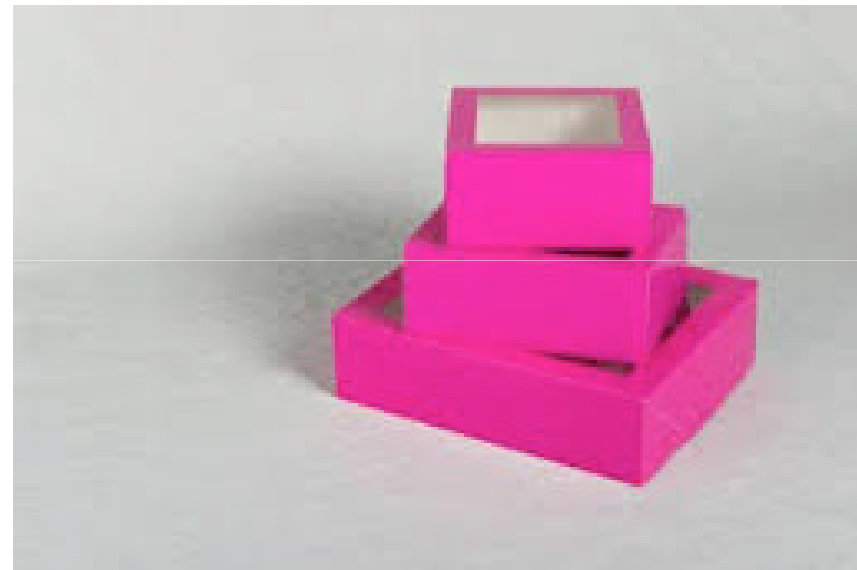


Epigenetic mechanisms: gene-specific DNA methylation

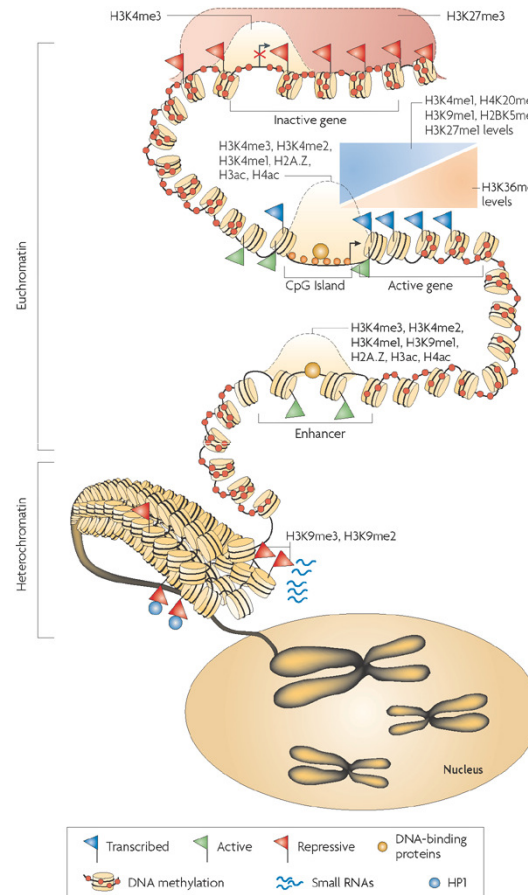


Epigenetic mechanisms

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

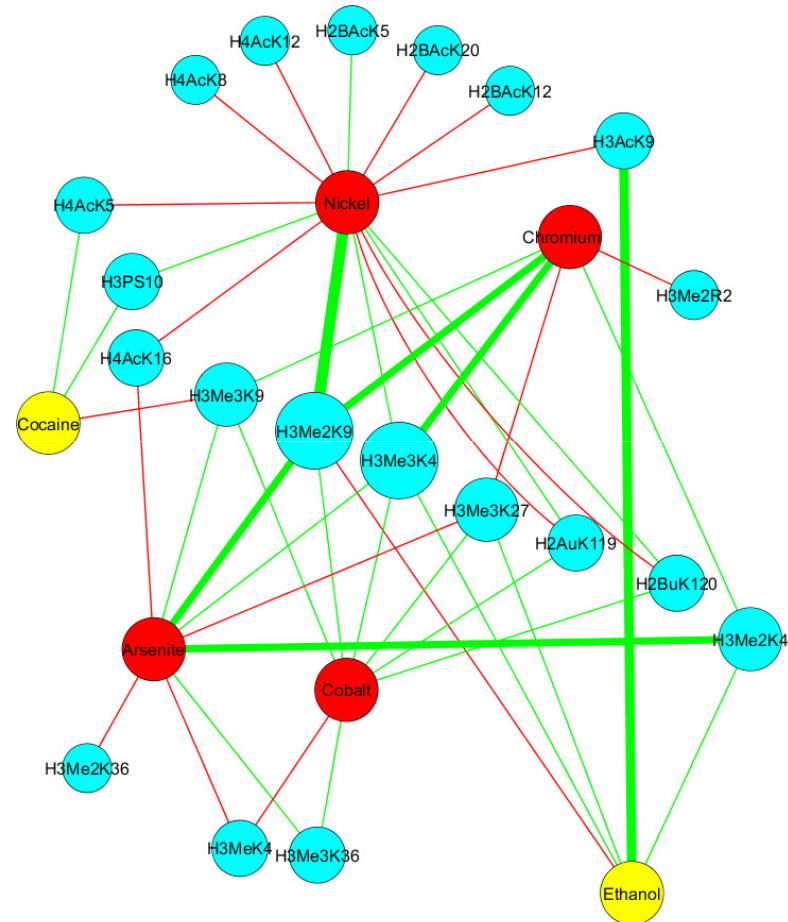


Epigenetic mechanisms: histone modification



Nature Reviews | Genetics

Epigenetic mechanisms

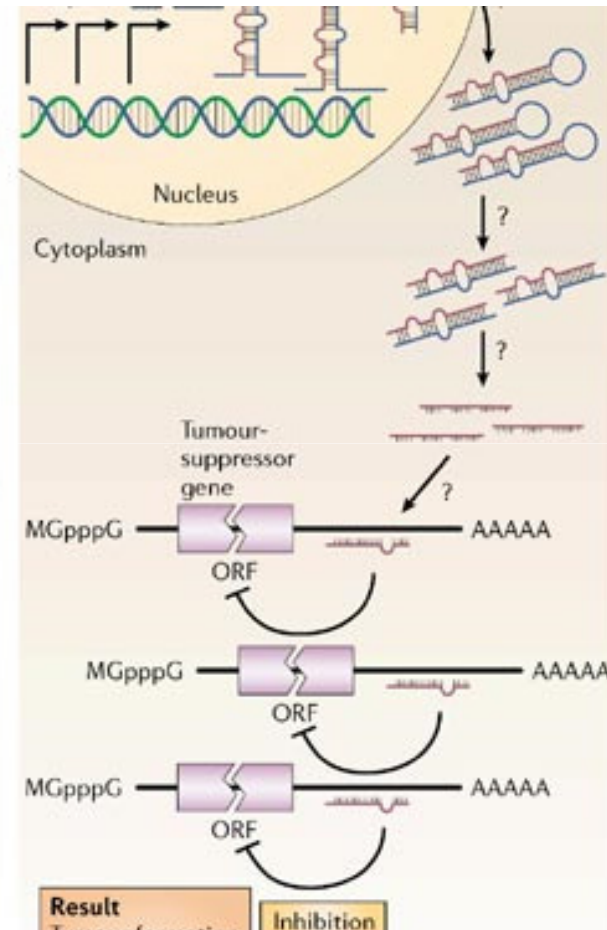
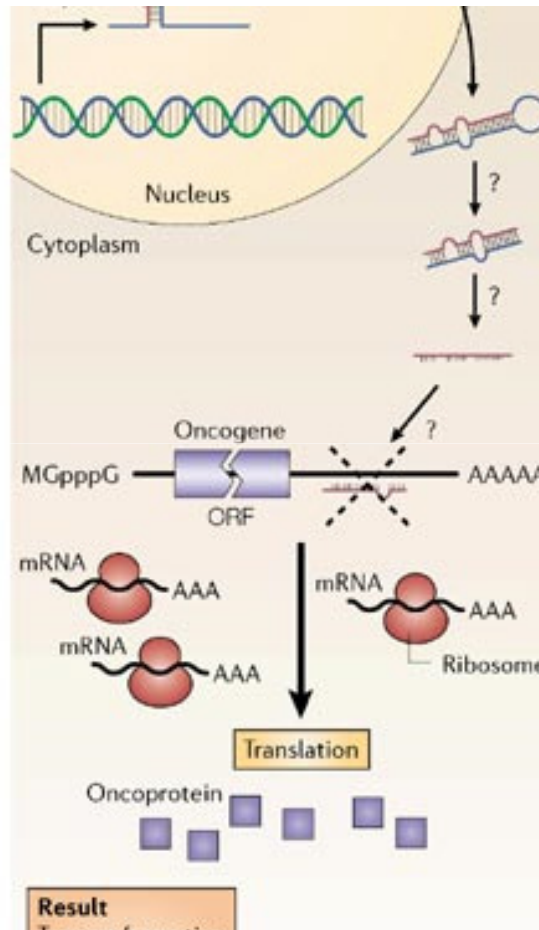
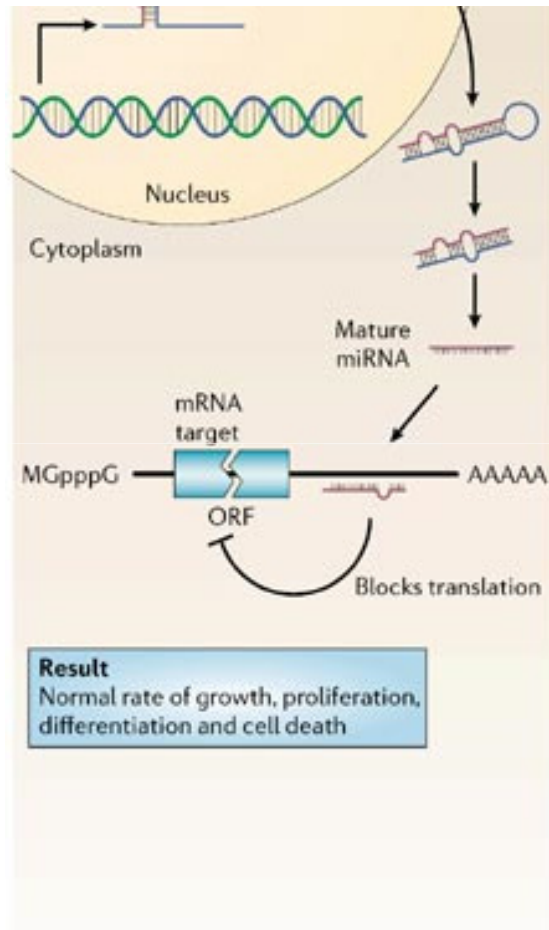


Epigenetic mechanisms

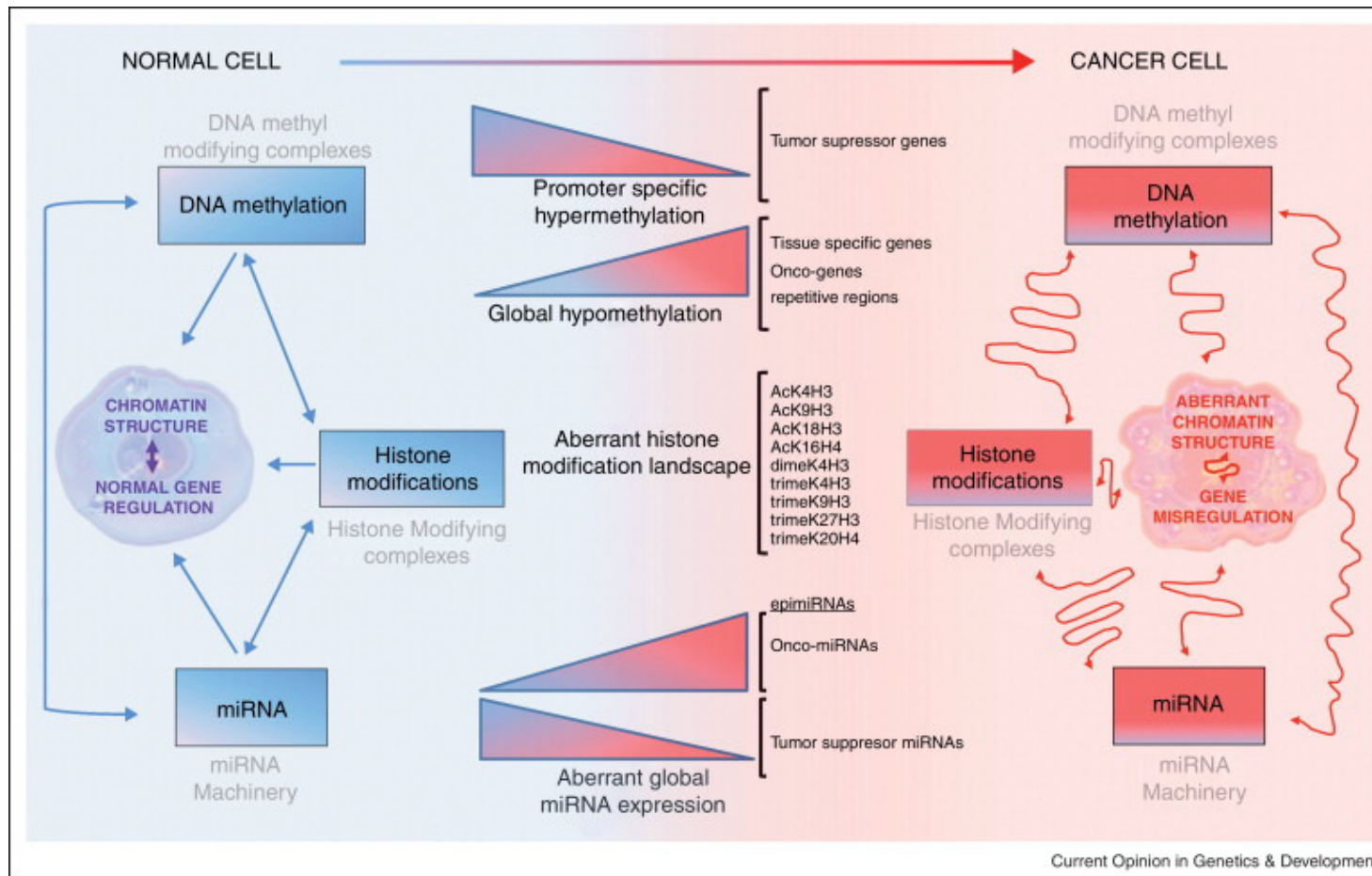
- DNA methylation
- Histone modification
- **Non-coding RNA**



Epigenetic mechanisms: non coding RNA



Epigenetic mechanisms



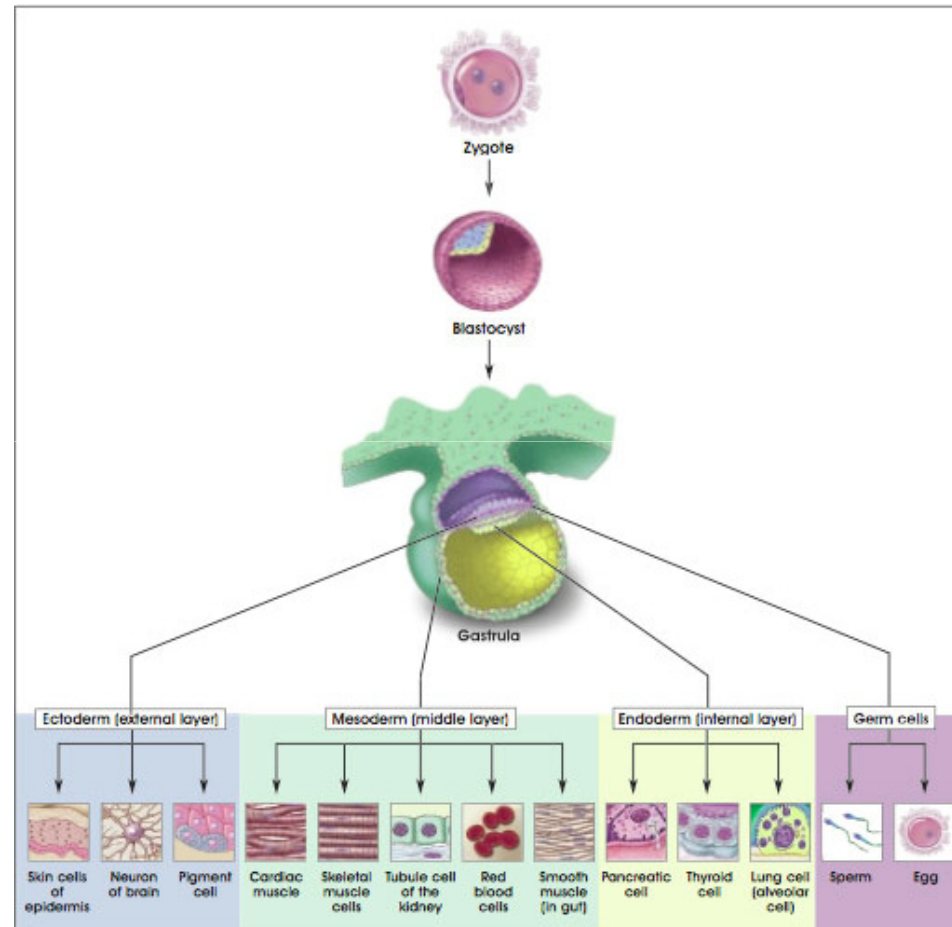
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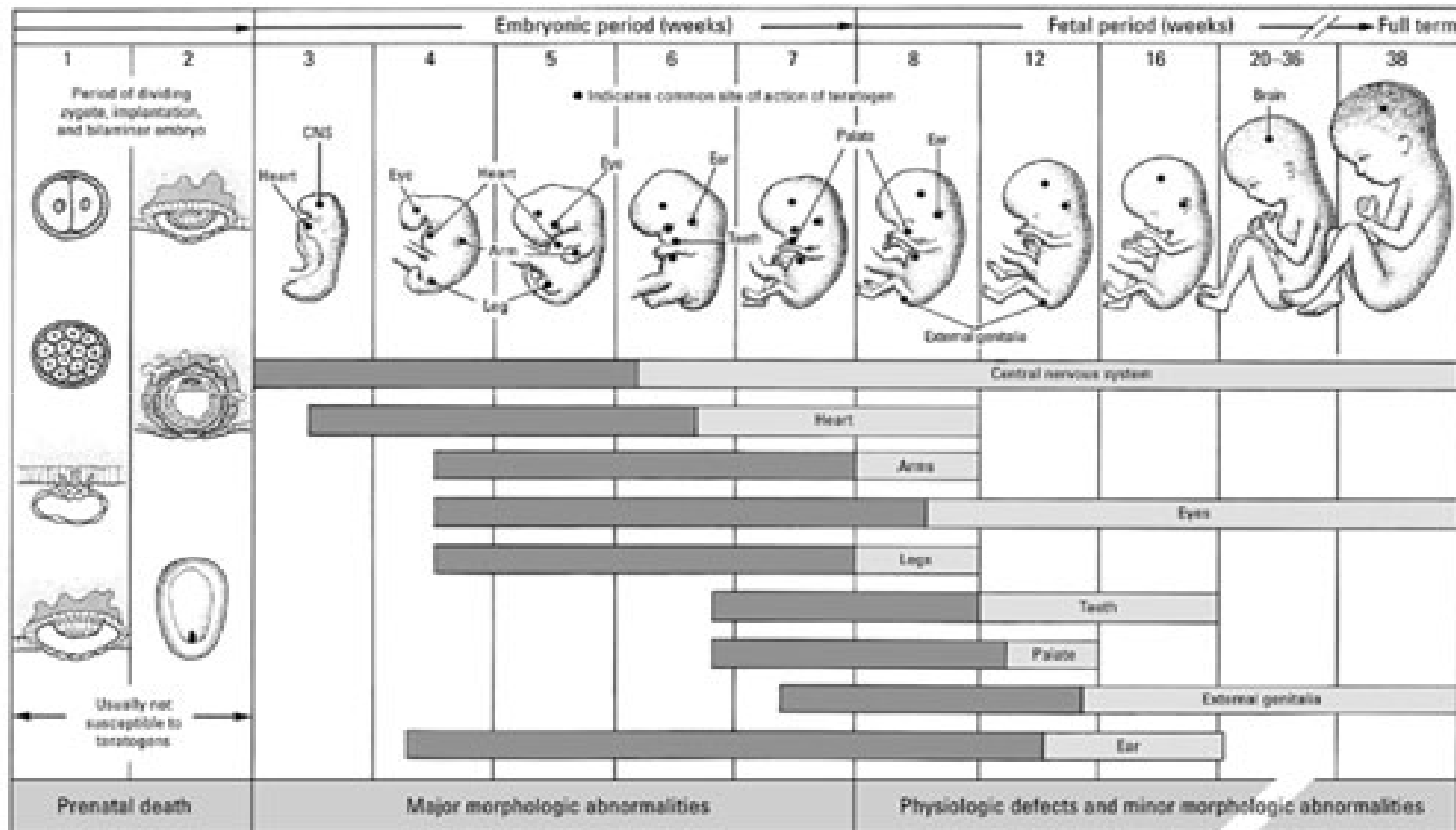
Impact environment on development through epigenetics



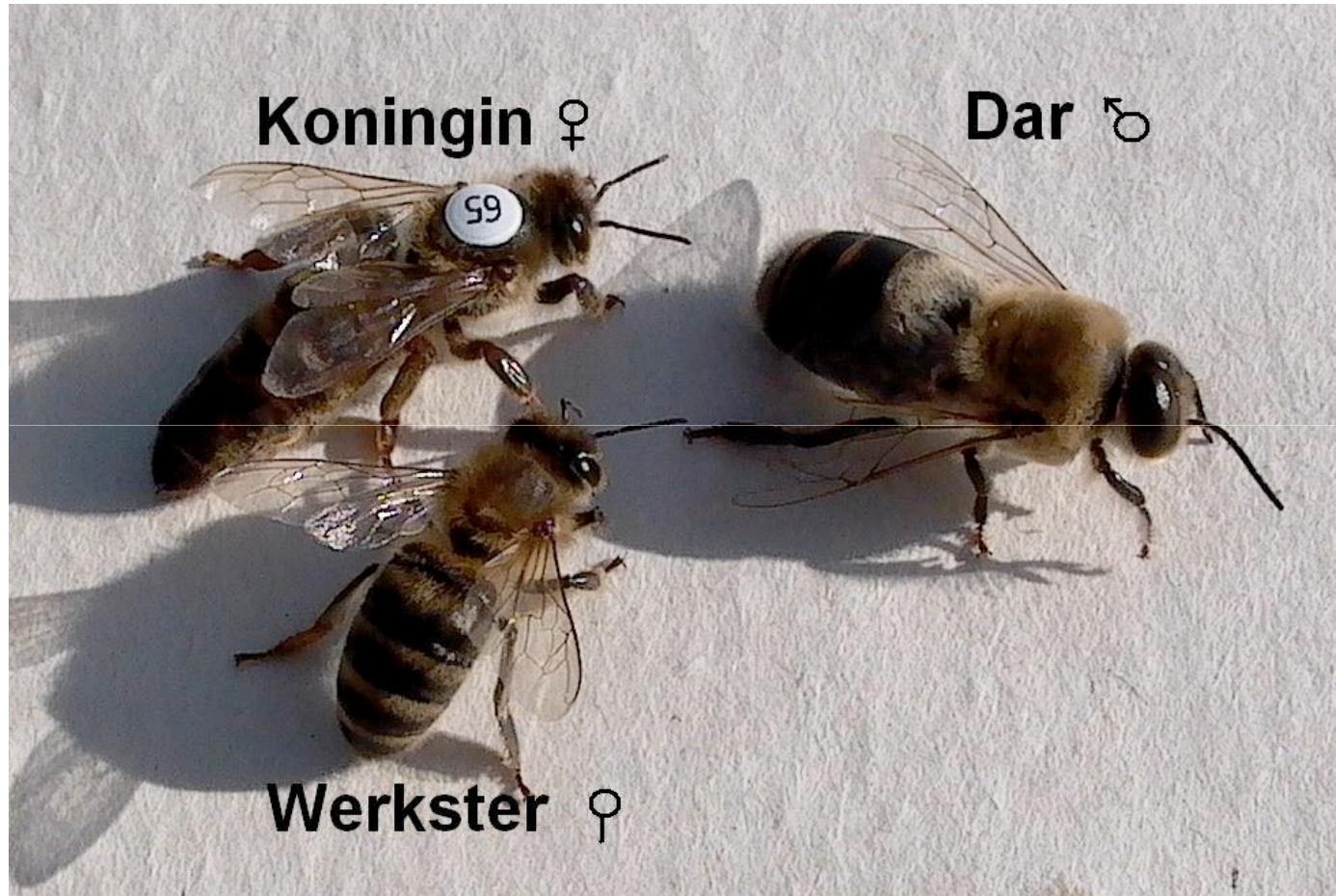
Epigenetics, a natural mechanism



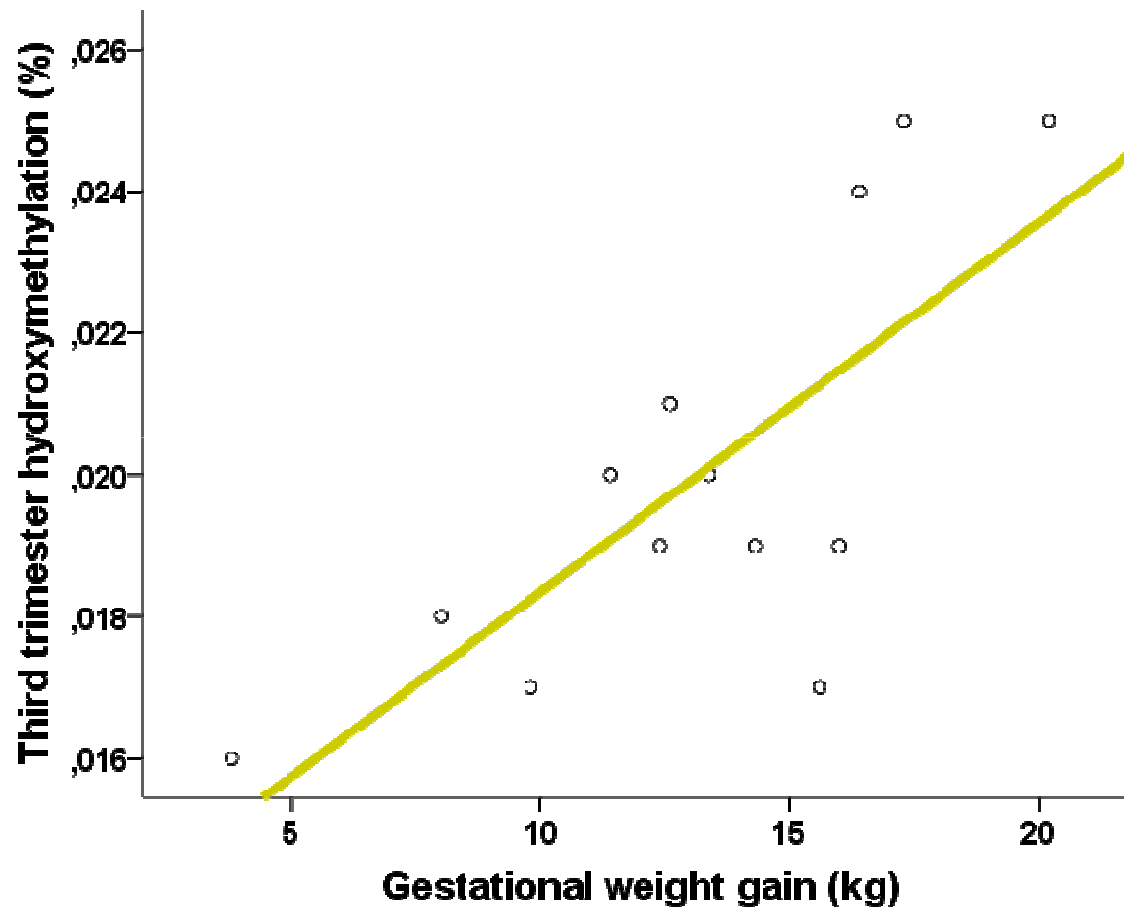
Impact environment on development through epigenetics



Cradle and environment do matter



Cradle and environment do matter



Outline

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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

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

Andrea Baccarelli^{1,2},
Franca Rusconi³,
Valentina Bollati²,
Dolores Catelan⁴,
Gabriele Accetta⁴,
Lifang Hou⁵,
Fabio Barbone⁶,
Pier Alberto Bertazzi²
& Annibale Biggeri⁴

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 75214

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

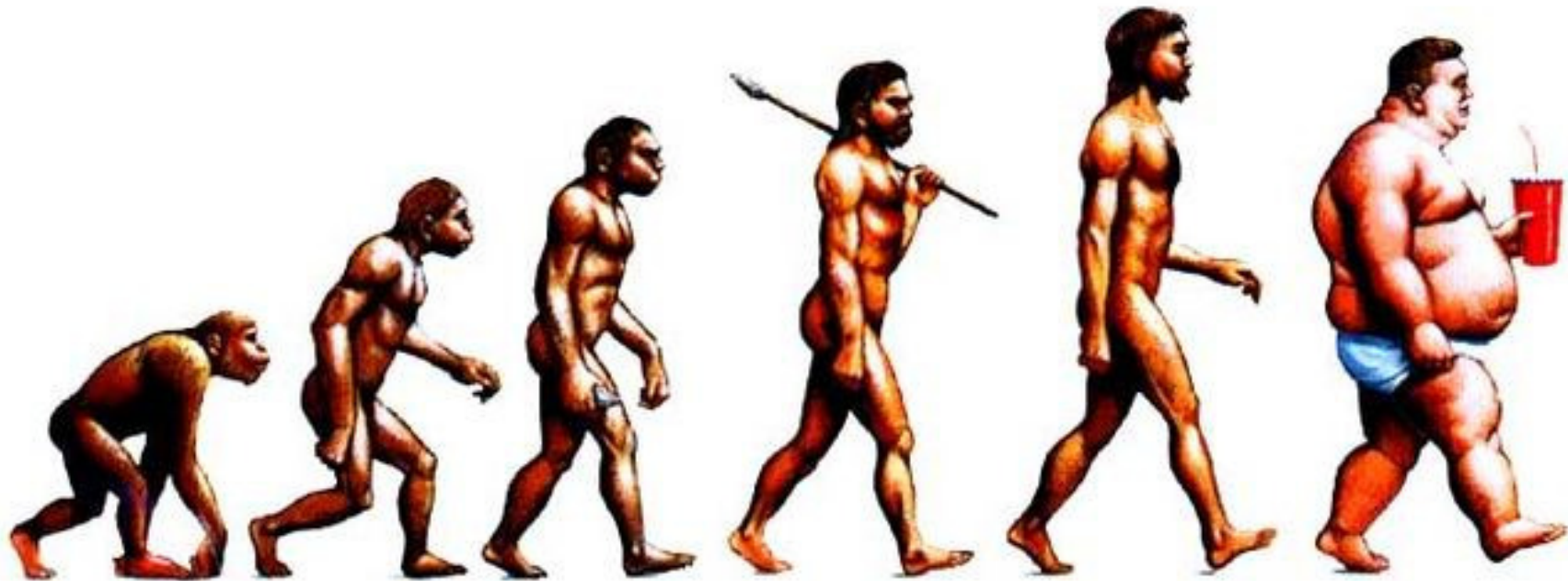
Weiliang Qiu¹, Andrea Baccarelli², Vincent J. Carey¹, Nadia Boutaoui³, Helene Bacherman¹, Barbara Klanderman¹, Stephen Rennard⁴, Alvar Agusti⁵, Wayne Anderson⁶, David A. Lomas⁷, and Dawn L. DeMeo^{1,8}

Review

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

Lucia Migliore^{1,*}, Fabio Coppedè^b

Conclusion



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