Nutrigenomica e gravidanza

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Plan

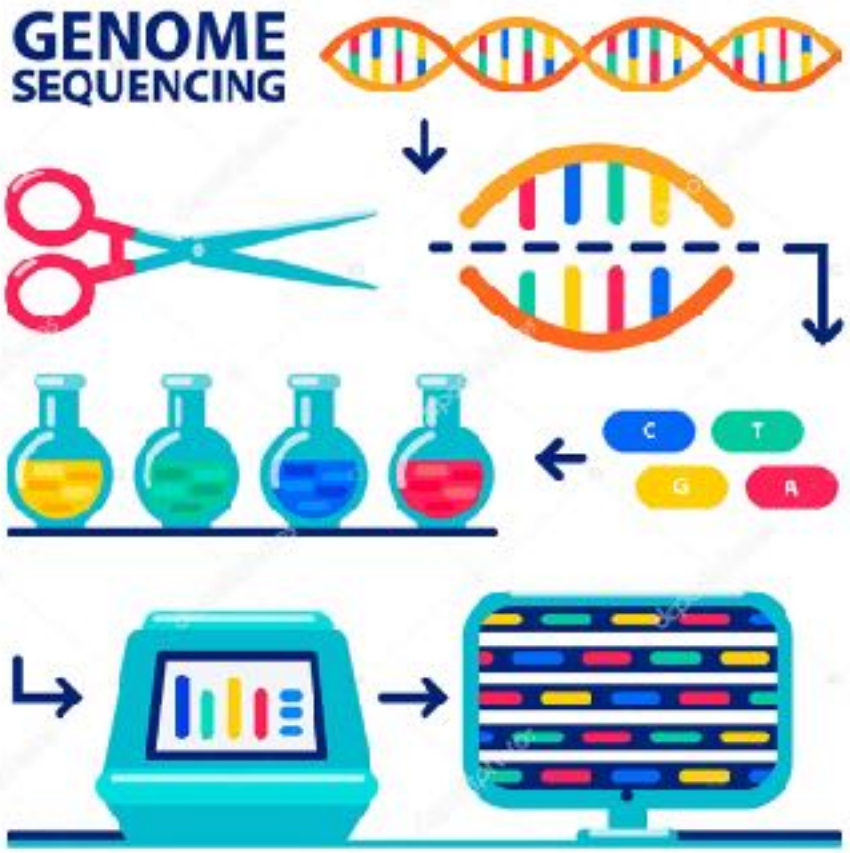
1. System Biology
2. Pregnancy and nutrigenomic
3. Lifestyle

The human genome

2022

1990 - 2001

PROGETTO GENOMA UMANO



«I fatti accertati logicamente vi aiutano a dormire meglio, il che è essenziale, anche quando ci sono creature ululanti nel buio e nutrizionisti che scrivono libri.»

«Non ho mai pensato che ci siano domande che non si possono fare.»

Nozioni di base….definizioni!!!

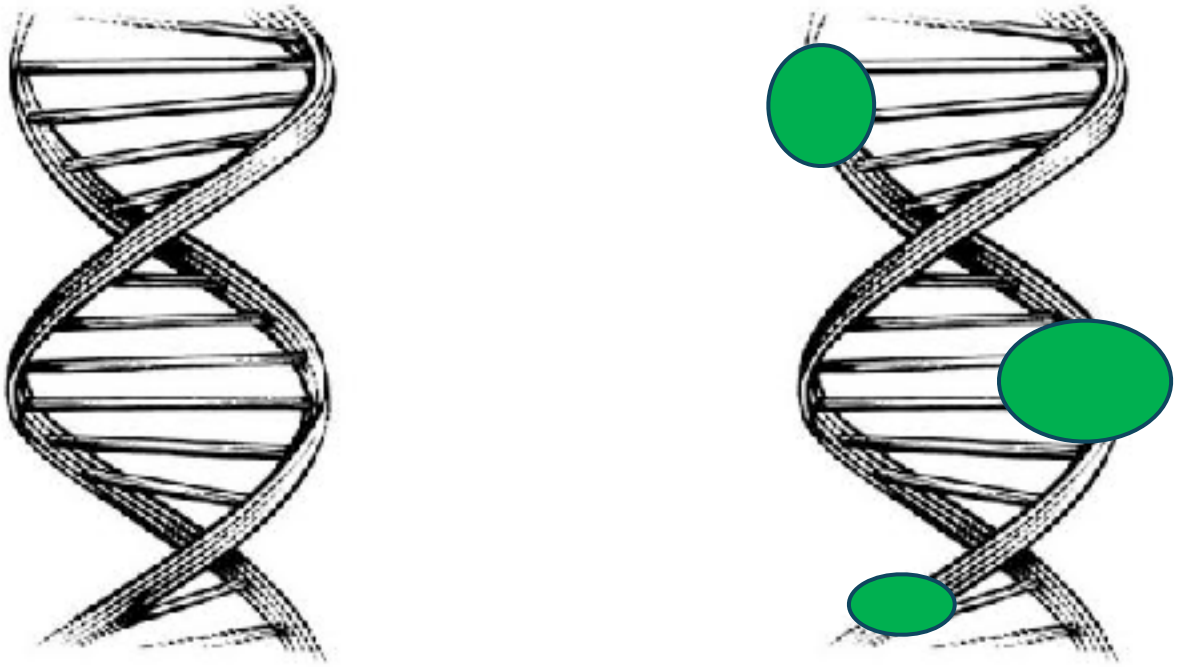
La **GENETICA** è la branca della biologia che studia i geni, l'ereditarietà e la variabilità genetica negli organismi viventi, focalizzandosi sulla comprensione dei meccanismi alla base di questi fenomeni, noti sin dall'antichità ma spiegati solo nella metà del 1800 dal biologo ceco Gregor Mendel.

L'**EPIGENETICA** è quell'aspetto della biologia che vuole studiare la relazione causale tra i geni ed i loro prodotti cioè le proteine. Una possibile definizione di epigenetica è "la serie di modificazioni al materiale genetico che cambia il modo in cui i geni vengono accesi o spenti ma non altera i geni in sé".

Nozioni di base….definizioni!!!

Genoma = DNA

EPIGENOMICA = SOPRA IL GENOMA

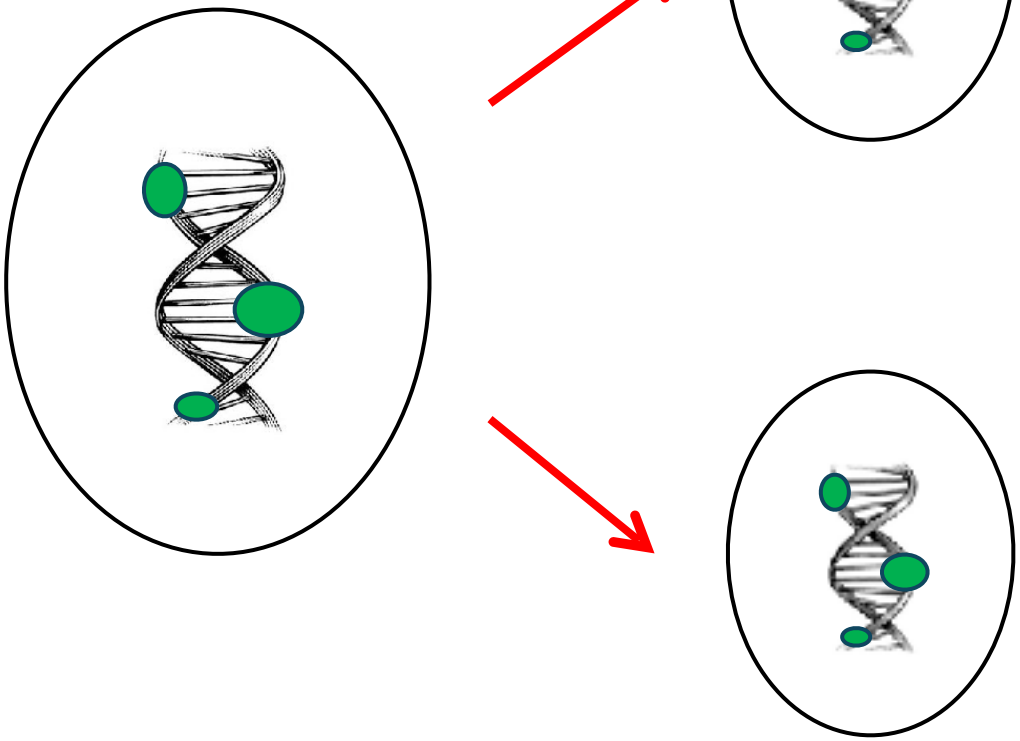


1 Genoma → n epigenomi

Tutte le cellule di un organismo hanno lo stesso genoma ma differiscono l'una dall'altra perché hanno un epigenoma

MEMORIA EPIGENETICA

CELLULA



CELLULE FIGLIE

Stress comportamentale
Metalli pesanti
Inquinanti e pesticidi
Fattori nutrizionali

↓

Alterazioni del pattern epigenetico

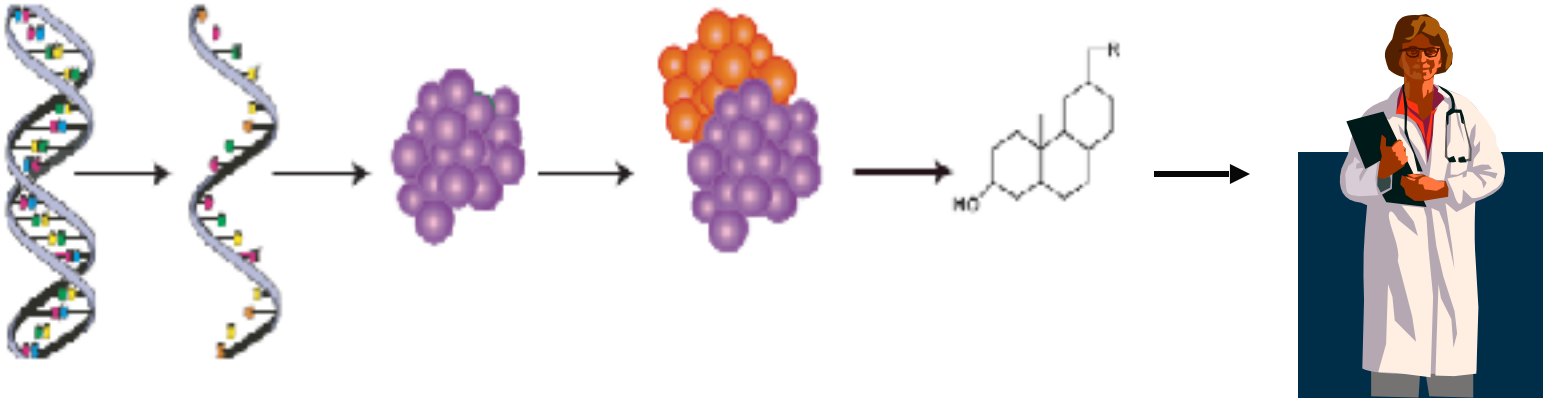
↓

Alterazioni dell'espressione genica

↓

PATOLOGIA

Systems Biology and Pathobiology



Genomics

Proteomics

Native *Modified*

Metabolomics

Metabonomics

Phenomics

Pathophenomics

Transcriptomics

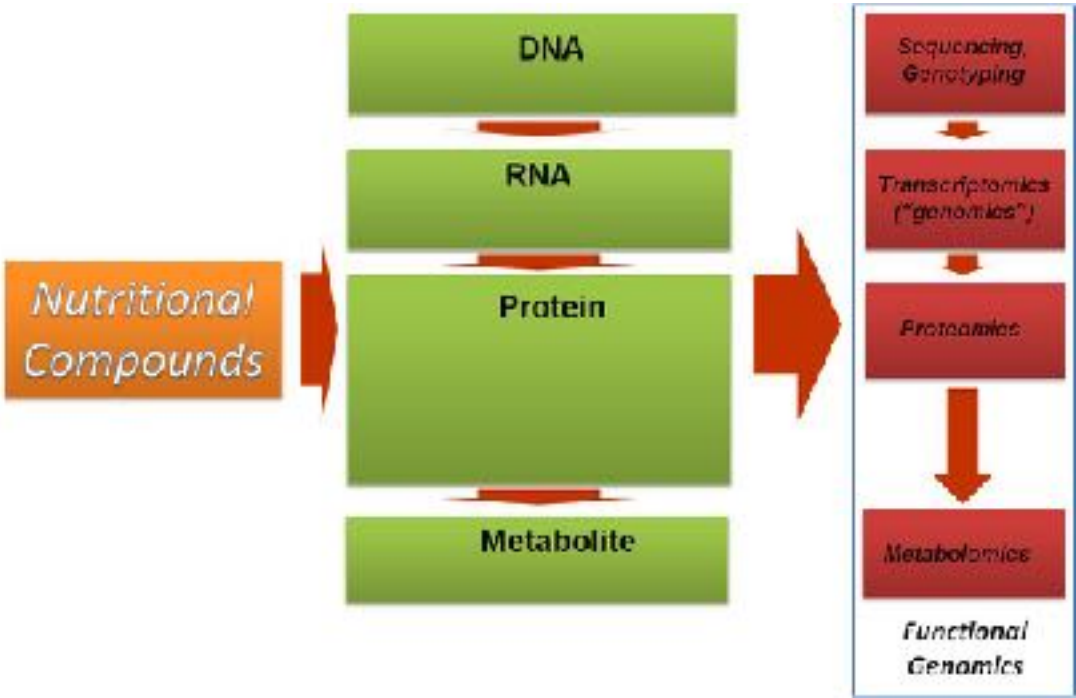
Functional Genomics/Proteomics

Environmental Perturbations

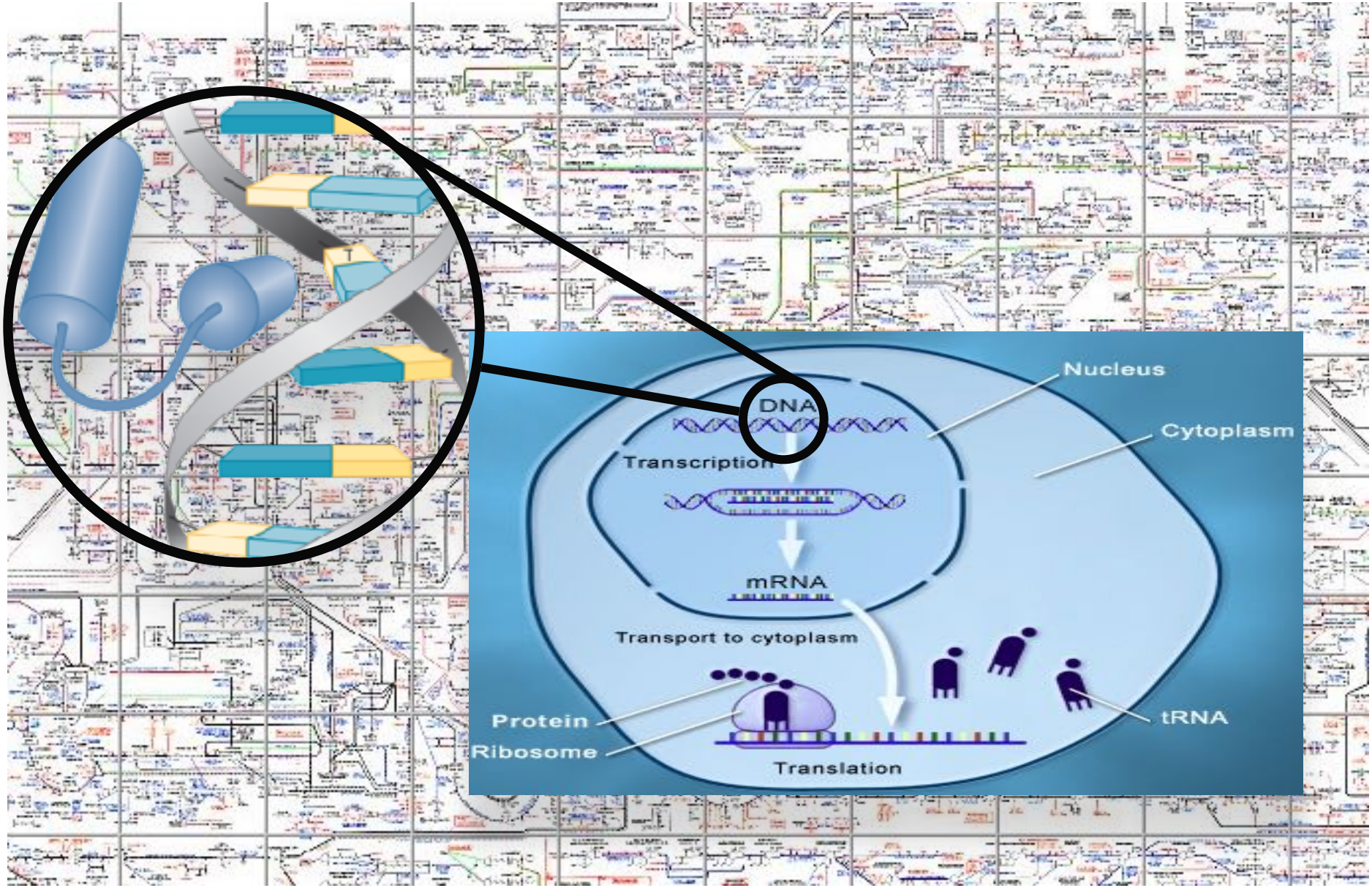
Systems Biology/Pathobiology

Facts on Nutritional Genomics

- The DNA sequence brings only the “genetic code”
- Phenotype is the resultant of the interaction of this genetic code with the environment
- Genes are turned “on” or “off” by:
    - Environmental influences



Nutrients can modify gene transcription



The nuclear receptor superfamily

Endocrine Receptors

Steroid Receptors

GR	glucocorticoid
MR	mineralocorticoid
PR	progesterone
AR	androgen
ERα,β	estrogen

Heterodimeric Receptors

TRα,β	thyroid hormone
RARα,β,γ	retinoic acid
VDR	vitamin D (bile acid)

Adopted Orphan Receptors

Lipid sensors

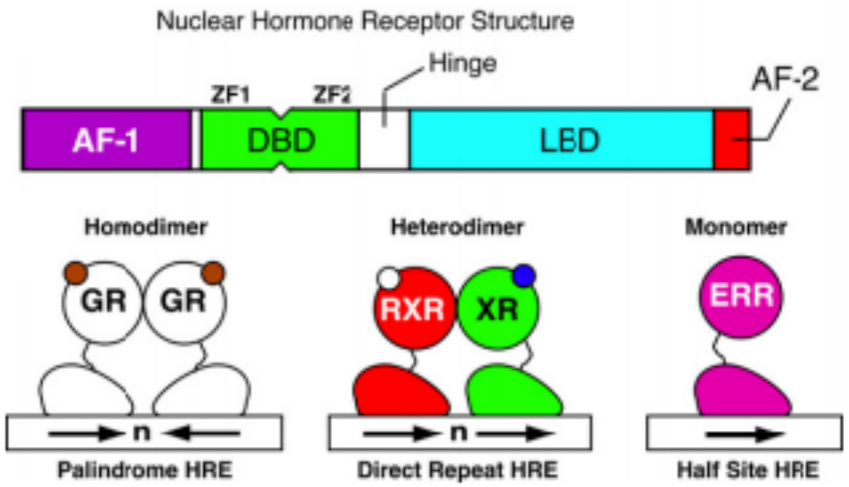
RXRα,β,γ	9cRA
PPARα,δ,γ	fatty acids
LXRα,β	oxysterol
FXR	bile acids
PXR	xenobiotics

Enigmatic Orphans

CAR	androstane
HNF-4α,γ	fatty acids
SF-1/LRH-1	phospholipids
RORα,β,γ	cholesterol / retinoic acid
ERRα,β,γ	estrogen?

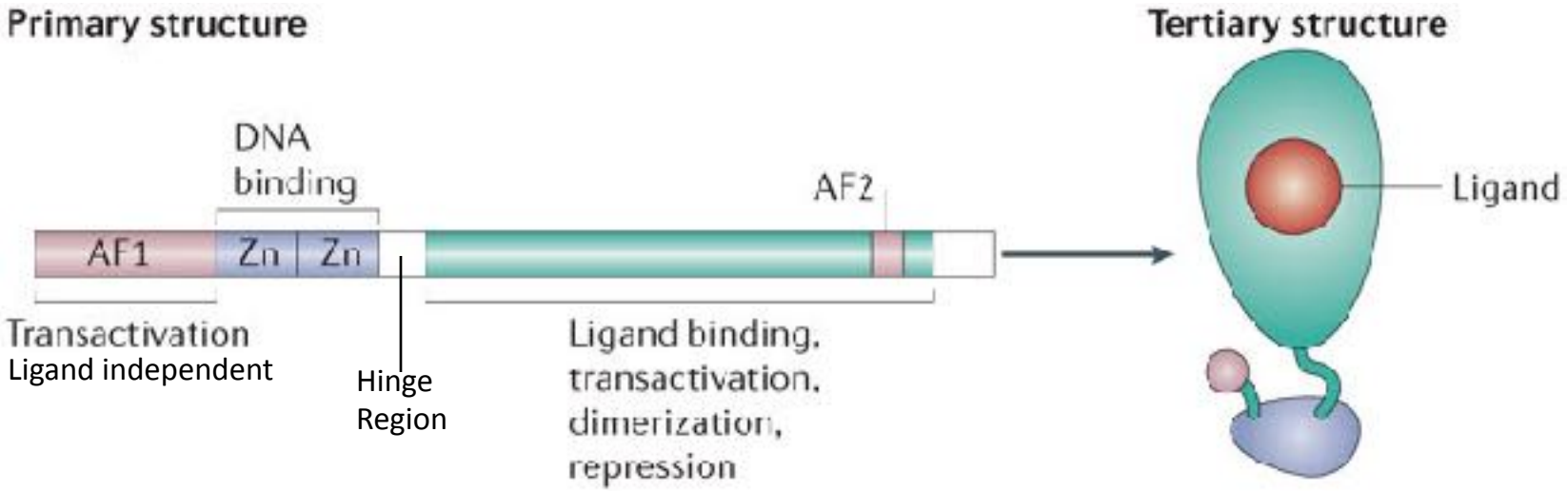
Orphan Receptors

SHP	?
DAX-1	?
TLX	?
PNR	?
GCNF	?
TR2,4	?
NR4Aα,β,γ	?
Rev-erbα,β	?
COUP-TFα,β,γ	?



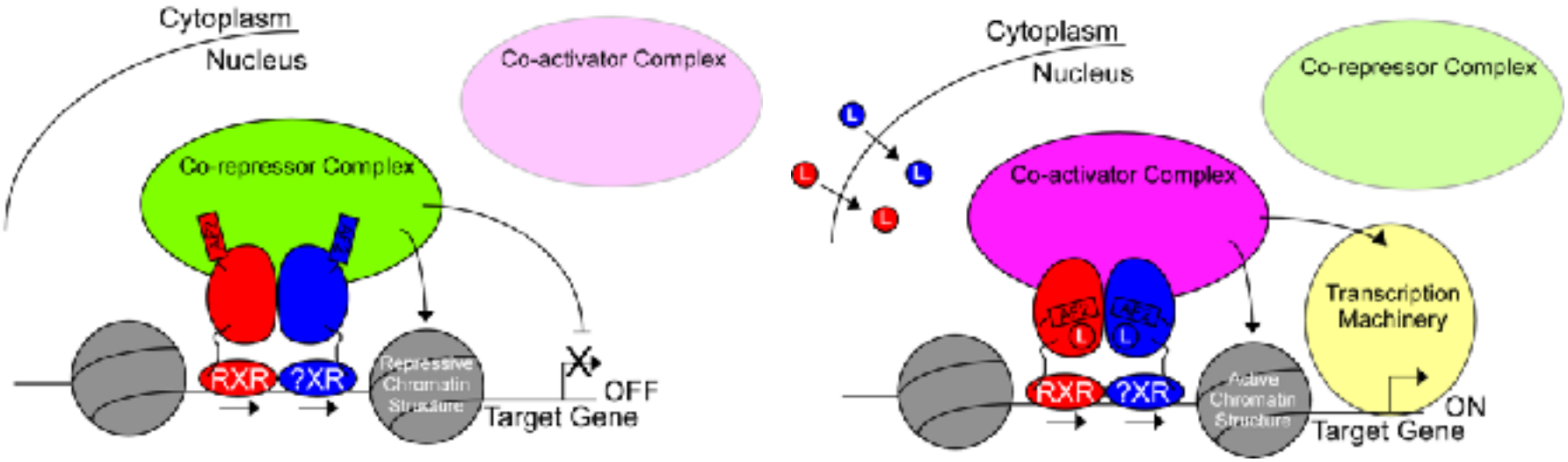
Sonoda et al., FEBS Letters 2008

Domain structure of a Nuclear Receptor



Christopher KG & Sumito O (2006) Nat Rev Immu ***6***: 44–55 doi:10.1038/nri1748

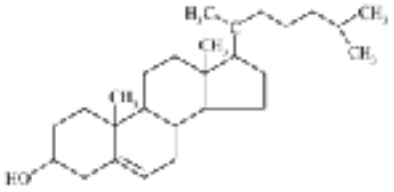
RXRs

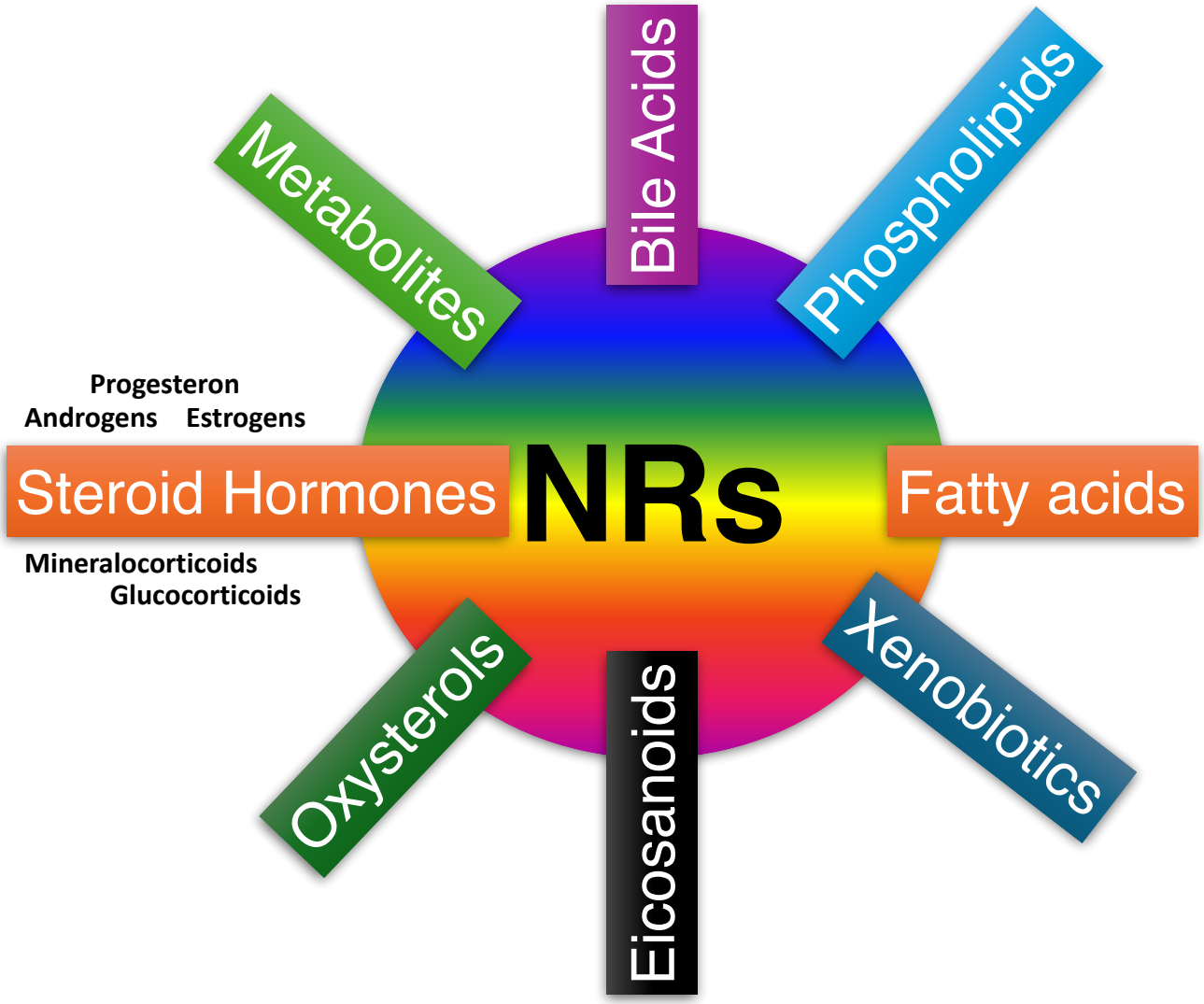


De Girolamo & Moschetta. Trends in Mol Med 2012
Moschetta & Kliewer. J Clin Invest 2005

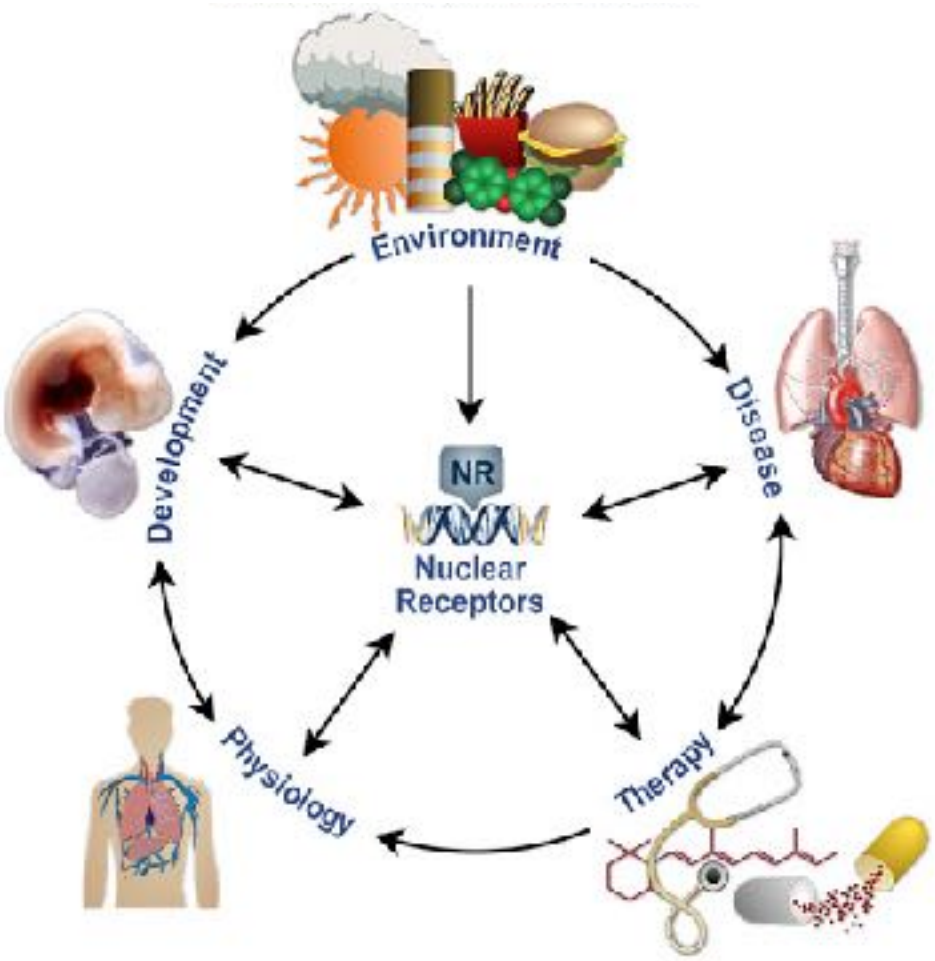
What activates nuclear receptors?

Cholesterol





Activated NRs and physiopathology



EPIGENOMIC FACTORS

Executive summary

- Lifestyle includes different factors such as nutrition, behavior, stress, physical activity, working habits, smoking and alcohol consumption.
- Environmental and lifestyle factors may influence epigenetic mechanisms.

Nutrition

- Folate and vitamin B12 intake
  - Epidemiological data support the anticarcinogenic property of folate.
  - A protective effect of low folate status against colorectal cancer was reported.
  - Contrasting results suggest that folic acid supplementation could exert a negative effect on already existing lesions.
- Polyphenols
  - Polyphenols can impact DNA methyltransferases, histone acetylases and histone deacetylases inducing reversibility of epigenetic dysregulation.
- Selenium
  - Selenium can impact the DNA methylation status interacting directly with DNA methyltransferases.

Obesity & physical activity

- Macronutrient composition of the diet could help to develop obesity through epigenetic mechanisms.
- Epigenetic mechanisms may be implicated in mediating the effects of physical activity.

Tobacco smoke

- Tobacco smoke effects have been examined through different epigenetic studies, but the results are still under debate.
- Smoking during pregnancy has been associated with an increased risk of developing diseases in fetal or later life, through epigenetic mechanisms.

Alcohol consumption

- Alcohol is an antagonist of folate metabolism and may have effects on DNA methylation.

Environmental pollutants

- Arsenic
  - Hypo/hypermethylation was observed in DNA of blood samples from subjects exposed to toxic level of arsenic.
- Air pollution
  - Particulate air pollution may affect human health through DNA methylation alterations.
- Aromatic hydrocarbons and other organic compounds
  - Repetitive element hypomethylation as well as either hyper- or hypo-methylation of specific genes has been reported for benzene and polycyclic aromatic hydrocarbon exposures.

Psychological stress

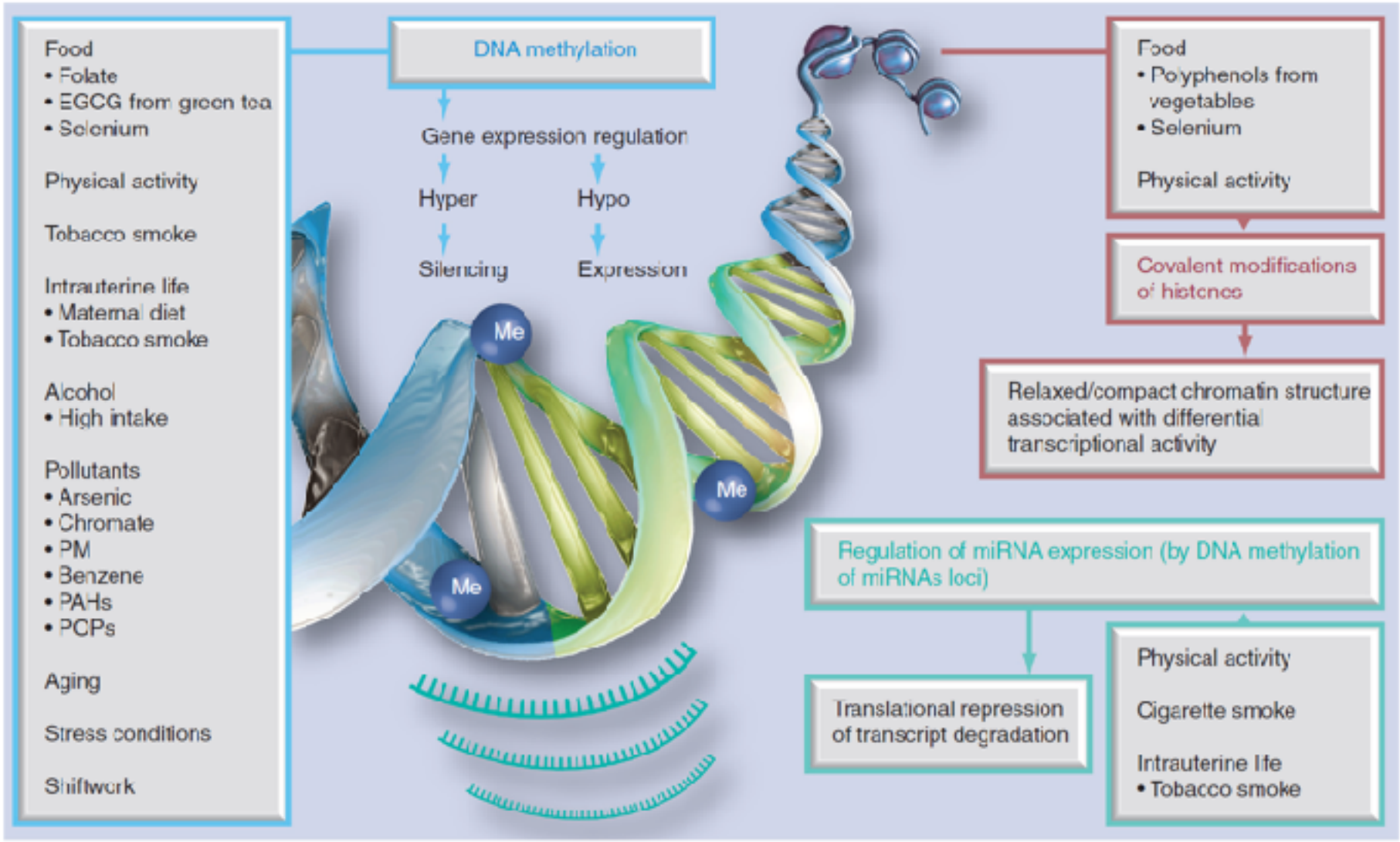
- DNA methylation is sensitive to environmental stressful exposures early in development and later in life.

Shiftwork

- An epigenetic reprogramming of circadian genes, changes in Alu repetitive elements methylation and gene-specific methylation of *IFN-γ* and *TNF-α* promoters have been observed.

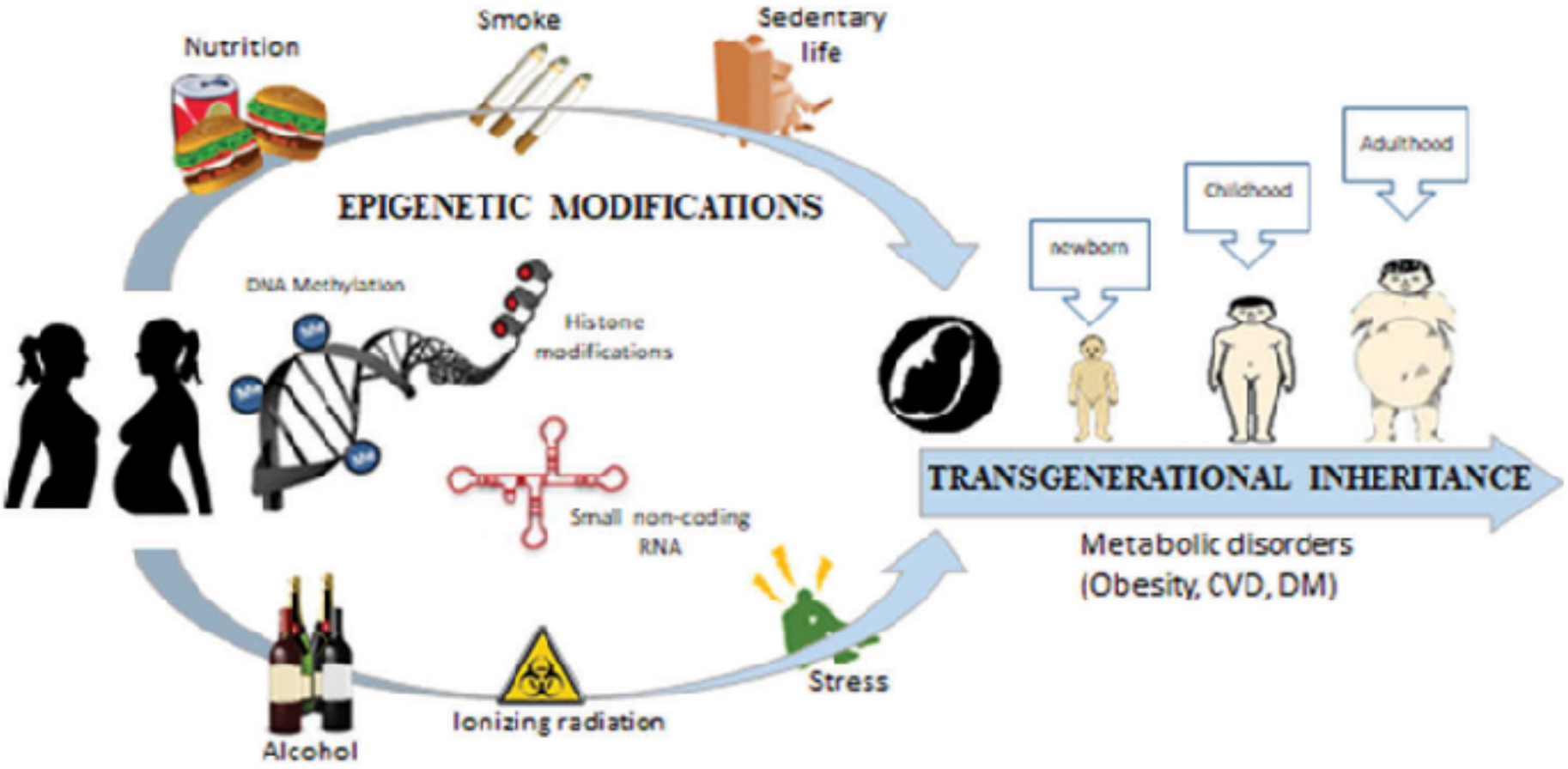
Alegría-Torres JA, et al. Epigenomics. 20

Lifestyle factors participating in environment–epigenetic interactions



Alegría-Torres JA, et al. Epigenomics. 20

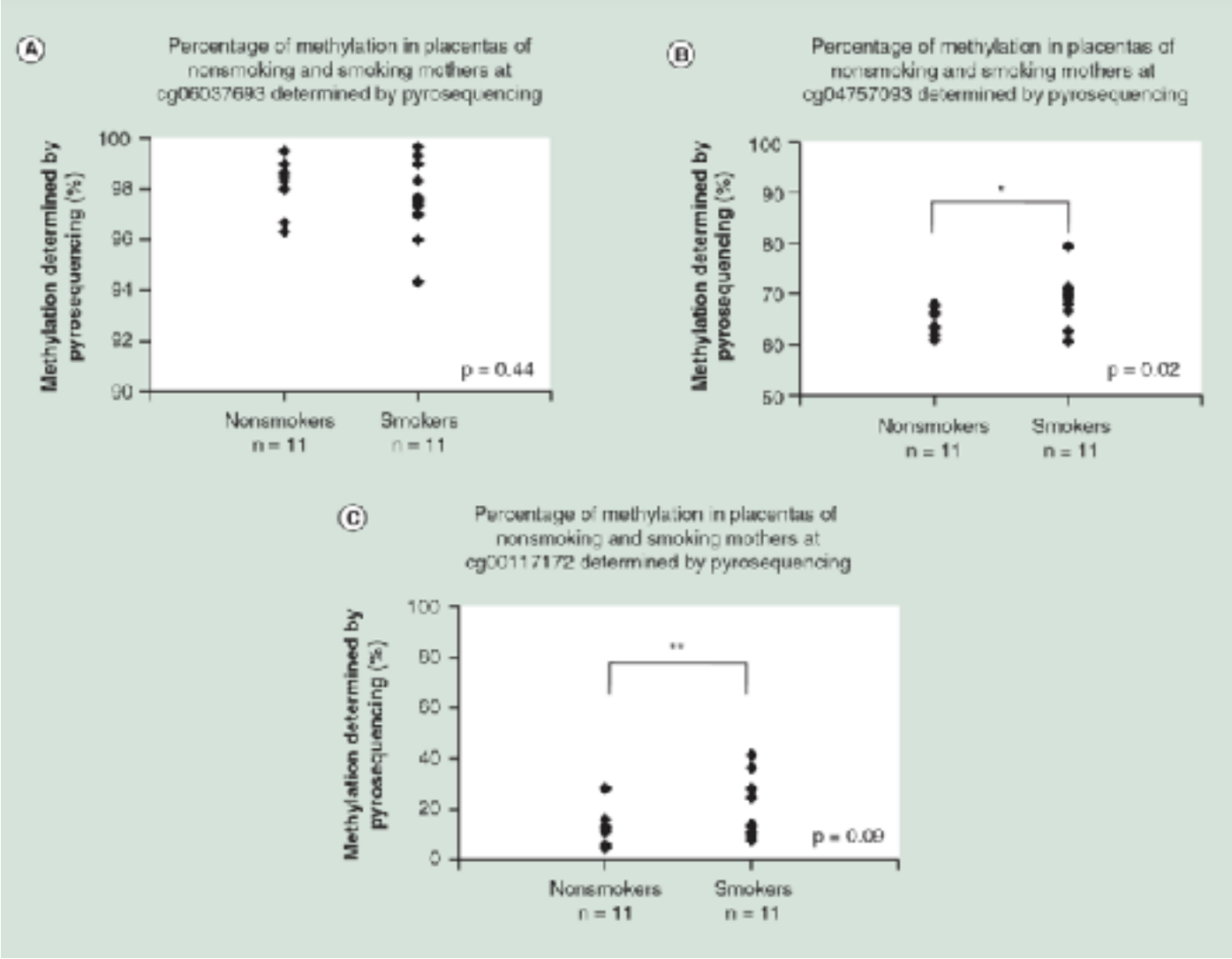
EPIGENETIC AND PREGNANCY



Epigenetic modifications are a modifiable component of the intergenerational transmission of phenotypic traits and thus can provide new exciting findings for susceptibility to obesity, diabetes, CVD, neuropsychiatric disorders and cancers.

Franzago M, et al. Epigenetics. 20

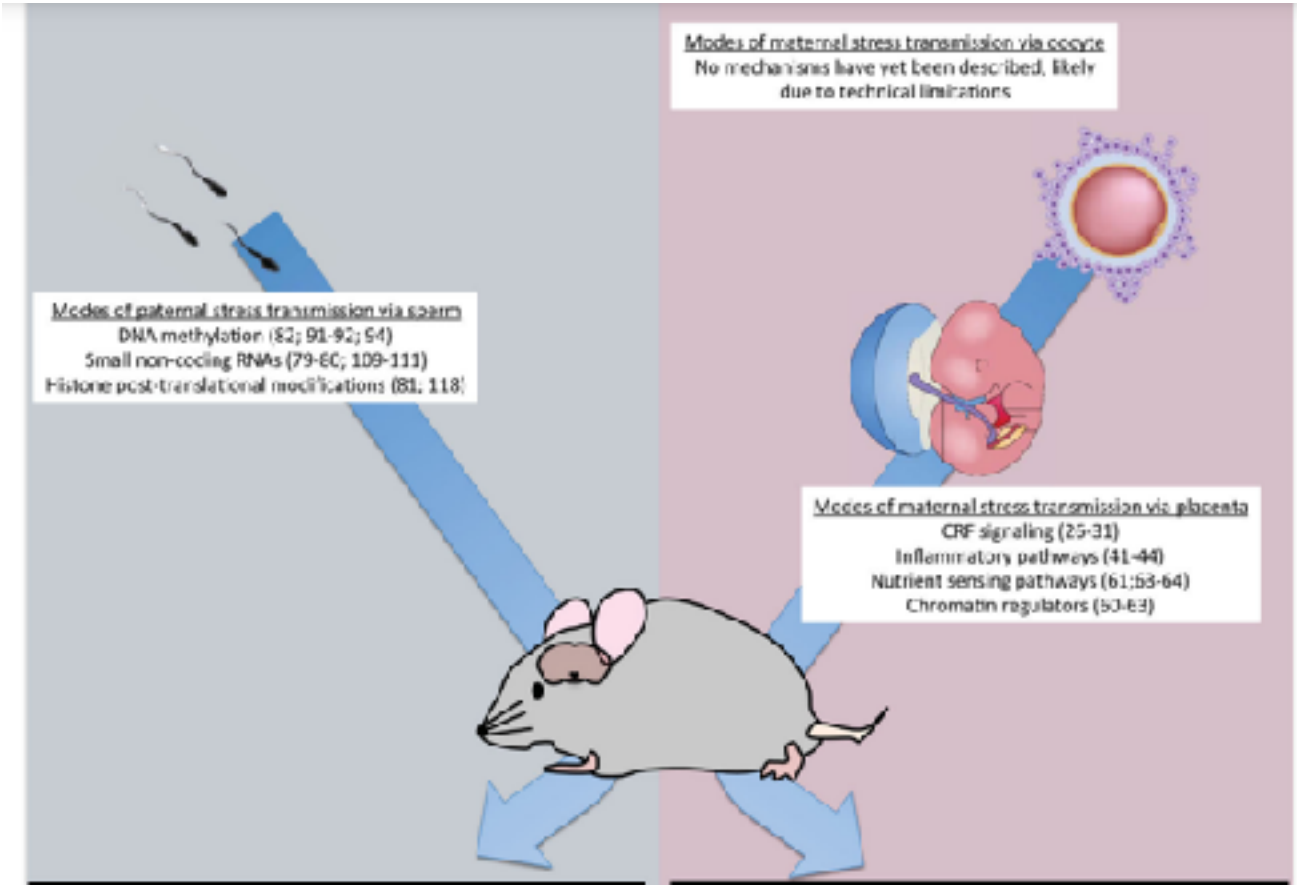
Placental DNA methylation alterations associated with maternal tobacco smoking at the RUNX3 gene



maternal smoking-induced changes in DNA methylation at specific loci, suggest a mechanism by which in utero tobacco smoke exposure could exert its detrimental effects upon the health of the fetus

Maccani JZ, et al. Epigenomics. 201

Intergenerational transmission of maternal and paternal stress can impact offspring neurodevelopment



Exposure	Species	Offspring outcomes	Ref
Jewish famine	Humans	Increased longevity and decreased risk for cardiovascular disease in grandsons	83-85; 95
Preconception trauma	Humans	Reduced cortisol levels, reduced GR sensitivity, increased risk of depression and PTSD	74; 86
Chronic vasopressin stress	Mice	Reduced HPA stress axis responsivity in male and female offspring	79
Social defeat	Mice	Increased depressive-like and anxiety-like behaviors, increased glucocorticoid levels	98
Odor-cued fear conditioning	Mice	Increased odor behavioral sensitivity in males	98
Maternal separation	Mice	Increased depressive-like behavior; altered exploratory behavior	98
Dietary challenge	Mice	Metabolic dysfunction, developmental defects	78; 80; 82

Exposure	Species	Offspring outcomes	Ref
Psychological stress during pregnancy	Humans	Increased risk of ASD and schizophrenia in males; increased risk for affective disorders in females	33-36
Infection during pregnancy	Humans	Increased risk of ASD and schizophrenia in males	34-40
Childhood abuse	Humans	Increased disruptive behavior, externalizing behavioral problems	71-73; 75
Preconception trauma	Humans	Poor perceived emotional health, increased depressive and anxiety symptoms, increased PTSD risk, greater glucocorticoid sensitivity	71; 74; 86
Prenatal chronic variable stress	Mice	Increased HPA stress axis sensitivity, cognitive dysfunction, metabolic dysfunction in males	21-23; 30
Prenatal infection	Mice	Social deficits; altered exploratory behavior; increased repetitive behavior	41-43
Prenatal glucocorticoids	Rats	Impaired coping and learning; reduced growth	31-32

Paternal stress exposures influence offspring outcomes (left table), potentially through changes in sperm epigenetic marks. Maternal stress during pregnancy alters placental signaling to reprogram offspring neurodevelopment (right table).

Chan JC, et al. Biol Psychiatry. 20

FOOD AND PREGNANCY

«We are what we eat»

(LW Feuerbach)

Ultra-processed foods

maternal obesity and shorter male infant anogenital distance

vegetables, fruits, nuts, and legumes

preeclampsia prevention

Leafy vegetable

improve the metabolic pathways in gestational diabetes pathogenesis and prognosis

Lifestyle


Gluten Free
Dairy Free
Soy Free
MONO DIET
Clean eating
BLOOD GROUP DIET
Vegan
I QUIT SUGAR!
Organic
Paleo?
Metabolism boosting
High Protein
low carb
Fat burning
Juice detox
INTERMITTANT FASTING

Mediterranean diet

Mediterranean diet

Mediterrean lifestyle inspired by the eating habits of Greece, Southern Italy, and Spain in the 1940s and 1950s years

In 2013, UNESCO added the Mediterranean diet to the Representative List of the Intangible Cultural Heritage of Humanity of Italy (promoter), Spain, Portugal, Morocco, Greece, Cyprus, and Croatia

Mediterrean lifestyle promotes conviviality and interpersonal relationships

Mediterranean diet

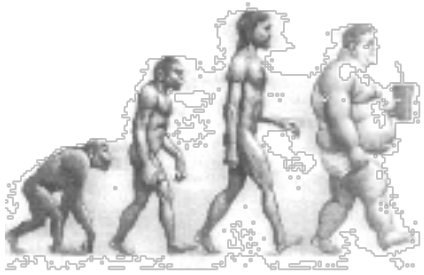
Mediterranean Lifestyle in Italy

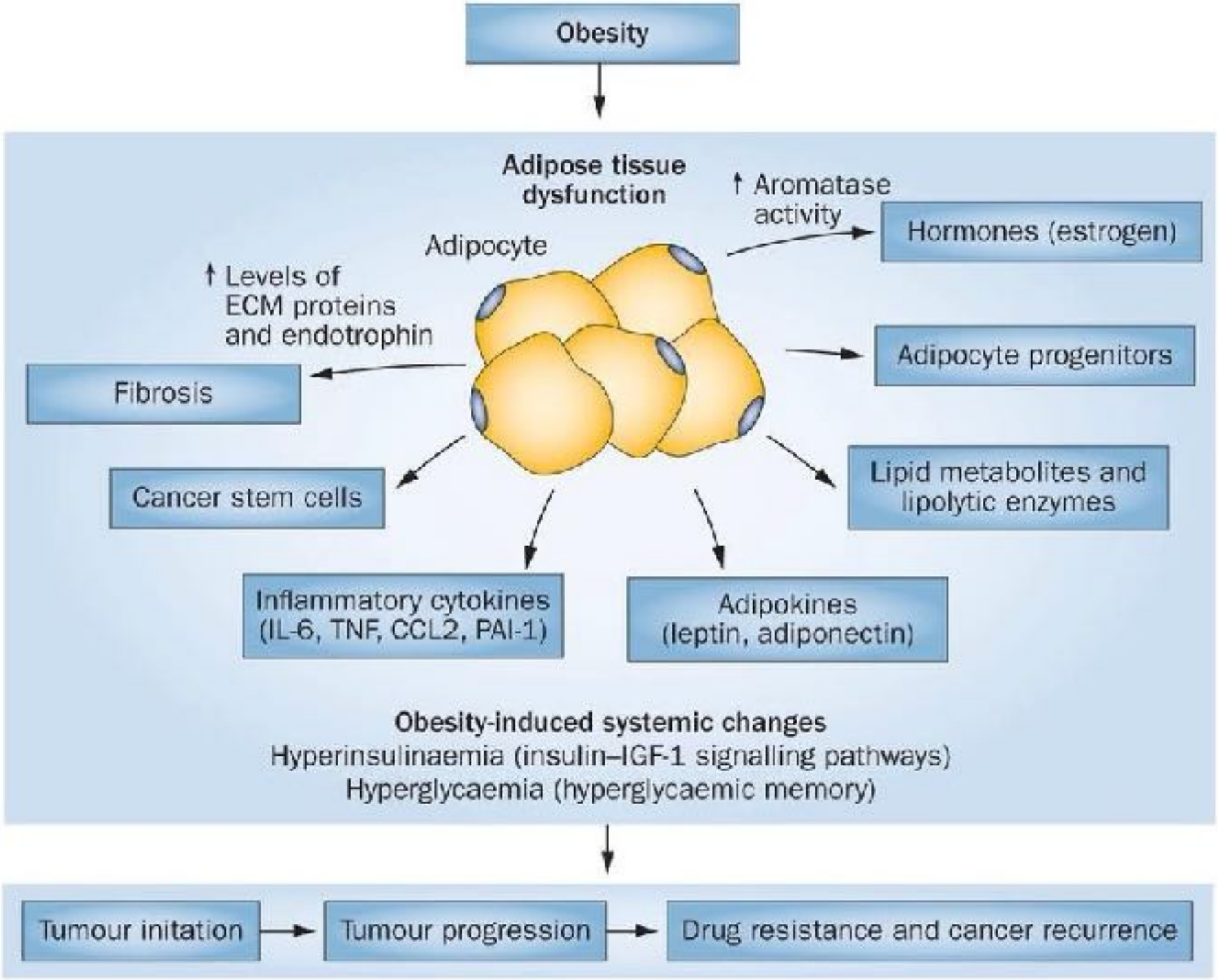
How it was in the past

- Low consumption of carbohydrates & saturated fats;
- High consumption of fibers & Olive Oil;
- Central Meal: **lunch**
- Dinner around 6 p.m.

How it is changed during the last decades:

- Increased consumption of sugars and fats;
- Reduced consumption of fibers;
- Central Meal: **dinner;**
- Dinner delayed to late evening;




Obesity
Adipose tissue dysfunction
↑ Aromatase activity
Hormones (estrogen)
Adipocyte
↑ Levels of ECM proteins and endotrophin
Fibrosis
Adipocyte progenitors
Cancer stem cells
Lipid metabolites and lipolytic enzymes
Inflammatory cytokines (IL-6, TNF, CCL2, PAI-1)
Adipokines (leptin, adiponectin)
Obesity-induced systemic changes
Hyperinsulinaemia (insulin–IGF-1 signalling pathways)
Hyperglycaemia (hyperglycaemic memory)
Tumour initation
Tumour progression
Drug resistance and cancer recurrence

Carbohydrate Overload Consequences

Carbohydrate Overload
(at high glycaemic index) increases:

- Plasma insulin;
- Insulin resistance;
- Plasma glucose;
- Plasma triglycerides;

- Visceral Obesity;
- Liver Steatosis;

Leading to MS

Carbohydrates fed during evening:

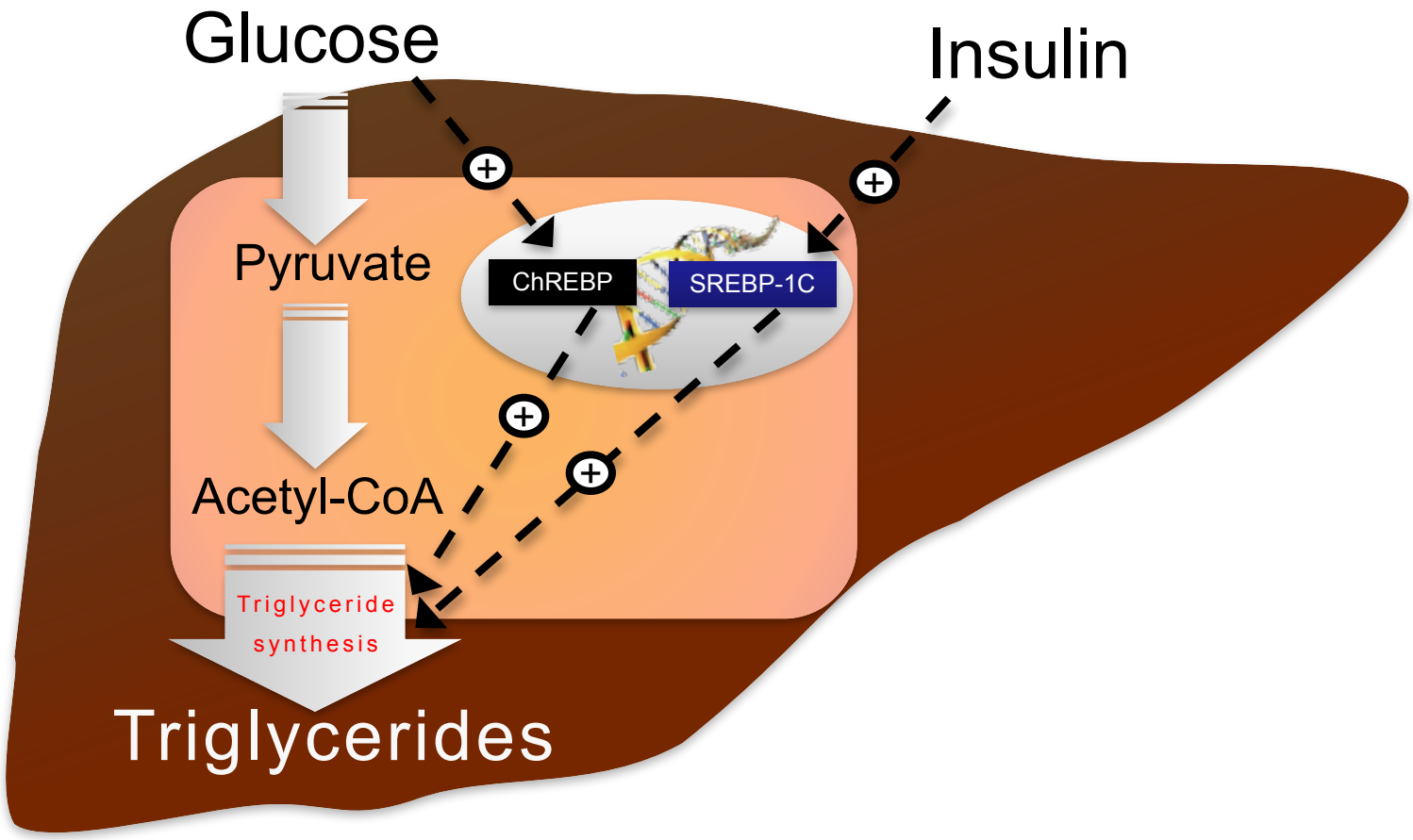
- Are converted into triglycerides by the liver via insulin (in absence of energy expenditure);

- Induces huge alterations in the physiology of the biological clock which is strictly related to metabolic homeostasis;

Alterations in biological clock lead to MS

PD Denechaud, J Clin Invest 2008; O Froy, Front Neuroendocrinol 2007; RM van Dam, Eur J Clin Nutr 2007

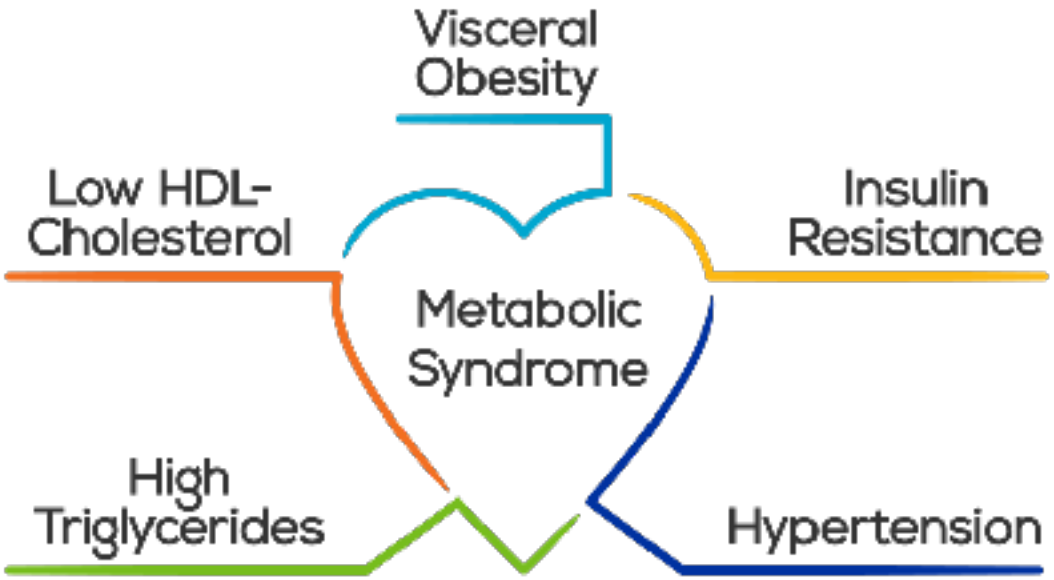
Carbohydrate Overload



PD Denechaud, J. Clin. Invest. 2008.

SINDROME METABOLICA

Disordine metabolico complesso, caratterizzato da un insieme di patologie (insulino-resistenza o diabete, obesità, ipertensione e dislipidemia)



La co-occorrenza di 3 delle 5 condizioni determina la diagnosi di sindrome metabolica.

SINDROME METABOLICA

Table 6
Risks of obesity in pregnancy

During Pregnancy	During Labor & Delivery	Postpartum Complications
Spontaneous miscarriage	Difficult fetal monitoring	Postpartum hemorrhage
Birth defects	Cesarean delivery	Wound infection
Limitations to ultrasound	Decreased success of a vaginal birth after cesarean delivery	Obesity in offspring
Gestational diabetes		
Hypertensive disease		
Stillbirth	Difficult anesthesia	
Fetal growth abnormalities		

Kominiarek MA, Rajan P. Med Clin North Am. 2

Il mio piatto in gravidanza….

Scegli 2 o 3 porzioni al giorno di latte e yogurt magri, non zuccherati, o di bevande vegetali (es di soia, di riso, di mandorla).
Una porzione corrisponde a un vasetto o tazzina da 125 g.
Lo yogurt è ottimo anche come spuntino.
Puoi aggiungere un cucchiaino di miele (max 2/die)

Assumi 2-3 porzioni di verdura al giorno, possibilmente di stagione, cercando di variare.
Es. broccoli, cavoli, carote, peperoni, spinaci, erbette.

Scegliere preferibilmente cereali e farine integrali

Condisci preferibilmente con olio extravergine di oliva (un cucchiaio da tavola). Mangia semi oleosi (noci nocciole, mandorle) e avocado, una volta al giorno.

Scegliere preferibilmente fonti proteiche di origine vegetale: fagioli, nocciole o pesci azzurri, formaggi a basso contenuto di grassi, limitare la carne rossa e gli insaccati.

Scegli la frutta fresca, spremute o frullati di frutta fresca, evita i succhi di frutta confezionati. La frutta è ottima anche come spuntino.

Bevi 6-8 bicchieri di acqua al giorno, evita le bevande zuccherate e riduci l'assunzione di tè o caffè.

Infine…almeno 30 minuti di attività fisica tutti i giorni

Tabella sintetica della porzioni settimanali di alimenti.

Frutta	2-3 frutti al giorno
Verdura	2-3 porzioni di verdura al giorno
Pane, pasta, cereali	ogni giorno, una porzione ad ogni pasto, meglio se integrali
Pelate	2 volte/settimana
Pesce	Fino a 3 volte alla settimana il pesce azzurro (es alici), 2 volte/sett il salmone, evitare se possibile, pesci di grosse dimensioni (spada, tonno).
Carne bianca (preferire)	1-2 volte/settimana (pollo, tacchino)
Carne rossa (non cruda in gravidanza)	1 volta/settimana
Uova	Un uovo 2-4 volte / settimana
Salumi	In gravidanza si può mangiare solo prosciutto cotto, fesa di tacchino e mortadella, con moderazione in quanto sono molto ricchi di grassi saturi/colesterolo quest'ultimi. Non più di una volta/sett. Tutti gli altri vanno evitati per via del rischio di TOXOPLASMOSI e a causa dell'elevato contenuto in nitrati e nitriti utilizzati per la conservazione.
Legumi	2-3 volte a settimana
Frutta secca con guscio (noci, nocciole mandorle, pistacchi, pinoli), non tostati, salati	Due porzioni (es 3 noci o mandorle, o 5 pistacchi) al giorno, dopo i pasti principali e anche come spuntino.
Frutta secca morbida (prugne, fichi secchi, datteri, uvetta, albicocche)	NON sostituisce quella fresca. Se ne possono assumere 2-4 al giorno, soprattutto le prugne sono molto indicate, in quanto aiutano anche a combattere la stitichezza. Vanno integrate nell'apporto calorico.
Latte e yogurt	2-3 porzioni al giorno
Formaggi (come secondo)	2 volte/settimana
Alcolici	Consumo occasionale, in quantità limitate (2 bicchieri di vino rosso da 125 ml ciascuno, alla settimana).
Caffè	2 tazzine/die (o una di tè e una di caffè)
Bibite zuccherate e succhi	NO
Cioccolato fondente (>70% cacao)	2-3 quadratini al giorno (30 g /settimana)
Dolci	Consumo occasionale
Gelati	Consumo occasionale
Zucchero	Consumo occasionale
Dolcificanti	NO
Marmellata/miele	Sì, una porzione al mattino. Preferire marmelate fatte con una percentuale di frutta > 50%
Olio e burro	Preferire olio extravergine a crudo: 2 cucchiai /die

Acknowledgement

Antonio Moschetta's Lab