KOÇ UNIVERSITY

ENDOCRINE DISRUPTING CHEMICALS INDUCE OXIDATIVE STRESS

Prof. Dr. N. Nuray Ulusu
nulusu@ku.edu.tr

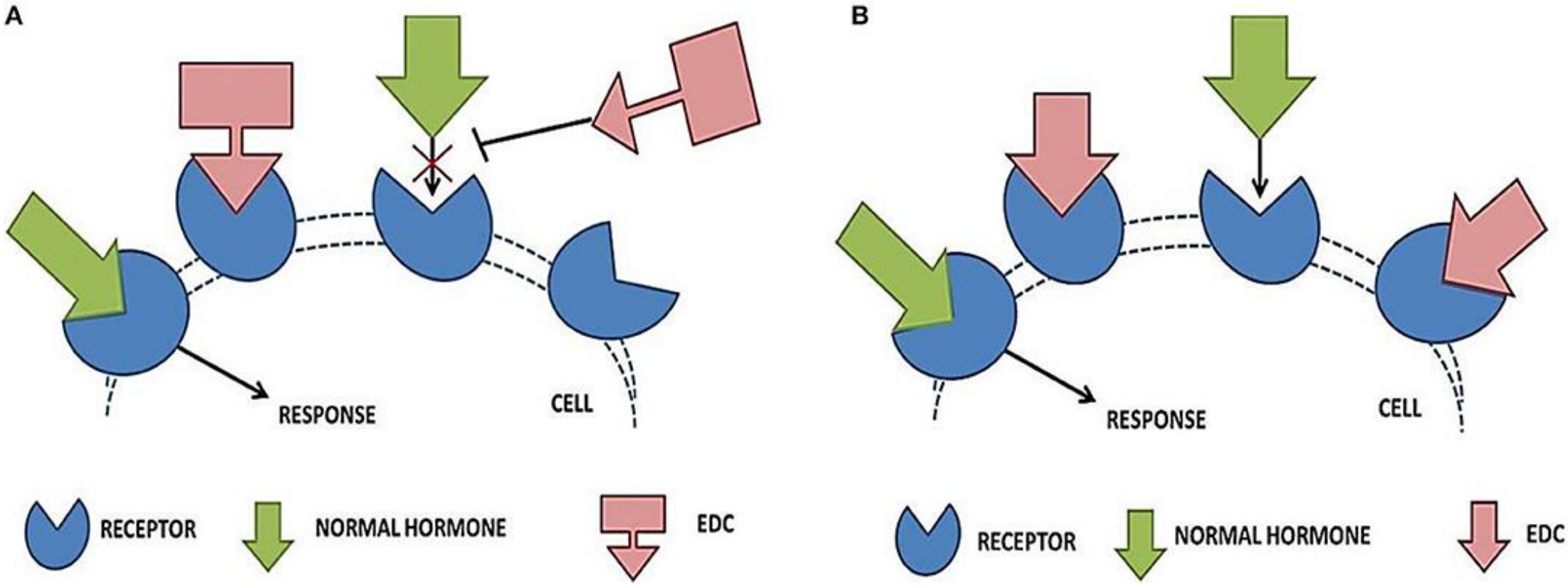
BCLF BALKAN CLINICAL LABORATORY FEDERATION

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

EFLM EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

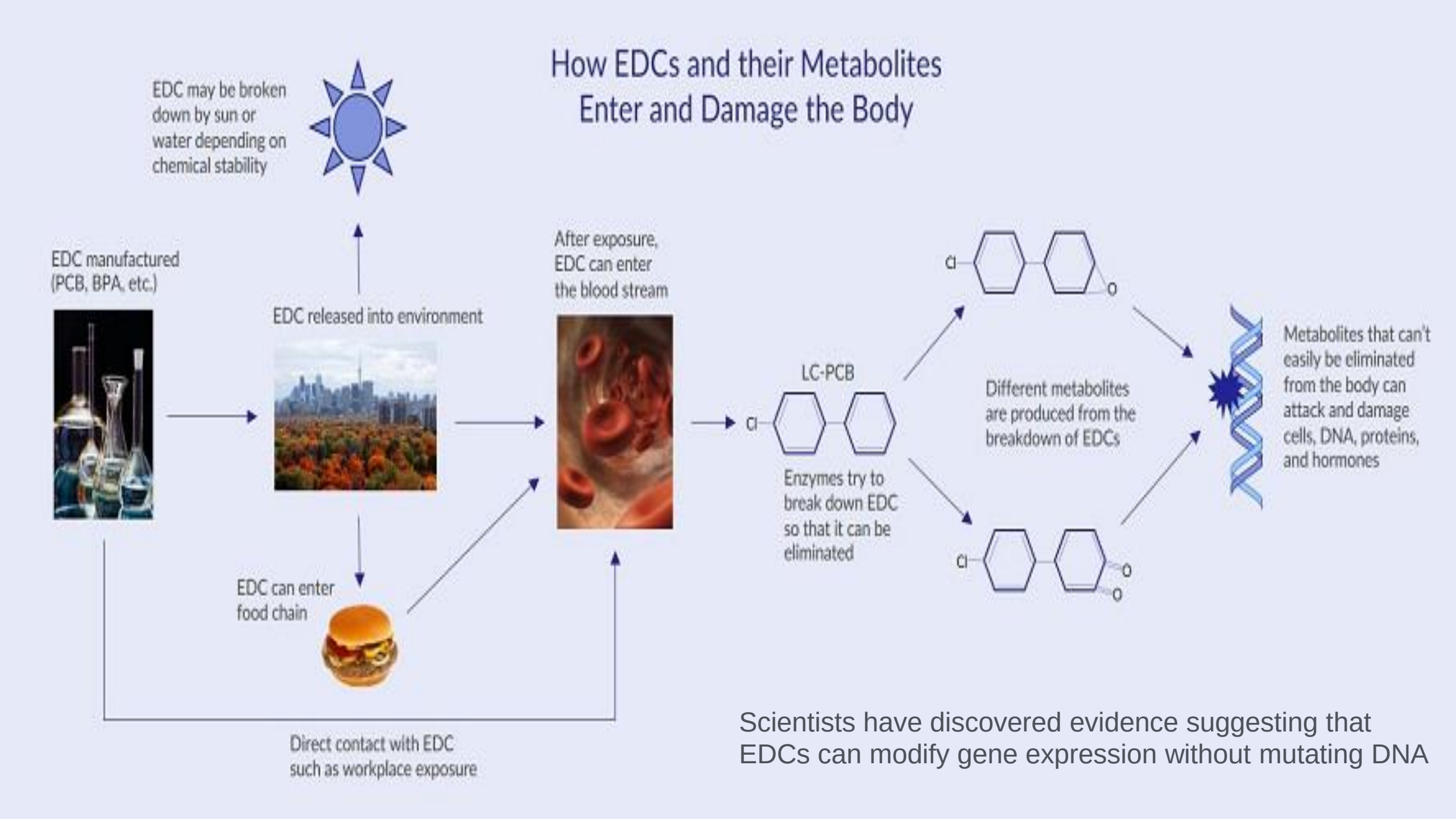
Effect of EDCs on receptor—hormone interaction

Mimic or interfere with functions of endogenous hormones

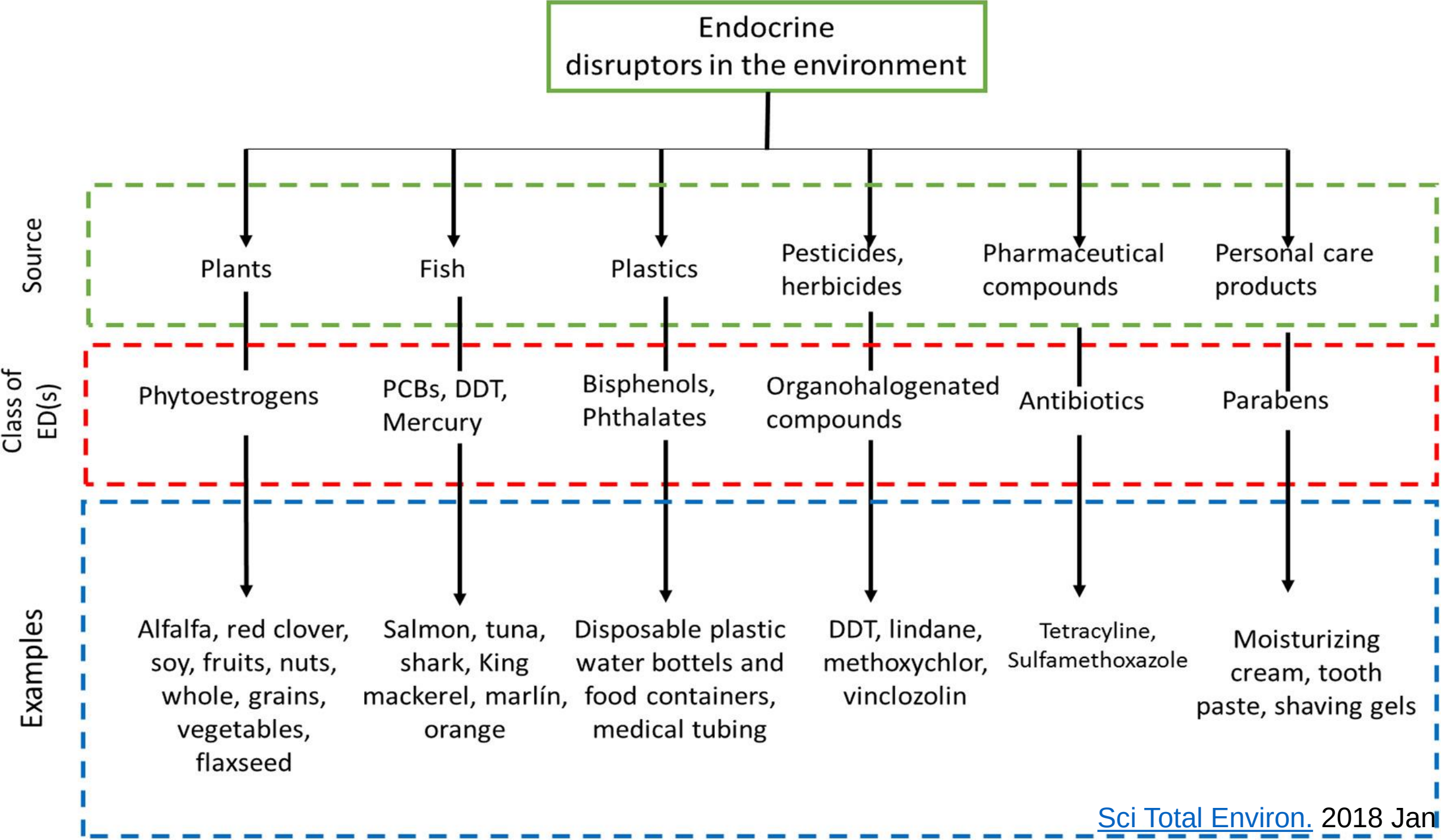


Front. Endocrinol., 26 November 2018

How EDCs and their Metabolites Enter and Damage the Body



Scientists have discovered evidence suggesting that EDCs can modify gene expression without mutating DNA



Sci Total Environ. 2018 Jan 15;6

Routes of EDC release to the environment and effects on human biological systems

Sources of EDCs emission to the environment

Pesticides

Food Packaging

Contraceptives

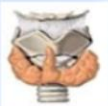
Air pollution

Occupational Environmental Exposure

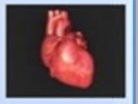
Toxicologically affected Biological systems/organs

CNS

Thyroid



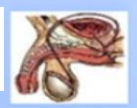
Heart



Pancreas

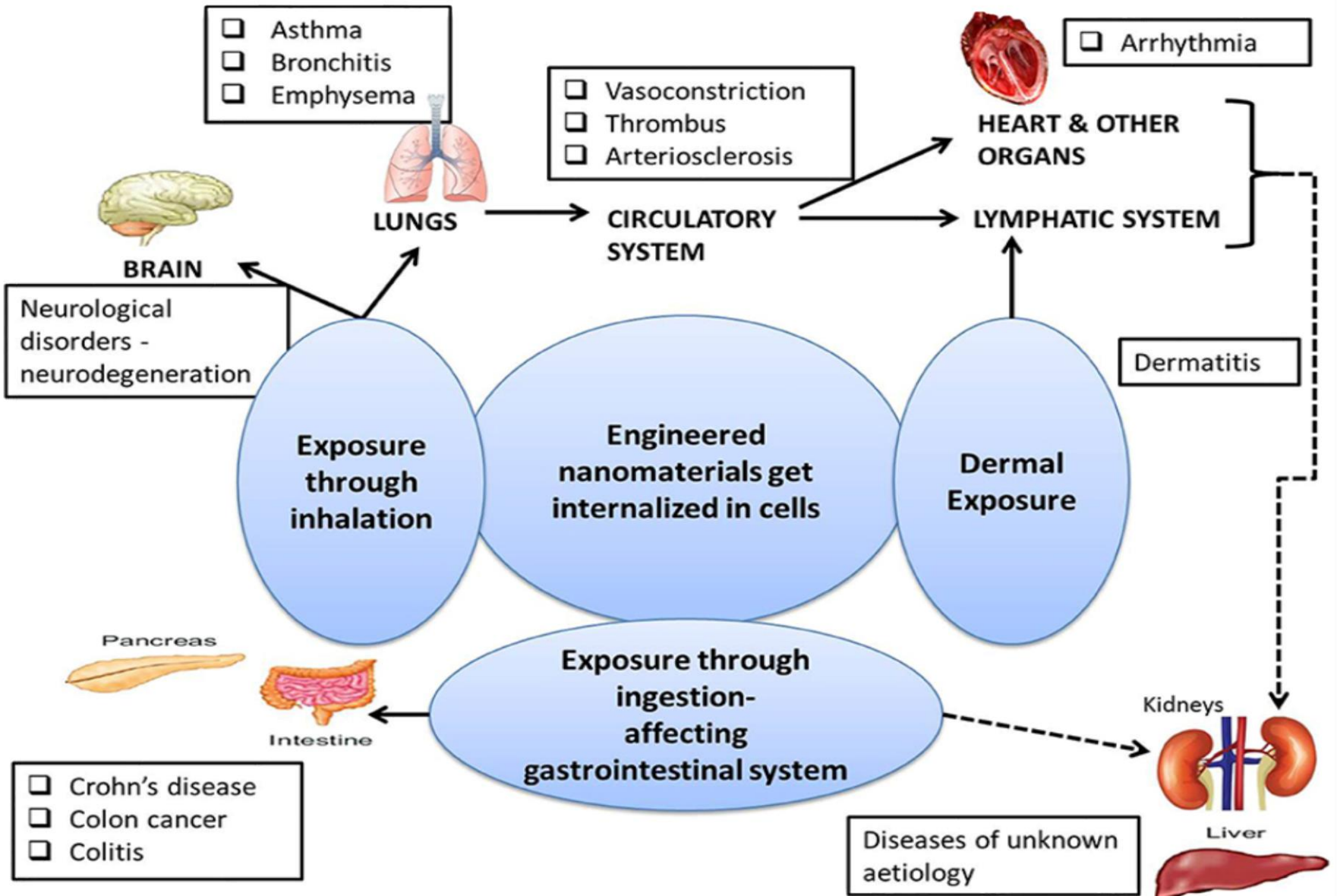
Ovary

Testis

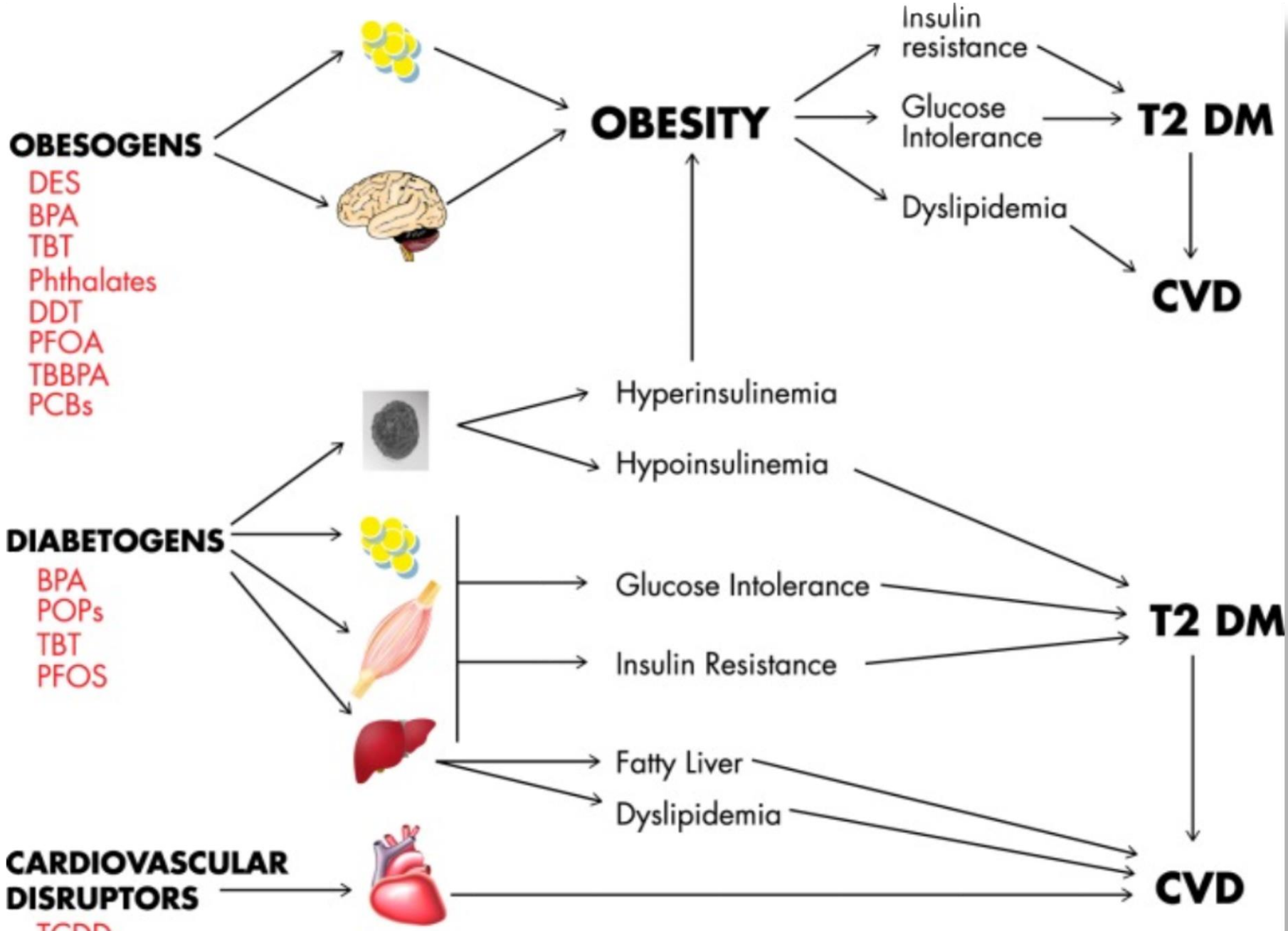


Life Sci. 2016 Ja

The exposure to EDCs & affected organs

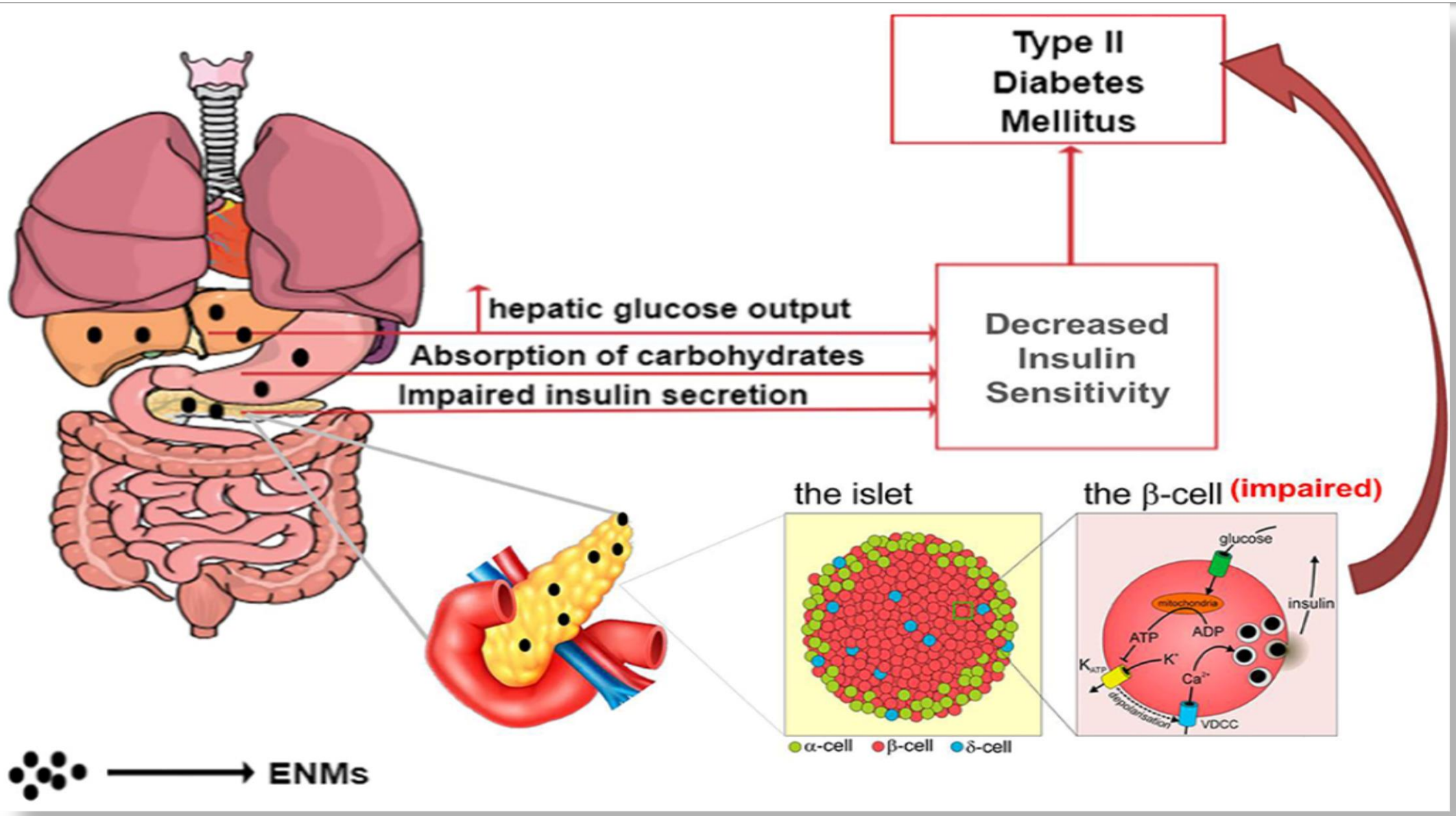


Front. Endocrinol., 2018



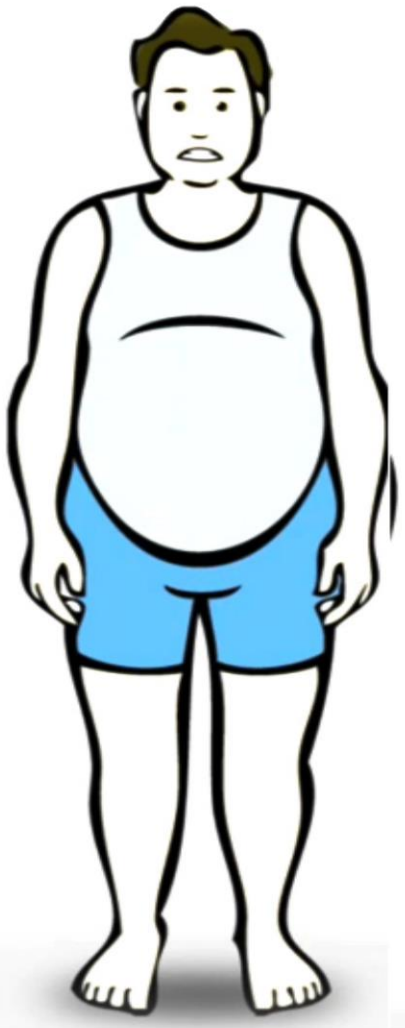
Endocr Rev. 2018 Dec; 36(6): E1–E

Effects of EDCs on the gastrointestinal system, development of T2DM.

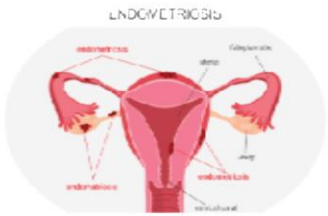


Front. En
| https://d

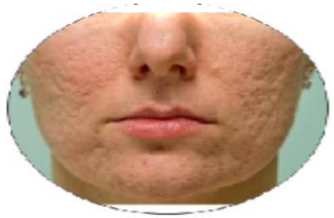
EDCs & health problems



OBESITY & METABOLIC SYNDROME



ENDOMETRIOSIS

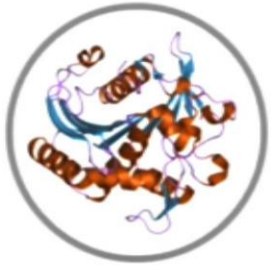


ACNE

AUTISM

Childhood social impairment

HEART DISEASE

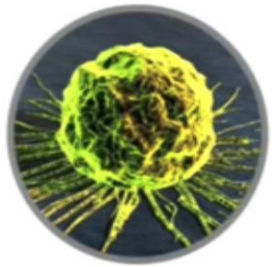


LIPID PROBLEMS

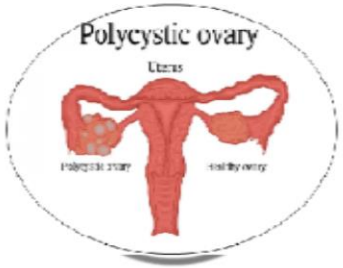
HYPERTENSION

TYPE 2 DIABETES

DEMENTIA



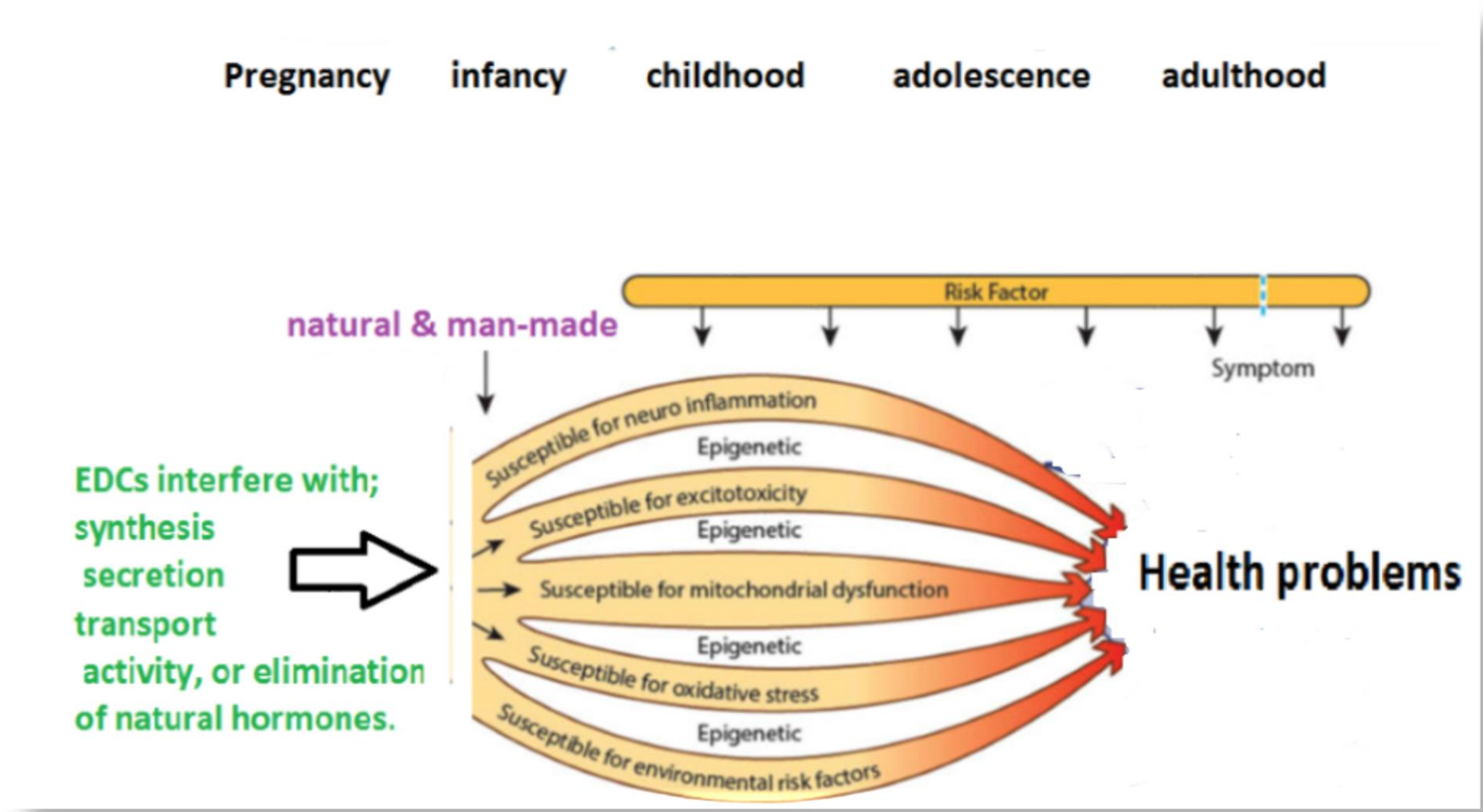
CANCER



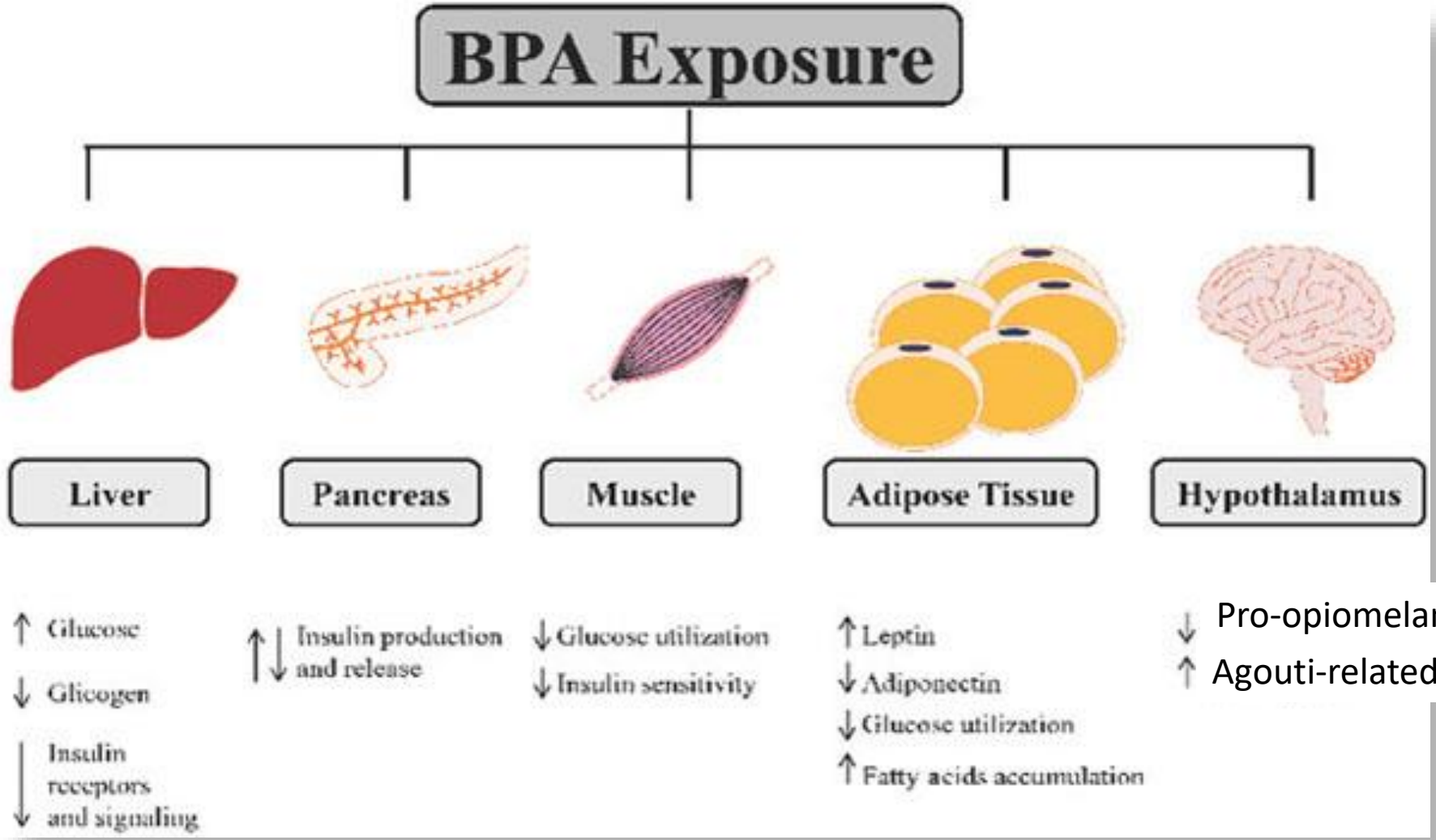
POLYSYSTIC OVARIAN SYNDROME

NON-ALCOHOLIC FATTY LIVER DISEASE

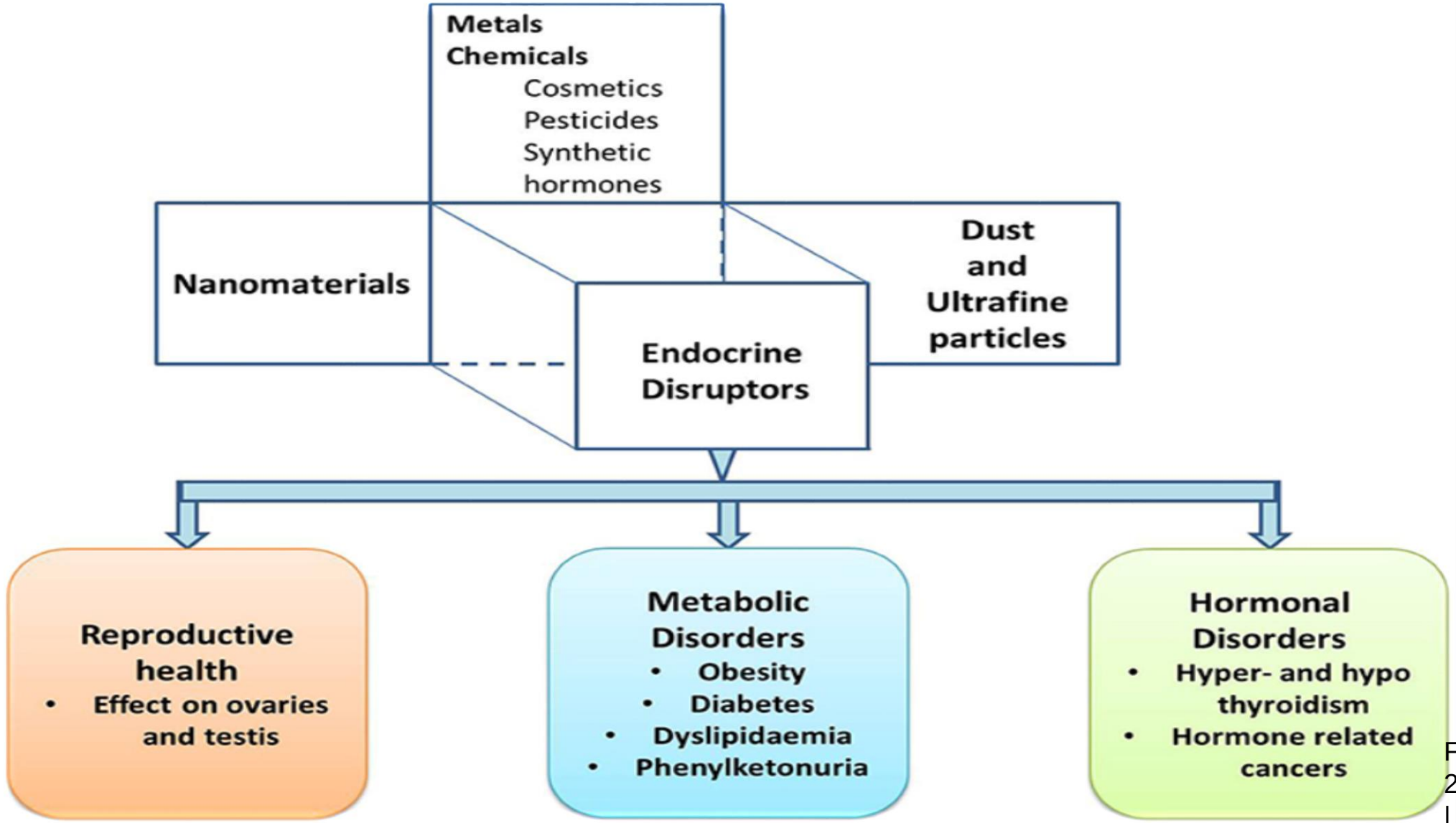
EDCs interfere with the hormone sytem
&
produce adverse effects by aging



BPA exposure may lead to metabolic dysfunction affecting glucose homeostasis



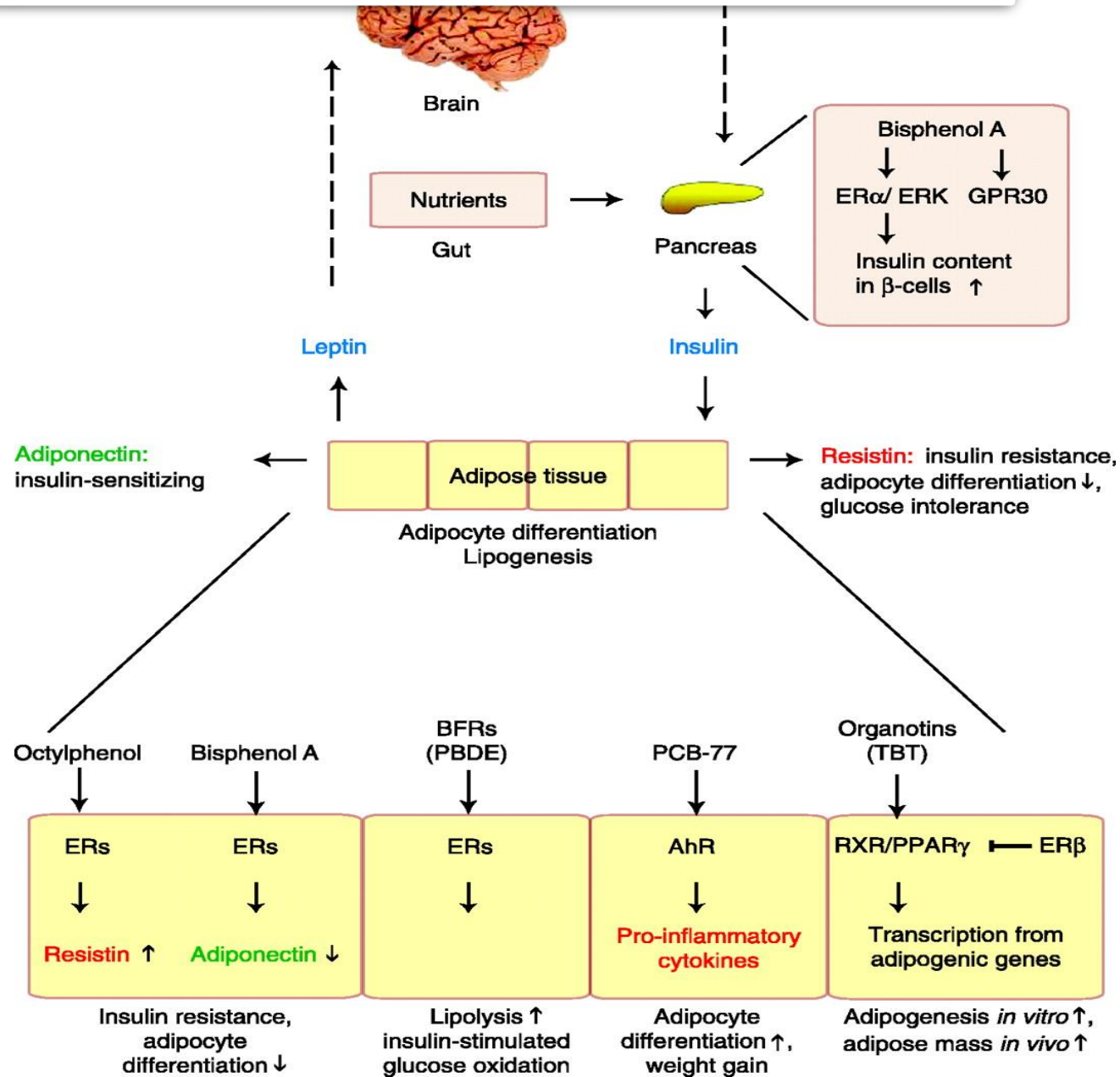
Different types of EDCs & the associated endocrine disorders



Front. Endocrinol., 2018 | https://doi.org/10.3

Regulation of glucose uptake
How this can link EDC exposure to metabolic disorders

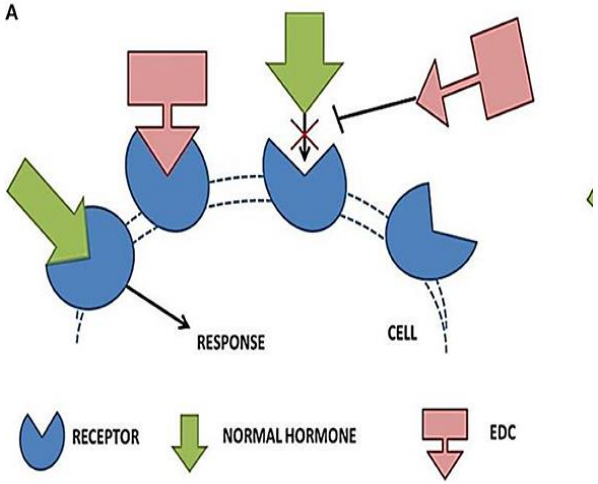
- Leptin**, regulates energy homeostasis** by **stimulating energy use** and limiting food intake.
- If it is lacking, food intake may be uncontrolled, causing obesity.

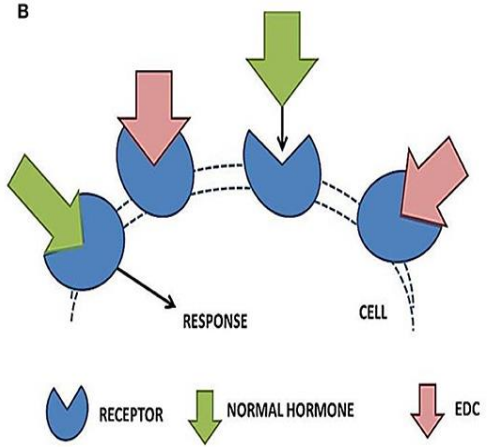


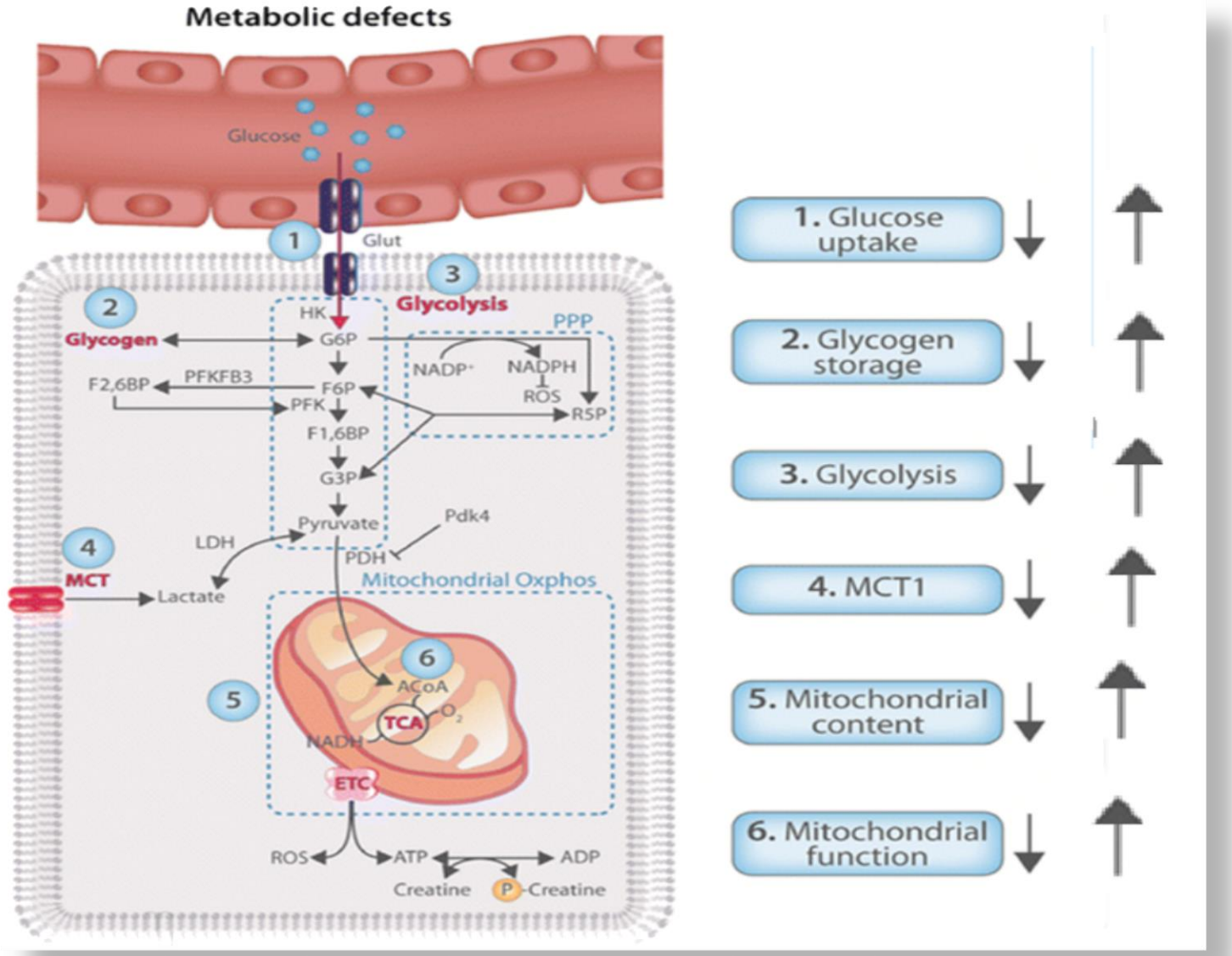
AhR: **aryl hydrocarbon receptor**

multiple phase I and II xenobiotic chemical metabolizing enzyme genes

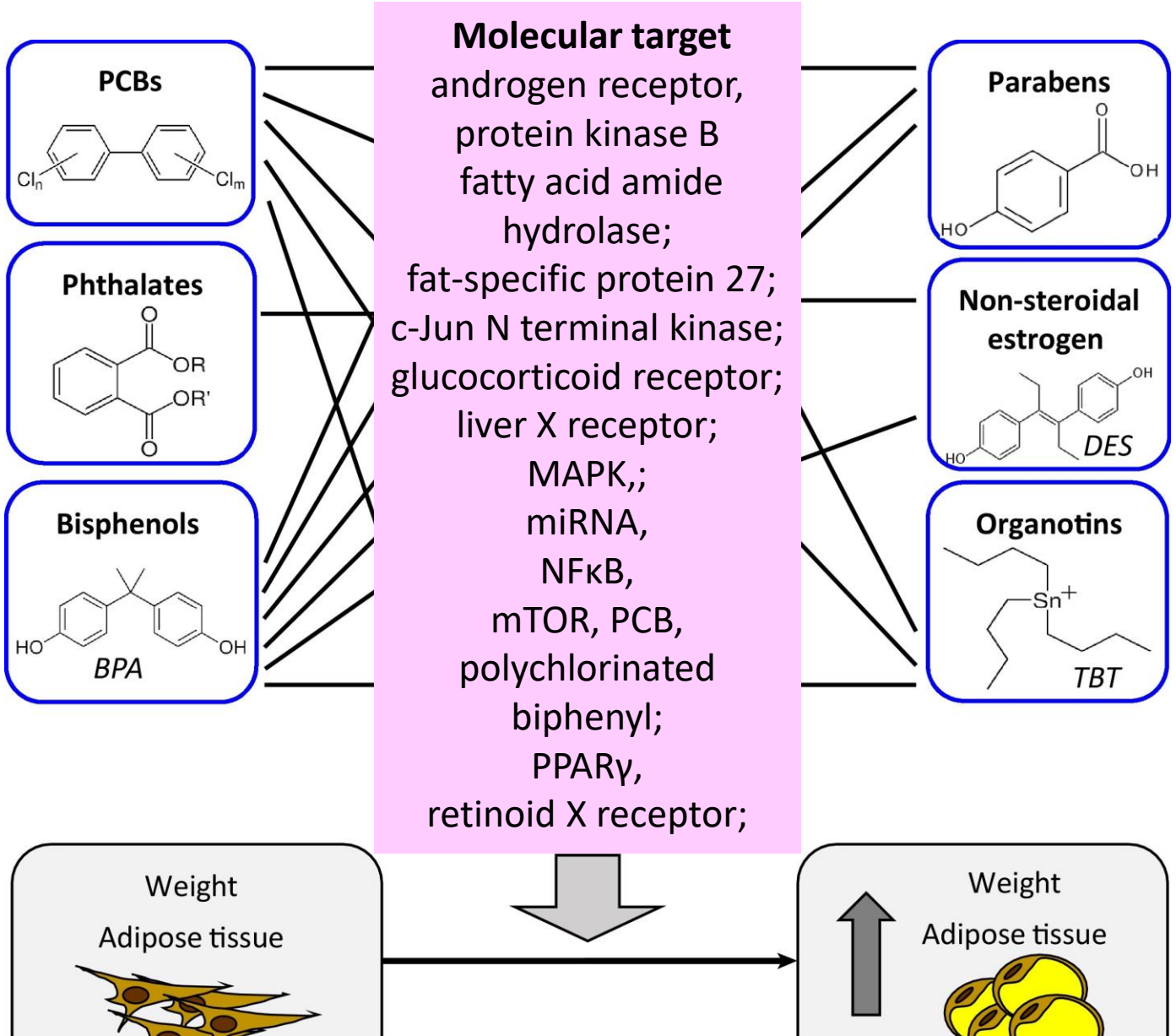
EDCs disrupt energy homeostasis





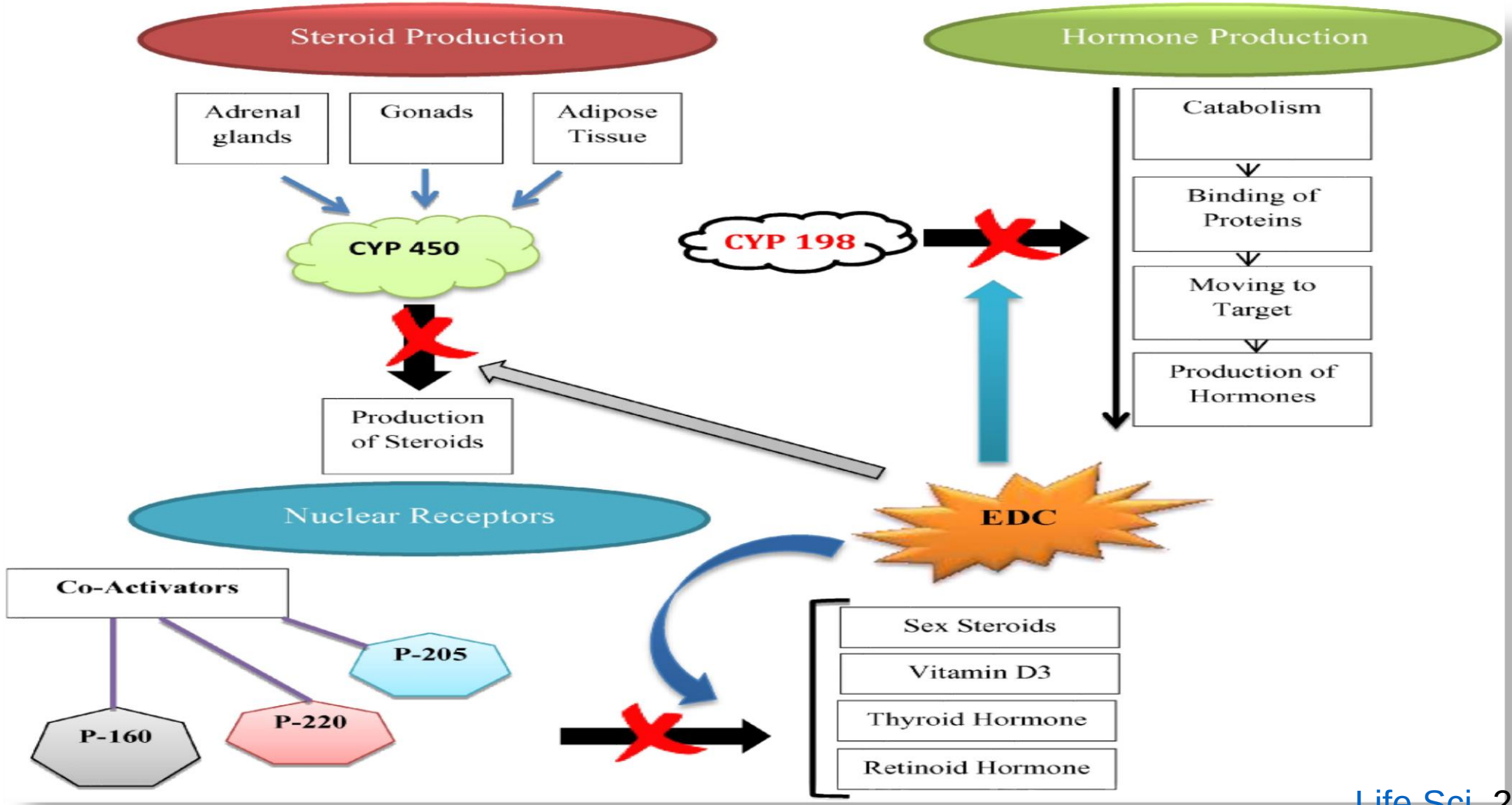


EDCs & targets



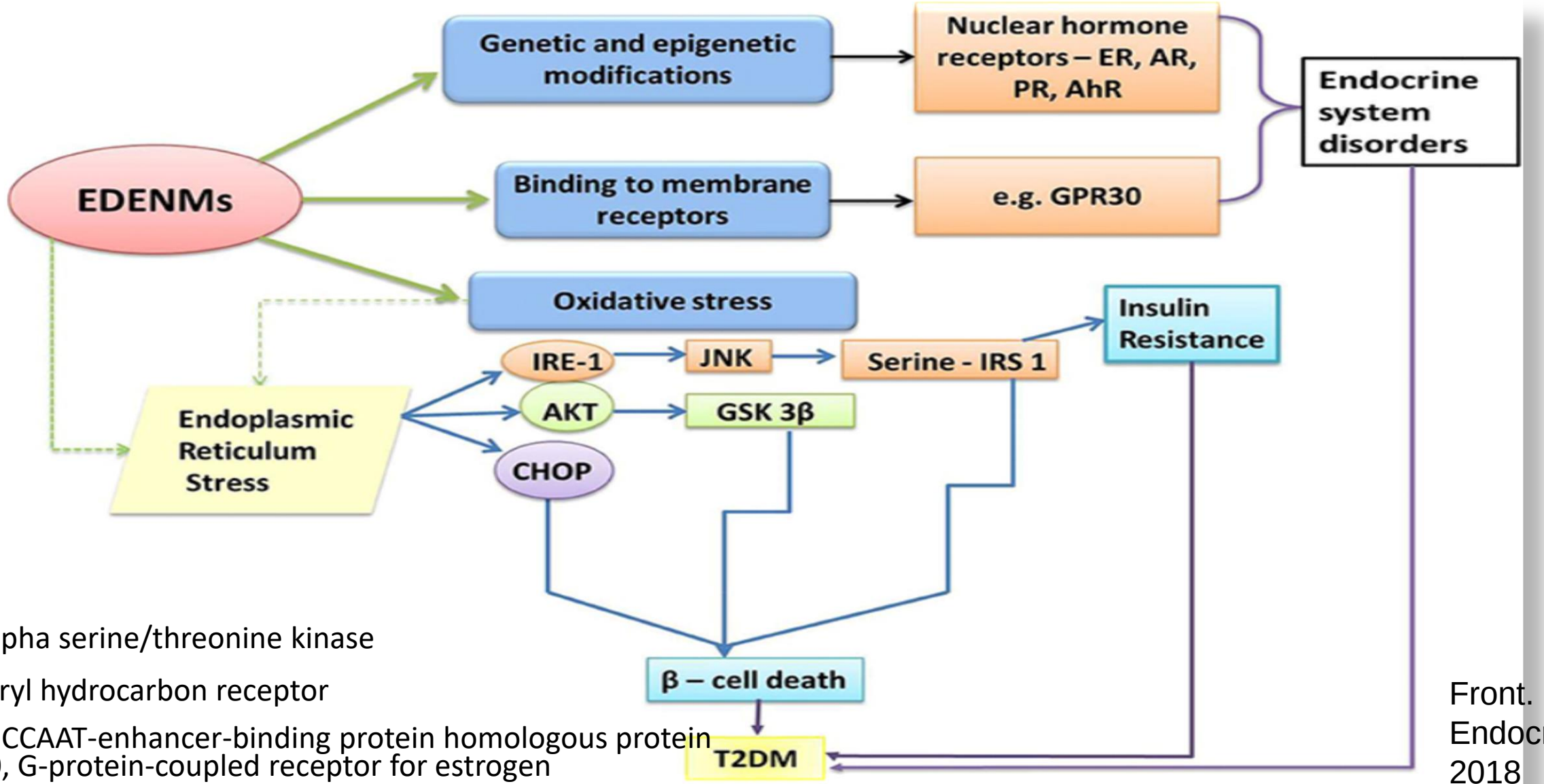
Trends Endocrinol Metab. 2018

Mechanism of EDCs at hormonal & receptor level



Life Sci. 2016 Jan 15;145:265-73

Role of ED in the Pathogenesis of Type 2 Diabetes Mellitus



AKT, alpha serine/threonine kinase

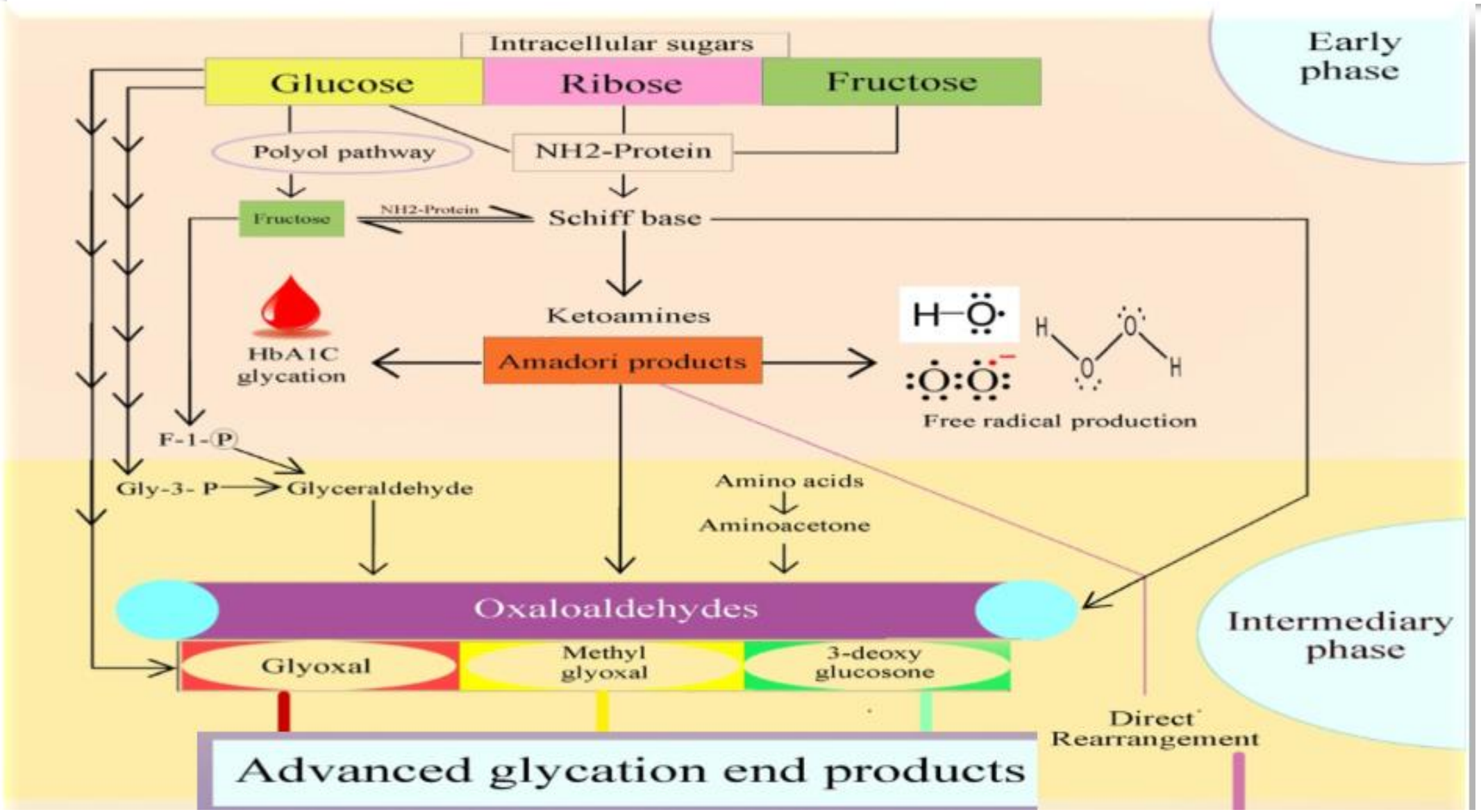
AhR, aryl hydrocarbon receptor

CHOP, CCAAT-enhancer-binding protein homologous protein

GPR30, G-protein-coupled receptor for estrogen

Front. Endocrinol., 2018

Effects advanced glycation end products



Environment International Volume 123, February 2019, Pages 486-500

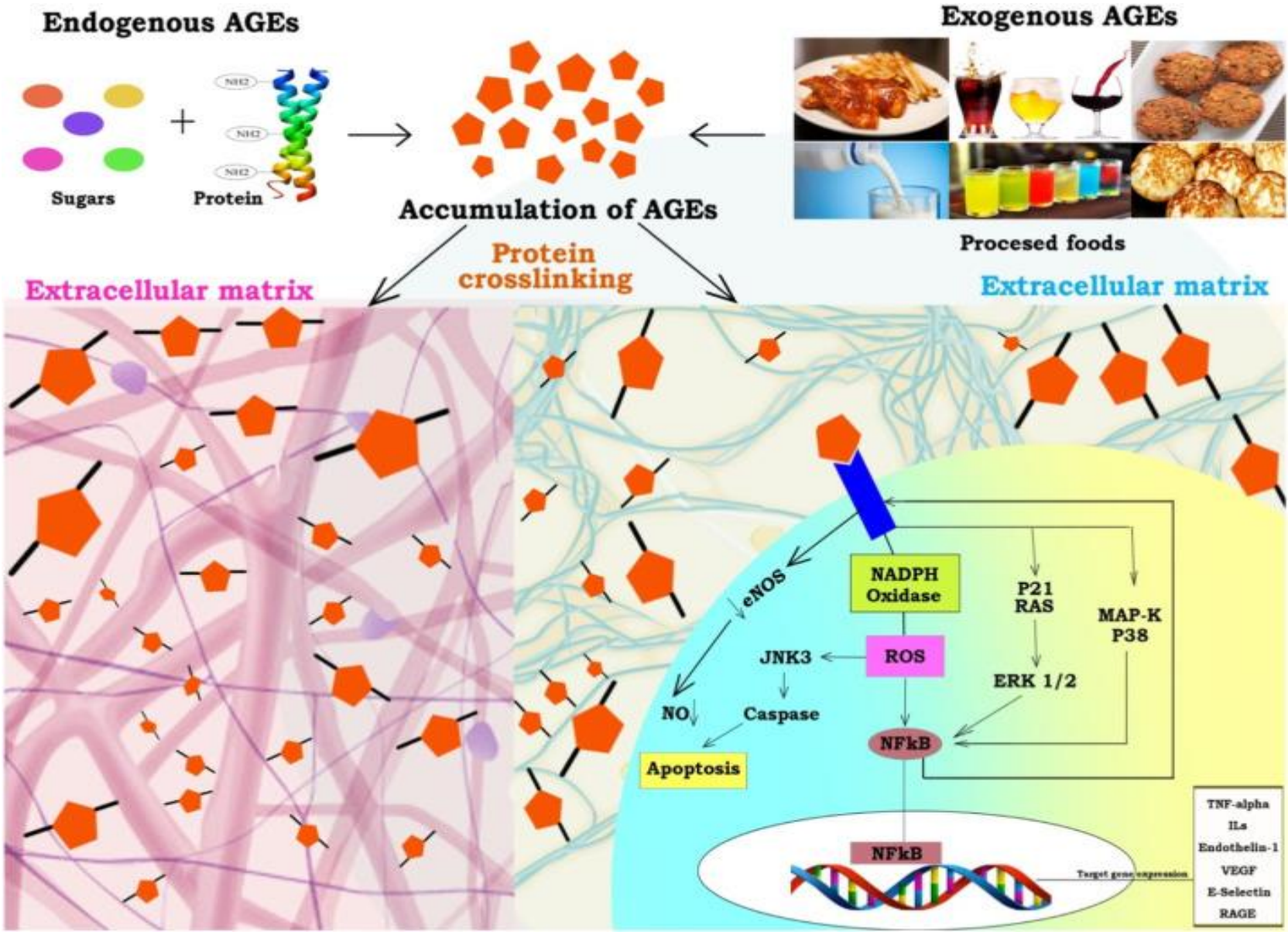
Effects of AGEs

Advanced glycation end products form:

- covalent cross-links with proteins,
- increase oxidative stress,
- upregulate inflammation.

Proteins that constitute the extracellular matrix are among the longest lived and most susceptible to AGE modification

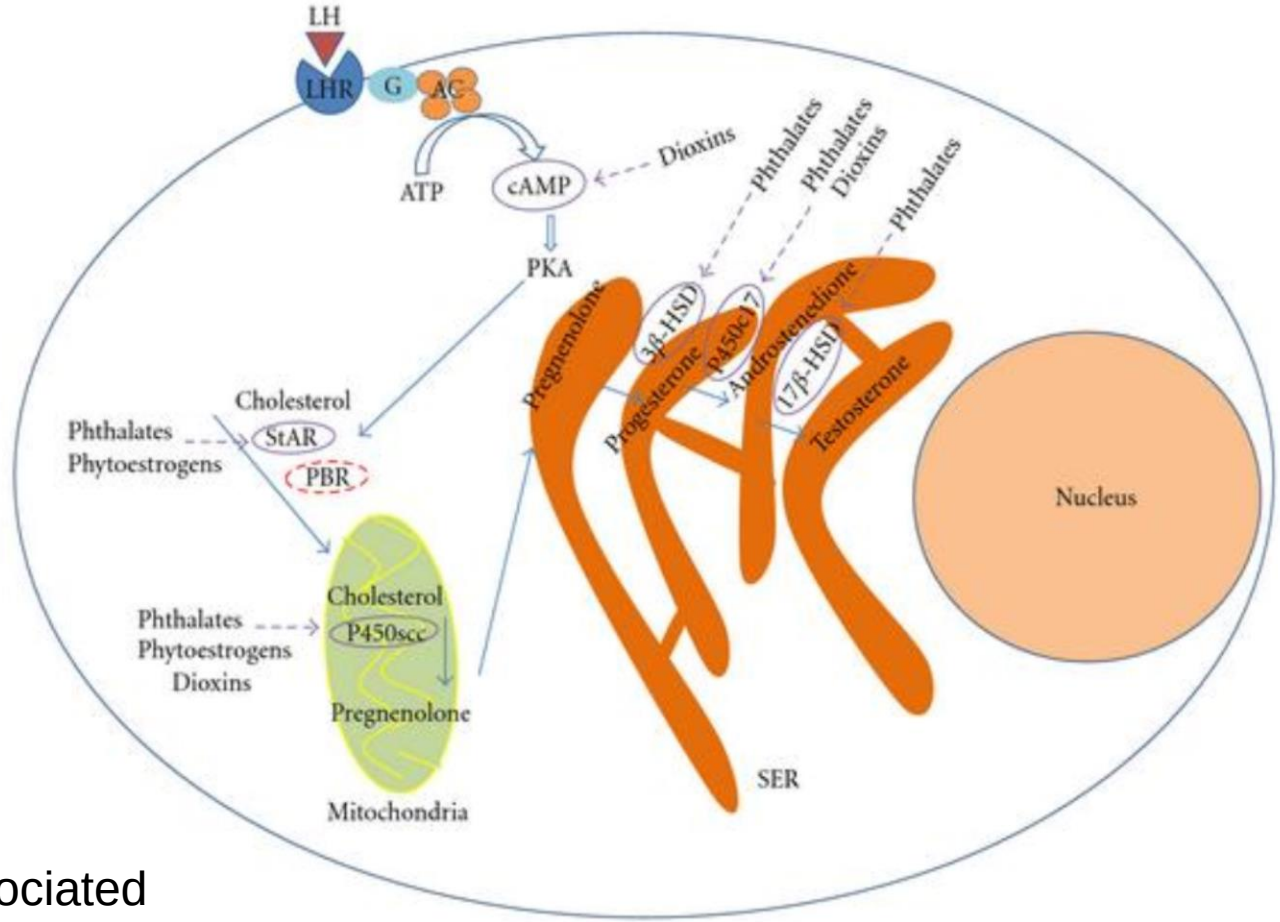
Environment International Volume 123, February 2019, Pages 486-500



Inhibitory actions of EDCs on androgen biosynthesis

P450scc is a mitochondrial enzyme that catalyzes **conversion of cholesterol** to **pregnenolone.**

P450 scc: cholesterol side-chain cleavage enzyme



3BHSD- 3-beta (β)-hydroxysteroid dehydrogenase

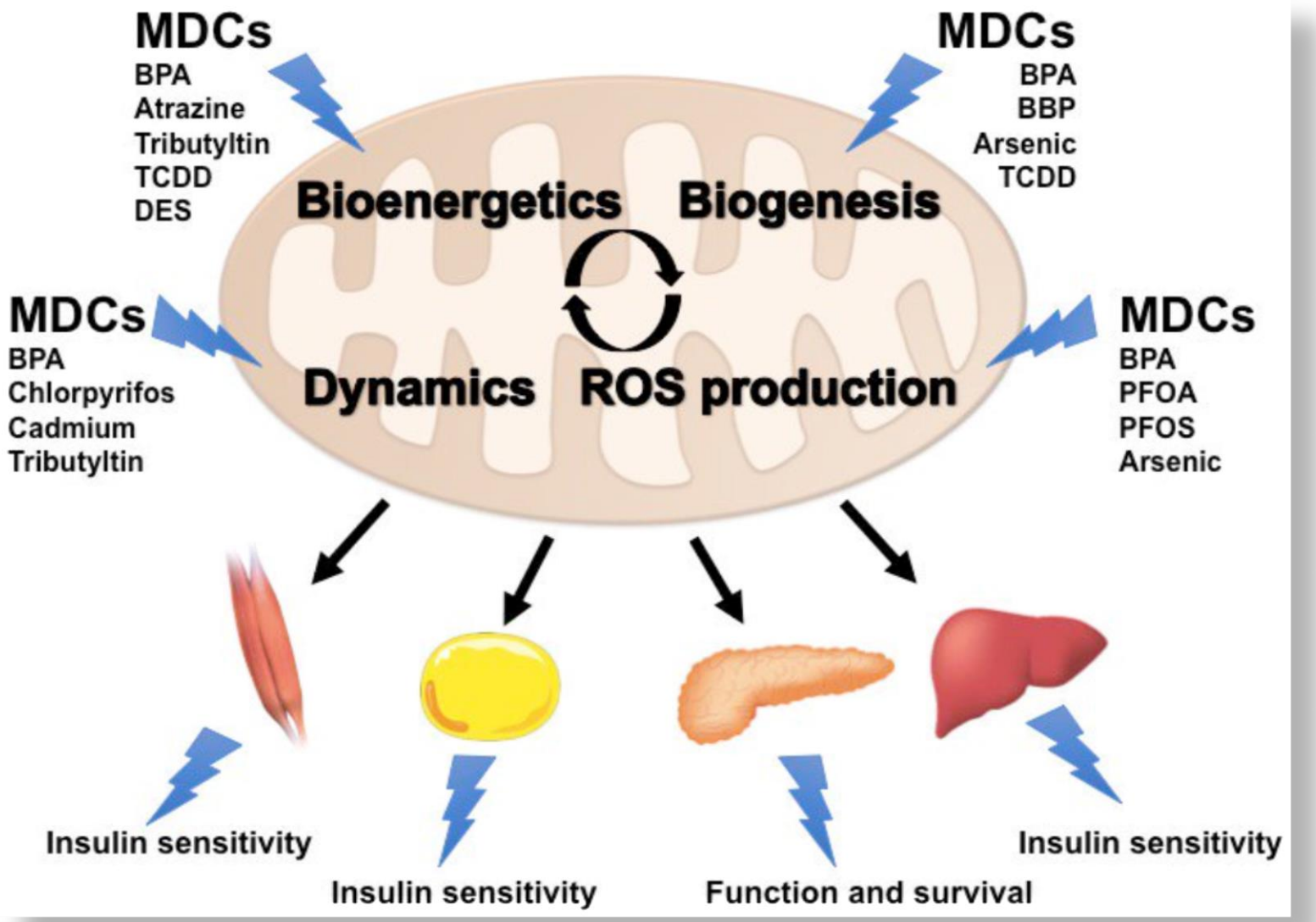
17 beta-hydroxysteroid dehydrogenase

PBR- Peripheral-type benzodiazepine receptor associated protein

StAR-Steroidogenic acute regulatory protein

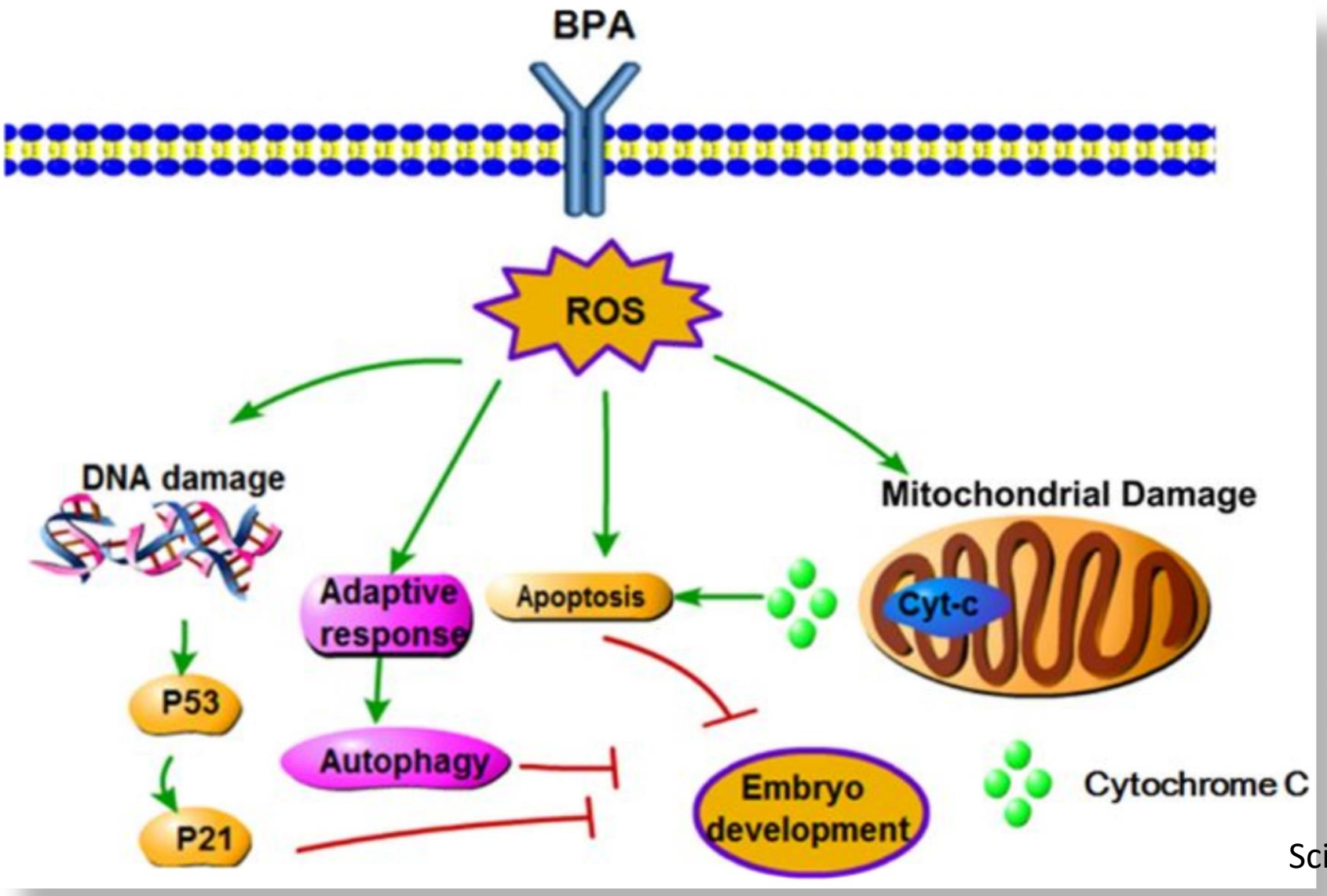
Cytochrome P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase)

EDCs and Mitochondria



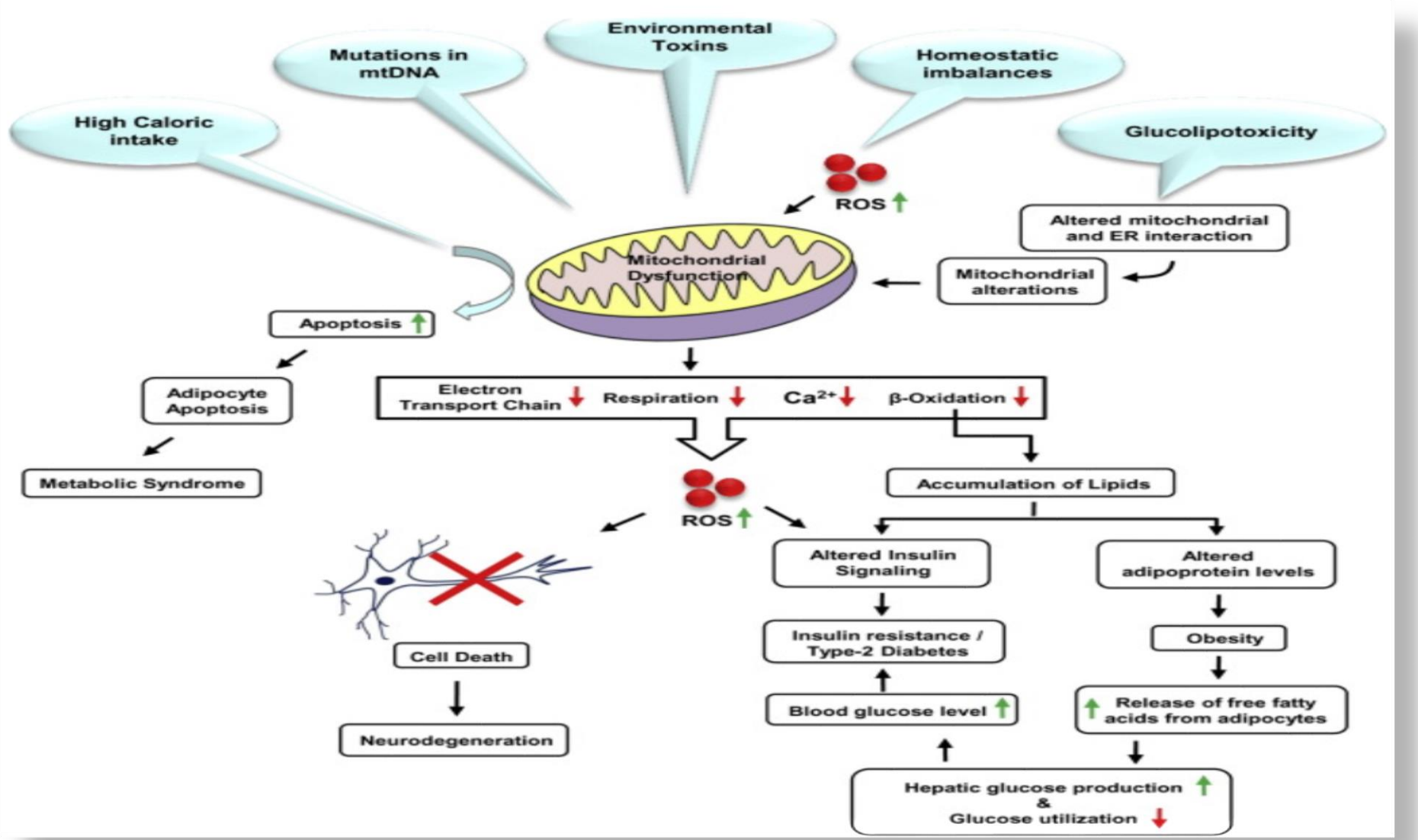
J. Endoc 2018

Adverse effect of BPA during early embryonic development



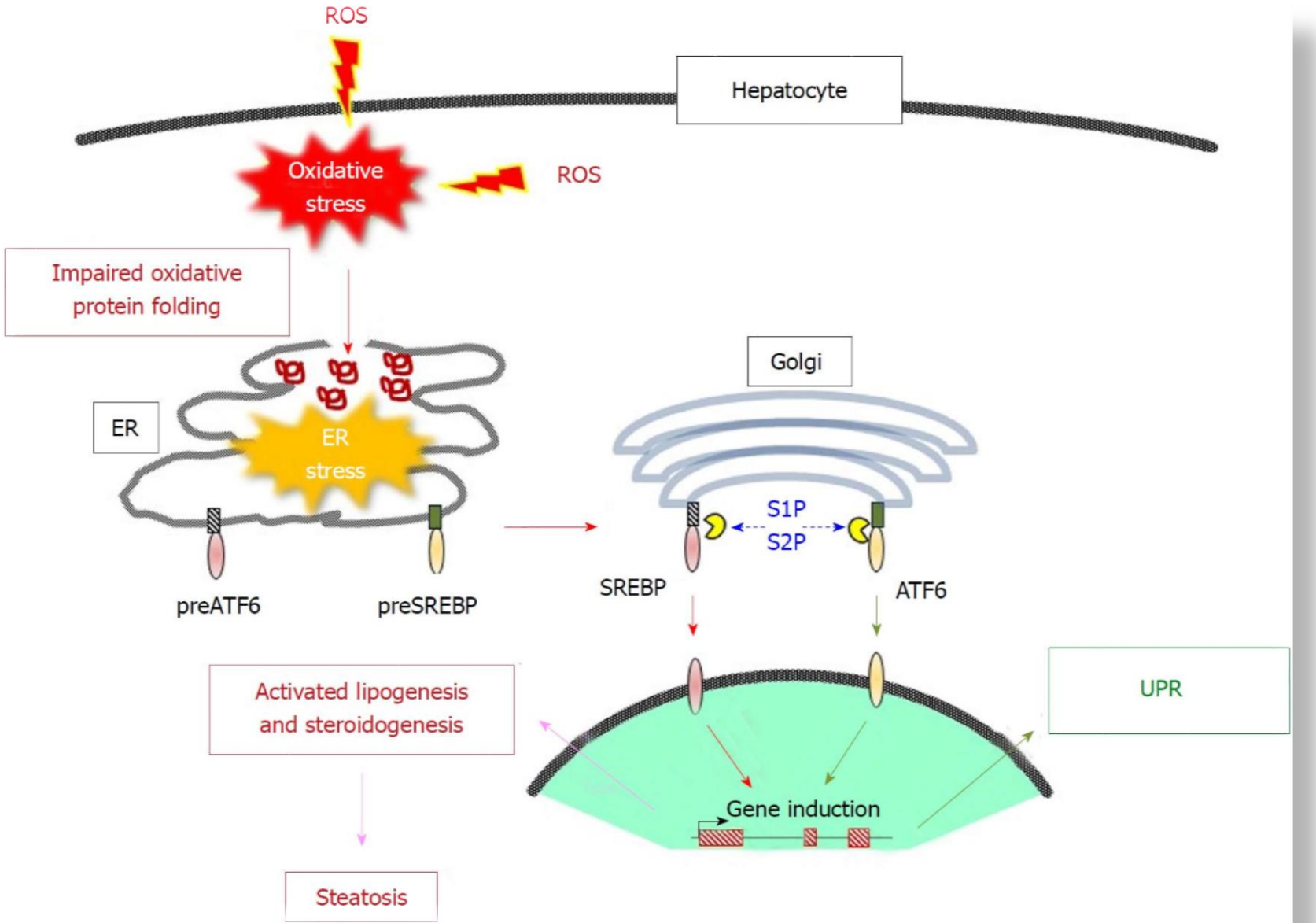
Scientific Reportsvolume

EDCs cause mitochondrial dysfunction

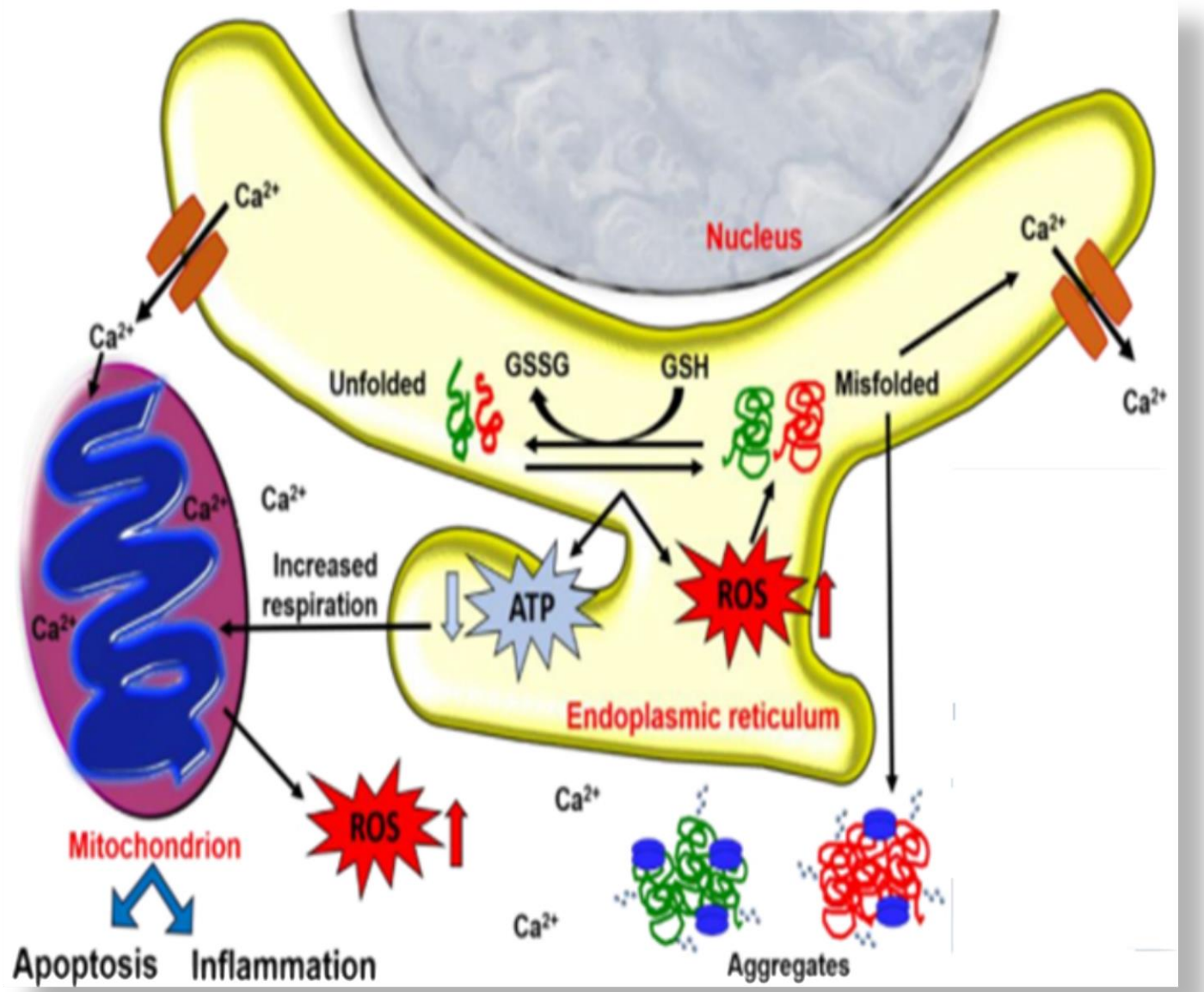


BBActa 2019

Oxidative stress and endoplasmic reticulum stress in liver steatosis

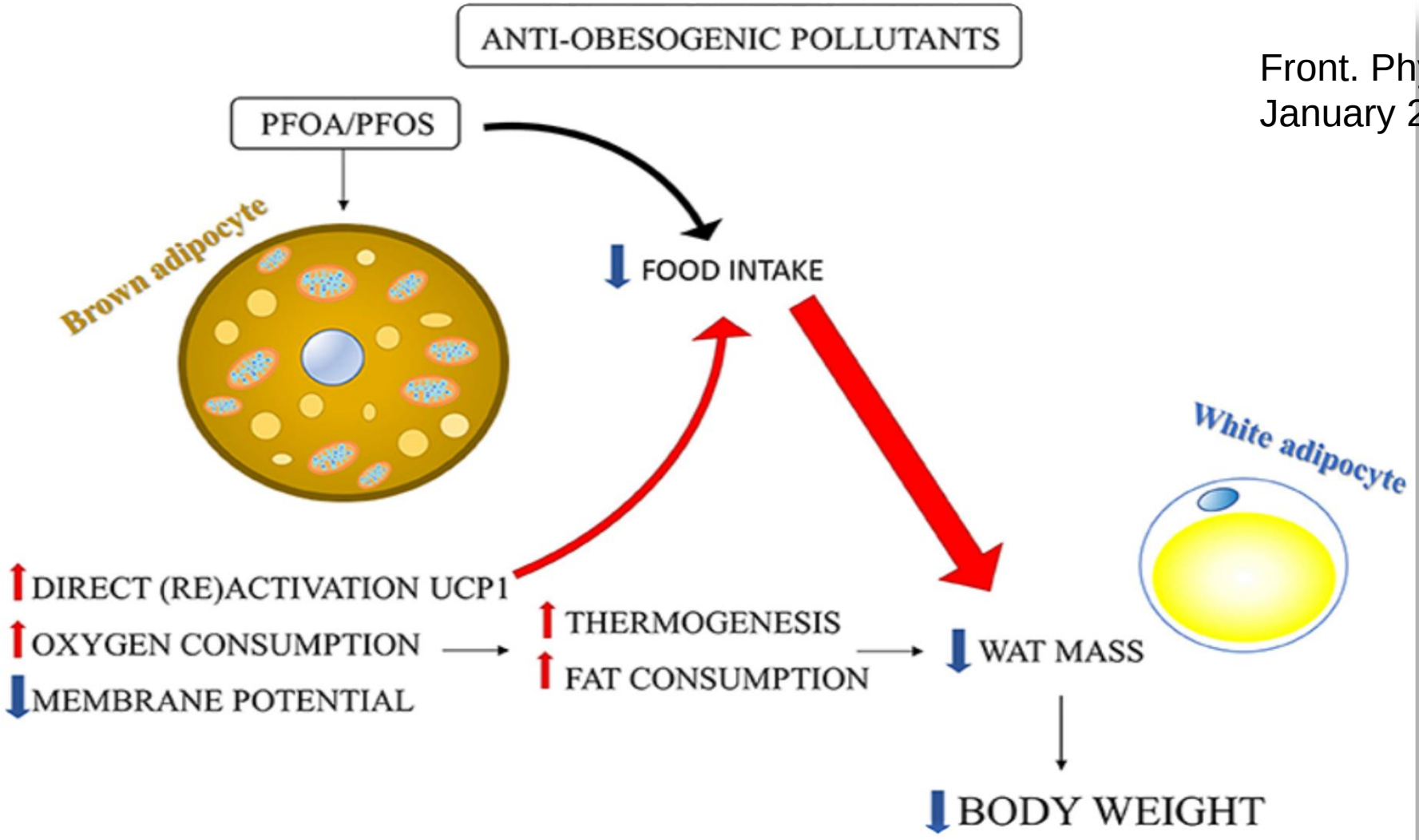


EDCs & Glutathione metabolism



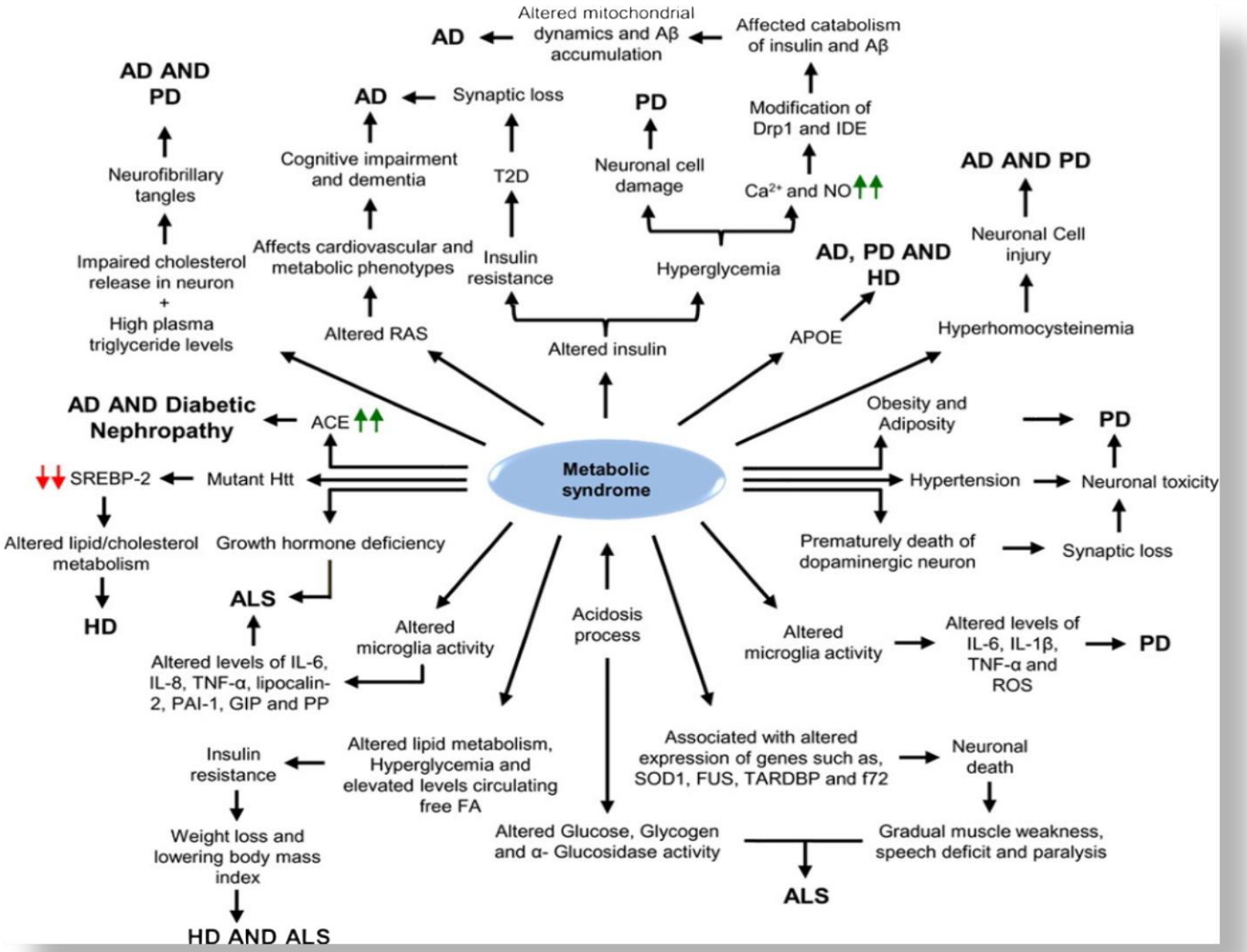
Environmental pollutants-induced body weight reduction: involvement of BAT activation.

Brown adipose tissue have thermogenic function **due to the presence** of the mitochondrial **uncoupling protein 1** (UCP1), has been positively associated with improved resistance to obesity and metabolic diseases.



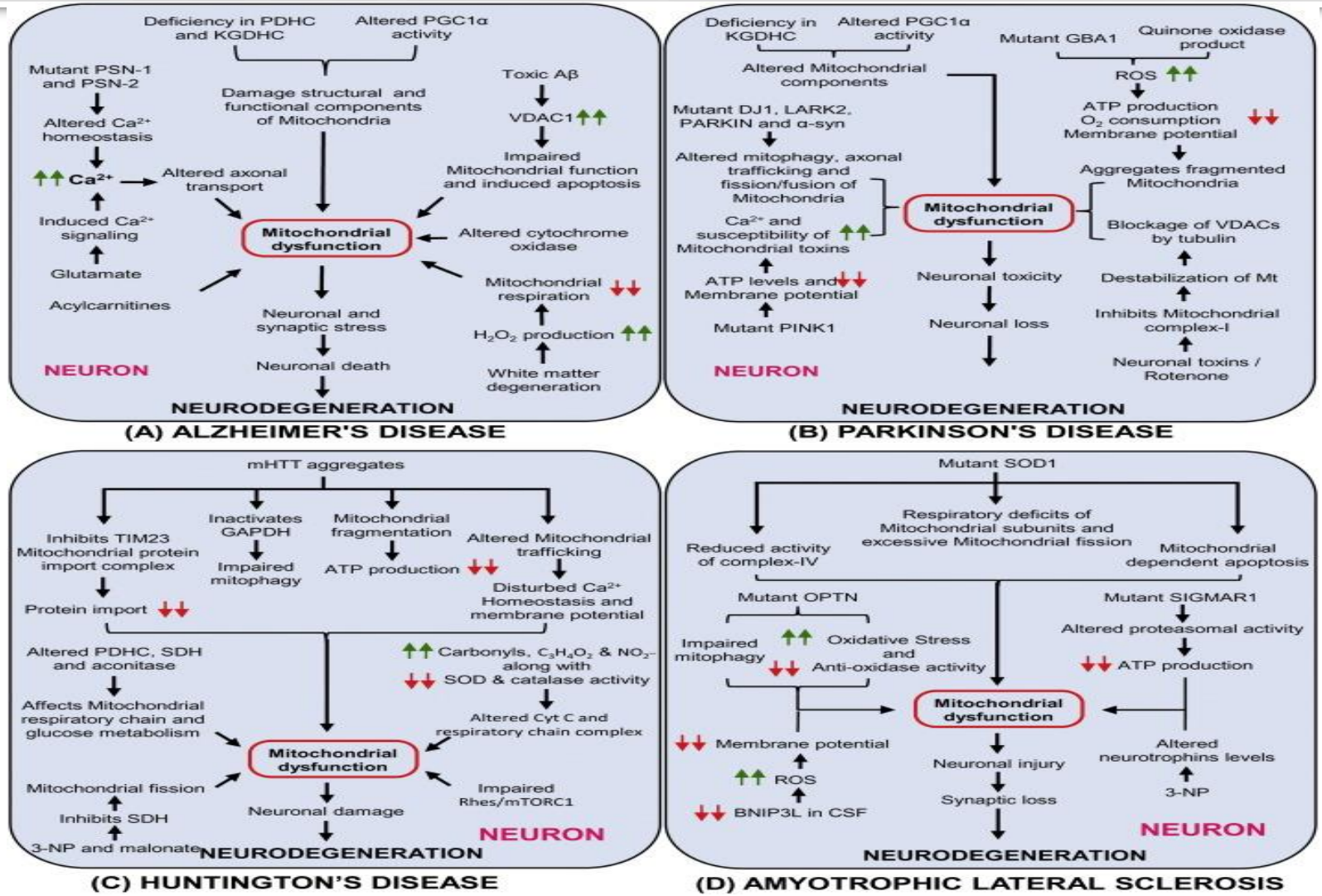
Front. Physi
January 201

EDCs & Metabolic syndrome associated neurodegeneration



BBActa 2019

Molecular mechanism involved in mitochondrial dysfunction mediated pathophysiology of neurodegenerative disorders by EDCs



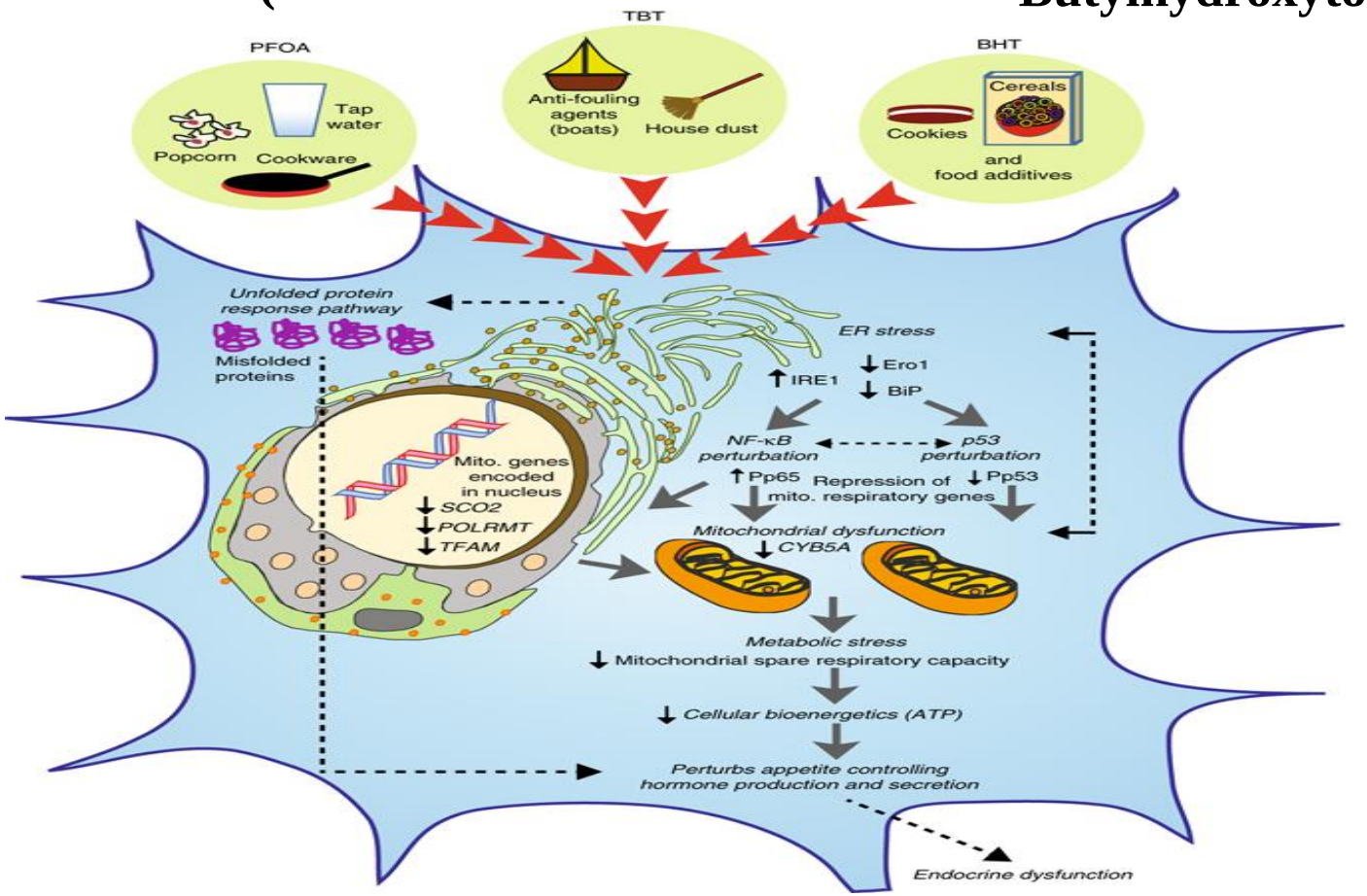
BbActa 2019

EDC-mediated dysregulation in developing endocrine tissues

perfluoro-octanoic acid (PFOA

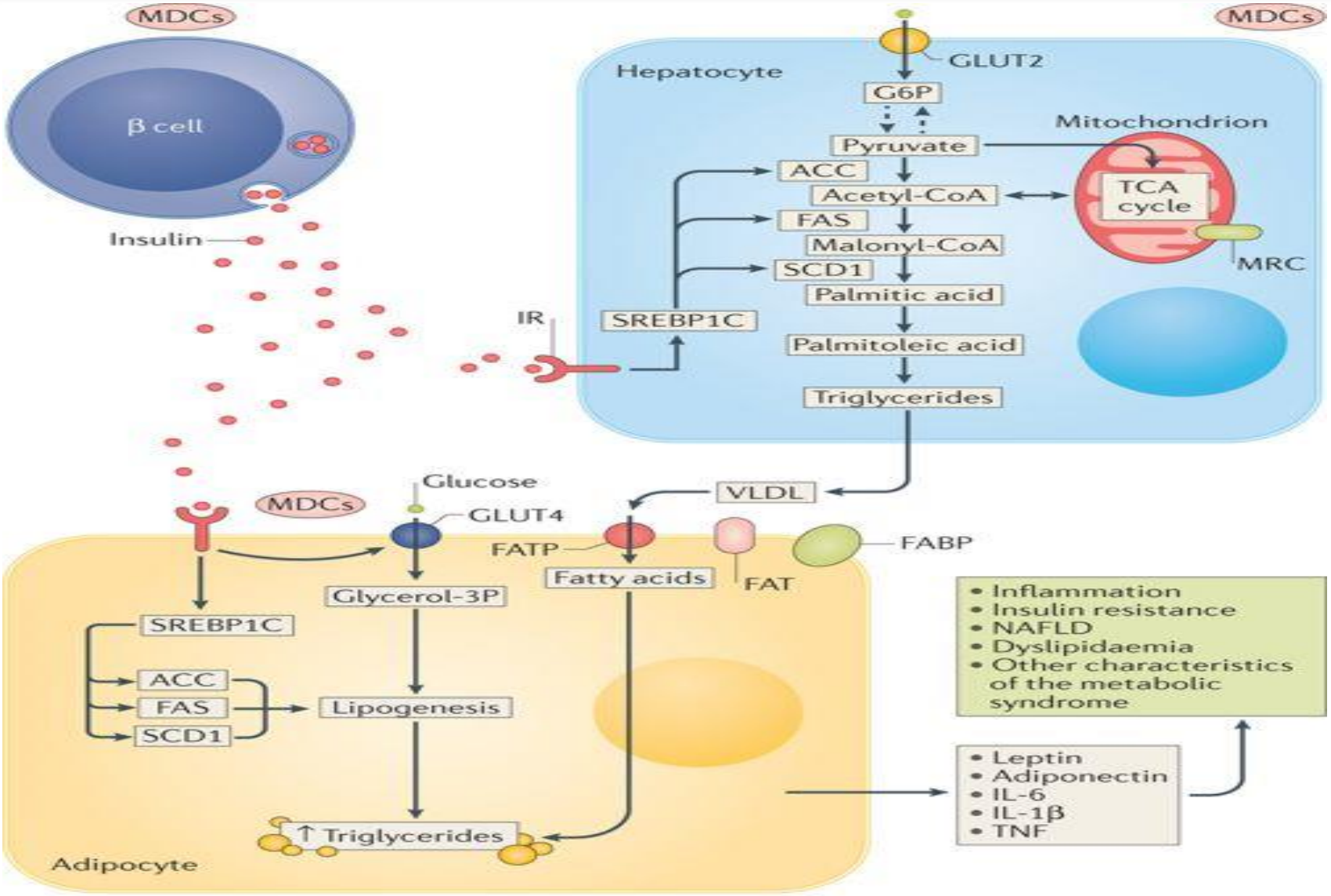
Tributyltin (TBT)

Butylhydroxytoluene (BHT)



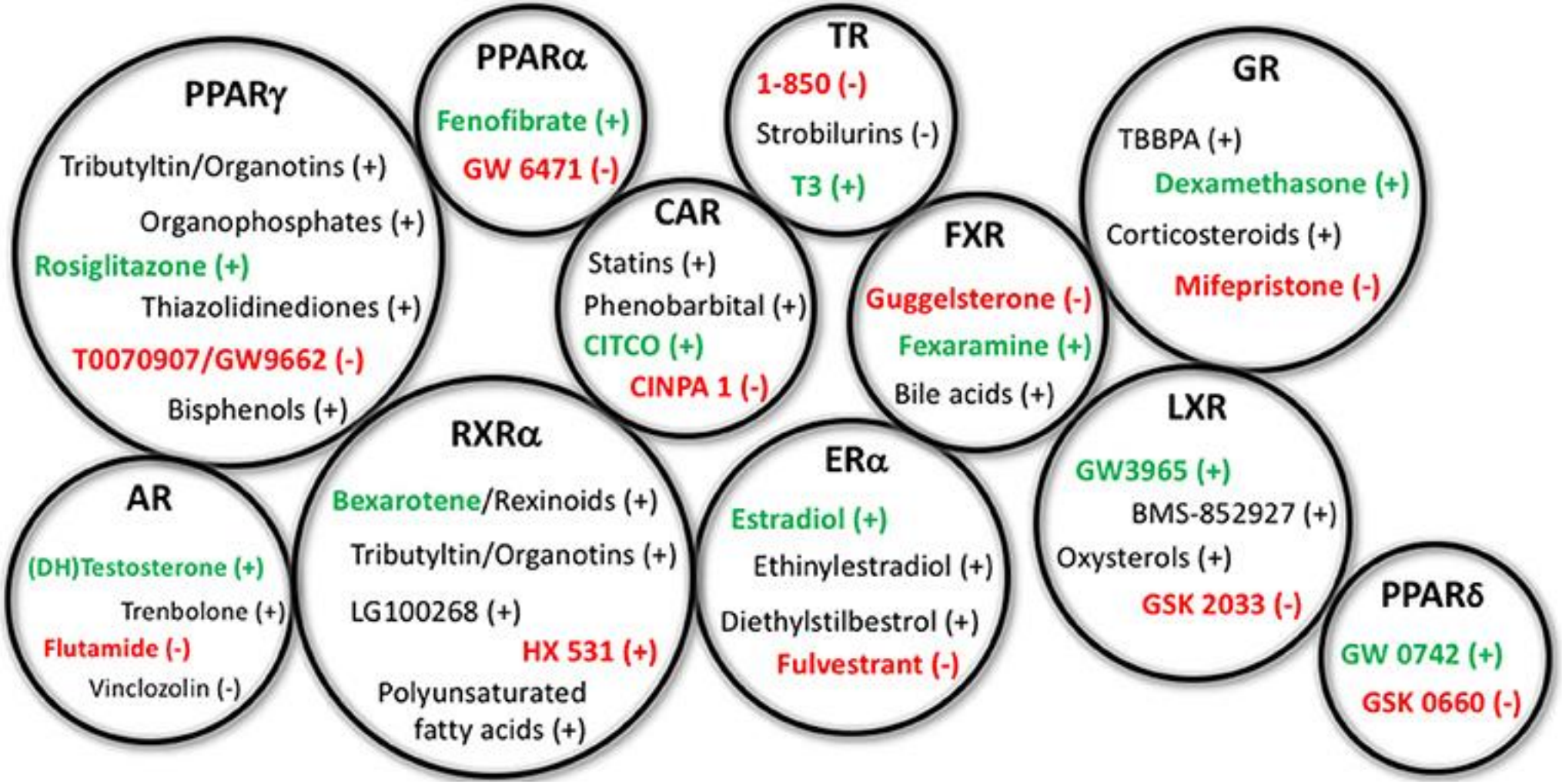
Nat Commun. 2019;

Lipid metabolism & metabolism-disrupting chemicals



Nature Reviews | Endocrinology

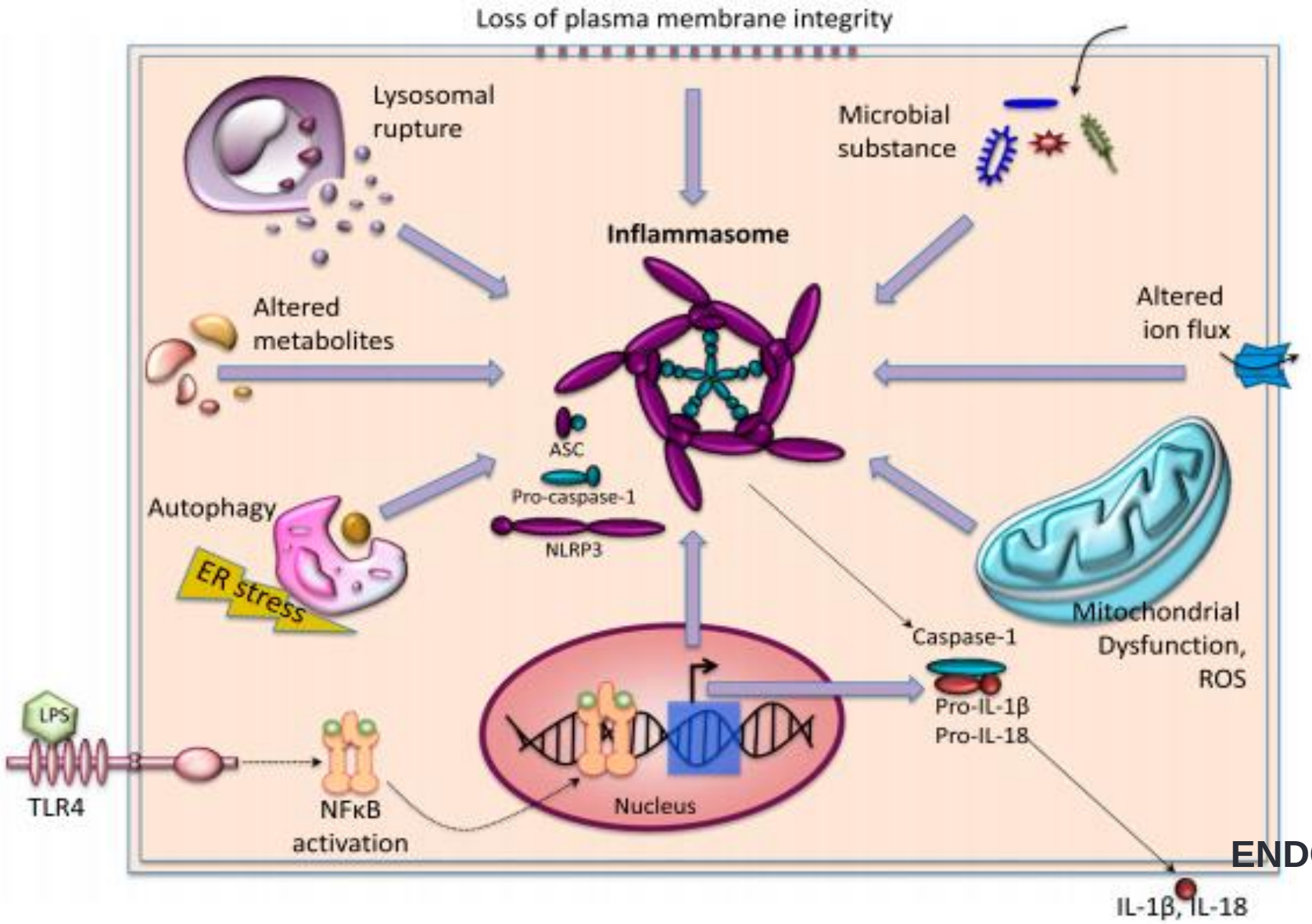
EDCs Capable of Affecting Adipogenesis



PPAR, peroxisome proliferator activated receptor; RXR, retinoid X receptor; AR, androgen receptor; ER, estrogen receptor; CAR constitutive androstane receptor; TR, thyroid receptor; FXR, farnesoid X receptor; LXR, liver X receptor; GR, glucocorticoid receptor.

Front. Endocrinol., 07 February 2019

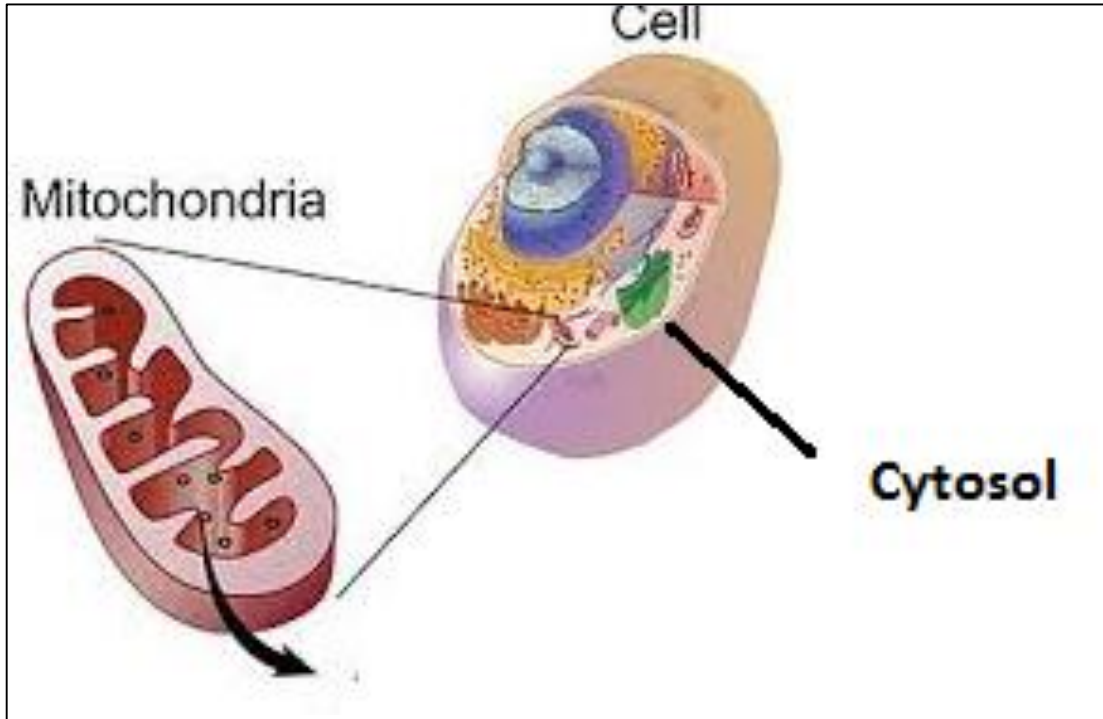
Activation signals of inflammasomes



ENDOCRINOLOGY 2018

Research in Ulusu lab.

1. Oxidative stress enzymes
2. Neurotransmitter metabolism
3. Lipid metabolism & free fatty acid analysis (GC-MS& HPLC)
4. Trace elements & minerals
5. Mitochondria & Endoplasmic reticulum
6. Inflammation
7. Energy metabolism
8. Novel markers



KOÇ UNIVERSITY

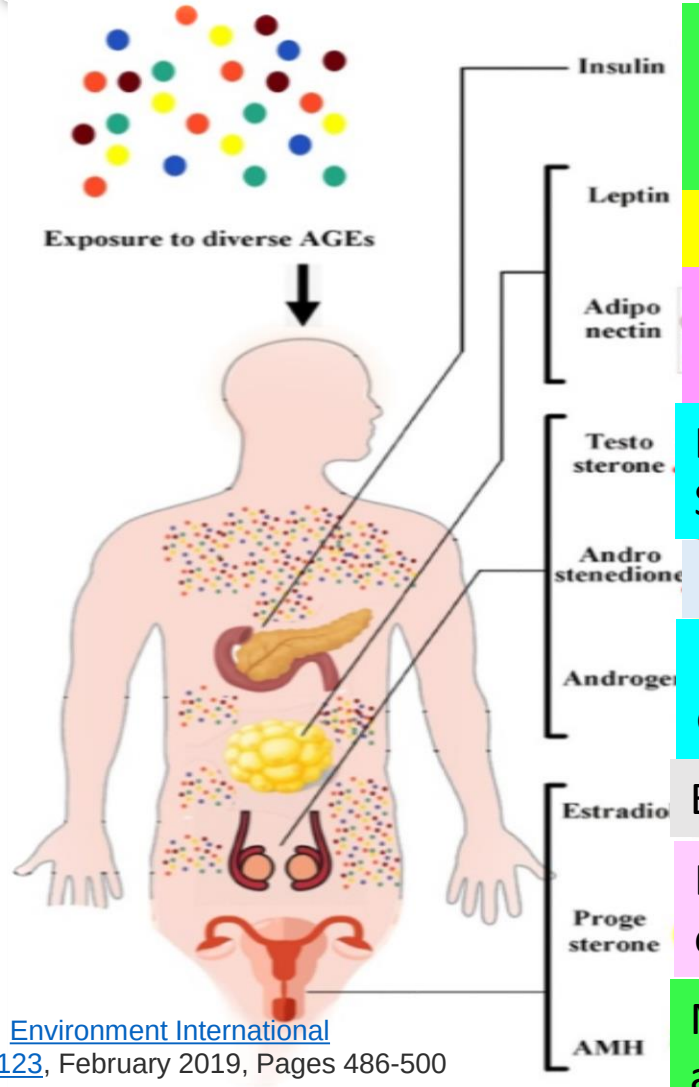
Prof. Dr. N. Nuray Ulusu

School of Medicine

Department of Biochemistry

nulusu@ku.edu.tr

Endocrine disruption by AGEs and their possible mechanism of action



Glucose & AA uptake
Glucagon protein and fatty acid Synthesis

Fod intake & insulin sensitivity

Glucose metabolism, fatty acid oxidation

Development of male reproductive organs
Secondary sexual characteristics

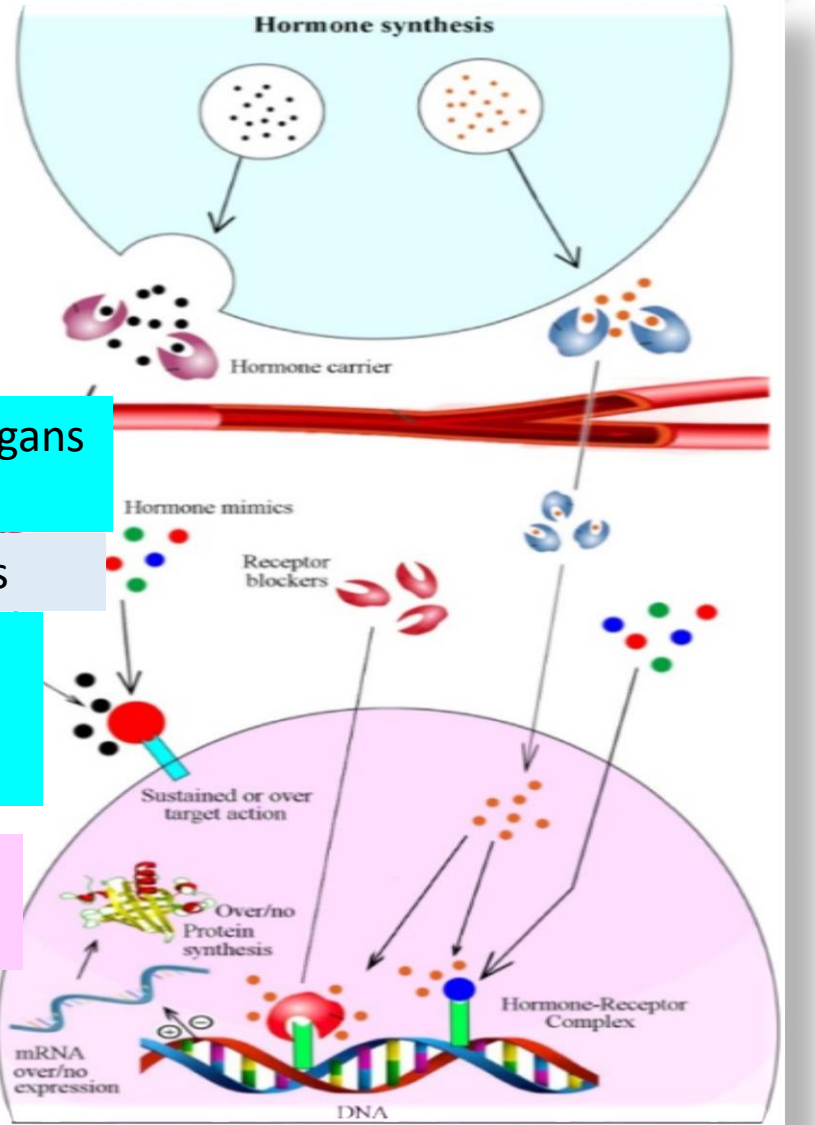
Male reproductive hormone synthesis

Development of male reproductive organs

Egg implantation and pregnancy

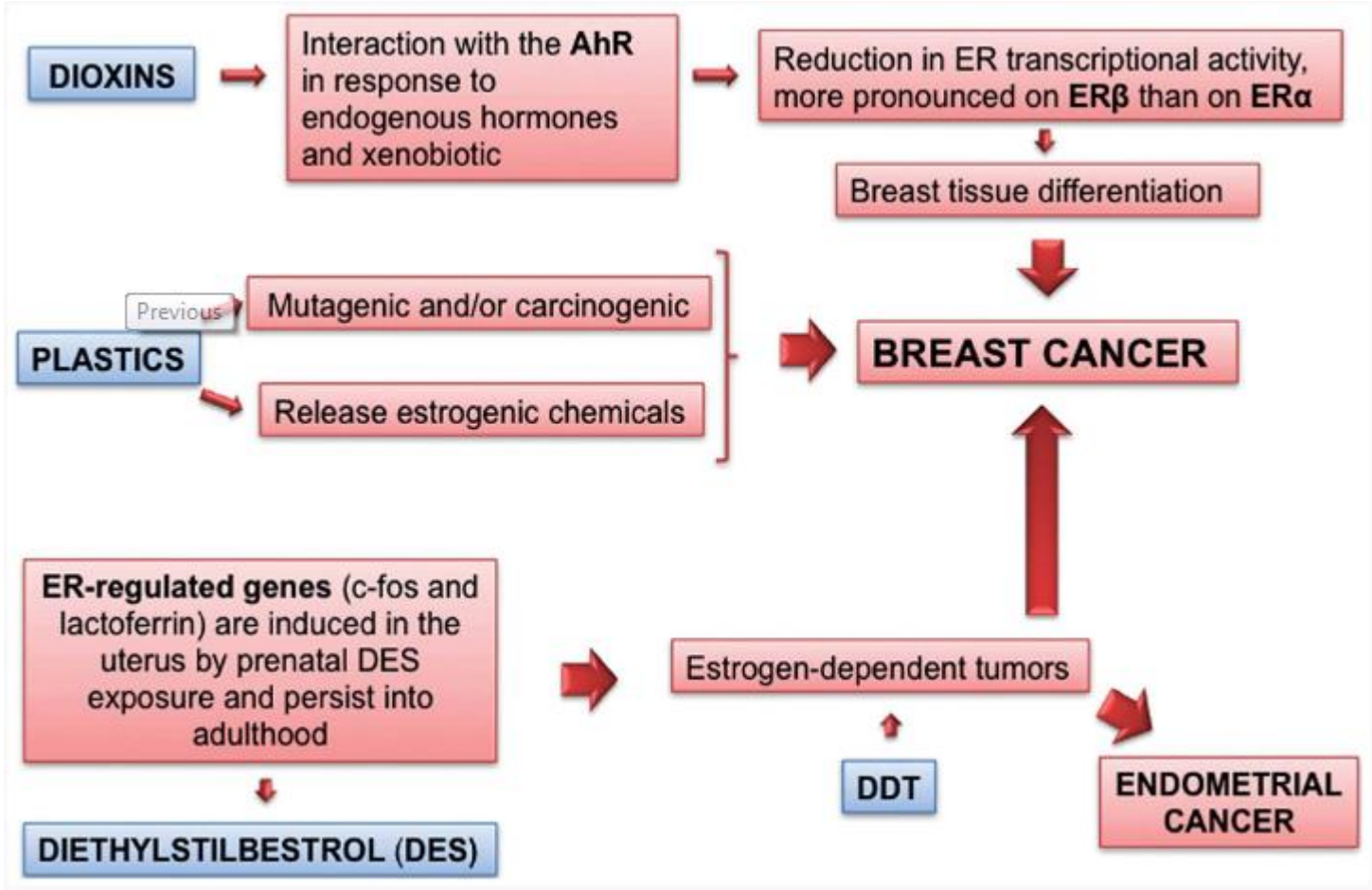
Development of female reproductive organs estrous & menstrual cycle

Mullerian inhibition
anovalation

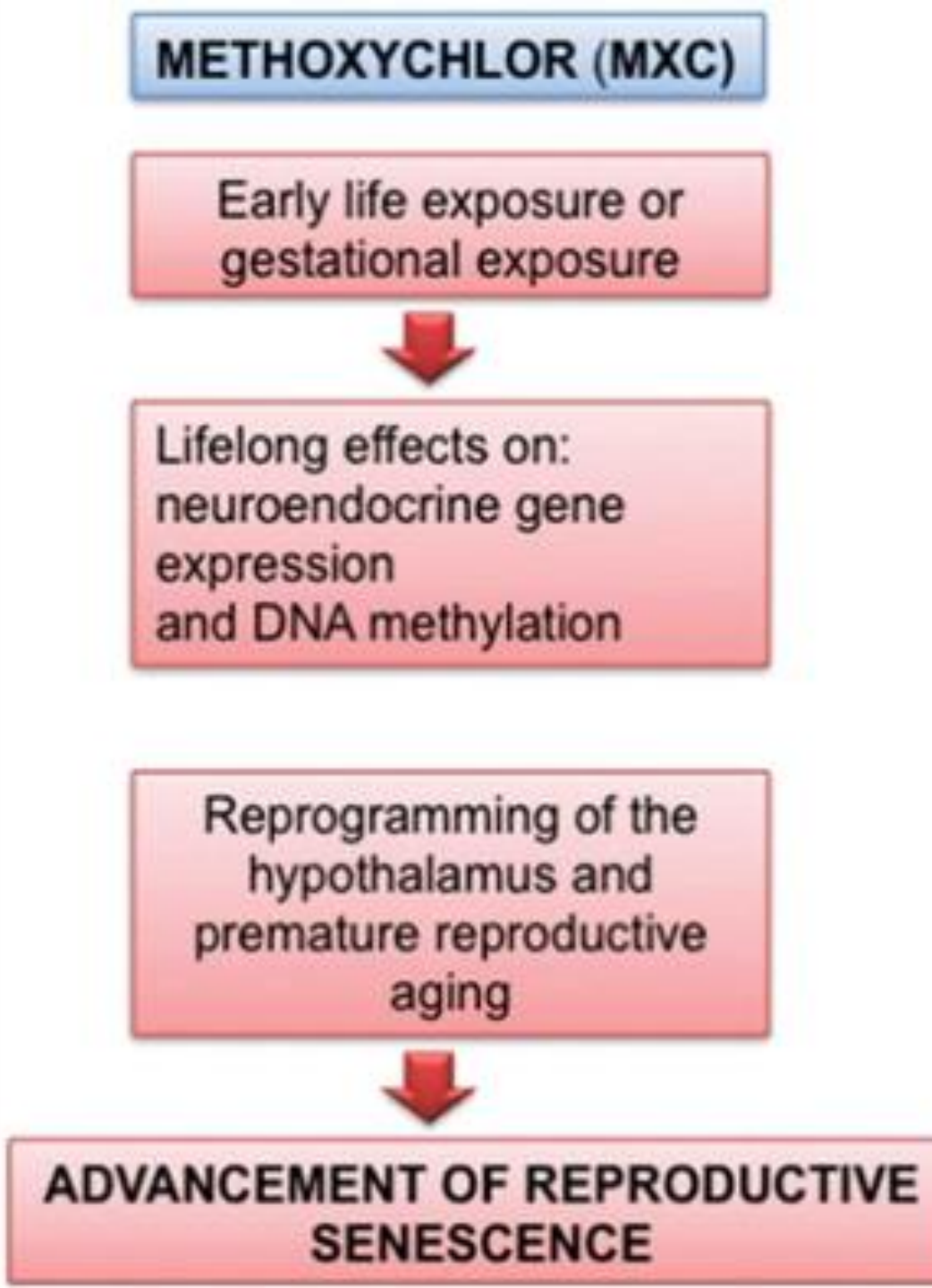


Environment International
Volume 123, February 2019, Pages 486-500

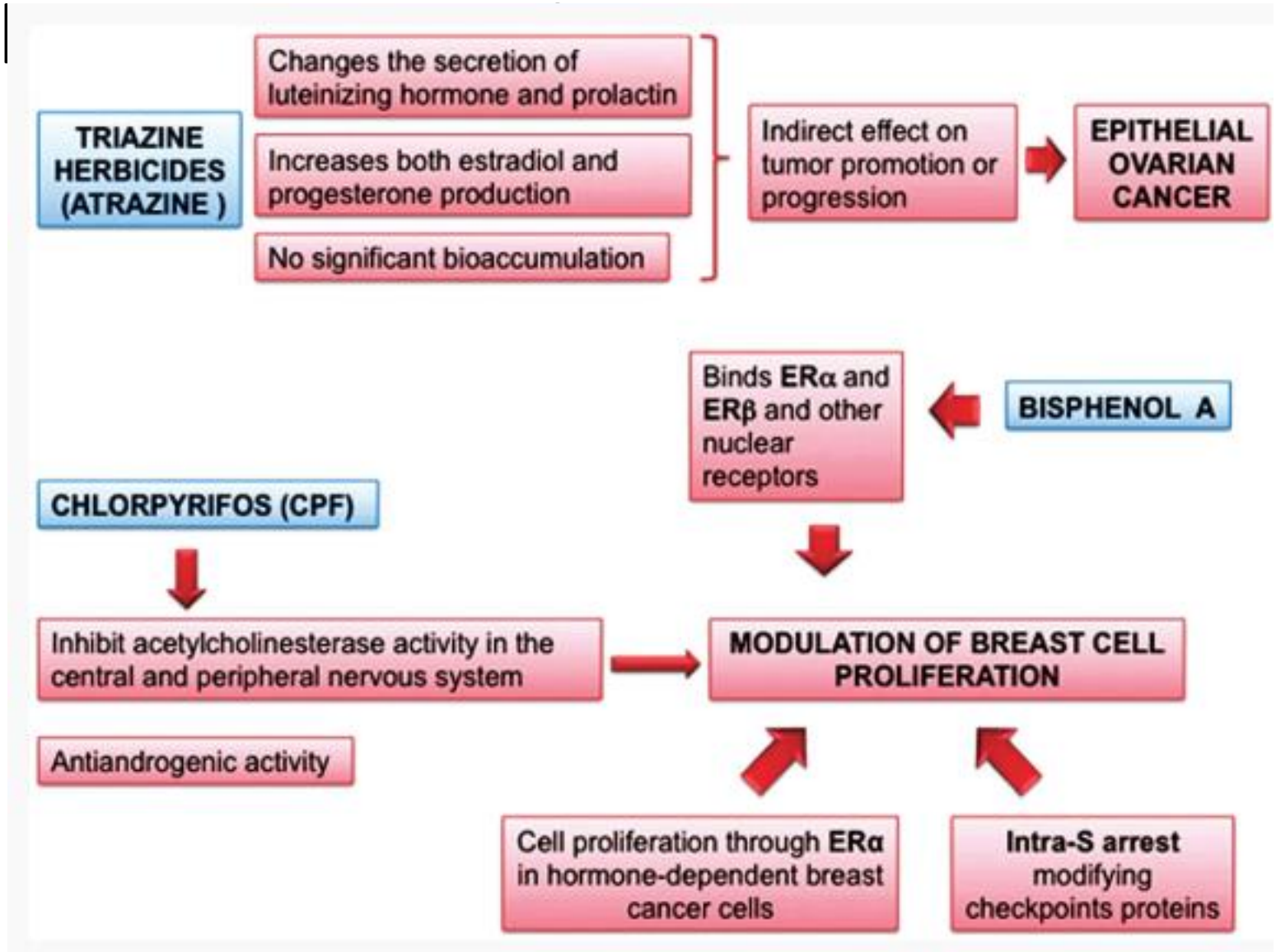
the action of dioxins, plastics, DDT and diethylstilbestrol (DES) on the modulation of breast and endometrial cell proliferation.



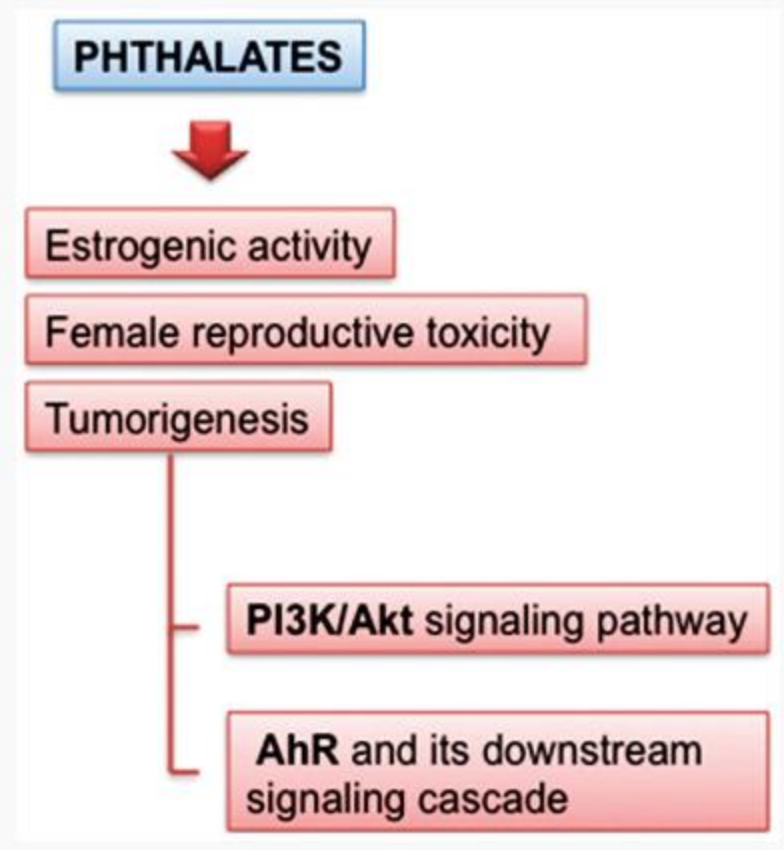
the action of methoxychlor advancement of reproducti



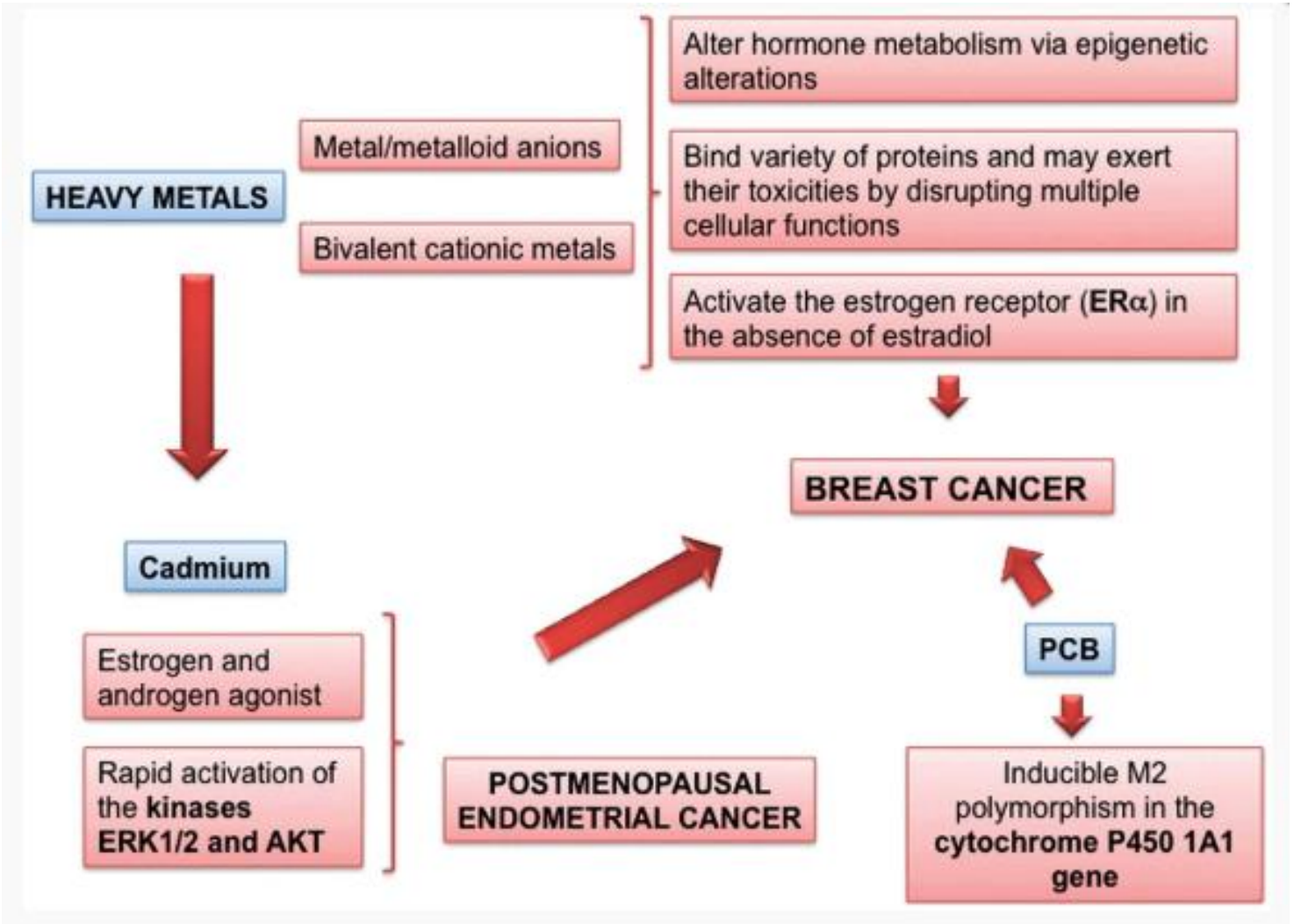
the action of triazine herbicides (atrazine), bisphenol A and chlorpyrifoson in the modulation of



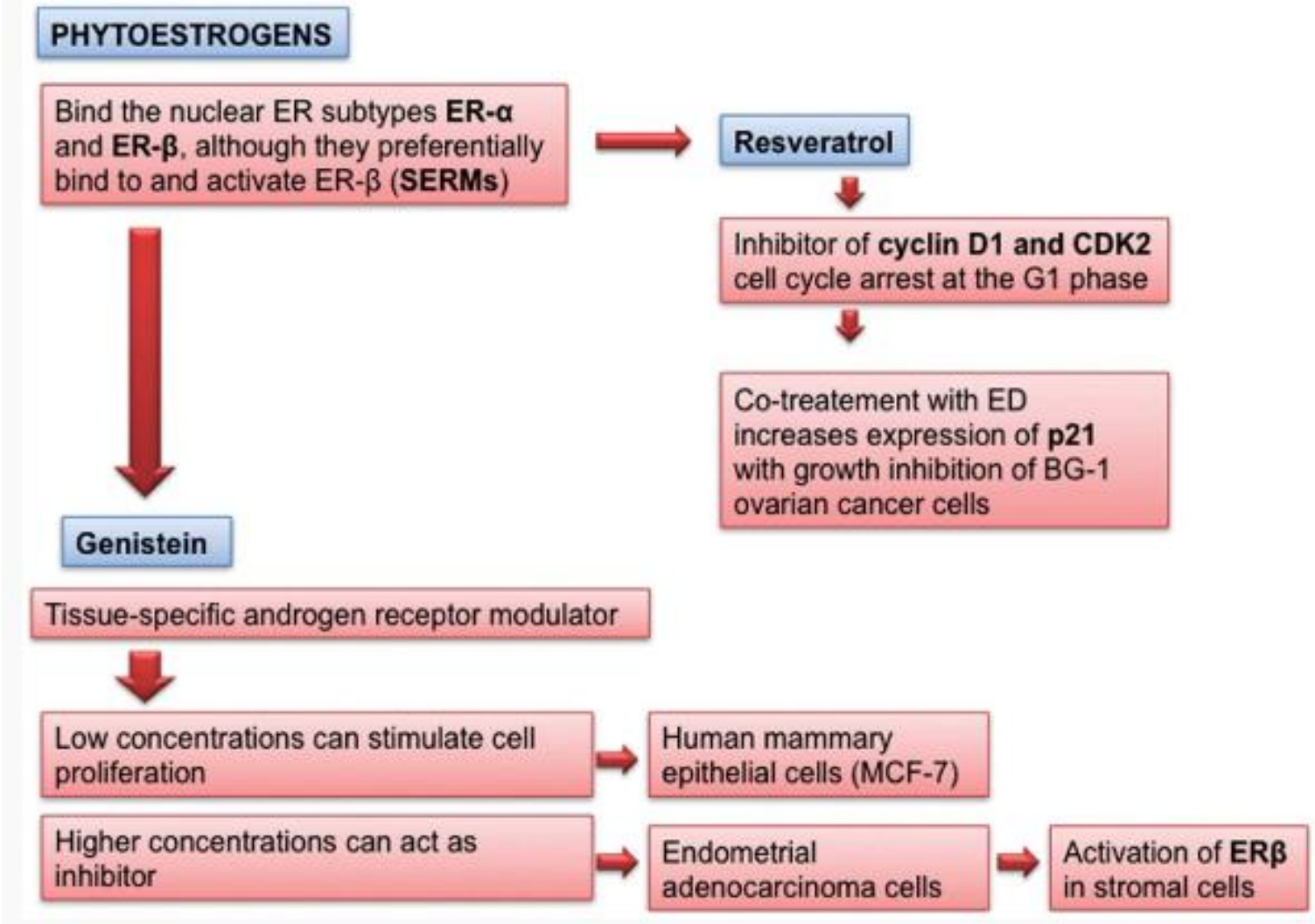
the action of phthalates on tumorigenesis pathways.



the action of heavy metals and polychlorinated biphenyls (PCBs) on the development of breast and postmenopausal endometrial cancer.

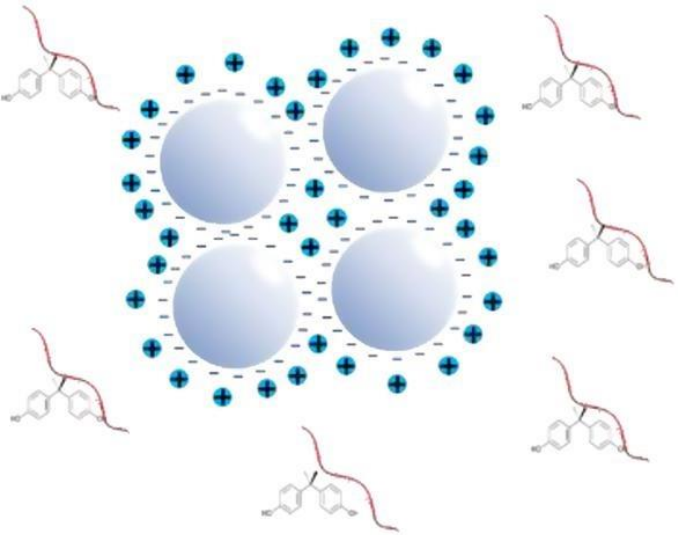


the action of phytoestrogens and polychlorinated biphenyls (PCBs) on the development of breast and postmenopausal endometrial cancer.

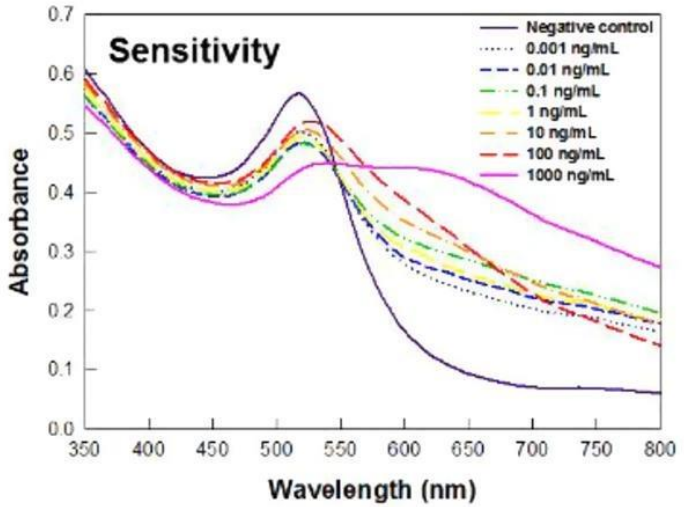


Simple and rapid detection of bisphenol A using a gold nanoparticle-based colorimetric aptasensor.

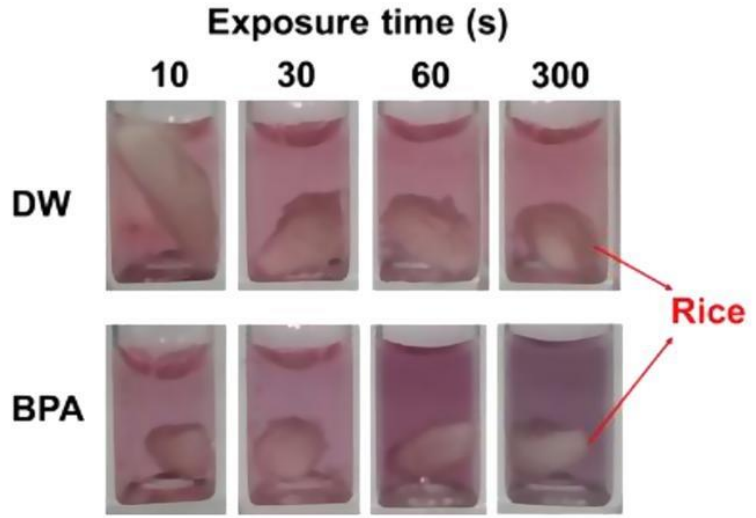
Colorimetric aptasensor



Performance verification



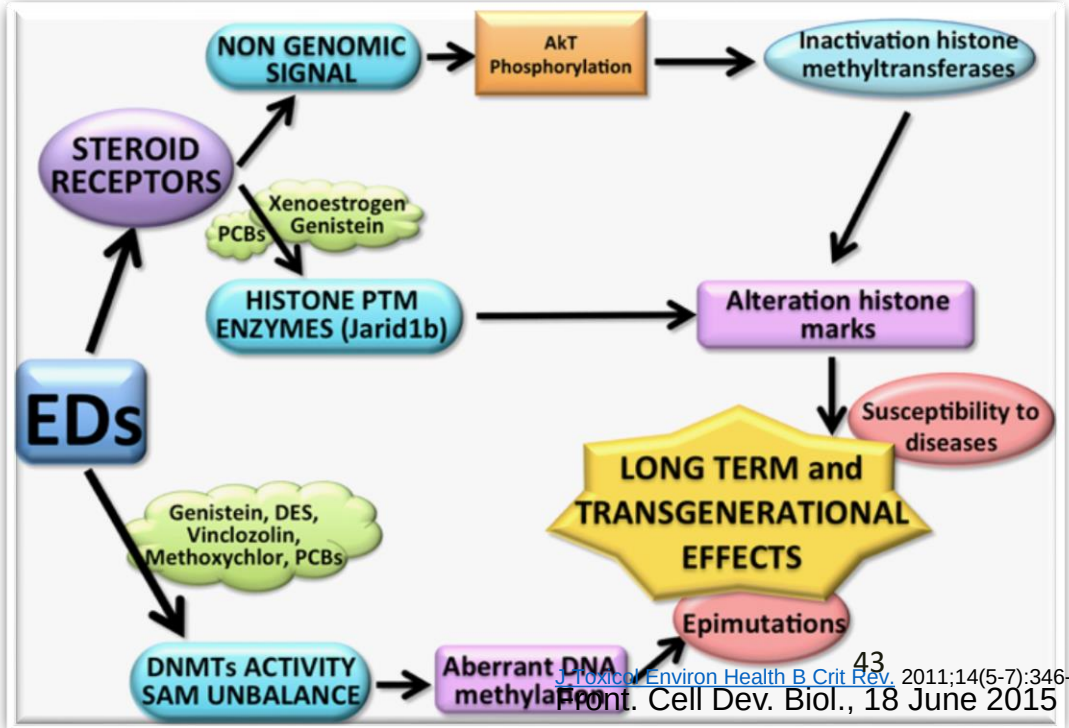
Bisphenol A detection in food



Food Chem. 2019 Jul 30;287:205-213. doi: 10.1016/j.foodchem.2019.02.079

EB dopaminerjik neuronlar üzerine etkileri

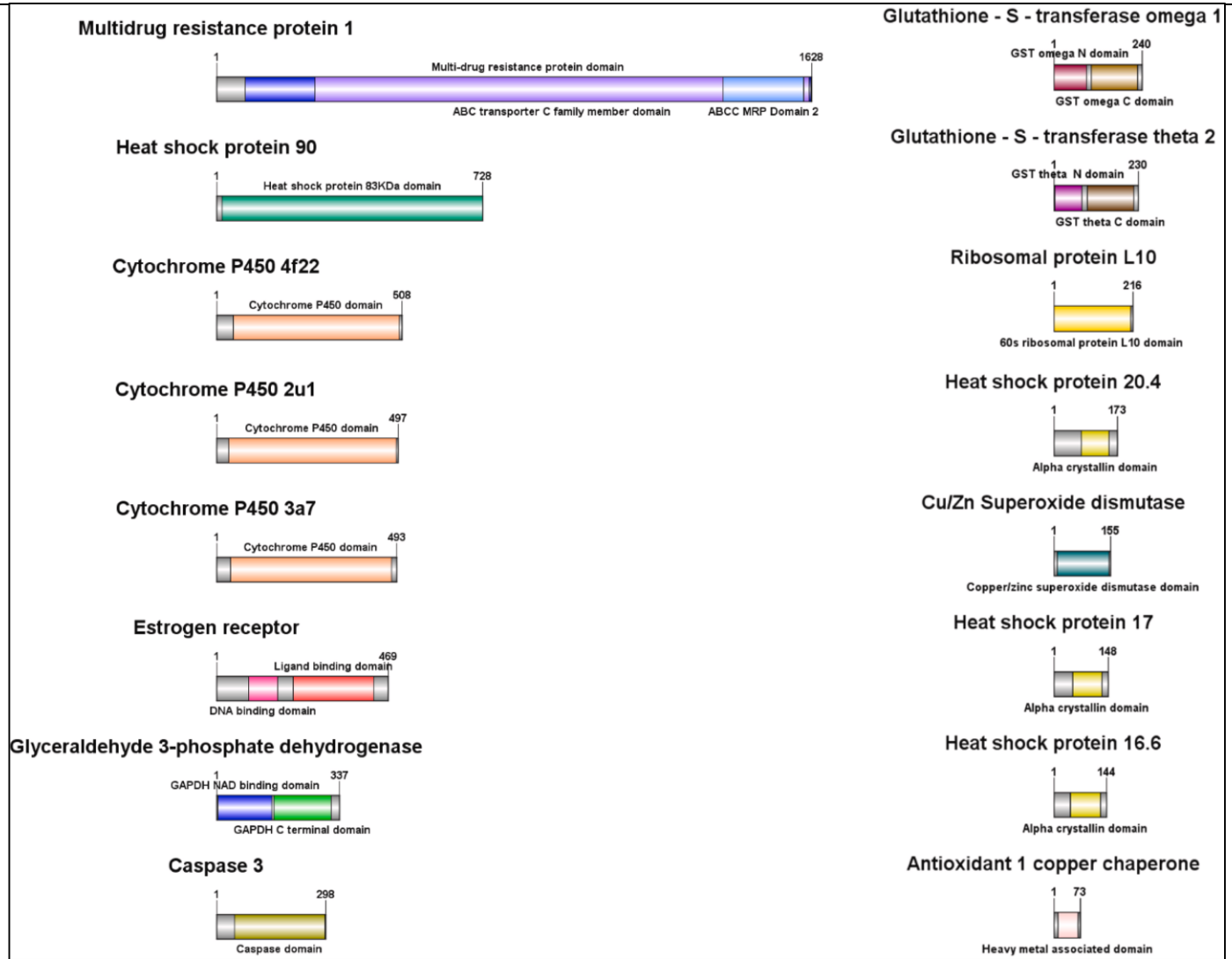
- Epigenom da farklılıklar
- Steroid reseptörlerle etkileşime giriyor
- Histon posttranslasyonel enzimlerini inhibe diyor
- DNA metilasyonunda farklılıklara neden oluyor
- Epimutasyonlara neden olarak çeşitli hastalıklar oluşturuyor



DNA methyltransferases (DNMTs)

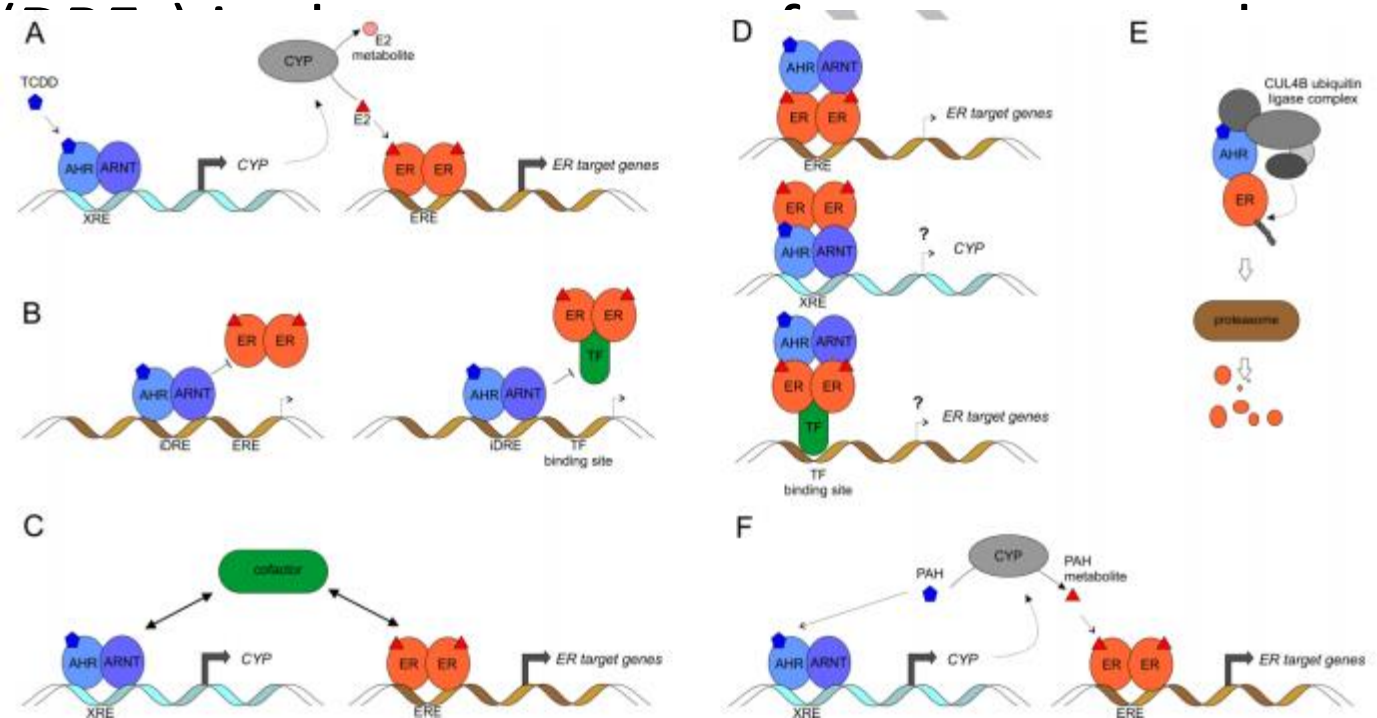
J Toxicol Environ Health B Crit Rev. 2011;14(5-7):346-6
Front. Cell Dev. Biol., 18 June 2015

Different cellular pathways, detoxification and stress



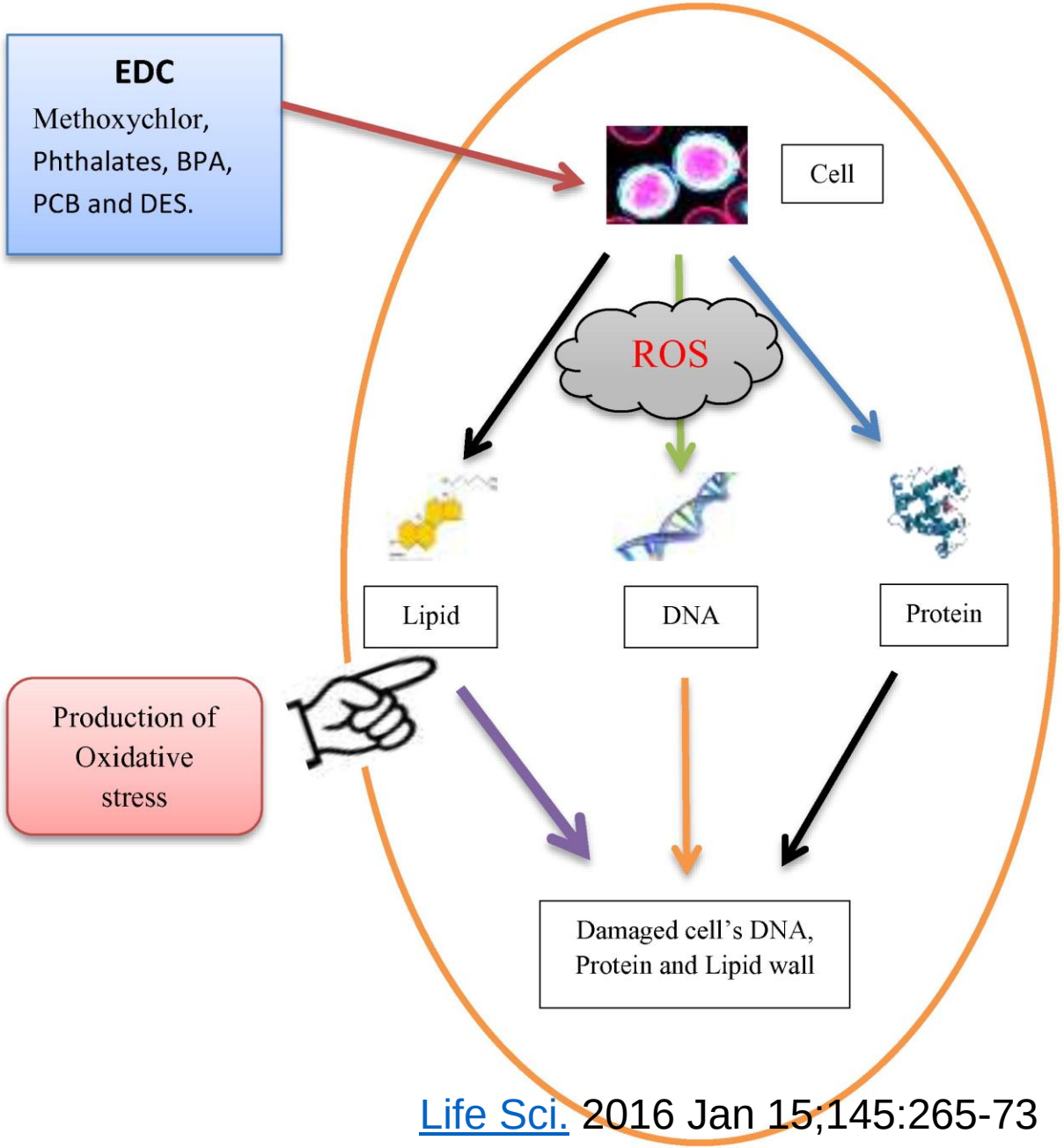
Ecotoxicol Environ Saf. 2019 Apr 1
10.1016/j.ecoenv.2018.

- Overview of the interactions of AHR and ER signalling pathways. (A) AHR induces expression of cytochrome P450-dependent monooxygenases (CYPs) involved in the degradation of endogenous estrogens. (B) Activated AHR binds to inhibitory dioxin responsive elements (genes. (C) AHR and ER co itment of AHR/ARN E) AHR induced proteason xylation of PAHs to es for further explanatic



Mechanism of action of endocrine disrup oxidative stress.

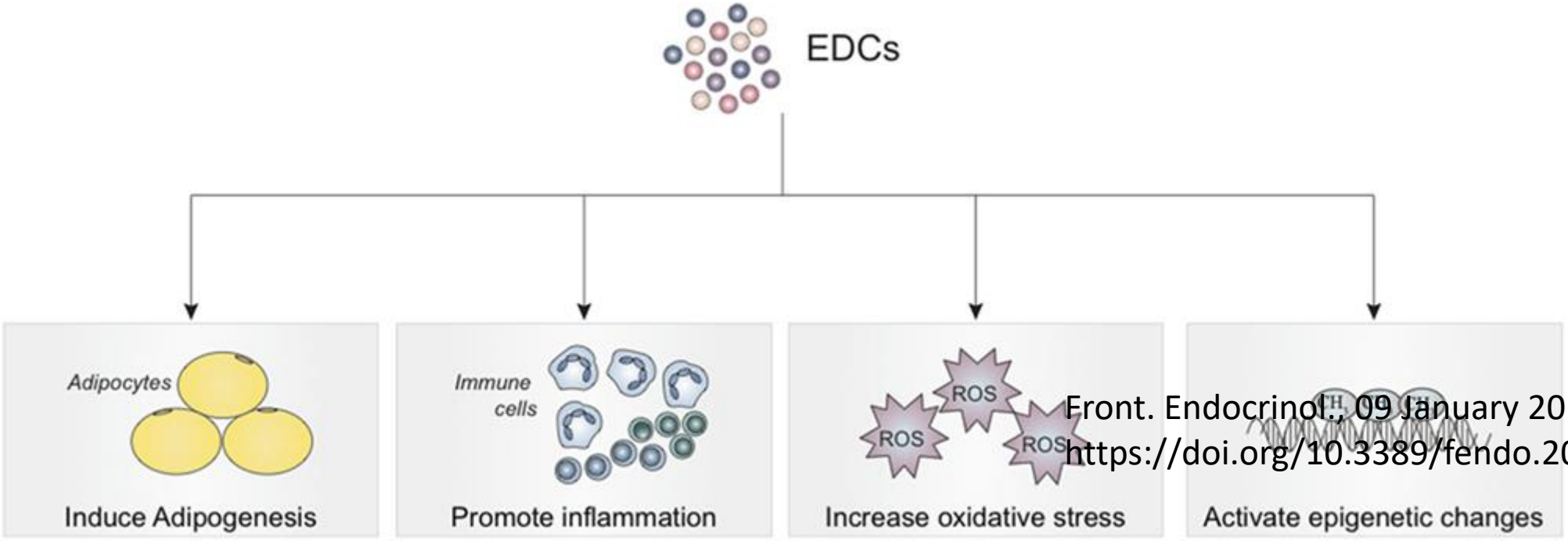
- alter the function of the endocrine system, producing adverse health effects in exposed organisms and their offspring



Life Sci. 2016 Jan 15;145:265-73

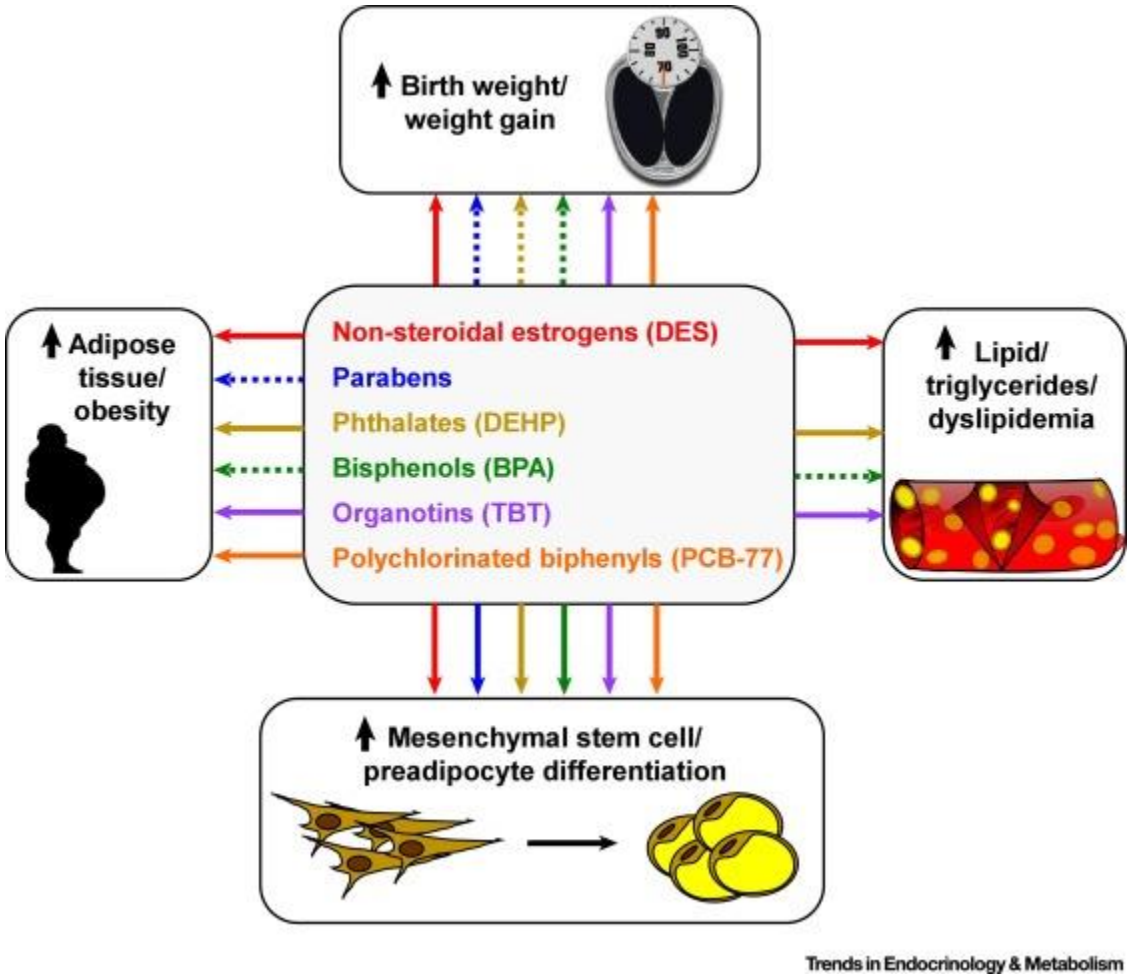
Effects of EDCs on mesenchymal stem cells

- 100 pM to 1 nM, EDCs have been demonstrated to exert effects
- Structural similarities between these EDCs and endogenous hormones indicate that the ability of EDCs to affect homeostasis may be through activation of hormone receptors. Like hormones, EDCs are



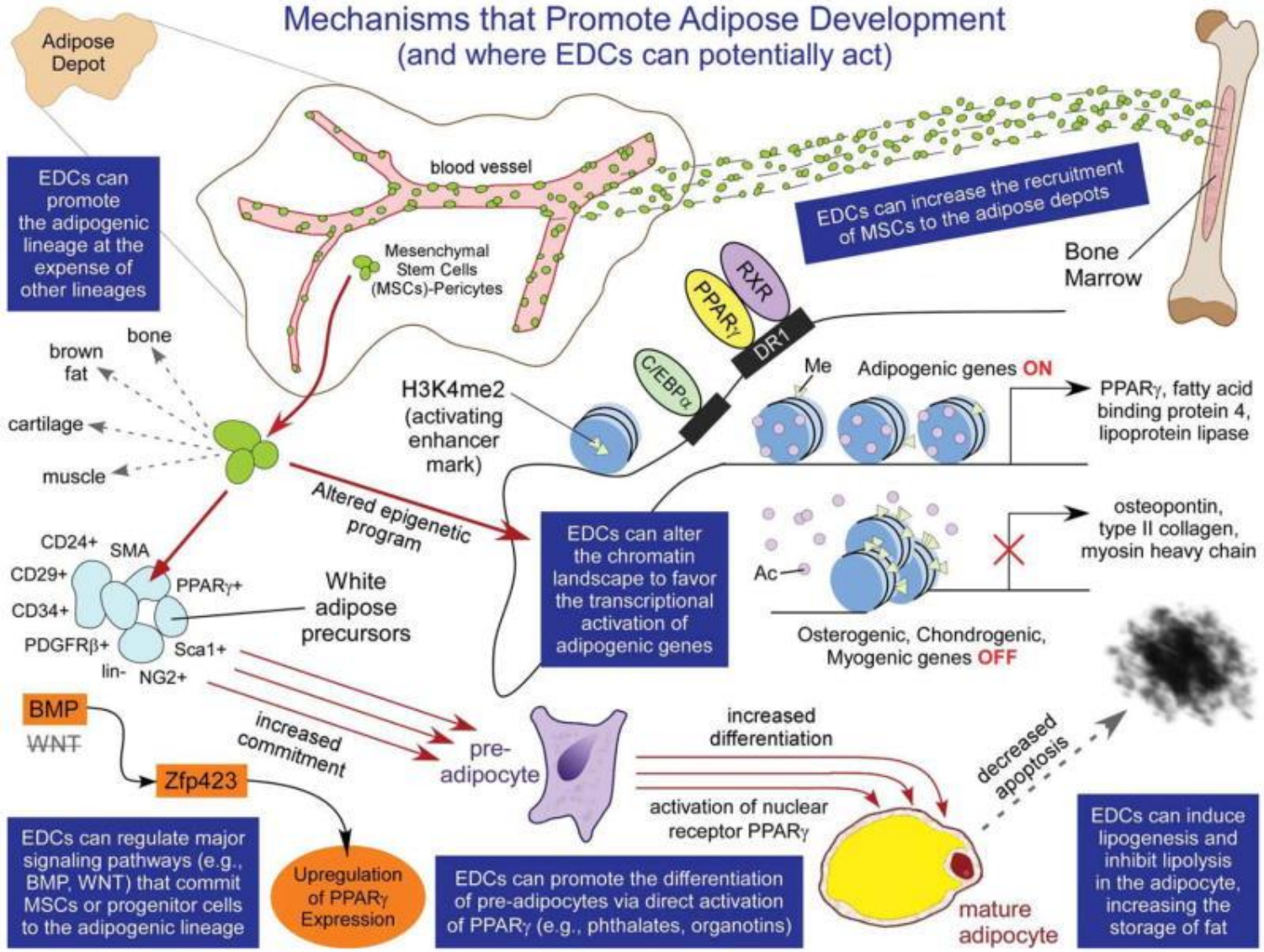
Front. Endocrinol., 09 January 2017 | https://doi.org/10.3389/fendo.2016.00171

Known Obesogenic Effects of the Six Classes of Endocrine Disrupting Chemicals



Trends Endocrinol Metab. 2018 Sep;29(9):607-625.

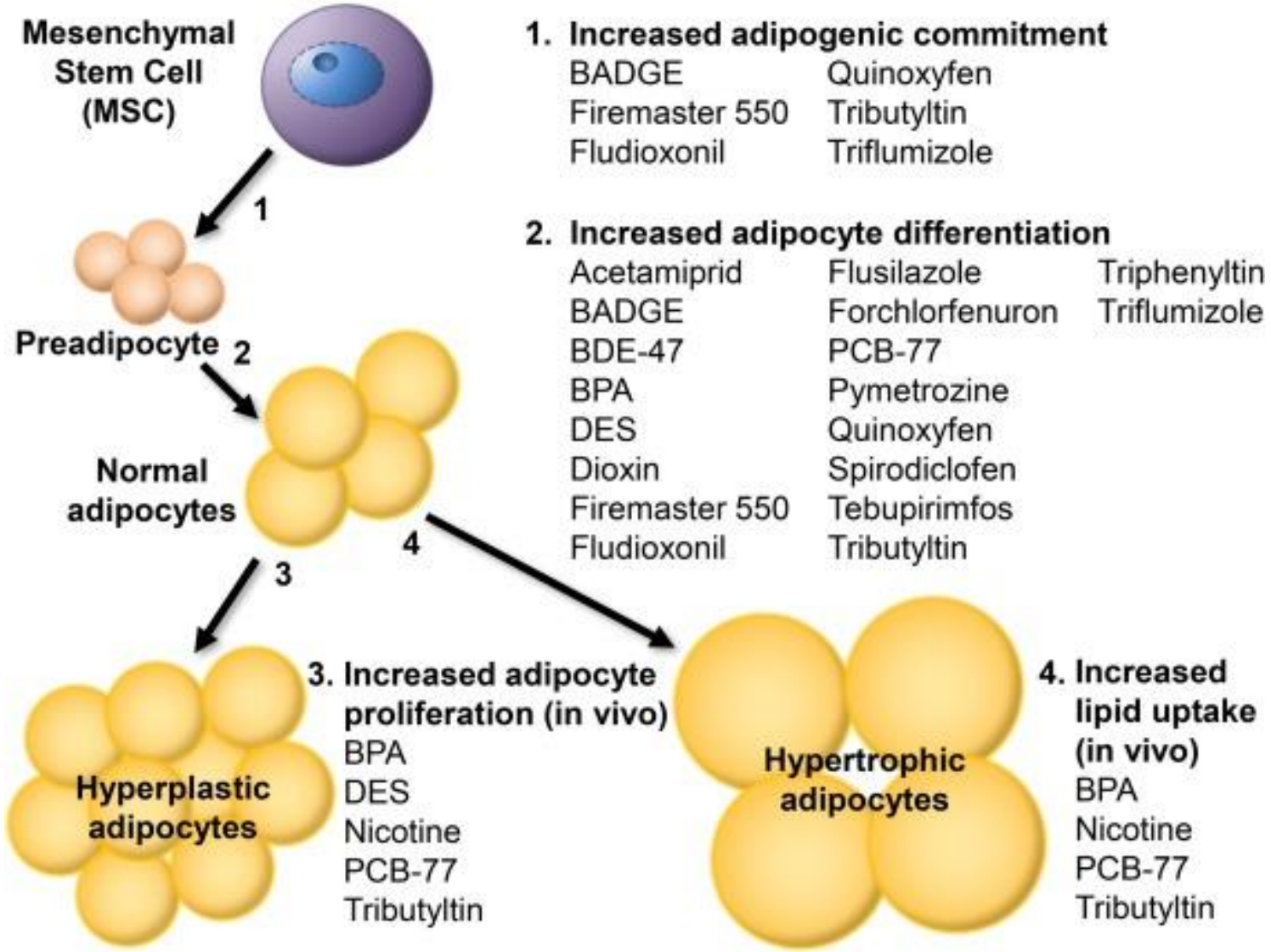
The potential interactions of endocrine disrupting chemicals during various stages of adipose tissue development.



Birth Defects Res C Embryo Today. 2011 Mar; 93(1): 34–

- dipogenesis is the differentiation of preadipocytes into adipocytes and is important for storage of lipids and metabolism in the human body. Adipogenesis requires a supportive environment and a peroxisome proliferator-activated receptor gamma (PPARγ) ligand

Mechanisms of Adipocyte Formation and Sites of Action of Metabolism Disruptors.

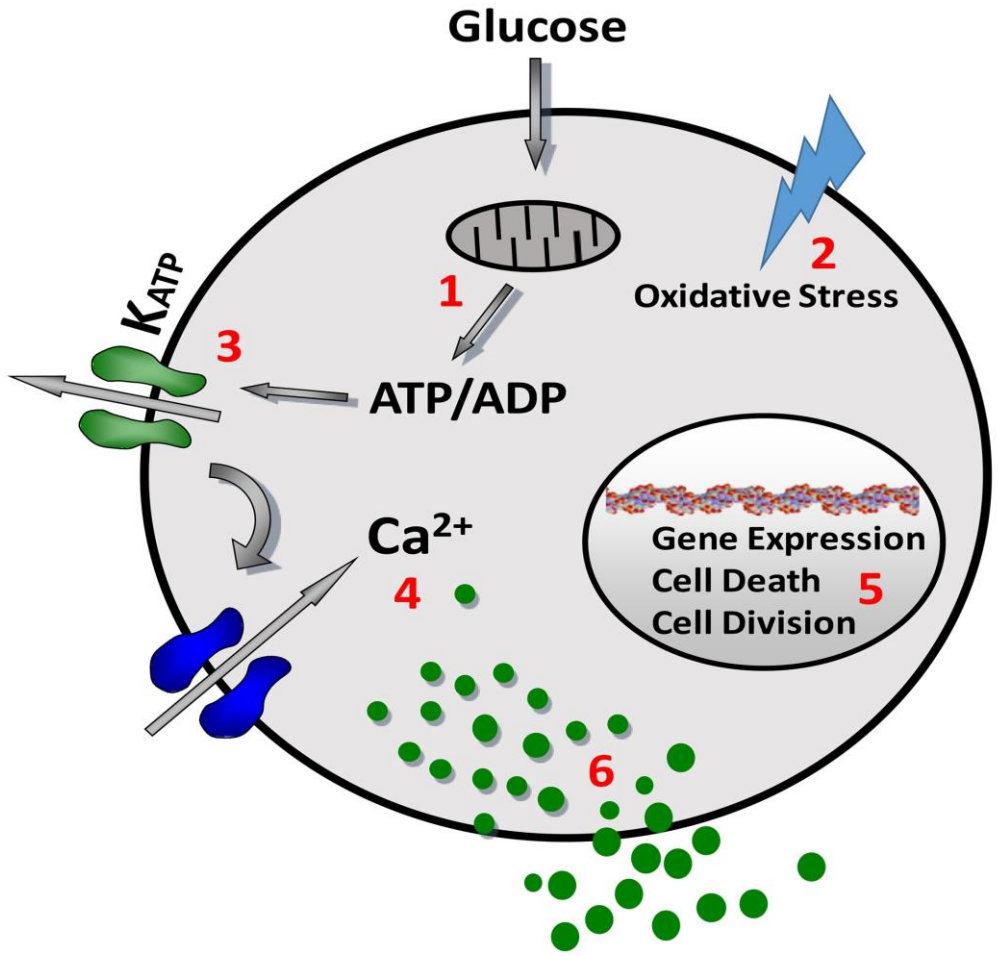


Weight loss is a frequent intervention to reduce the risk of metabolic disease

- however, weight loss has paradoxical effects on circulating levels of lipid-soluble EDCs. For example, a weight loss intervention among obese participants resulted in elevated levels of serum organohalogenated contaminants and their hydroxylated metabolites

Front. Endocrinol., 04 February 2019

Regulationofpancreasbetacellcontrolofbloodglucoseandsitesofactionofmetabolismdisruptors



1 Bisphenol-A
Nonylphenol
Octylphenol
Triphenyltin

2 Mercury
Cadmium

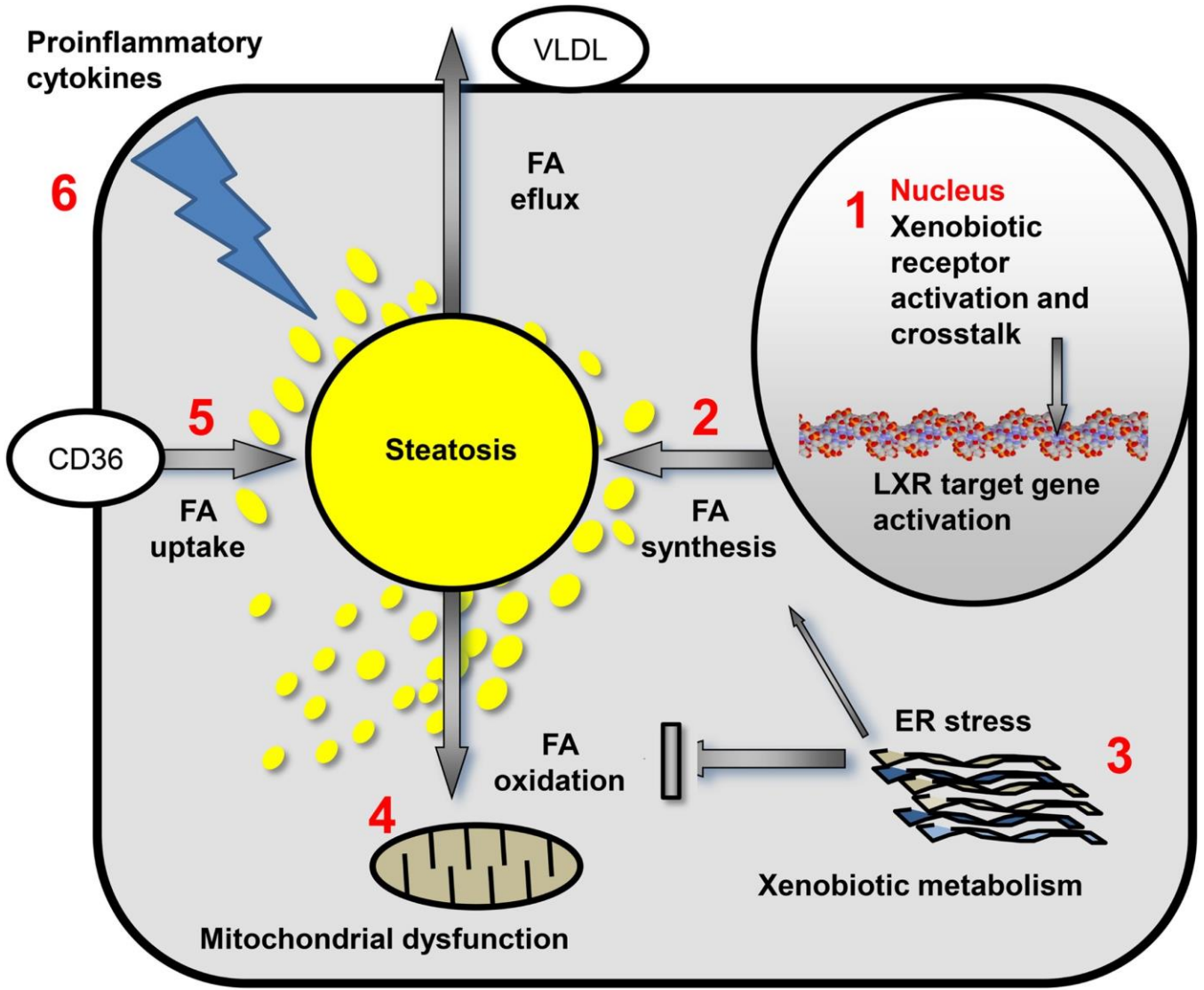
3 Bisphenol-A

4 Bisphenol-A
Arsenic
PCBs
Triphenyltin

5 Bisphenol-A
DEHP
Cadmium

6 Bisphenol-A
Dioxins
PCBs

Regulation of hepatic lipid metabolism and sites of action of metabolism disruptors



1 BPA, Dioxins, Pesticides, PCBs, PFCs, Phthalates, Organotins

2 BPA, PCBs, PFCs, Tributyltin, Metals

3 Acrolein, Metals

4 Acrolein, BPA, Metals, PCBs, Vinyl Chloride

5 BPA, Dioxins, PCBs

6 PCBs, Vinyl Chloride, VOCs, Metals

Dioxins

- Dioxins are mainly by-products of industrial processes but can also result from natural processes, such as volcanic eruptions and forest fires. Their half-life in the body is estimated to be 7 to 11 years. They accumulate in food chain and in the adipose tissue of human body. The most harmful dioxin is 2,3,7,8-tetrachlorodibenzo -p-dioxin (TCDD).

endocrine disrupting chemicals are metabolic disruptors

- Adipose tissue is an important regulator of metabolic health, as increased adiposity is a wellrecognized risk factor for insulin resistance and diabetes, and impairments in adipose development and function are also associated with metabolic disease

Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.

- The transcription factor peroxisome proliferator activated receptor-γ (PPARγ) is a key regulator of normal adipocyte development
- PPARγ also influences glucose homeostasis by controlling expression of GLUT4,
- Humans with heterozygous loss of function. PPARγ mutations have lipodystrophy and insulin resistance [84]. Thus, disruption of PPARγ activity has multiple negative consequences on adipocyte development and function. Several MDCs disrupt PPARγ signaling, including organotins and phthalates

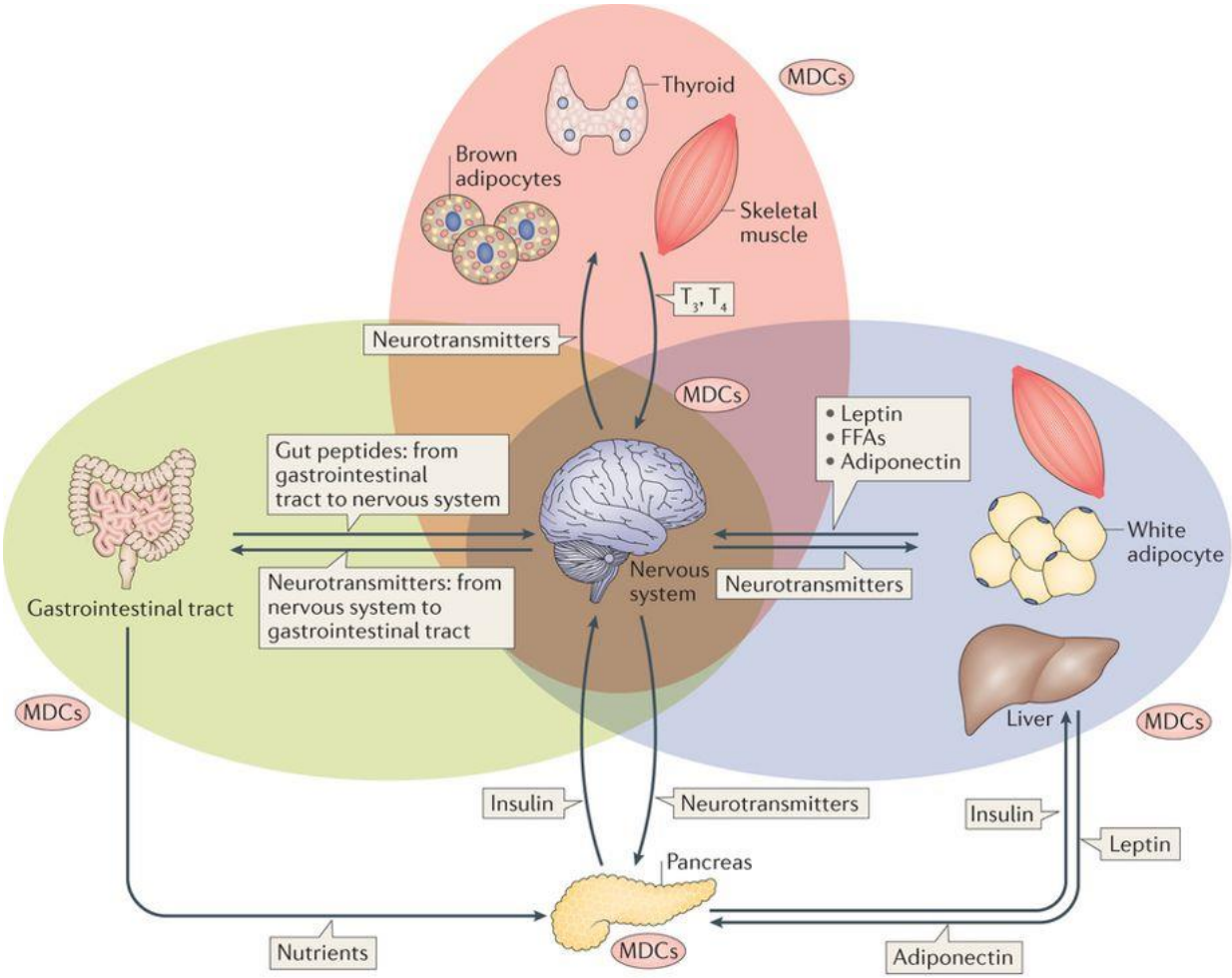
Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.

- Several MDCs disrupt PPARγ signaling, including organotins and phthalates [85]. Importantly, the classical obesogen TBT, has been shown to promote adipogenesis in multiple model systems via PPARγ activation [86], while generating a dysfunctional adipocyte with reduced expression of the beneficial adipokine adiponectin

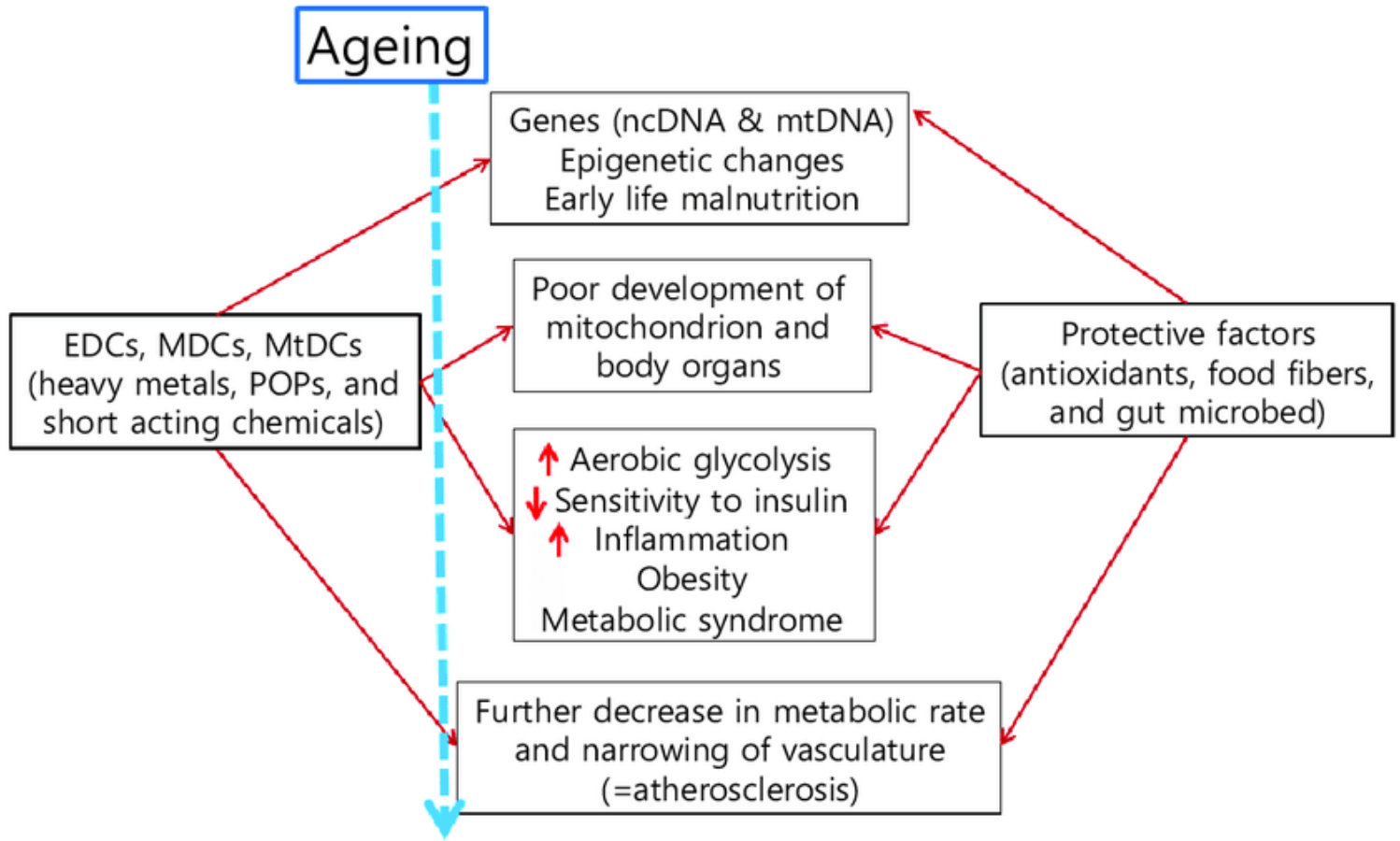
Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.

Organs targeted by metabolism-disrupting chemicals.

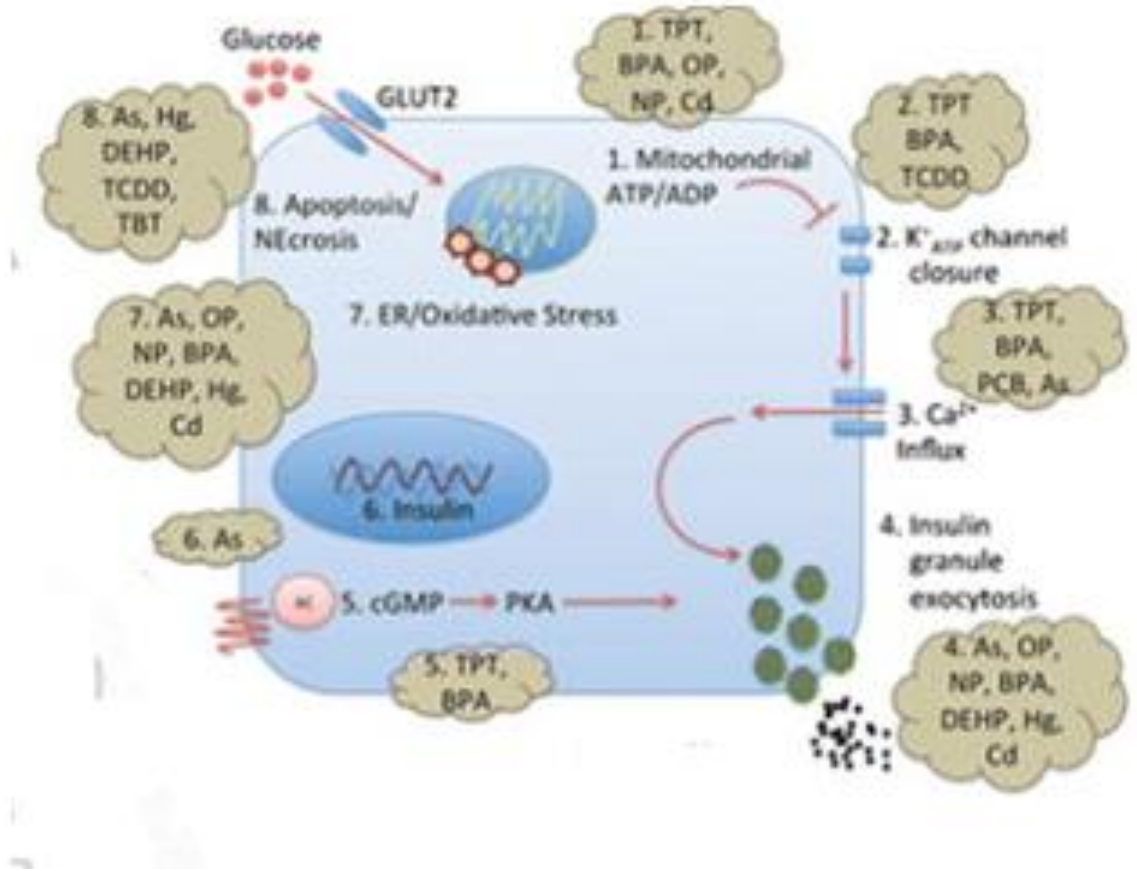
- Humans are exposed to a cocktail of common metabolism-disrupting chemicals (MDCs) that affect every aspect of energy balance
- MDCs alter energy intake by targeting the gut cells involved in nutrient transport and peptide secretion, as well as the gut microbiota and hypothalamic neurons
- Energy expenditure is affected by the influence of MDCs on brown adipose tissue function, skeletal muscle metabolism and thyroid hormone production and action
- MDCs act on the most important metabolic tissues involved in energy storage: the endocrine pancreas, the liver, white adipose tissue and skeletal muscle
- MDCs disrupt insulin secretion in pancreatic β cells and alter insulin-dependent glucose metabolism in the liver, skeletal muscle and adipocytes, modifying lipogenesis and glucose metabolism after altering the expression of essential genes
- MDCs also affect energy homeostasis, as they alter the metabolic cues that connect the different organs involved in metabolism



Nature Reviews Endocrinology **volume13**, pages536-546 (2017)

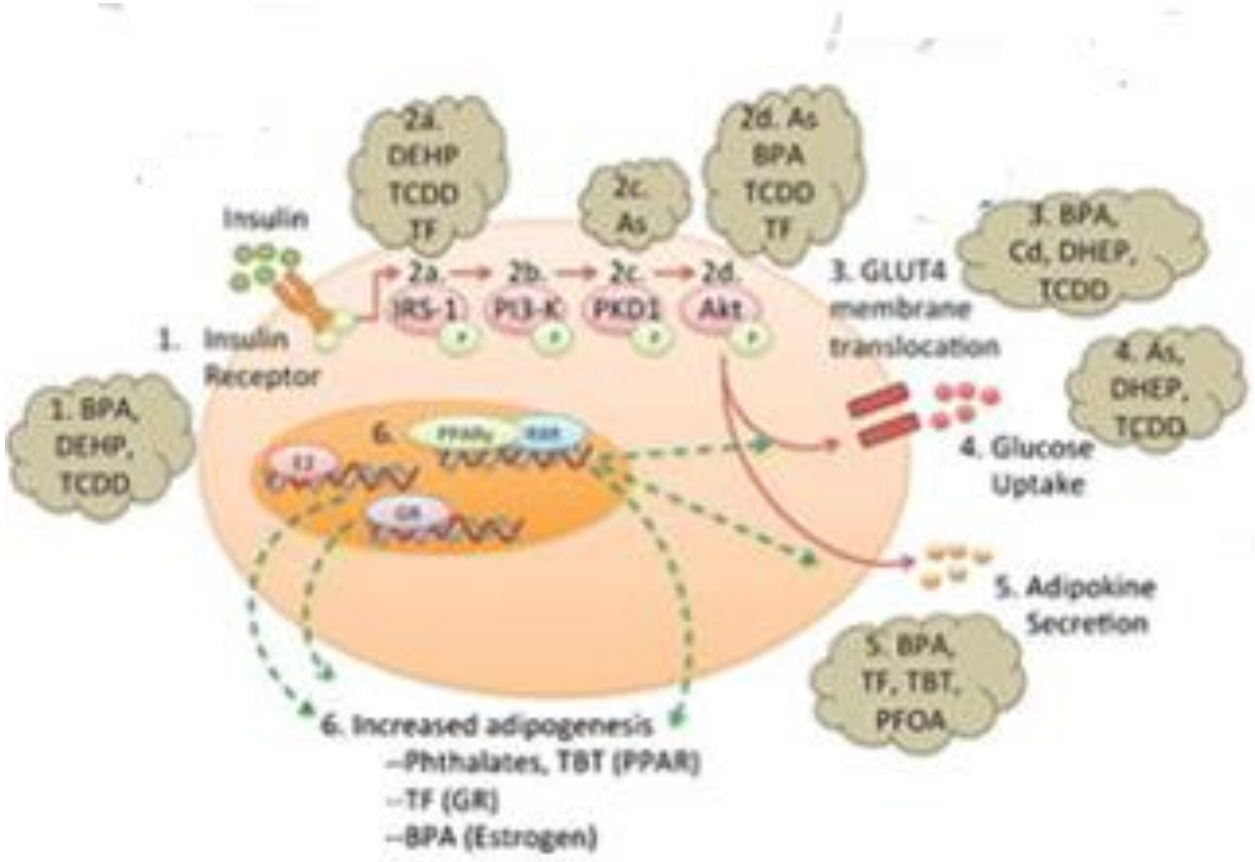

Ageing
Genes (ncDNA & mtDNA)
Epigenetic changes
Early life malnutrition
EDCs, MDCs, MtDCs
(heavy metals, POPs, and
short acting chemicals)
Poor development of
mitochondrion and
body organs
Protective factors
(antioxidants, food fibers,
and gut microbed)
↑ Aerobic glycolysis
↓ Sensitivity to insulin
↑ Inflammation
Obesity
Metabolic syndrome
Further decrease in metabolic rate
and narrowing of vasculature
(=atherosclerosis)

metabolism disrupting chemicals disrupt energy homeostasis in the β-cell,



Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.

metabolism disrupting chemicals disrupt energy homeostasis in the adipocyte.

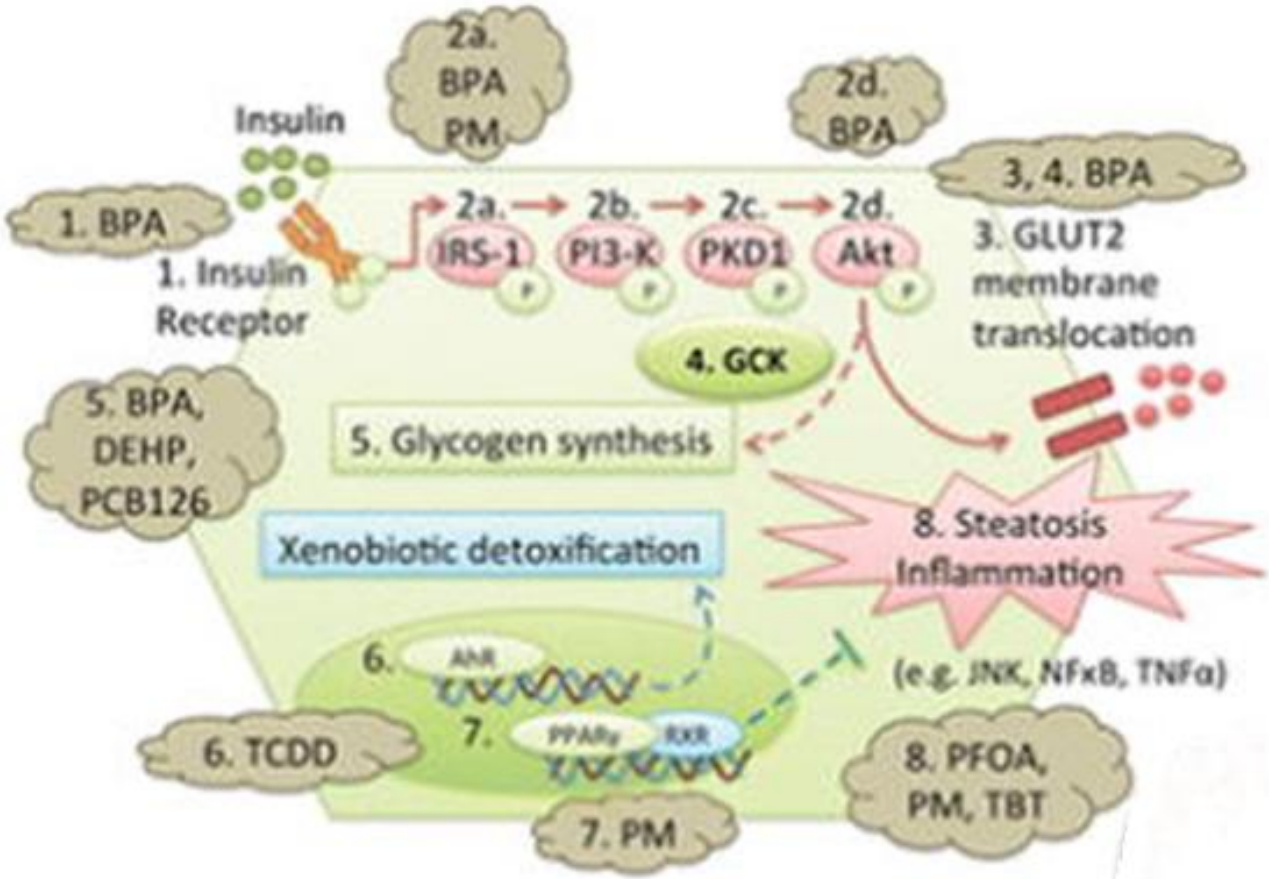


Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.

metabolism disrupting chemicals disrupt energy homeostasis in the myocyte,

Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.

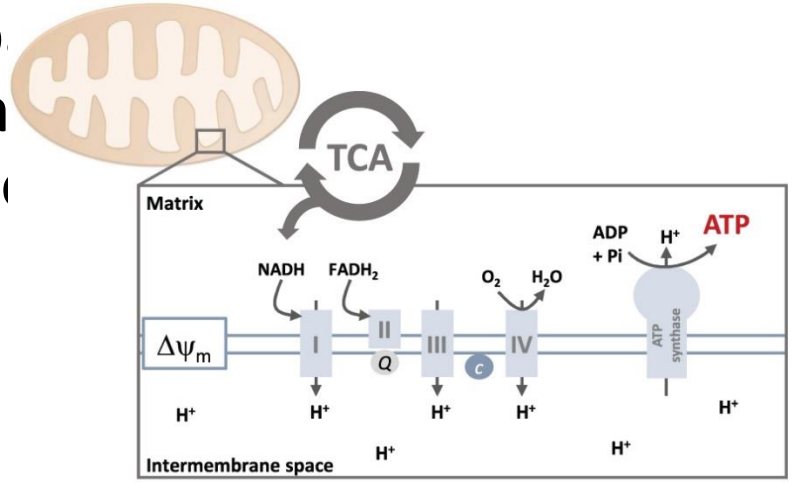
metabolism disrupting chemicals disrupt energy homeostasis in, hepatocyte

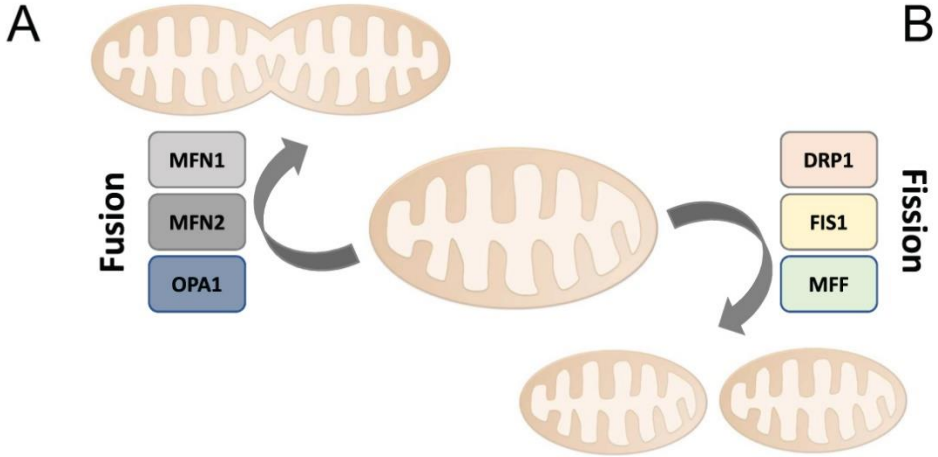


Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.

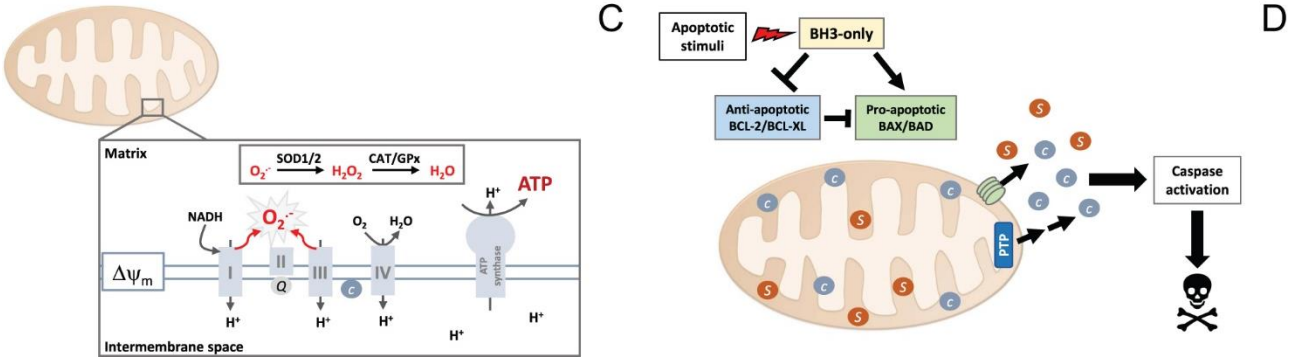
EDCs and Mitochondria

- recognized as the powerhouse of the cell,
- (TCA), which takes place in the mitochondrial matrix, generates NADH and FADH2, whose free energy will be used to transport electrons in the electron transport chain (ETC, located in the inner mitochondrial membrane
- B) Mitochondrial dynamics: mitochondrial fusion (left), which generates large, interconnected mitochondrial networks, is mainly governed by the dynamin-related proteins, mitofusins 1 and 2 (MFN1 and MFN2) and optic atrophy 1 (OPA1). On the other hand, mitochondrial fission (right) leads to fragmented, sep ins, including dyn (FIS1), and the mit

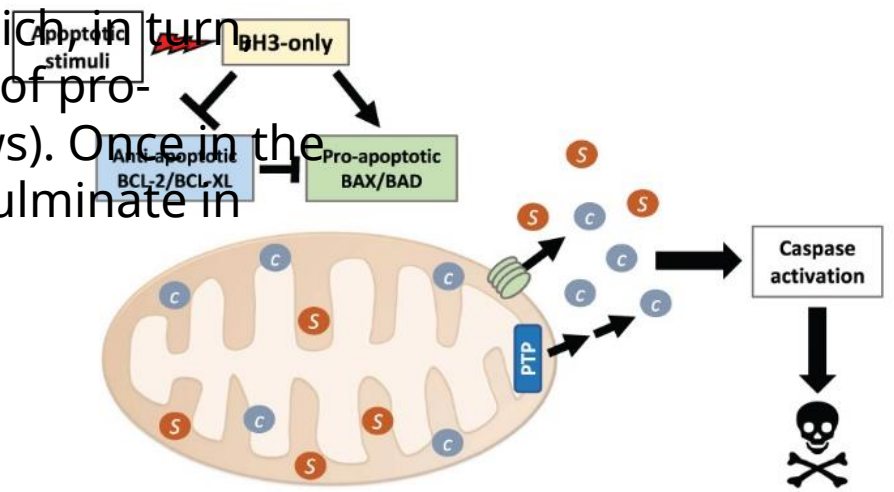




Mitochondria ROS generation and antioxidant activity. Due to its redox activity, the ETC generates reactive oxygen species (ROS) as a consequence of electron leak during the oxidative phosphorylation. The figure depicts the main sites of ROS production in the ETC, i.e. complexes I and III. Of note, there are at least 11 different sites linked to ROS production in the mitochondria, such as the α-ketoglutarate dehydrogenase and the glycerol 3-phosphate dehydrogenase. Complexes I and III generate superoxide radical ($O_2^{\cdot -}$), which can be dismutated to hydrogen peroxide (H_2O_2) by the enzymes superoxide dismutase (SOD) 1 (CuZnSOD, located in the intermembrane space) and 2 (MnSOD, located in the mitochondrial matrix). Other antioxidant enzymes, such as catalase (CAT) and glutathione peroxidase (GPx), can decompose H_2O_2 into H_2O and/or O_2.



Mitochondrial pathway of apoptosis. After an apoptotic stimulus, activated BH3-only proteins translocate to mitochondria where inactivate anti-apoptotic BCL-2 proteins and activate pro-apoptotic BAX and BAK. BAX oligomerization in the outer mitochondrial membrane (OMM) leads to OMM permeabilization and release of cytochrome *c* (*c*) and SMAC/DIABLO (*S*) from the intermembrane space into the cytosol. Under certain conditions (e.g. glucose deprivation and ischemia/reperfusion injury), long-lasting opening of the mitochondrial PTP may also contribute to cytochrome *c* release. In these situations, prolonged PTP opening leads to mitochondrial dysfunction (e.g. depolarization, and inhibition of oxidative phosphorylation and ATP synthesis) and matrix swelling, which in turn causes outer mitochondrial membrane rupture and release of pro-apoptotic factors, including cytochrome *c*(consecutive arrows). Once in the cytosol, cytochrome *c* drives caspase activation, which will culminate in activation of apoptosis.



- Under certain physiological or stressful conditions, activation of different signaling cascades culminates with the activation of transcription factors and co-regulators encoded by both nucleus and mitochondria. From the nuclear side, nuclear respiratory factors 1 and 2 (NRF1 and NRF2) are the two major transcription factors, directly modulating the expression of the mitochondrial transcription factor A (TFAM) and transcription factor B proteins (TFBs), two key regulators of the transcription and replication of mtDNA (Gleyzer *et al.* 2005, Scarpulla 2008).

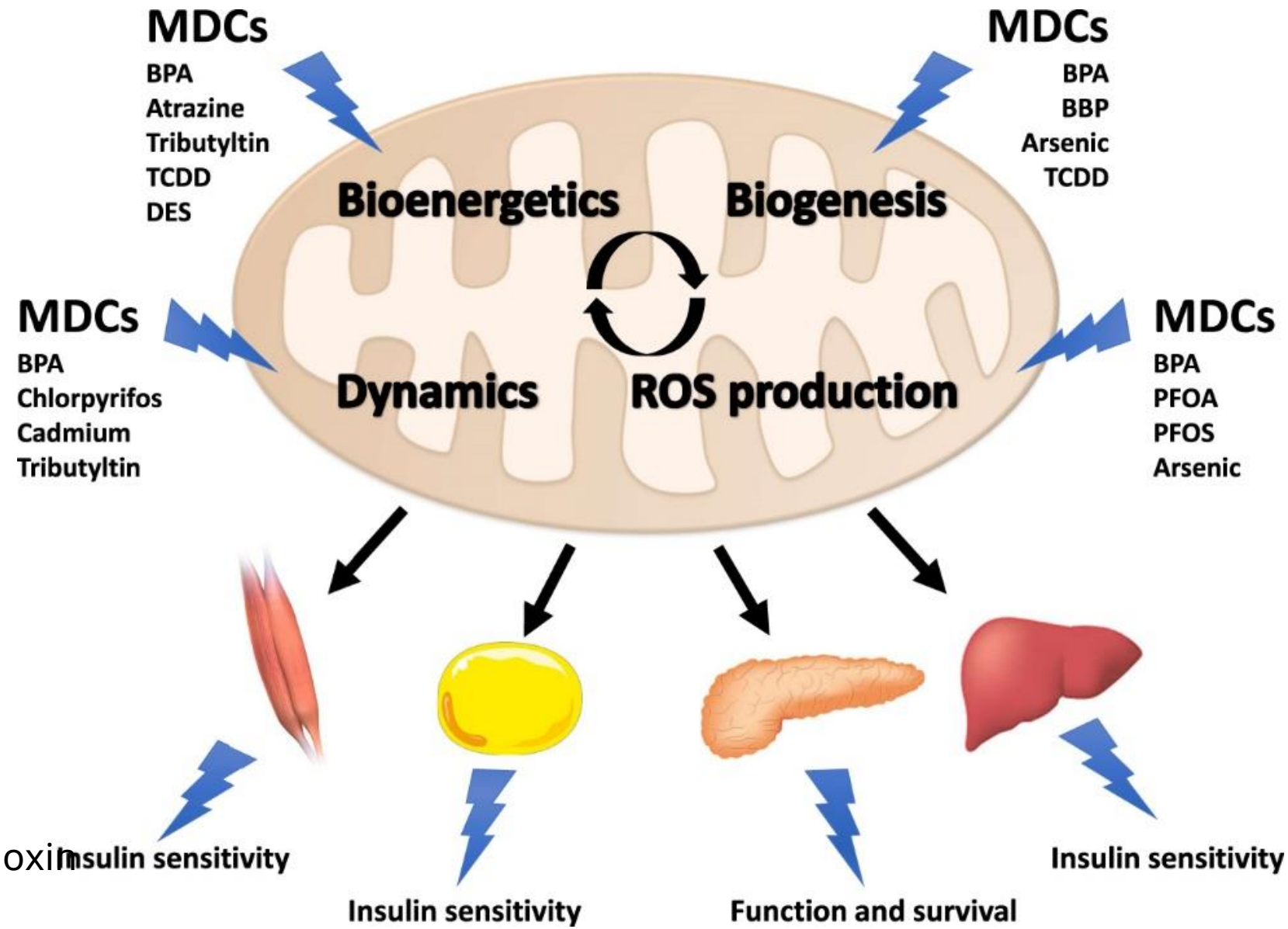
- Mitochondrial biogenesis is coordinated by members of the peroxisome proliferator-activated receptor (PPAR) coactivator-1 (PGC-1) family of coactivators, namely PGC-1α (PPARγ coactivator-1α), PGC-1β (PPARγ coactivator-1β) and PRC (PGC-1 related coactivator) (Puigserver *et al.* 1998, Wu *et al.* 1999, Andersson & Scarpulla 2001, Lin *et al.* 2002). PGC-1α is considered the master regulator of mitochondrial biogenesis, as its activation leads to activation of several transcription factors, such as PPARs, NRF1/NRF2, estrogen-related receptors (ERRα, ERRβ, ERRγ) and thyroid hormone receptors (TRα and TRβ) (Puigserver & Spiegelman 2003, Scarpulla 2011).

- Mitochondria are very dynamic organelles, exhibiting a wide variety of shapes, size and location that can change within a few seconds or minutes (Twig *et al.* 2010, Picard *et al.* 2016). These characteristics are related to active, regulated processes called mitochondrial fission and fusion (also known as mitochondrial dynamics), as well as the ability of mitochondria to build extensive intracellular networks through the formation of a tubular reticulum (Bereiter-Hahn 1990, Scott & Youle 2010, Prasai 2017). A proper control of mitochondrial dynamics is very important for several biological processes, such as regulation of neuronal development (Choi *et al.* 2013, Burté *et al.* 2015, Denton *et al.* 2018), ROS production (Yu *et al.* 2006, Huang *et al.* 2016, Ježek *et al.* 2018) and apoptosis (Frank *et al.* 2001, Olichon *et al.* 2003, Suen *et al.* 2008).

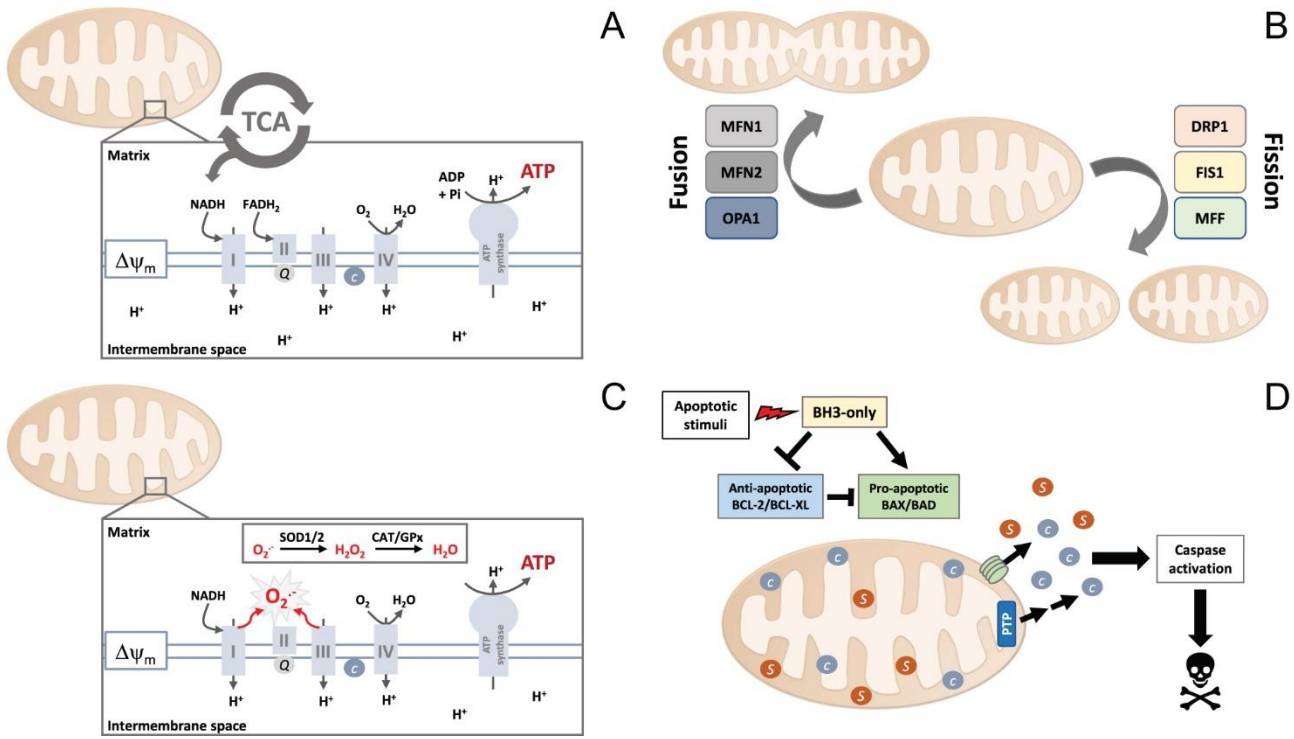
- Mitochondrial fission promotes fragmented, separated mitochondria in a process regulated by several proteins, including dynamin-related protein 1 (DRP1), a master regulator of mitochondrial division in eukaryotic cells and mitochondrial fission protein 1 (FIS1). Conversely, mitochondrial fusion generates large, interconnected mitochondrial networks. Three dynamin-related proteins, namely mitofusins 1 and 2 (MFN1 and MFN2), and optic atrophy 1 (OPA1), mediate mitochondrial fusion in mammals (Suárez-Rivero *et al.* 2016, Williams & Ding 2017). Both processes contribute to keep a healthy pool of mitochondria by actively participating in mitophagy, the mitochondrial quality control process by which damaged or dysfunctional mitochondria are eliminated by selective autophagy (Lemasters 2005, Williams & Ding 2017). The mitophagic process is mainly orchestrated by two main proteins, namely phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) and Parkin (PARK2). More recently, other proteins participating in mitophagy have been identified, including the E3 ubiquitin ligase ariadne RBR E3 ubiquitin protein ligase 1 (ARIH1) and the inner mitochondrial membrane protein, prohibitin 2 (PHB2) (Palikaras & Tavernarakis 2014, Villa *et al.* 2017, Wei *et al.* 2017).

- ROS and oxidative stress
- Mitochondria are considered the major source of intracellular ROS, which are mainly produced as consequence of electron leak from the ETC during the OXPHOS. Mitochondria present at least 11 different sites associated with ROS generation; it is generally well accepted that complexes I and III are the two major sites (Brand 2016).
- ROS act as a double-edged sword for the cells. Physiological concentrations of ROS act as second messengers in diverse cellular and mitochondrial processes and signaling pathways (Sena & Chandel 2012). Conversely, excessive ROS can react with lipids, nucleic acids (including mtDNA) and proteins, causing oxidative damage and, eventually, cell death (Circu & Aw 2010). To keep ROS levels under control and avoid their potentially detrimental effects, mitochondria have evolved an antioxidant defense composed by non-enzymatic (e.g. ascorbic acid and α-tocopherol) and enzymatic (e.g. catalase and superoxide dismutase, SOD) systems (Sies 1993). Moreover, it has been suggested that UCP2 and UCP3 might be involved in the control of ROS production (Arsenijevic *et al.* 2000, Mailloux & Harper 2011, Pons *et al.* 2015). When antioxidant defenses fail to cope with excessive ROS production, cells undergo oxidative stress, which has been associated with IR and T2DM (Houstis *et al.* 2006, Anderson *et al.* 2009, Tangvarasittichai 2015).

- Mitochondria and cell death
- Along with their role in energy production, mitochondria are also implicated in several signaling pathways. For instance, mitochondria play a crucial role in the intrinsic pathway of apoptosis, which requires permeabilization of the outer mitochondrial membrane (OMM). Regulation of OMM permeabilization depends on the balance between anti- and pro-apoptotic B-cell lymphoma 2 (BCL-2) family proteins. This family comprises three groups of proteins: anti-apoptotic (e.g. BCL-2 and BCL-XL), pro-apoptotic (e.g. BAX and BAK) and BH3-only proteins (e.g. PUMA, and BIM) (Youle & Strasser 2008). Upon exposure to cell death stimuli (e.g. DNA damage), BH3-only proteins translocate to mitochondria, where they bind and inactivate anti-apoptotic BCL-2 proteins. Subsequently, BH3-only proteins stimulate BAX and BAK, causing OMM permeabilization and release of pro-apoptotic proteins, such as cytochrome *c* and SMAC/DIABLO, from the intermembrane space. Additionally, long-lasting opening of the mitochondrial permeability transition pore (PTP) also contributes to cytochrome *c* release under certain conditions (e.g. glucose deprivation and ischemia/reperfusion injury). Once in the cytosol, cytochrome *c* binds to the apoptotic protease activating factor 1, leading to the activation of caspase-9 and -3, and, ultimately, apoptosis (Ow *et al.* 2008, Youle & Strasser 2008).



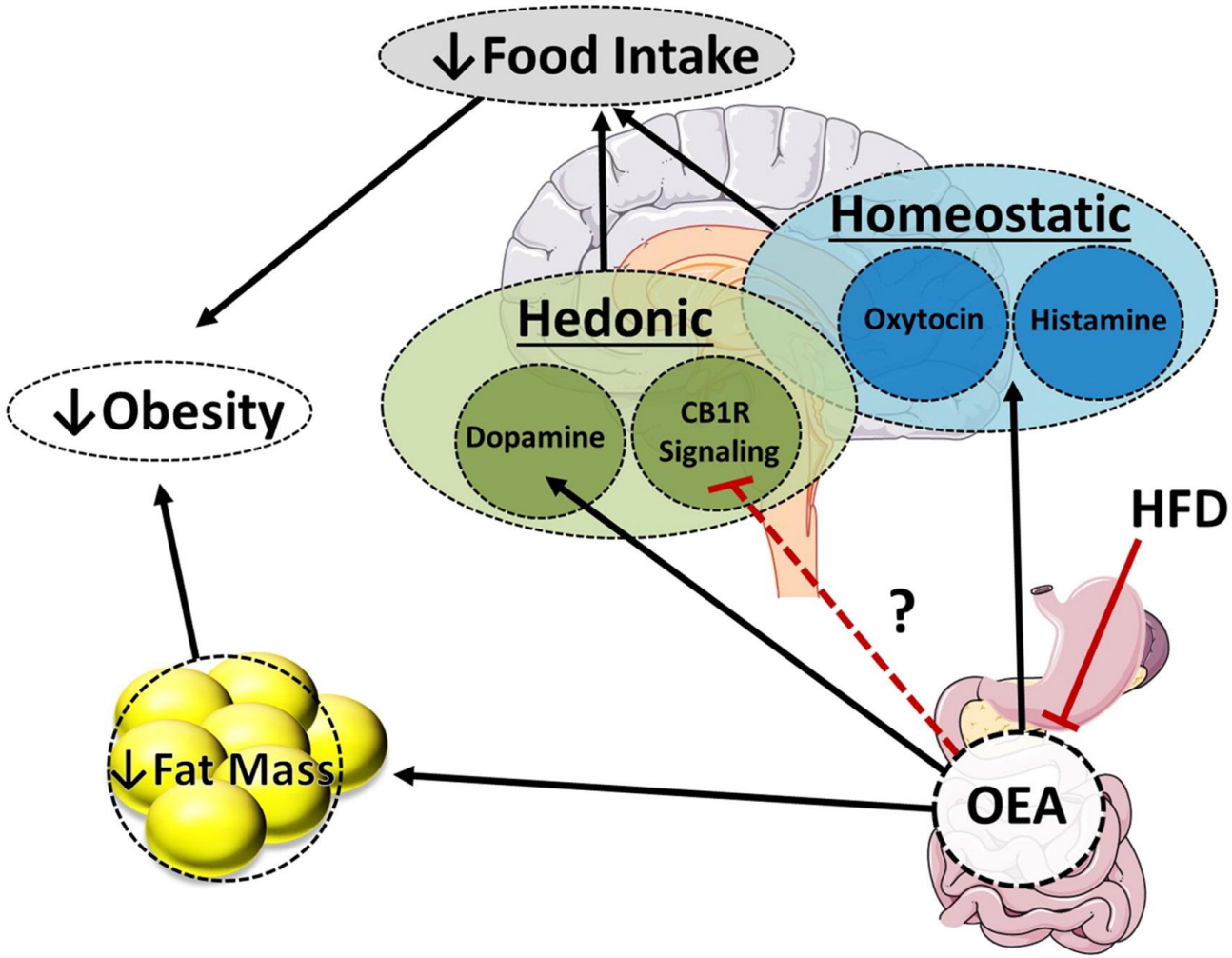
TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin
polychlorinated biphenyls (PCBs),
Perfluorooctanoic acid (PFOA)
perfluorooctane sulfonate (PFOS),
dichlorodiphenyltrichloroethane (DDT).


A
TCA
Matrix
NADH
FADH2
ADP
+ Pi
ATP
O2
H2O
ΔΨm
I
II
Q
III
IV
c
ATP synthase
H+
Intermembrane space
B
Fusion
MFN1
MFN2
OPA1
Fission
DRP1
FIS1
MFF
C
Matrix
SOD1/2
CAT/GPx
O2·-
H2O2
H2O
NADH
ATP
ΔΨm
Intermembrane space
D
Apoptotic stimuli
BH3-only
Anti-apoptotic BCL-2/BCL-XL
Pro-apoptotic BAX/BAD
PTP
Caspase activation

Oleoylethanolamide: A fat ally in the fight against obesity

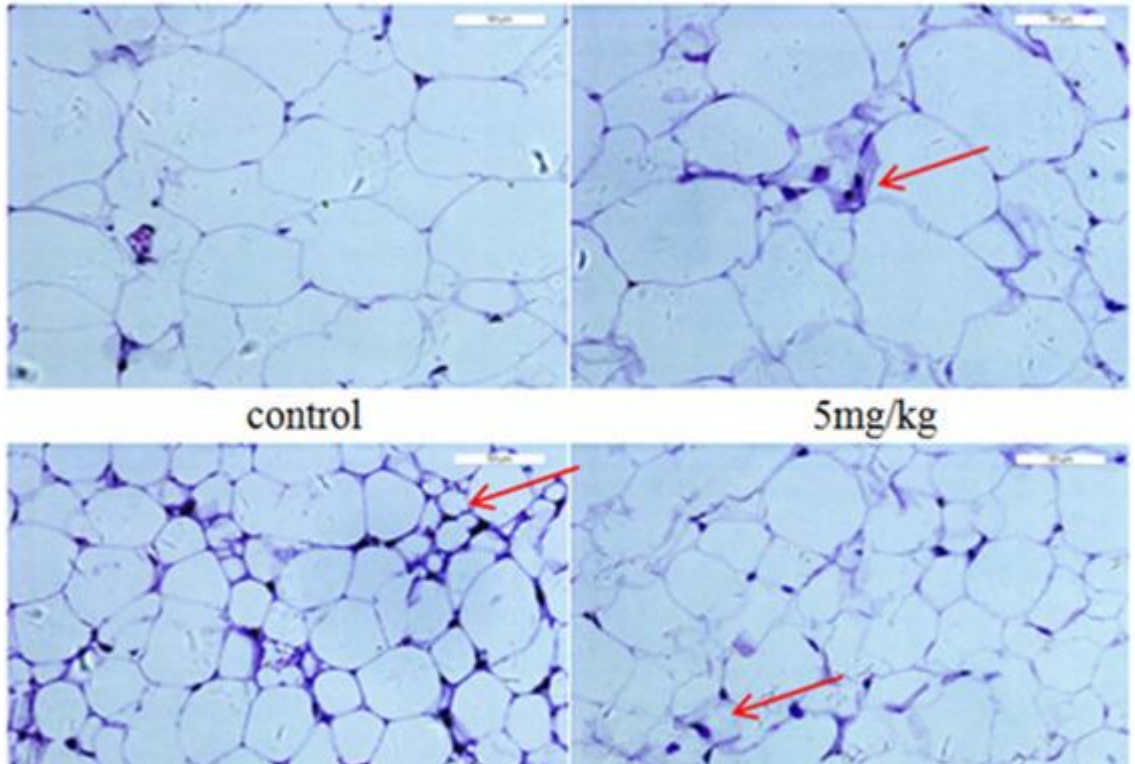
- Oleoylethanolamide (OEA) is an endocannabinoid-like lipid that induces hypophagia and reduces fat mass
- PPAR-α has been the most widely accepted mediator of the hypophagic action of OEA via signaling to homeostatic brain centers.
- OEA may also reduce food intake via effects on dopamine and endocannabinoid signaling within hedonic brain centers
- Limited study of OEA supplementation in humans has provided some encouraging insight into OEA-based weight loss therapy,
- As a potential link between homeostatic and hedonic regulation of food intake, OEA is a prime starting point for the development of more effective obesity therapies.

The anti-obesity actions of oleoylethanolamide



Effect of DEHP on adipose tissue histopathology of rats

- Plasticizer di-2-ethylhexyl phthalate (DEHP) can induce lipid metabolic disorder. There was a chronic low level inflammatory response in adipose tissue of patients with lipid metabolic disorder.

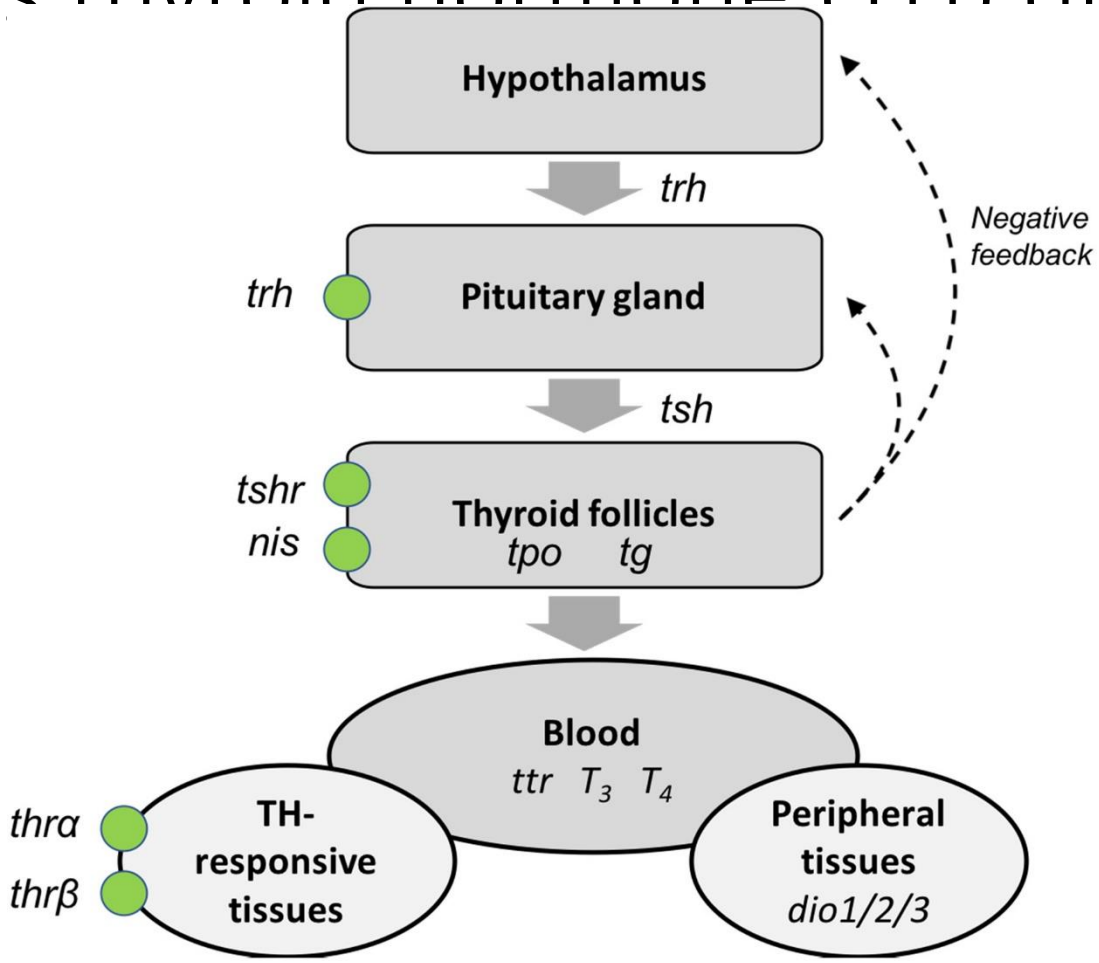


Exposure to DEHP promoted the secretion of IL-1β, TNF-α and led to the inflammation.

DEHP disturbed the normal lipid metabolism and lead to lipid metabolic disorders.

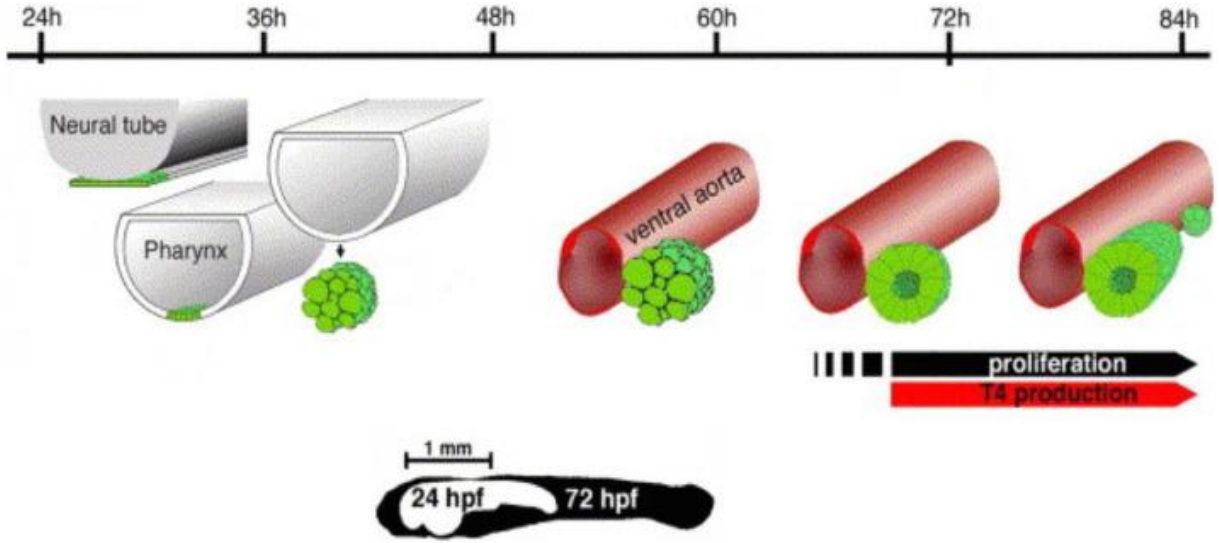
Inflammation may play a regulatory role in lipid metabolic disorders induced by DEHP.

many organic compounds found in our environment can interfere with the thyroid system and act as thyroid hormone (TH) disruptor.



Science of The Total Environment
Volume 656, 15 March 2019, Pages 1238-1249

the time line for thyroid development in zebrafish.



Science of The Total Environment
Volume 656, 15 March 2019, Pages 1238-1249

İlginiz için teşekkür ederim

- **Prof. Dr. N. Nuray Ulusu**

  Koç Üniversitesi,

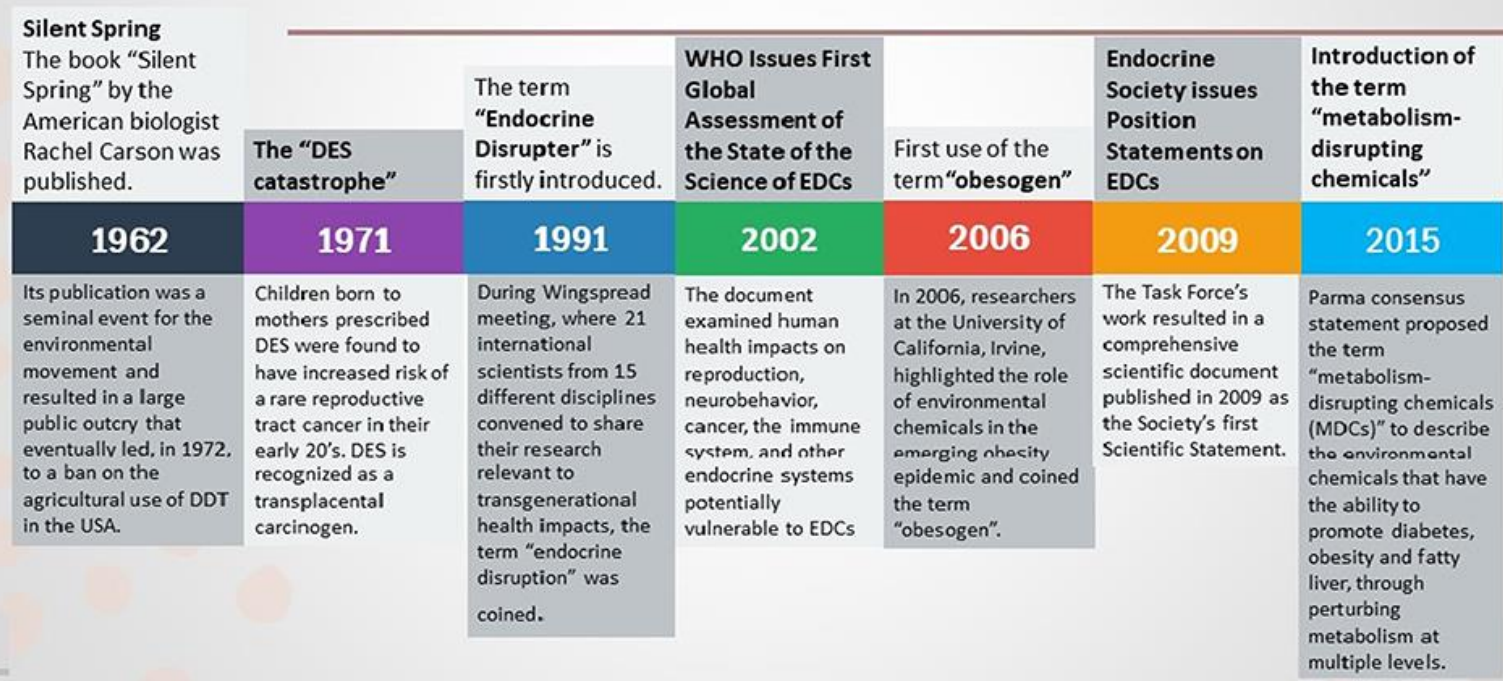
  Tıp Fakültesi

  Rumelifeneri yolu

  Sarıyer-İstanbul

  nulusu@ku.edu.tr

Historical landmarks in the EDCs Research



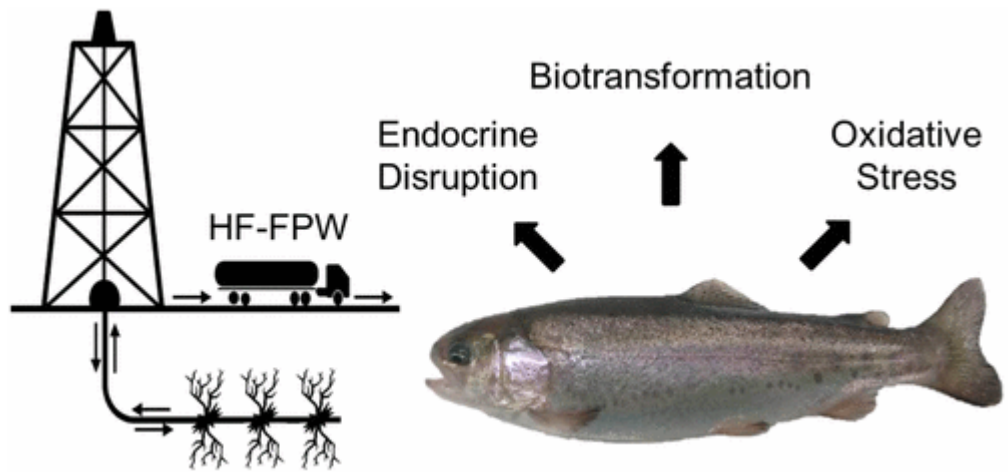
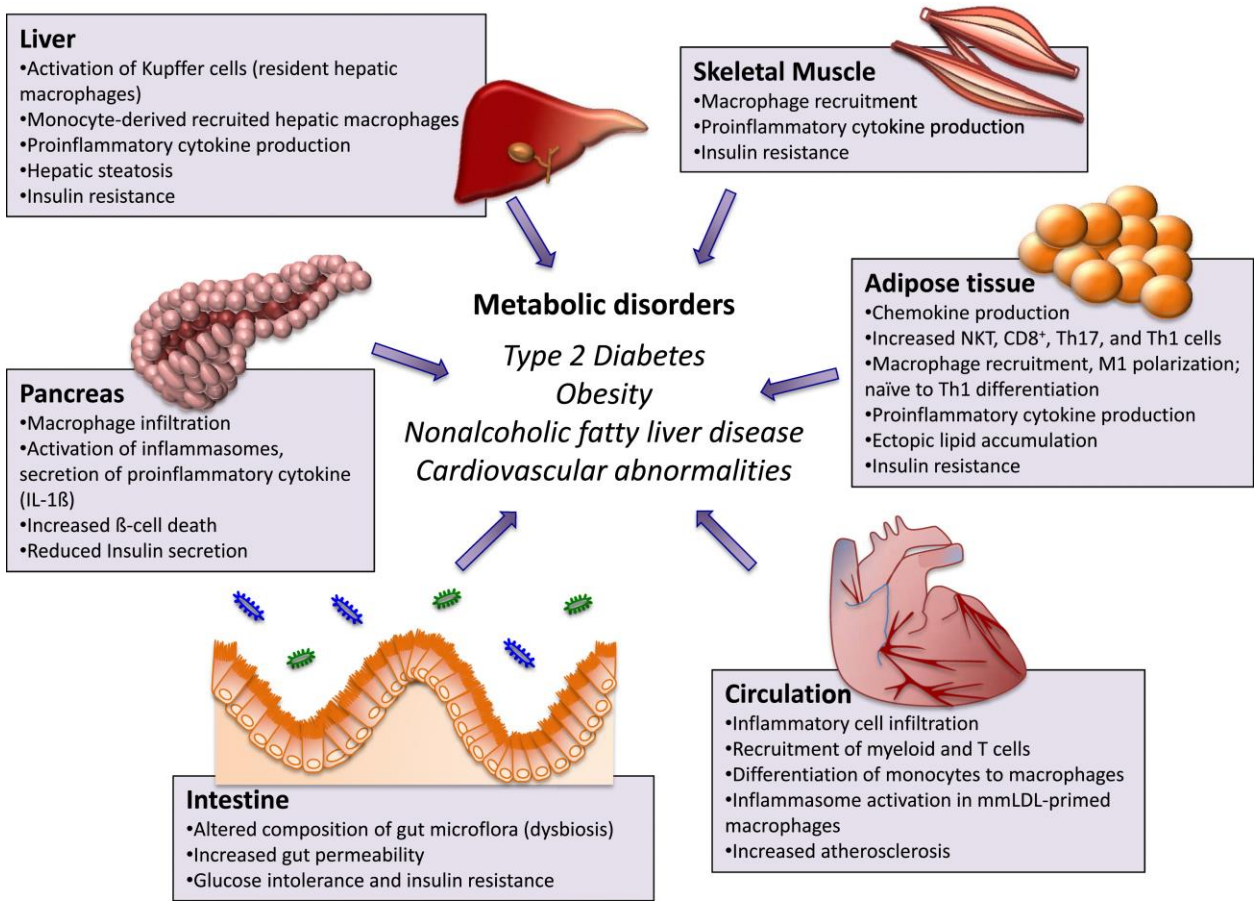
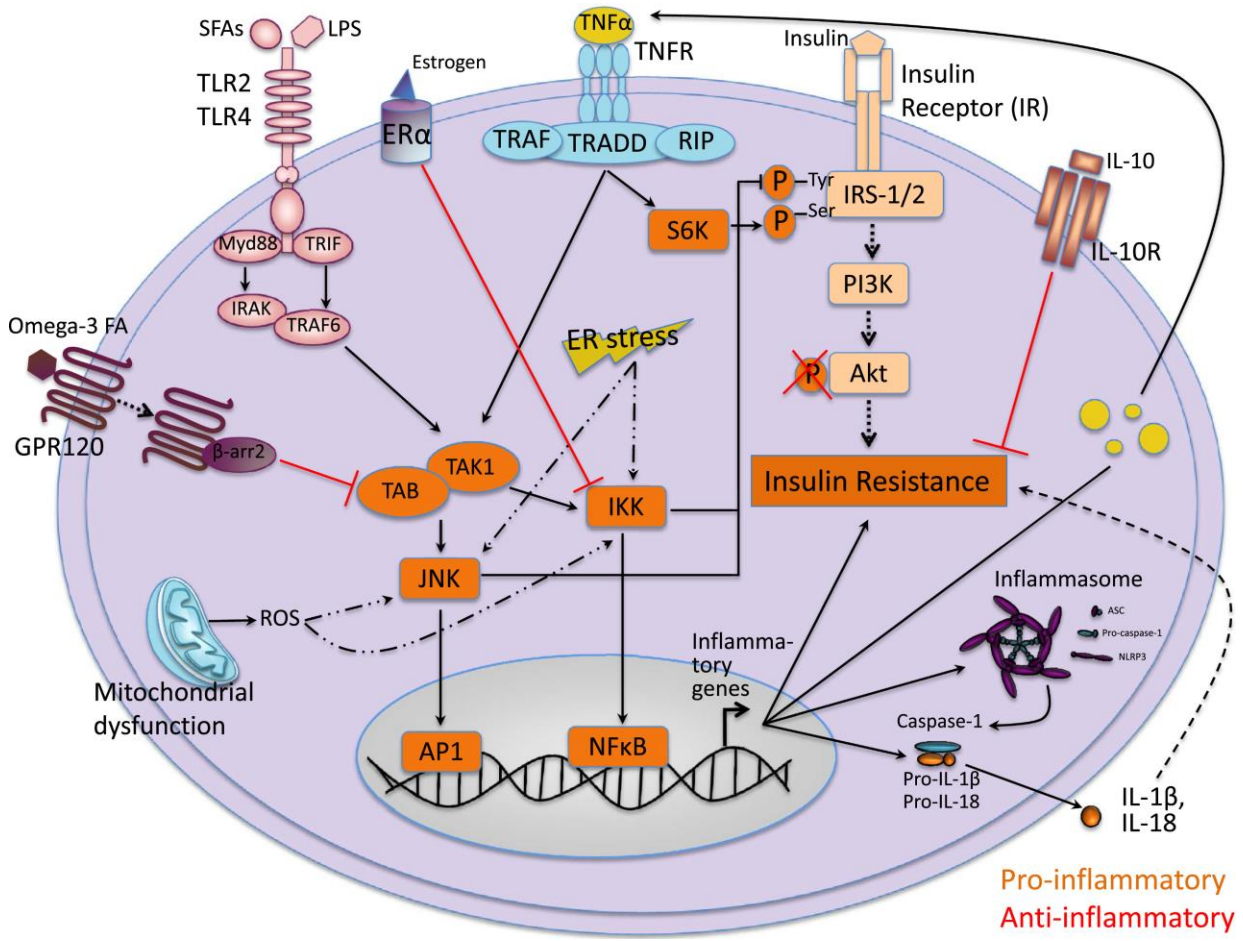

Biotransformation
Endocrine
Disruption
Oxidative
Stress
HF-FPW

Figure 1. Role of immune system in mediating metabolic phenotype. The liver contains Kupffer cells (resident hepatic ...



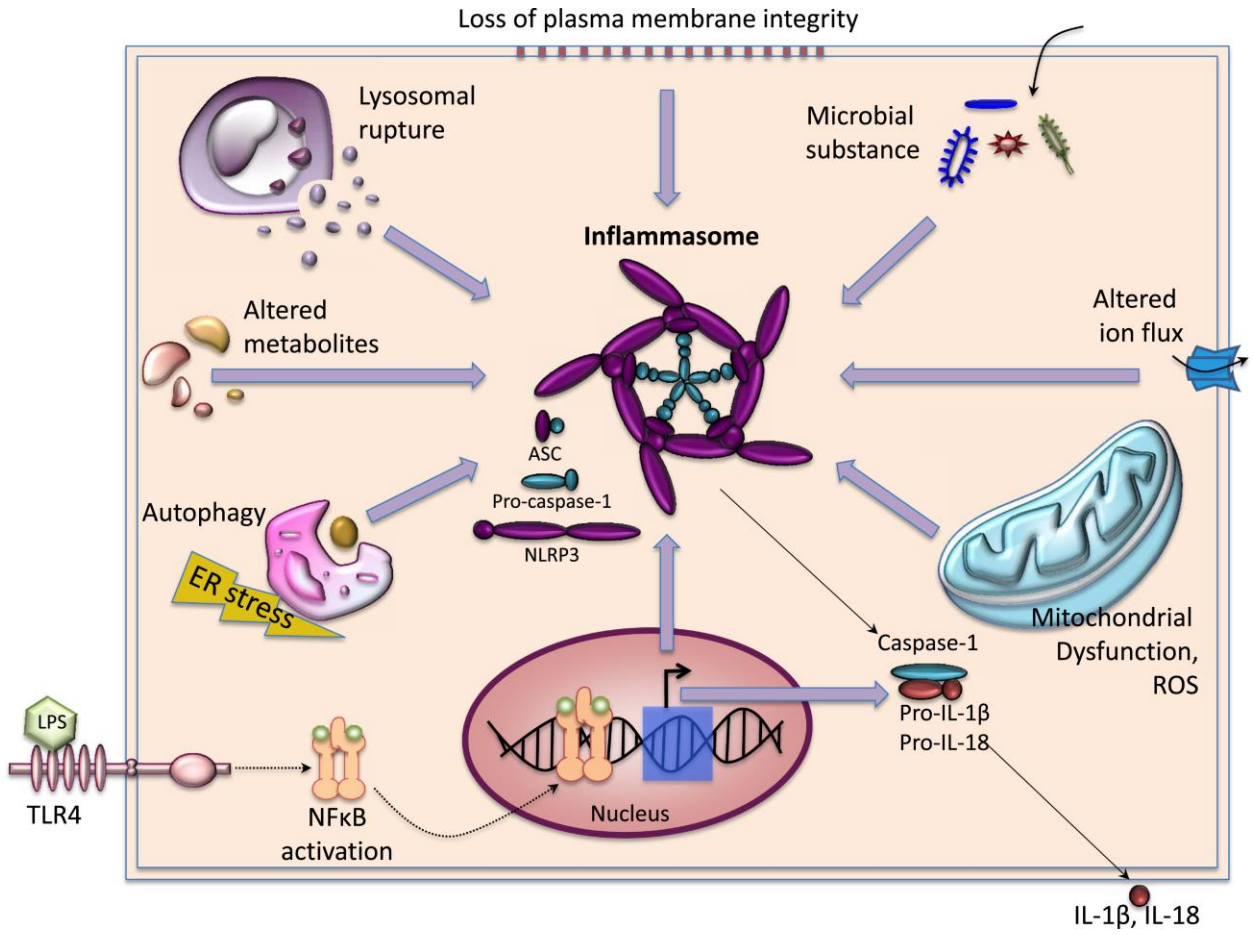
Endocrinology, Volume 159, Issue 1, January 2018, Pages 32–45, https://doi.org/10.1210/en.2017-00882

Figure 2. Inflammation-associated signaling pathways involved in insulin resistance. Proinflammatory signaling induces ...



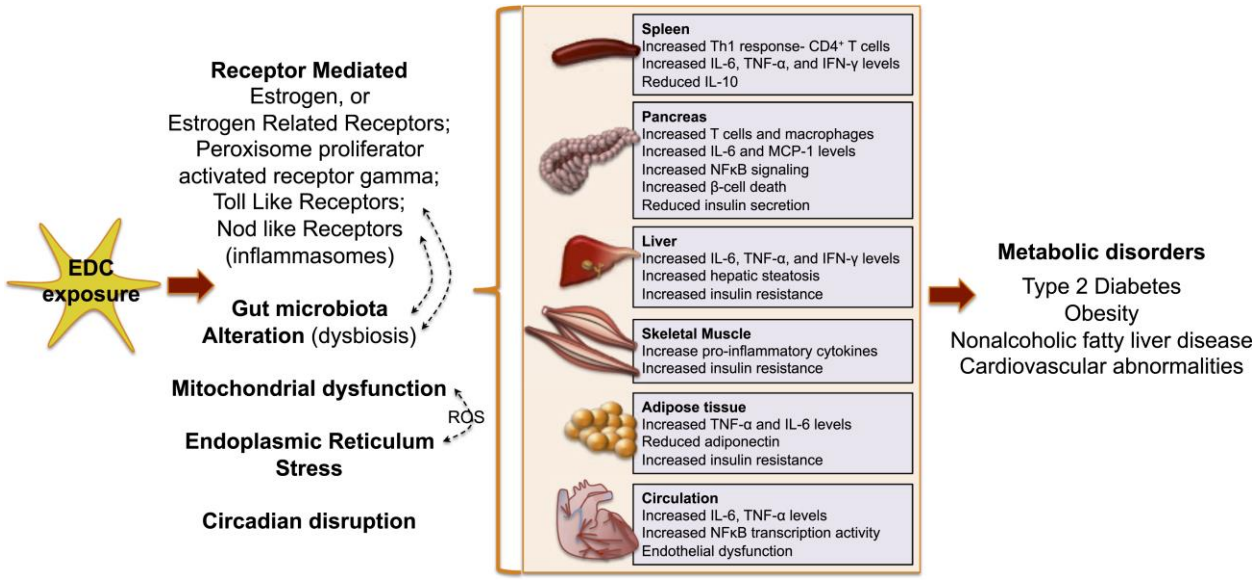
Endocrinology, Volume 159, Issue 1, January 2018, Pages 32–45, https://doi.org/10.1210/en.2017-00882

Figure 3. Activation signals of inflammasomes. Signal 1 is provided by ligands of other pattern recognition receptors ...



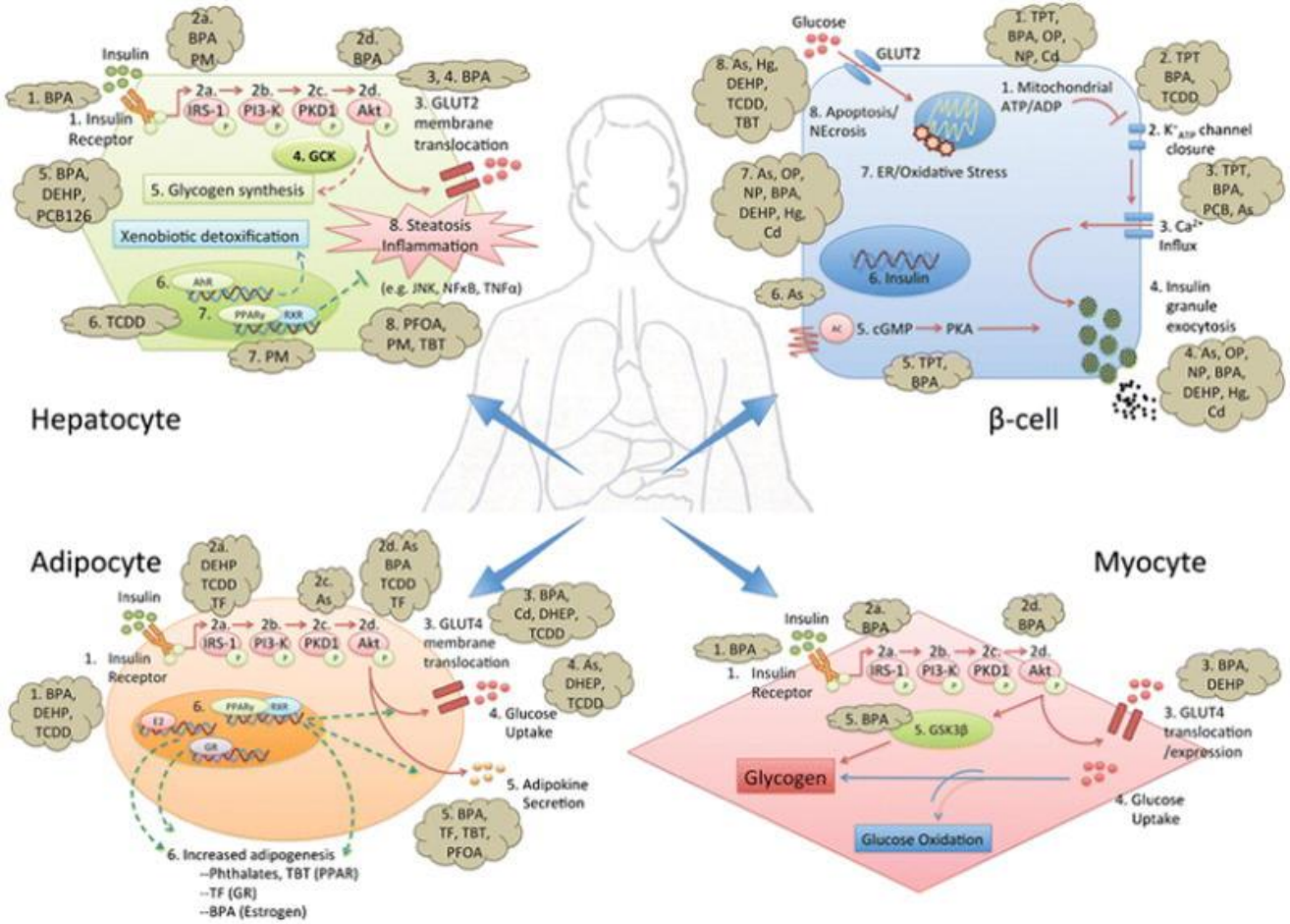
Endocrinology, Volume 159, Issue 1, January 2018, Pages 32–45, https://doi.org/10.1210/en.2017-00882

Figure 4. Possible routes of EDC action on the immune system contributing to metabolic disorders. By interacting with ...

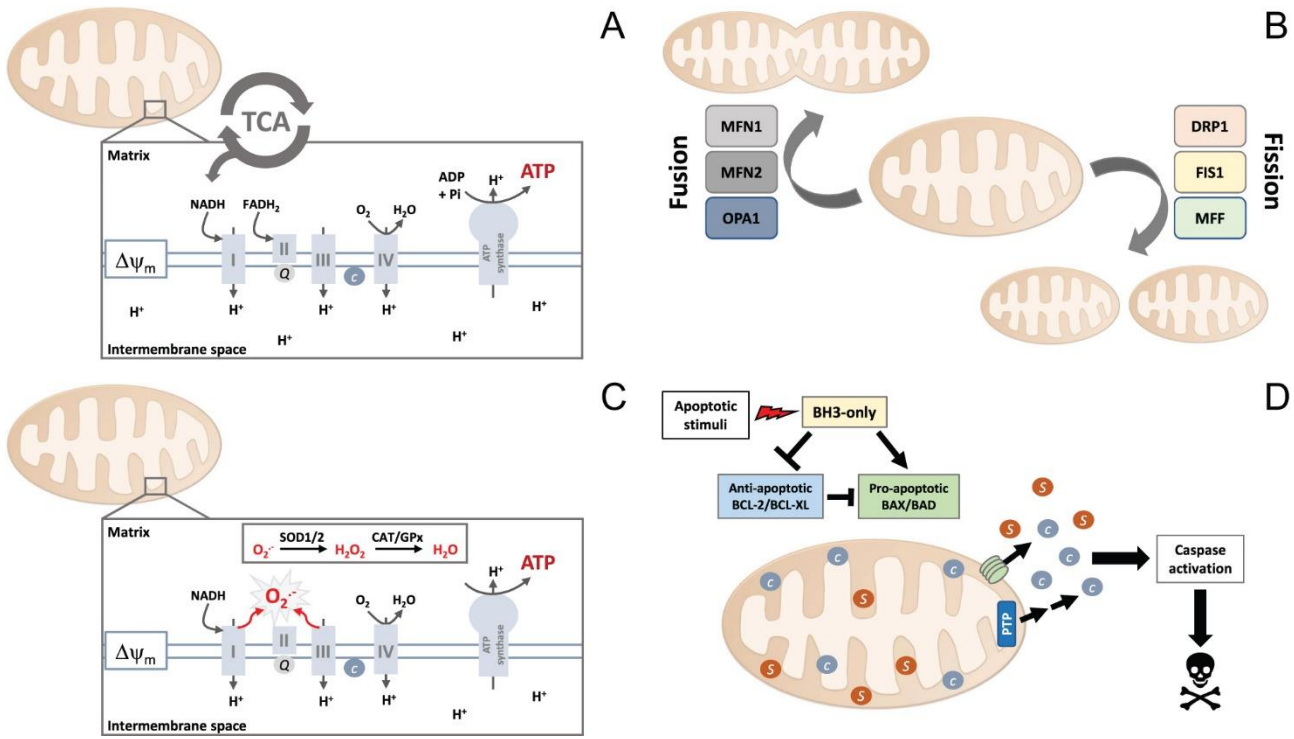


Endocrinology, Volume 159, Issue 1, January 2018, Pages 32–45, https://doi.org/10.1210/en.2017-00882

Overview of the molecular mechanisms by which metabolism disrupting chemicals MDCs disrupt energy homeostasis in the β-cell, myocyte, hepatocyte, and adipocyte.



Curr Environ Health Rep. 2017 June ; 4(2): 208–222.
doi:10.1007/s40572-017-0137-0.


A
TCA
Matrix
NADH
FADH2
ADP
+ Pi
ATP
O2
H2O
ΔΨm
I
II
Q
III
IV
c
ATP synthase
H+
Intermembrane space
B
Fusion
MFN1
MFN2
OPA1
Fission
DRP1
FIS1
MFF
C
Matrix
SOD1/2
CAT/GPx
O2·-
H2O2
H2O
NADH
ATP
ΔΨm
Intermembrane space
D
Apoptotic stimuli
BH3-only
Anti-apoptotic BCL-2/BCL-XL
Pro-apoptotic BAX/BAD
PTP
Caspase activation

- BPA is a component of polycarbonate plastics often used in food and beverage containers as well as numerous other product
- Trough the increase of oxidative stress, BPA induces inflammation in liver cells resulting in a development and progression of several liver diseases such as non-alcoholic fatty liver disease (NAFLD)7. In vitro studies also indicated that BPA increased insulin resistance and inflammation in HepG2 cells confirming a direct effect of BPA on liver and adipose tissue

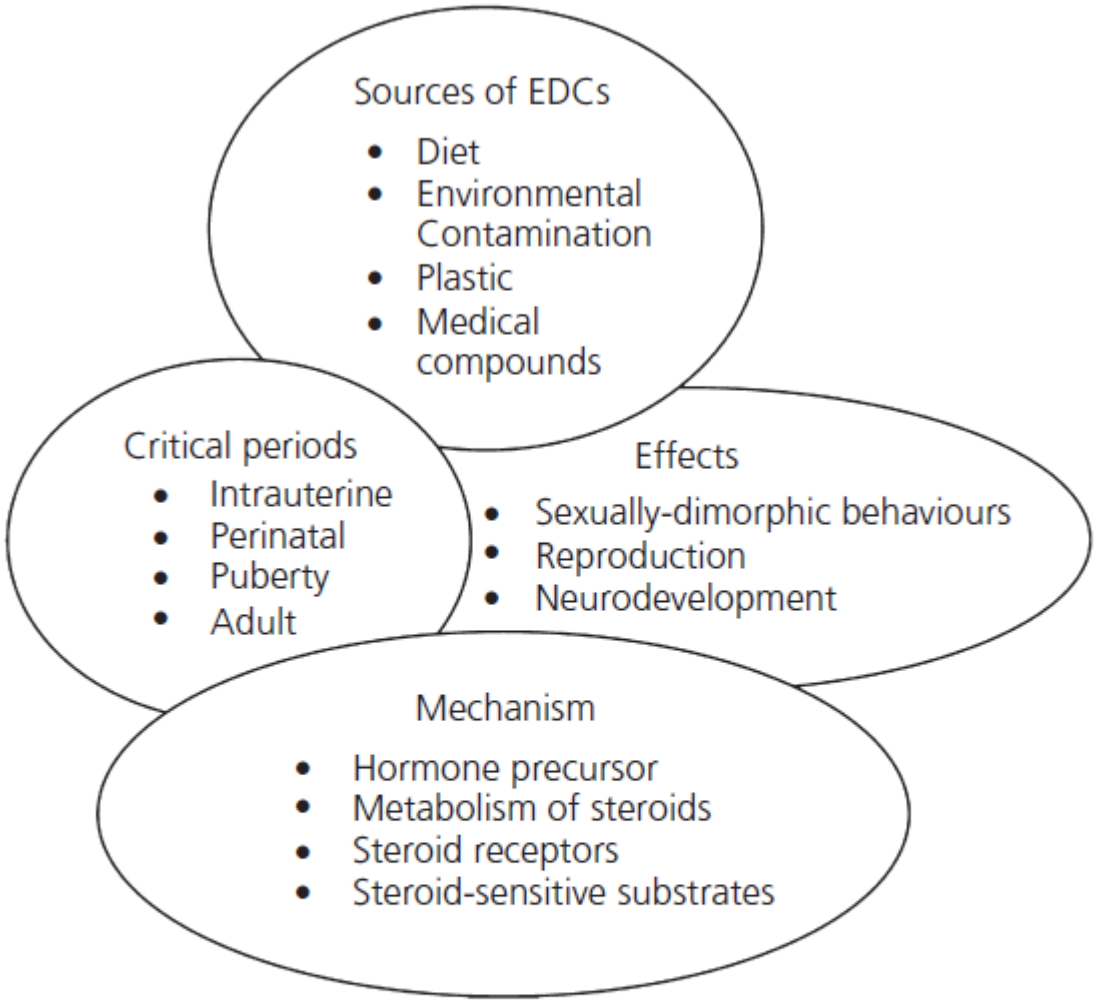
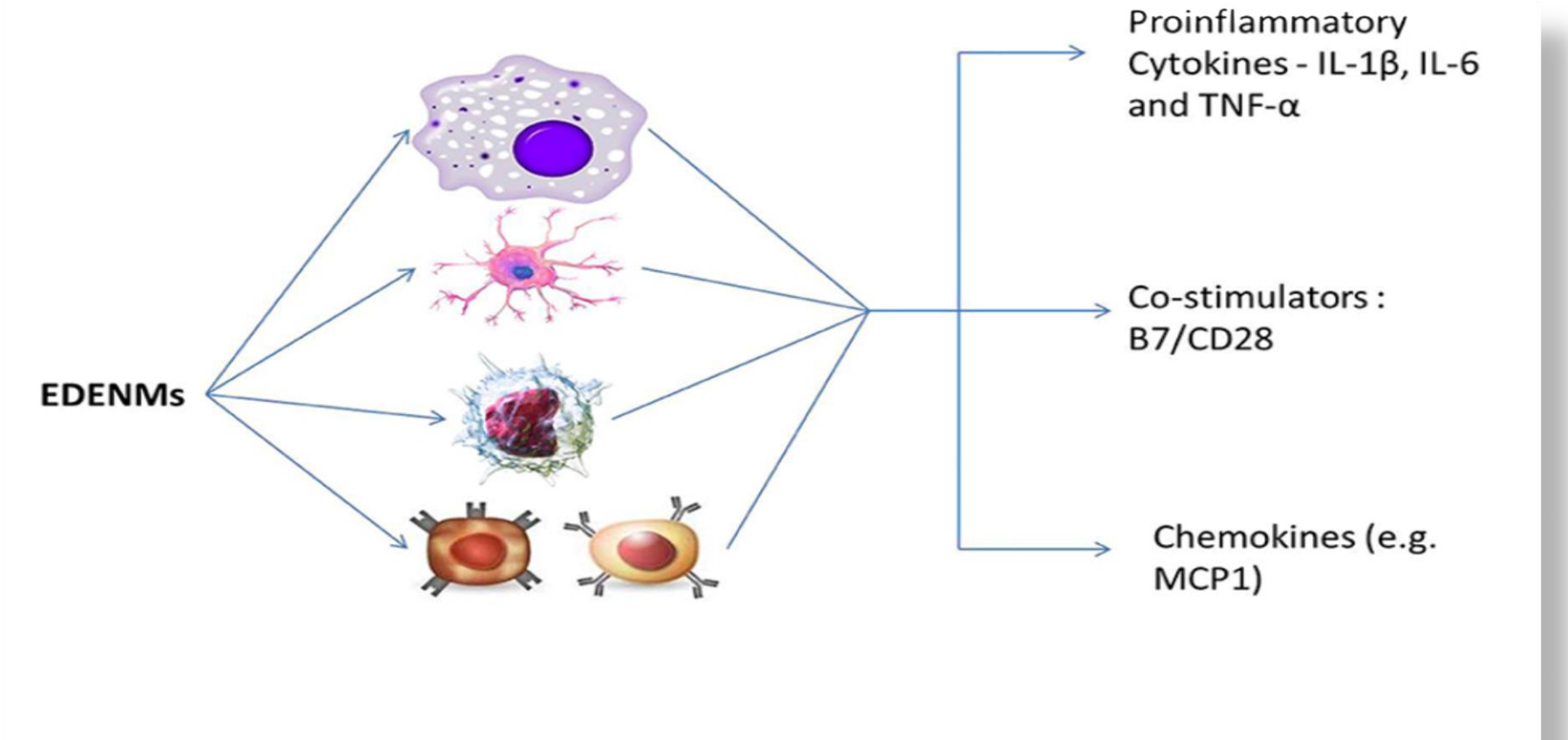


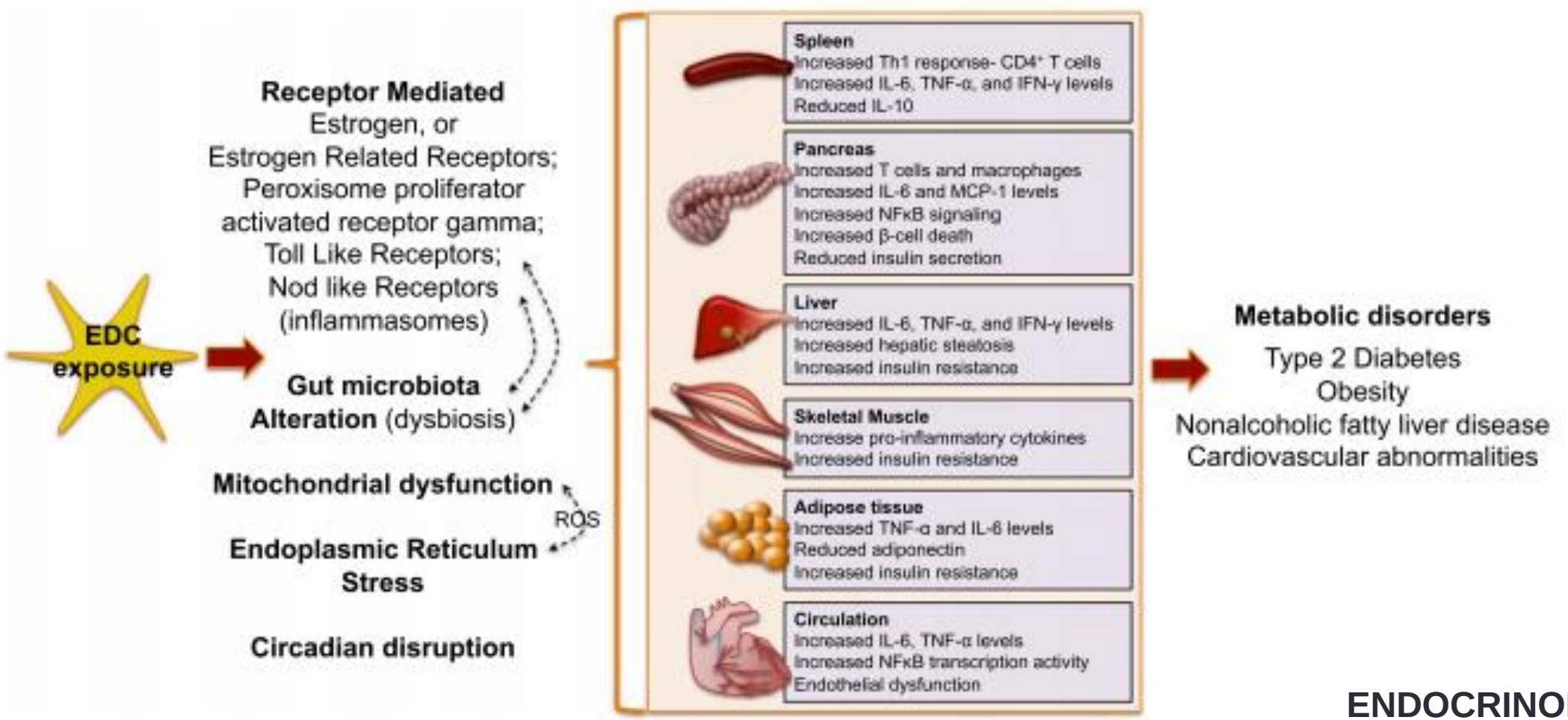
Fig. 1. A schematic representation of varied sources of endocrine disrupting chemicals (EDCs) and how they may influence sexually-dimorphic, repro-

Role of EDe Pathogenesis of Type 2 Diabetes Mellitus



Front. Endoc
| https://doi.c

Possible routes of EDC action on the immune system contributing to metabolic disorders



ENDOCRINOLOGY 2018