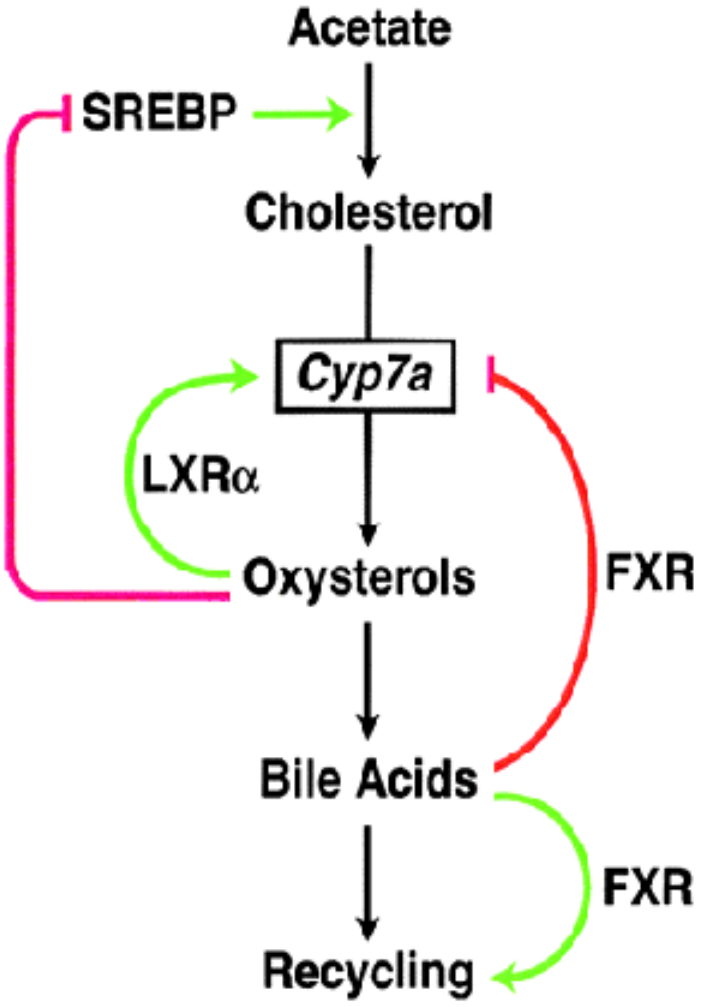
VITAMINS

VLA 23.4.2019

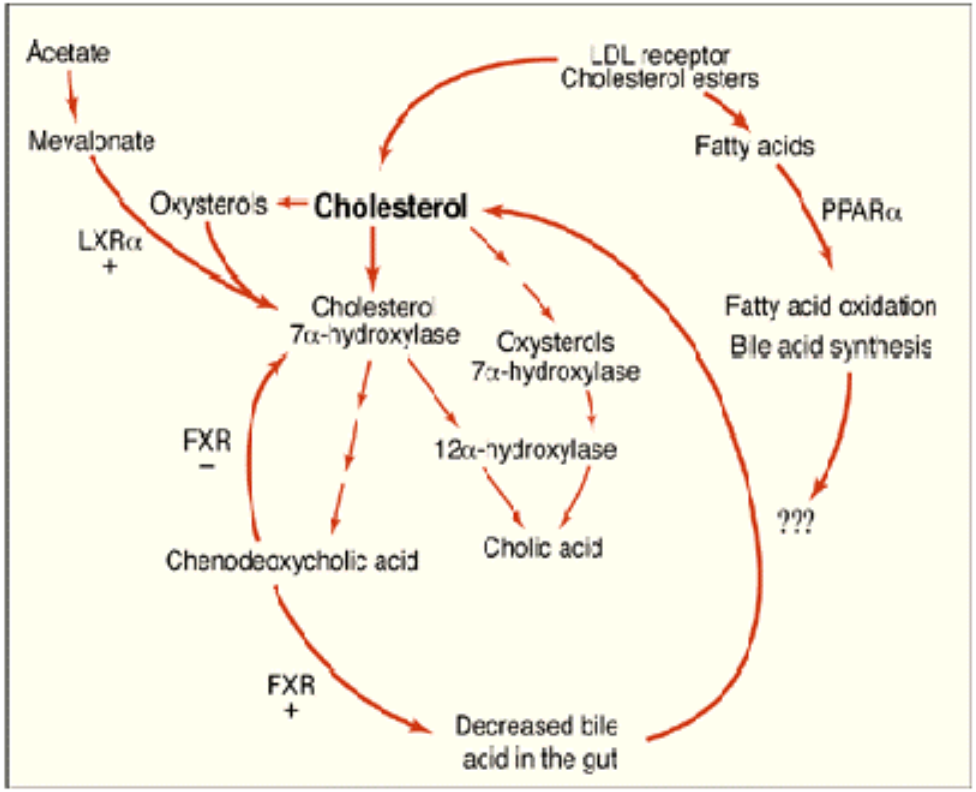
Regulatory Loops in Cholesterol Metabolism



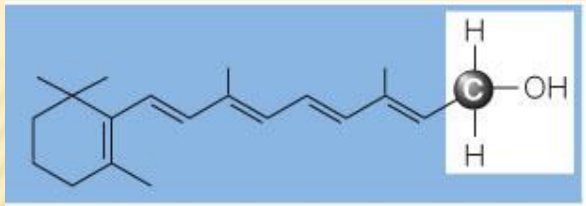
Black arrows indicate metabolic pathways involving cholesterol and bile acids.
The cholesterol 7α-hydroxylase target gene (Cyp7a) is boxed. Green arrows indicate positive regulation. Red brakes indicate negative regulation.

Bilious Biochemical Pathways

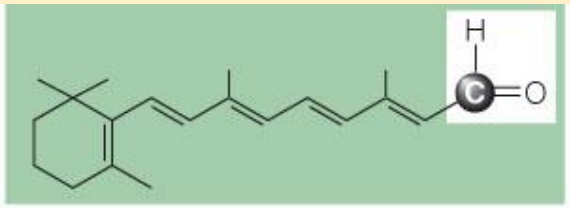
A number of nuclear receptors are involved in the biochemical pathways that regulate cholesterol homeostasis.



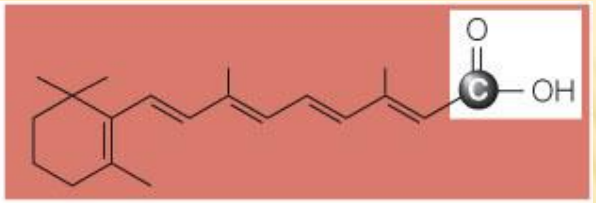
For example, FXR binds bile acids that are important in the disposal of cholesterol. When bound to bile acids, FXR switches off (-) production of cholesterol 7a-hydroxylase (which is the rate-limiting step in bile acid synthesis) and switches on (+) synthesis of bile acid transporter proteins, leading to a decrease in bile acid in the gut and an increase in cholesterol levels in the blood. Another nuclear receptor, LXRa, which binds oxysterols, induces the synthesis of bile acids by up-regulating (+) cholesterol 7a hydroxylase. In addition to the classical pathway of bile acid synthesis, there is an alternative pathway in which oxysterol 7a-hydroxylase is the rate-limiting enzyme.



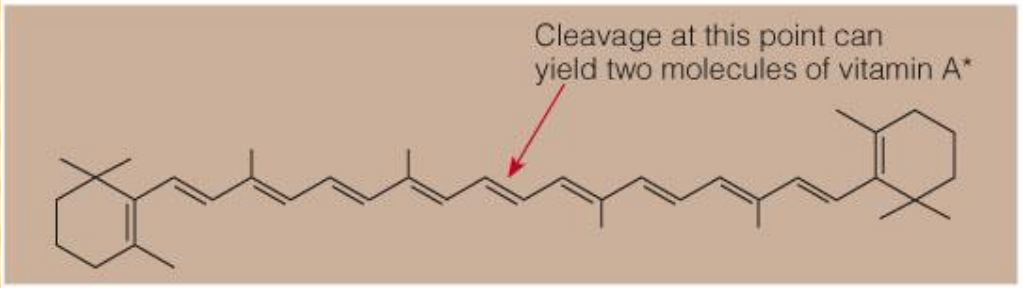
Retinol, the alcohol form



Retinal, the aldehyde form

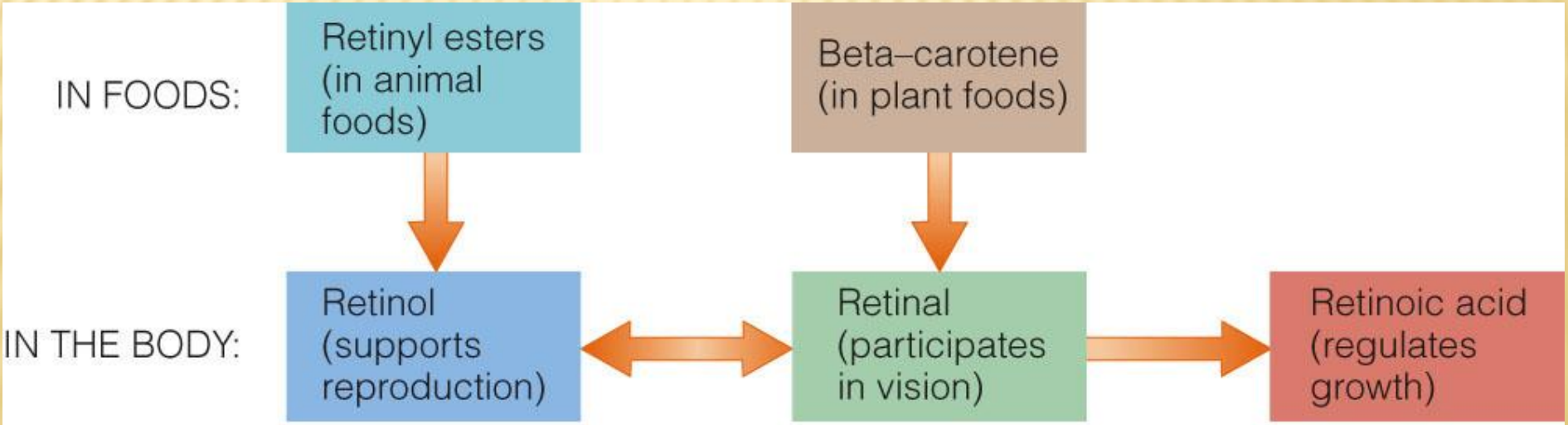


Retinoic acid, the acid form



Beta-carotene, a precursor

*Sometimes cleavage occurs at other points as well, so that one molecule of beta-carotene may yield only one molecule of vitamin A. Furthermore, not all beta-carotene is converted to vitamin A, and absorption of beta-carotene is not as efficient as that of vitamin A. For these reasons, 12 µg of beta-carotene are equivalent to 1 µg of vitamin A. Conversion of other carotenoids to vitamin A is even less efficient.



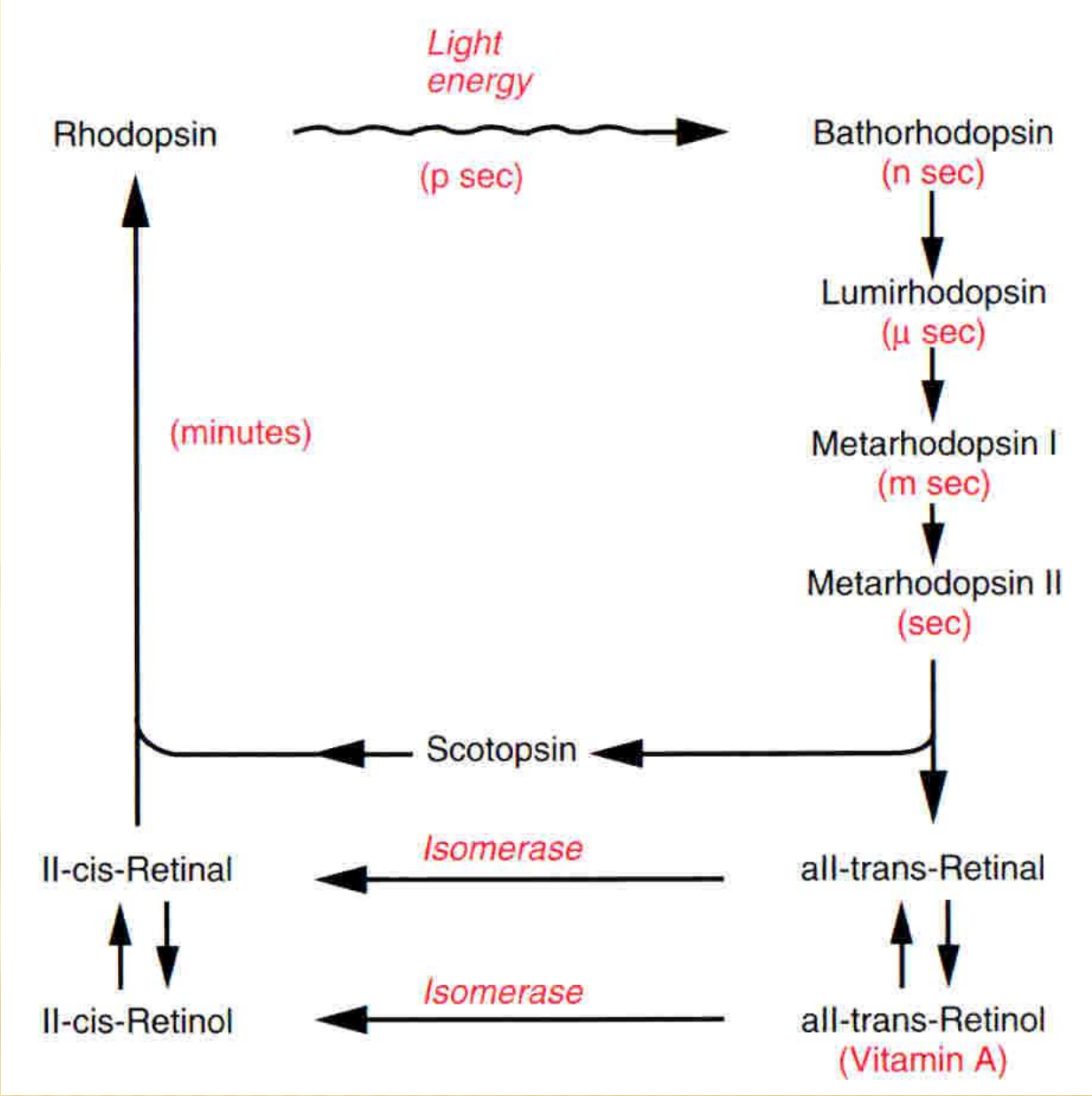
VITAMIN A

- Since the identification of fat soluble A a century ago, retinoids (vitamin A and its natural and synthetic analogs) have been the most extensively studied of the fat soluble vitamins.
- This research has identified essential roles for retinoids in many different aspects of mammalian physiology including embryonic development, adult growth and development, maintenance of immunity, maintenance of epithelial barriers and vision.

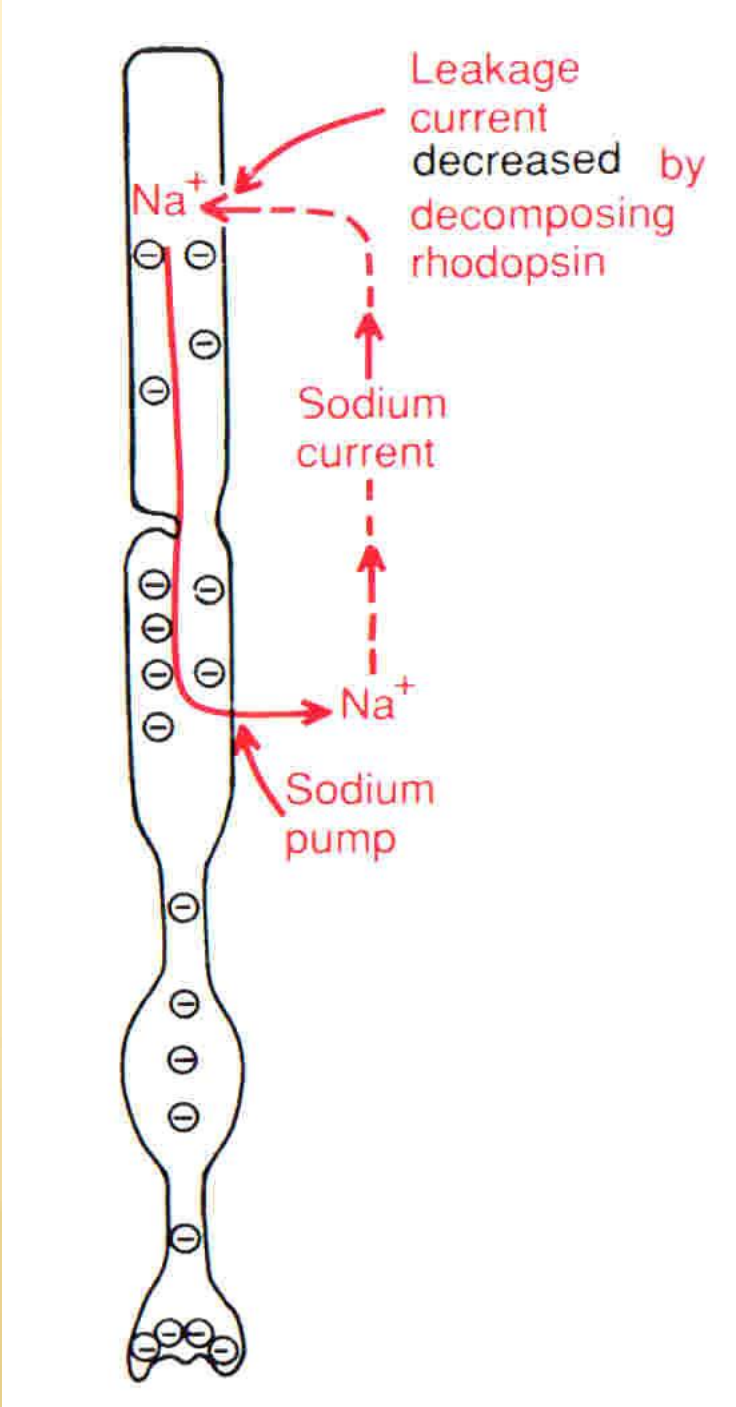
VITAMIN A AND BETA-CAROTENE

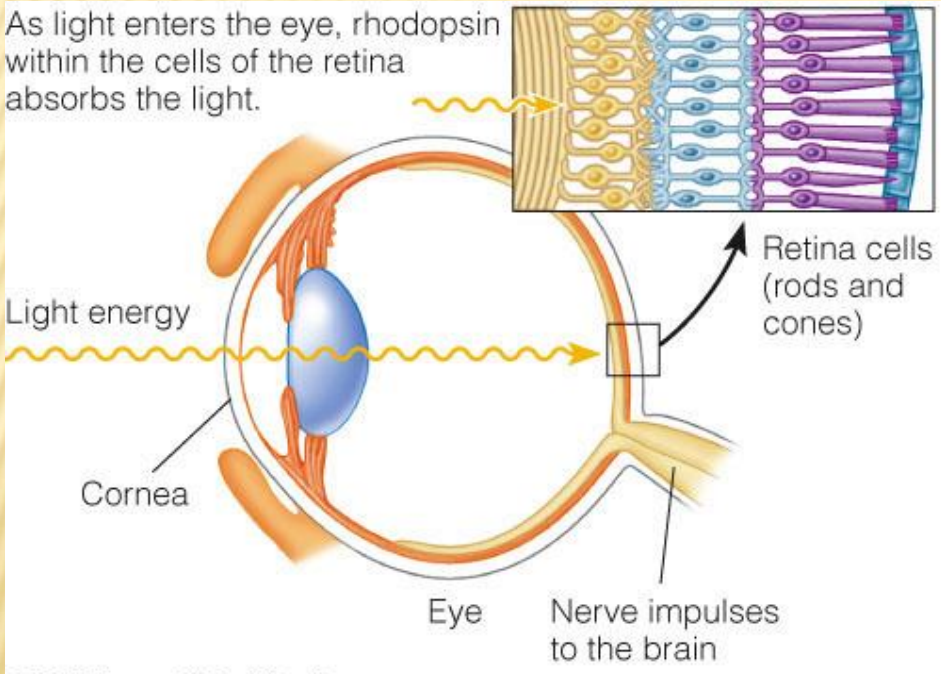
- Roles in the Body
  - Vitamin A in Vision
    - Helps to maintain the cornea
    - Conversion of light energy into nerve impulses at the retina
    - Rhodopsin is a light-sensitive pigment of the retina that contains a protein called opsin.

Rhodopsin retinal visual cycle

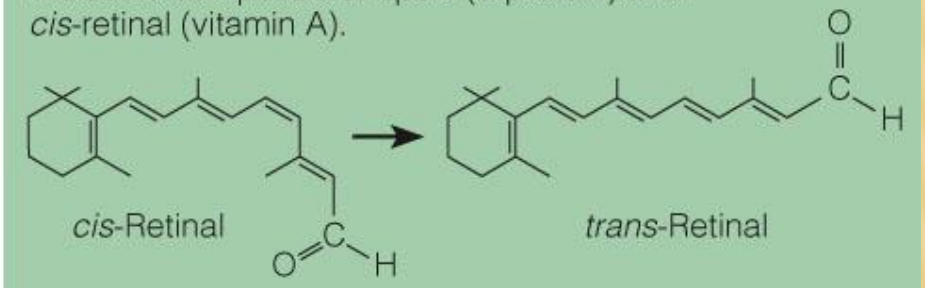


Hyperpolarization receptor potential formation due to decomposition of rhodopsin





The cells of the retina contain rhodopsin, a molecule composed of opsin (a protein) and *cis*-retinal (vitamin A).



As rhodopsin absorbs light, retinal changes from *cis* to *trans*, which triggers a nerve impulse that carries visual information to the brain.

VITAMIN A AND BETA-CAROTENE

- Roles in the Body
  - Vitamin A in Protein Synthesis and Cell Differentiation
    - Through cell differentiation, vitamin A allows cells to perform specific functions.
    - Epithelial cells
      - Epithelial tissues on the outside of the body form the skin.
      - Epithelial tissues on the inside of the body form the mucous membranes.

VITAMIN A AND BETA-CAROTENE

- Roles in the Body
  - Vitamin A in Reproduction and Growth
    - Sperm development in men
    - Normal fetal development in women
    - Growth in children
    - Remodeling of the bone involves osteclasts, osteoblasts, and lysosomes.
      - Osteoclasts are cells that destroy bone growth.
      - Osteoblasts are cells that build bones.
      - Lysosomes are sacs of degradative enzymes that destroy bones.

VITAMIN A AND BETA-CAROTENE

- Roles in the Body
  - Beta-Carotene as an Antioxidant
    - Beta-carotene helps protect the body from diseases, including cancer.

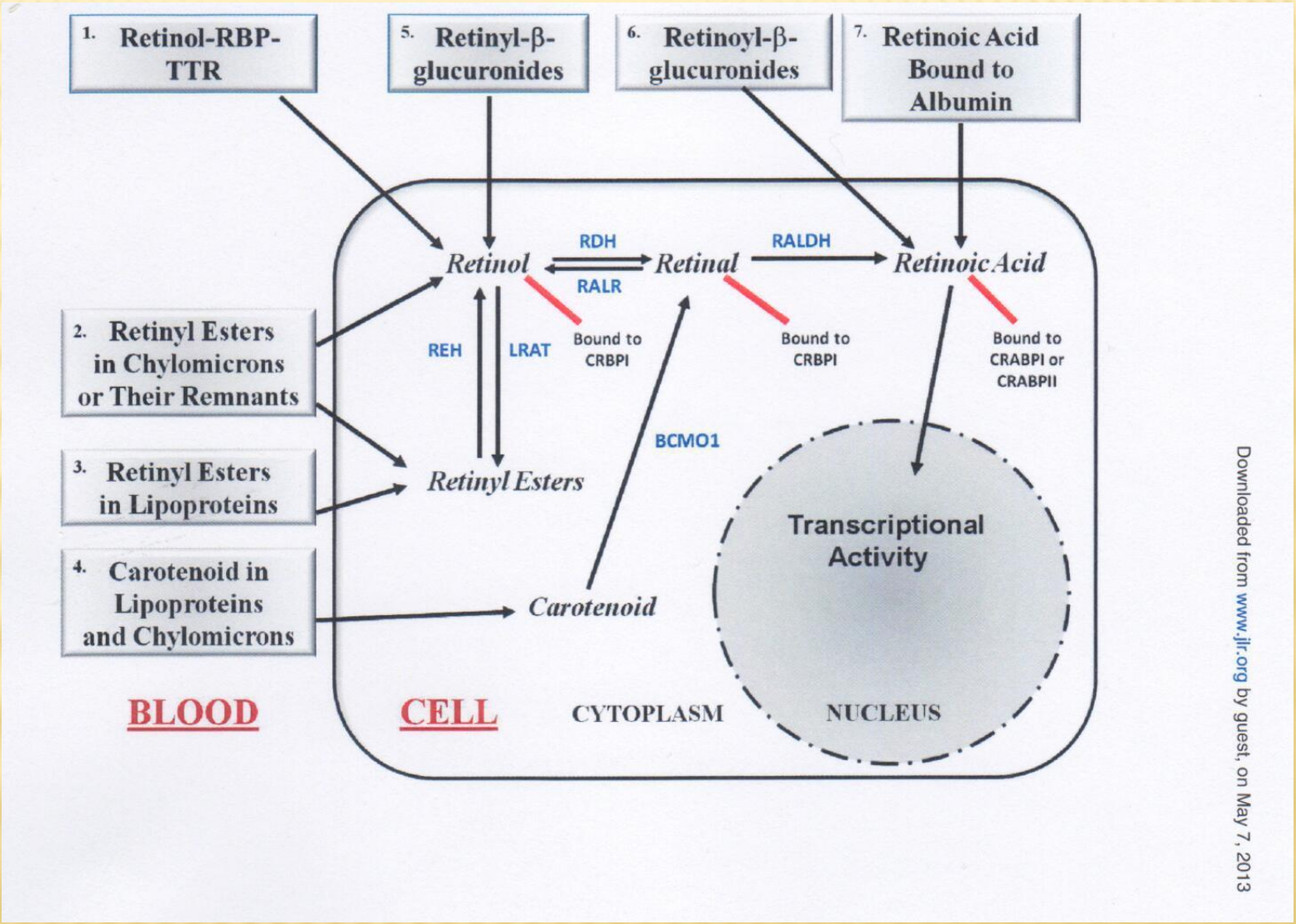
VITAMIN AND ITS METABOLITS

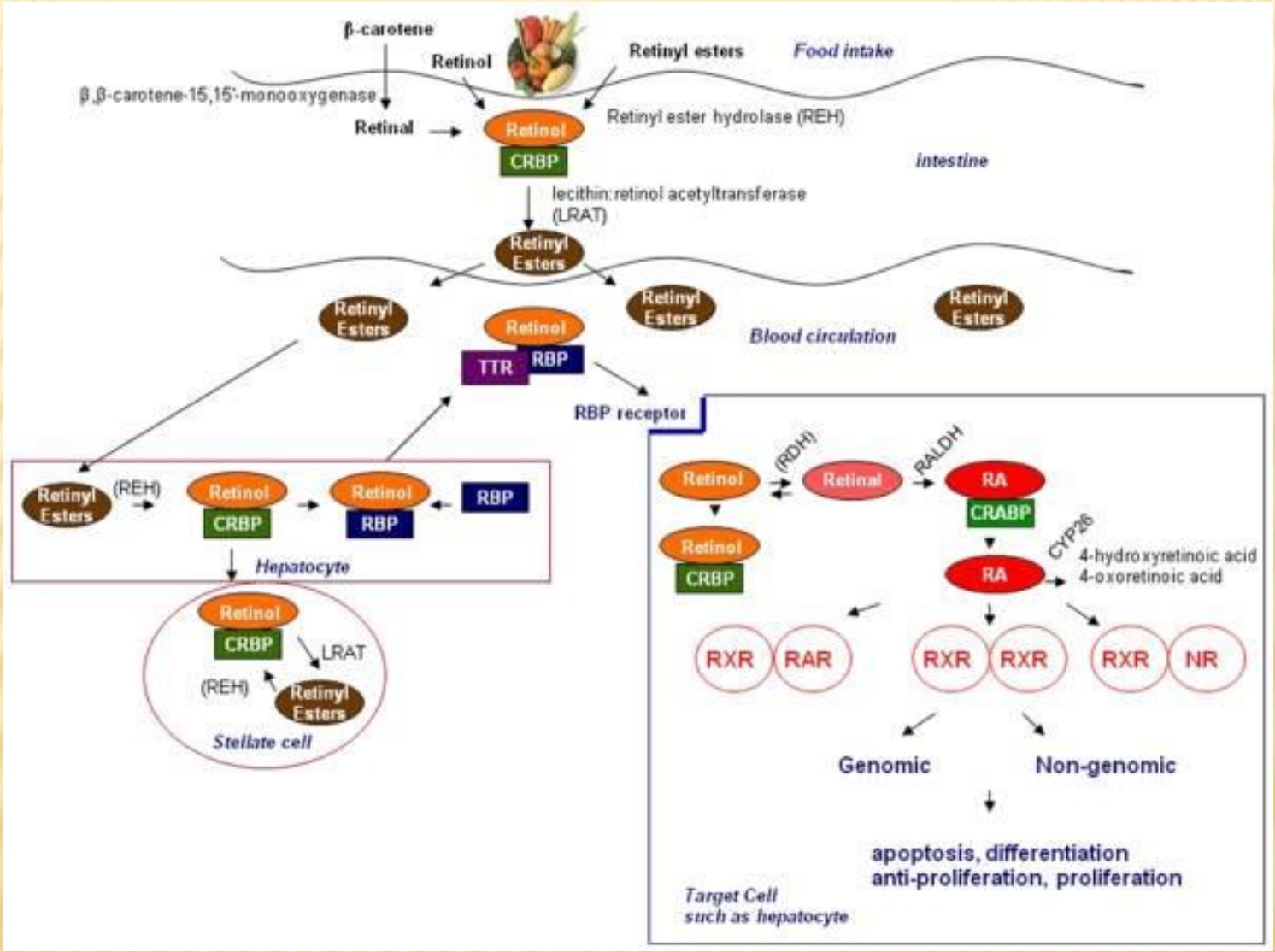
All-*trans*-retinoic acid (atRA) is a highly potent derivative of vitamin A that is required for virtually all essential physiological processes and functions because of its involvement in transcriptional regulation of over 530 different genes .

atRA is necessary for differentiation and development of fetal and adult tissues, stem cell differentiation, and apoptosis; for support of reproductive functions , immune response, and regulation of energy homeostasis

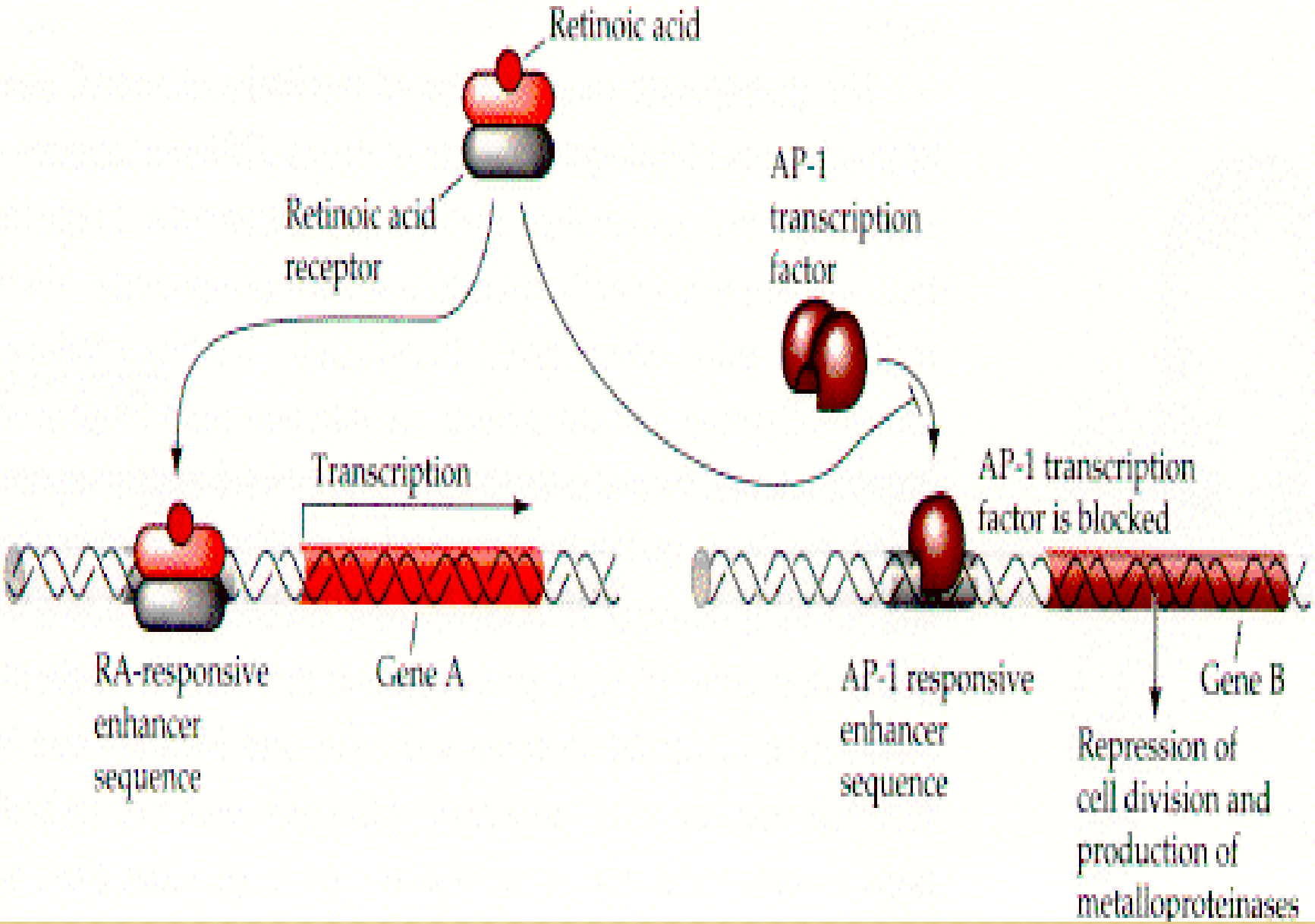
atRA exerts its actions by serving as an activating ligand of nuclear atRA receptors (RAR α, β, and γ) and peroxisome proliferator-activated receptors (PPAR β/δ), which form heterodimers with retinoid X receptors.

The concentration of atRA during embryonic development is tightly controlled in a spatial and temporal manner, and in adult tissues, it is maintained within a very narrow range that is specific for each given tissue. If the control mechanisms fail and the concentration of atRA exceeds or falls below the optimal range, tissues and cells undergo pathophysiological changes that in most severe cases can lead to disease. Thus, the maintenance of optimal atRA levels is essential for life.





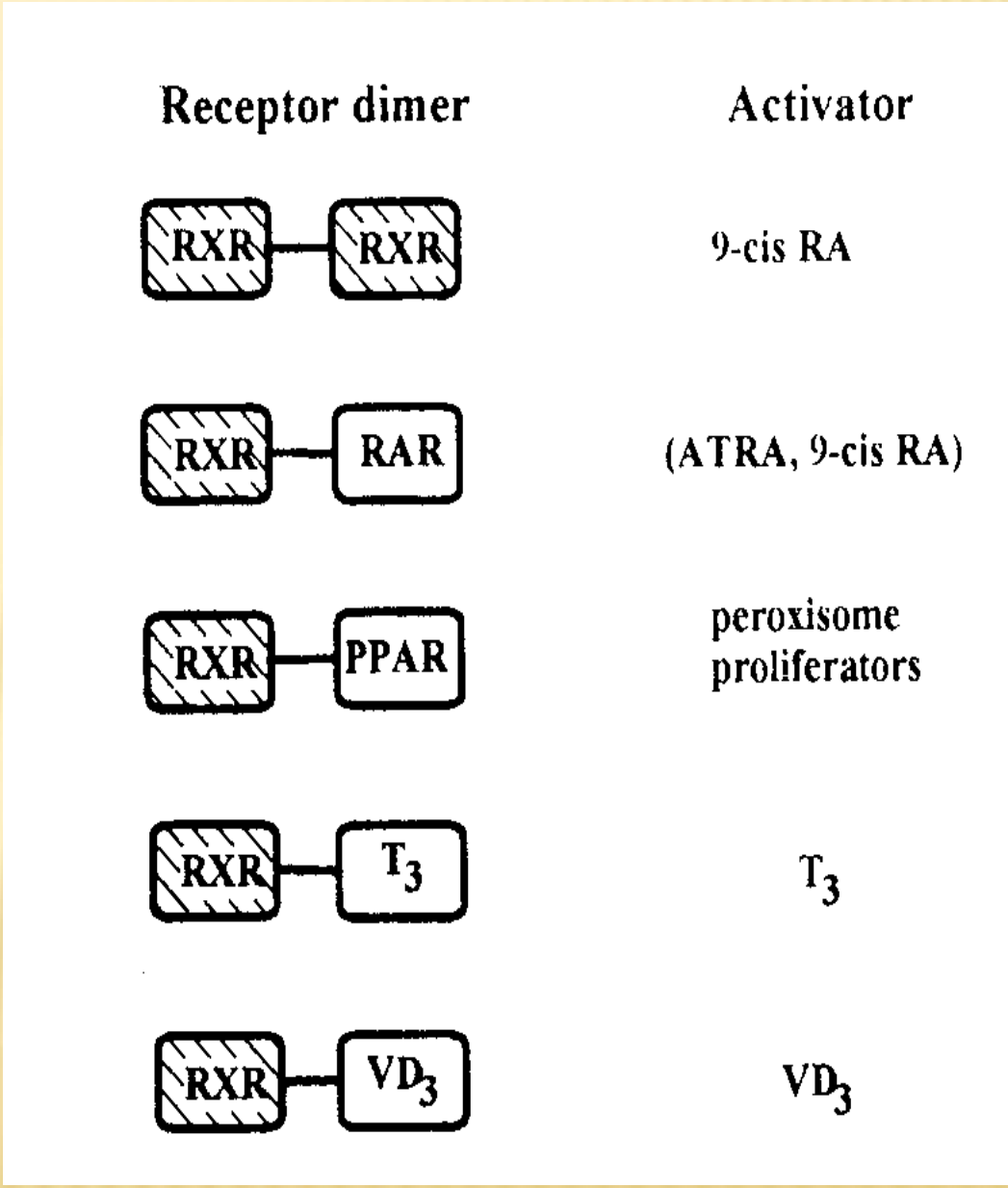
CRBP = cellular retinol binding protein


Retinoic acid
Retinoic acid receptor
AP-1 transcription factor
Transcription
AP-1 transcription factor is blocked
RA-responsive enhancer sequence
Gene A
AP-1 responsive enhancer sequence
Gene B
Repression of cell division and production of metalloproteinases

LIGANDS FOR RA

- RA IS FUNCTIONING BY:
- RAR (izoforms α, β and γ)
- RXR (izoforms α, β and γ)
- RAR:RXR heterodimers

RXR and its partners in nuclear receptor function



VITAMIN A AND BETA-CAROTENE

- Vitamin A Deficiency
  - Blindness
    - Xerophthalmia
      - Xerosis is the first stage where the cornea becomes dry and hard.
      - Keratomalacia is the softening of the cornea.
  - Keratinization
    - Epithelial cells secrete a protein called keratin—the hard, inflexible protein of hair and nails.
    - Changes in epithelial cells results in keratinization, rough, dry and scaly skin.
  - Deficiency disease is called hypovitaminosis A

XEROPHTHALMIA

VITAMIN A AND BETA-CAROTENE

- Vitamin A Deficiency
  - Because vitamin A is stored in the body, it would take a year or more to develop a deficiency in the presence of inadequate intake.
  - Infectious Diseases
    - Impaired immunity correlates with vitamin A deficiency in children.
    - The goals of worldwide health organizations include vitamin A supplementation.
  - Night Blindness
    - First detectable sign of vitamin A deficiency
    - Inability to see in dim light or inability to recover sight after a flash of bright light

VITAMIN A AND BETA-CAROTENE

- Vitamin A deficiency is a major health problem in the world.
- Toxicity is often associated with abuse of supplements.
- Plant foods provide carotenoids, such as beta-carotene, some of which have vitamin A activity.
- Animal foods provide compounds that are easily converted to retinol.
- Retinol binding protein (RBP) allows vitamin A to be transported throughout the body.

VITAMIN A AND BETA-CAROTENE

- Vitamin A Toxicity
  - Can occur with concentrated amounts of the preformed vitamin A from animal foods, fortified foods, or supplements.
  - Consuming excessive amounts of beta-carotene from supplements can be harmful.
  - Bone Defects
    - Increased activity of osteoclasts causes weakened bones and contributes to osteoporosis and fractures.

VITAMIN A AND BETA-CAROTENE

- Vitamin A Toxicity
  - Birth Defects
    - **Teratogenic** risk is possible, resulting in abnormal fetal development and birth defects.
    - Vitamin A supplements are not recommended the first trimester of pregnancy.
  - Not for Acne
    - Massive doses for teens are not effective on acne.
    - Accutane is made from vitamin A, but is chemically different. It is toxic during growth and can cause birth defects.
    - Retin-A fights acne, the wrinkles of aging, and other skin disorders.

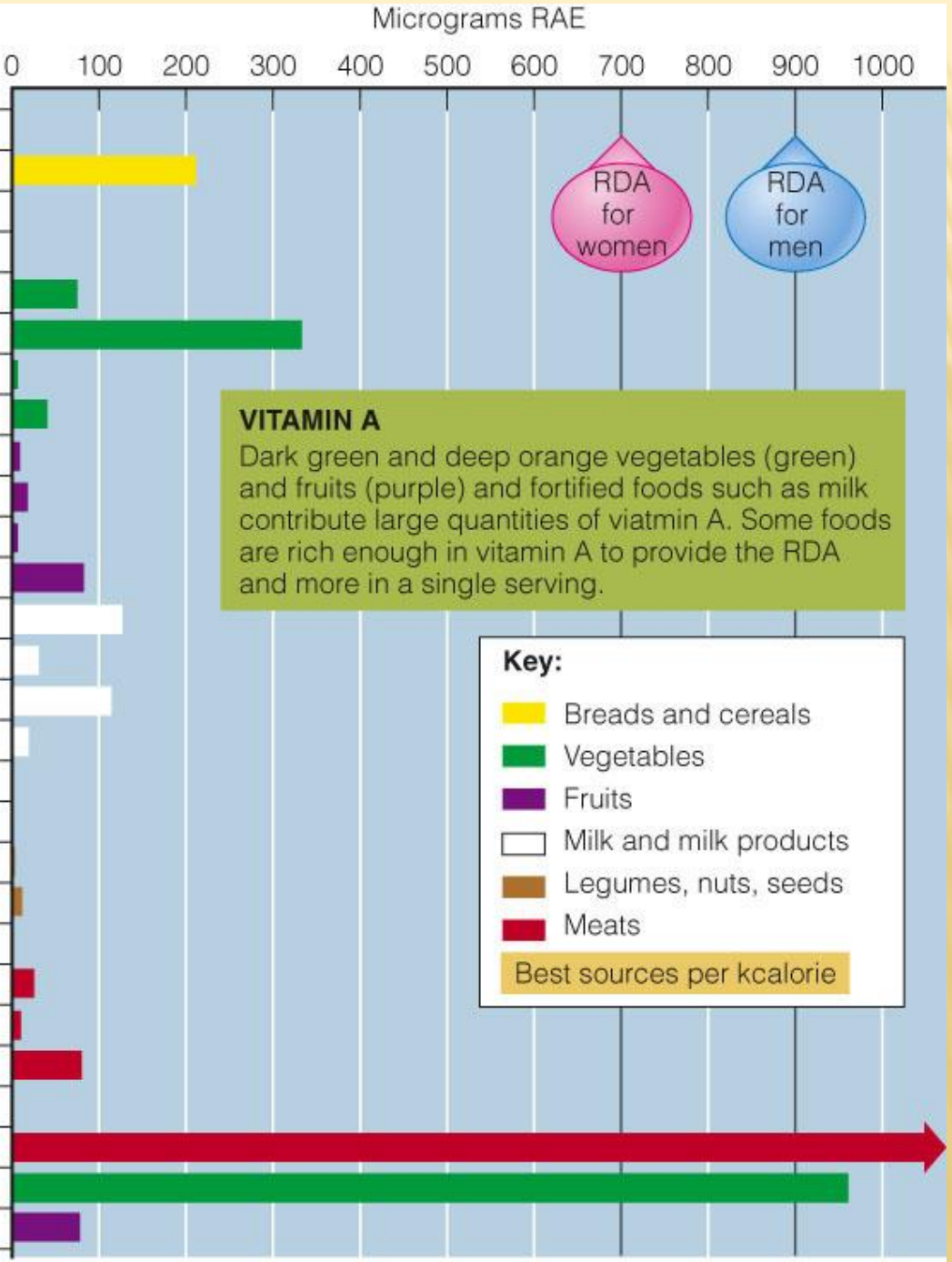
VITAMIN A AND BETA-CAROTENE

- Vitamin A Toxicity
  - Toxicity is called **hypervitaminosis A**
  - Chronic toxicity symptoms include liver abnormalities.
  - Acute toxicity symptoms include blurred vision, nausea, vomiting, vertigo, headaches, and pressure in the skull.
  - Upper level for adults: 3000 µg/day

VITAMIN A AND BETA-CAROTENE

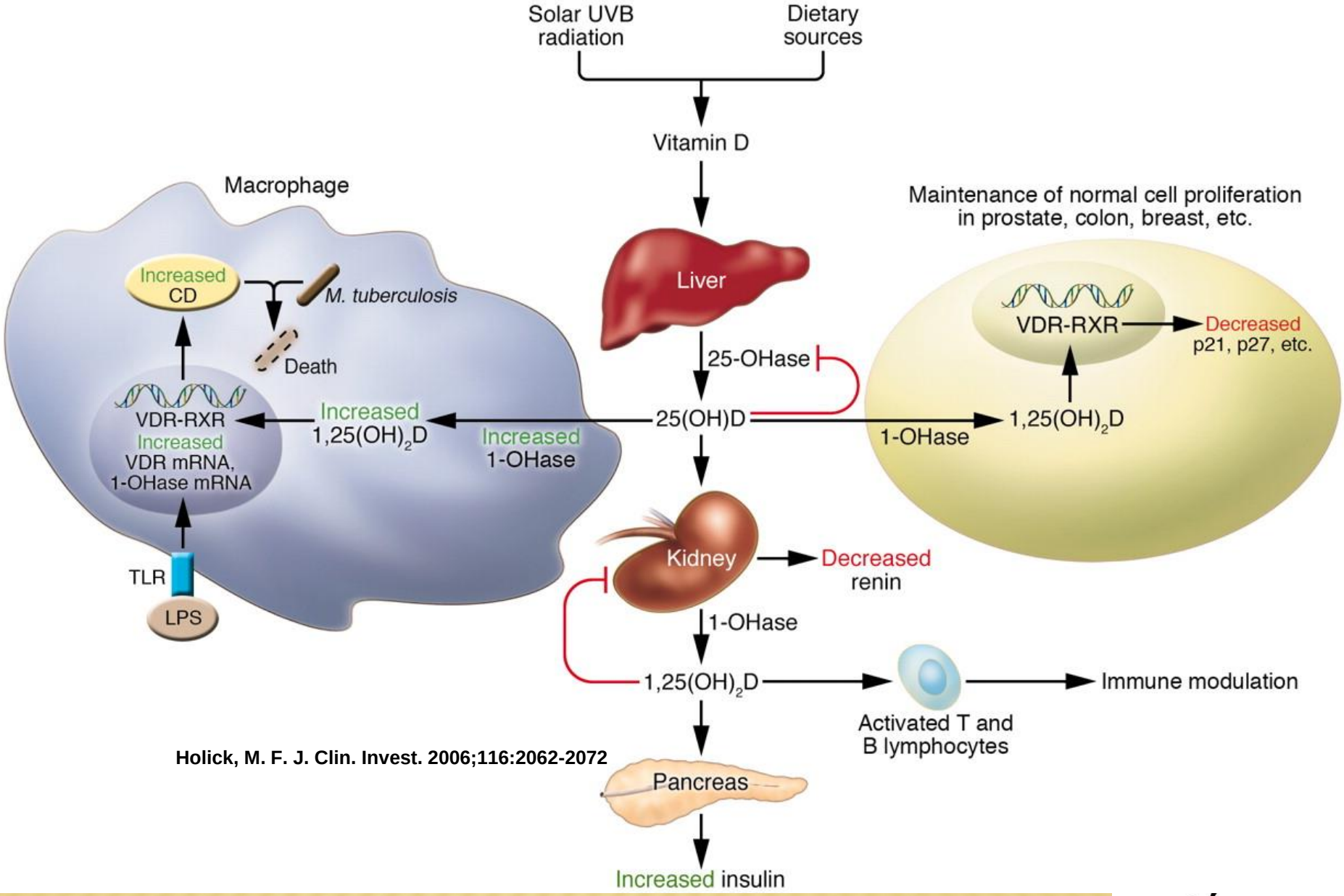
- Vitamin A in Foods
  - Retinol is found in fortified milk, cheese, cream, butter, fortified margarine, and eggs.
  - Beta-carotene
    - Spinach and other dark green leafy vegetables (chlorophyll pigment masks the color)
    - Deep orange fruits like apricots and cantaloupe
    - Deep orange vegetables like squash, carrots, sweet potatoes, and pumpkin
    - White foods are typically low in beta-carotene.
  - Liver is rich in vitamin A.

Food	Serving size (kcalories)
Bread, whole wheat	1 oz slice (70 kcal)
Cornflakes, fortified	1 oz (110 kcal)
Spaghetti pasta	½ c cooked (99 kcal)
Tortilla, flour	1 10"-round (234 kcal)
Broccoli	½ c cooked (22 kcal)
Carrots	½ c shredded raw (24 kcal)
Potato	1 medium baked w/skin (133 kcal)
Tomato juice	¾ c (31 kcal)
Banana	1 medium raw (109 kcal)
Orange	1 medium raw (62 kcal)
Strawberries	½ c fresh (22 kcal)
Watermelon	1 slice (92 kcal)
Milk, fortified	1 c reduced-fat 2% (121 kcal)
Yogurt, plain	1 c low-fat (155 kcal)
Cheddar cheese	1½ oz (171 kcal)
Cottage cheese	½ c low-fat 2% (101 kcal)
Pinto beans	½ c cooked (117 kcal)
Peanut butter	2 tbs (188 kcal)
Sunflower seeds	1 oz dry (165 kcal)
Tofu (soybean curd)	½ c (76 kcal)
Ground beef, lean	3 oz broiled (244 kcal)
Chicken breast	3 oz roasted (140 kcal)
Tuna, canned in water	3 oz (99 kcal)
Egg	1 hard cooked (78 kcal)
Excellent, and sometimes unusual, sources:	
Beef liver	3 oz fried (184 kcal)
Sweet potatoes	½ c cooked (116 kcal)
Mango	1 (135 kcal)



VITAMIN D

- Vitamin D is a nonessential nutrient that acts like a hormone in the body.
- The body can make vitamin D with help from sunlight.



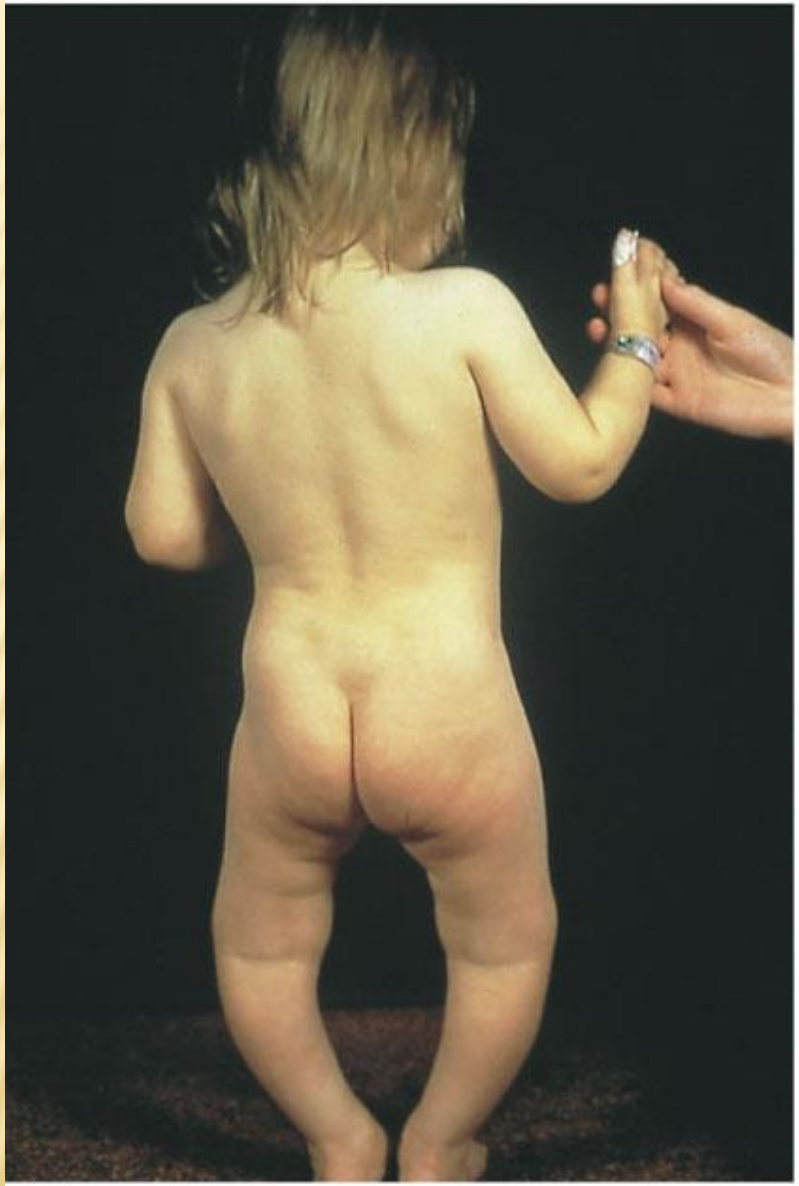
Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

VITAMIN D

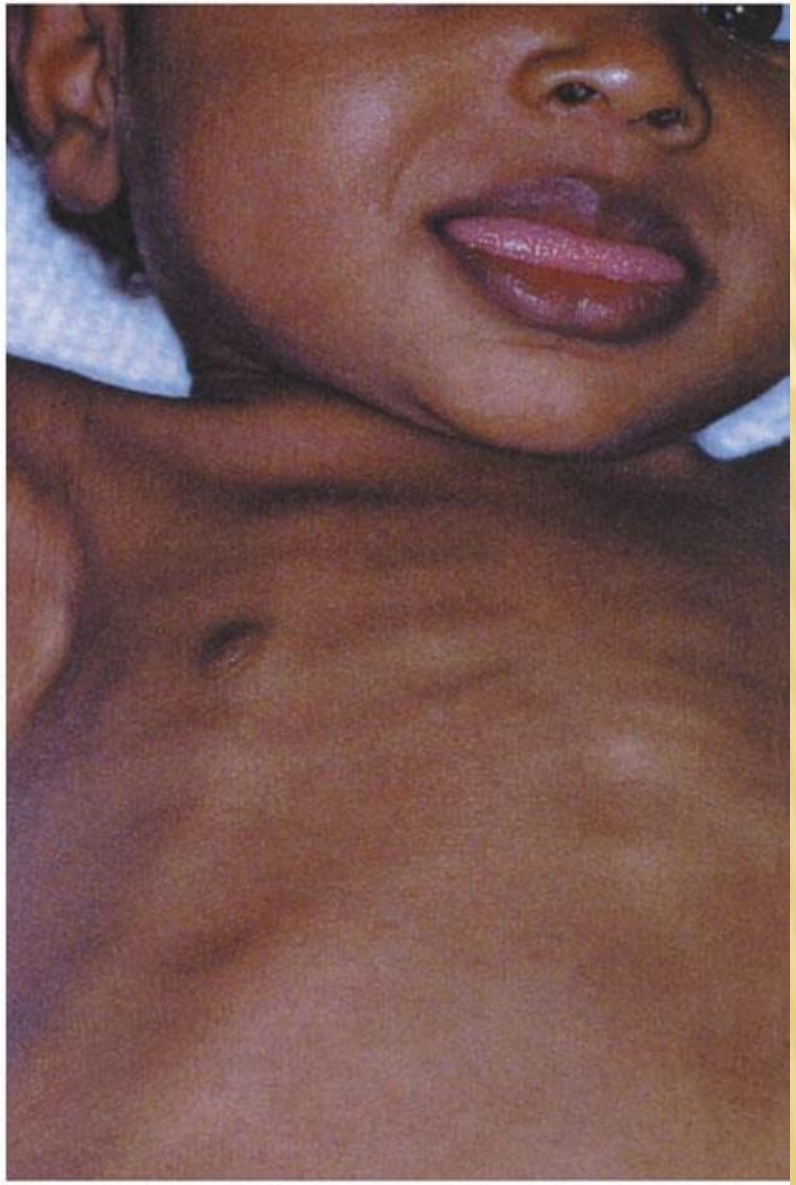
- Roles in the Body
  - Vitamin D in Bone Growth
    - Helps to maintain blood levels of calcium and phosphorus
    - Works in combination with other nutrients and hormones
      - Vitamin A, vitamin C, vitamin K
      - Parathormone and calcitonin
      - Collagen
      - Calcium, phosphorus, magnesium, and fluoride

VITAMIN D DEFICIENCY

- Rickets
  - Affects mainly children worldwide
  - Deficiency symptoms
    - Inadequate calcification of bones
    - Growth retardation
    - Misshapen bones- bowing of the legs
    - Enlargement of the ends of long bones
    - Deformities of ribs,
    - Lax muscles (resulting in a protruding abdomen) and muscle spasms



Bowed legs. In rickets, the poorly formed long bones of the legs bend outward as weight-bearing activities such as walking begin.

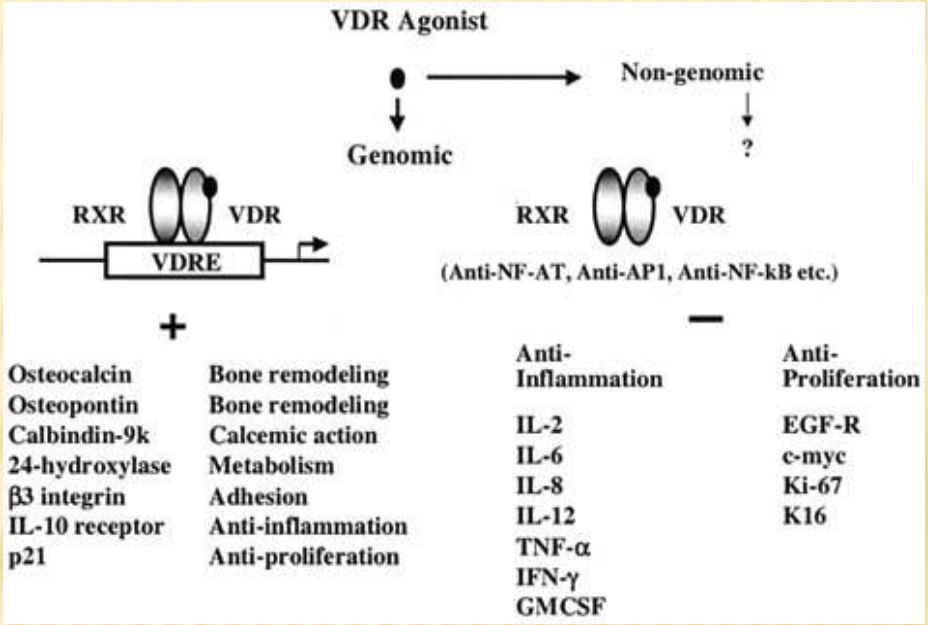


Beaded ribs. In rickets, a series of "beads" develop where the cartilages and bones attach.

CALCIUM, VITAMIN D, AND PARATHYROID HORMONE

- The active 1,25 dihydroxy vitamin D (calcitriol), is not only necessary for optimal intestinal absorption of calcium and phosphorus, but also exerts a tonic inhibitory effect on parathyroid hormone (PTH) synthesis, so that there are dual pathways that can lead to secondary hyperparathyroidism.
- Vitamin D deficiency and secondary hyperparathyroidism can contribute not only to accelerated bone loss and increasing fragility, but also to neuromuscular impairment that can increase the risk of falls.

Regulation of gene expresssion by VDR



TARGET GENES FOR VITAMIN D

Gene	***Transcription***
Receptor for vitamin D (VDR)	increased
Proteins bindingí Ca (calbindins)	increased
Calcium pump	increased
Osteokalcin	increased
Alkalic phosphatase	increased
24-hydroxylase	increased
PTH	decreased
1-hydroxylase	decreased
Collagen	decreased
Interleukin-2	decreased
Interferon γ	decreased

VITAMIN D DEFICIENCY

- Osteomalacia
  - Affects adults
  - Soft, flexible, brittle, deformed bones
  - Progressive weakness
  - Pain in pelvis, lower back, and legs

OSTEOMALACIA AND RICKETS

- Classically, the deficiency of vitamin D, essential for the absorption of calcium, has been the major cause of rickets in the child and osteomalacia in the adult resulting in absence or delay in the mineralization of growth cartilage or newly formed bone collagen.

OSTEOMALACIA AND RICKETS

- As a consequence of a low serum phosphate and normal serum calcium.
- Two such conditions are *x-linked hypophosphatemic rickets/osteomalacia* and *oncogenic osteomalacia*.
- When present, the signs of rickets and osteomalacia in the low serum phosphate states are indistinguishable from the classic hypocalcemic states.

X-LINKED HYPOPHOSPHATEMIC OSTEOMALACIA

- The condition is characterized by low tubular reabsorption of phosphate in the absence of secondary hyperparathyroidism.
- X-linked hypophosphatemia occurs in about 1 in 25,000 and is considered the most common form of genetically induced rickets.

ONCOGENIC OSTEOMALACIA

- Oncogenic osteomalacia is a paraneoplastic syndrome in which a bone or soft tissue tumor or tumor-like lesion induces hypophosphatemia and low vitamin D levels that reverse when the inciting lesion is resected.

ONCOGENIC OSTEOMALACIA

- In the past 15 or so years, a humoral factor, ***phosphotonin,*** has been identified in clinical and experimental studies as being responsible for the serum biochemical changes.
- Phosphotonin causes hyperphosphaturia by inhibiting the reabsorption of phosphate by the proximal renal tubules.
- Fibroblast growth factor 23, phosphate-regulating gene with homologies to endopeptides located on the 'x' chromosome (PHEX) and matrix extracellular phosphoglycoprotein (MEPE) are candidates proposed for the production of phosphatonin and the altered pathophysiology in oncogenic osteomalacia.

VITAMIN D TOXICITY

- More likely compared to other vitamins
- Vitamin D from sunlight and food is not likely to cause toxicity.
- High-dose supplements may cause toxicity.
- Toxicity symptoms
  - Elevated blood calcium
  - Calcification of soft tissues (blood vessels, kidneys, heart, lungs, and tissues around joints)
  - Frequent urination

VITAMIN E

- The principal role of vitamin E is to protect tissue against unwanted, destructive oxidation Vitamin E is the most effective lipid-soluble antioxidant present in our cells.
- Because vitamin E is an antioxidant, and because it has long been known that oxidation plays an important role in, it was presumed that vitamin E would be protective against cancer. However, perhaps because of the long induction times before overt tumors are observed and the long period over which supplementation must occur to provide protection, evidence for an anticancer effect for vitamin E in humans has developed more slowly than has evidence for the role of vitamin E in preventing heart disease.
- The hypothesis that links vitamin E and cardiovascular diseases (CVD) posits that the oxidation of unsaturated lipids in the LDL particle, as well as the complex sequelae that flow from this oxidation, play a crucial role in the pathogenesis of atherosclerosis. This theory is now generally accepted, and this theory provides a strong biological plausibility for the role of vitamin E in preventing CVD.

VITAMIN E

- There are four different tocopherol compounds, but only the alpha-tocopherol has vitamin E activity in human beings.
- Vitamin E as an Antioxidant
  - Stops the chain reaction of free radicals
  - Protection of polyunsaturated fatty acids and vitamin A
  - Protects the oxidation of LDLs

VITAMIN E

- Vitamin E Deficiency - Symptoms
  - Loss of muscle coordination and reflexes
  - Impaired vision and speech
  - Nerve damage
  - Erythrocyte hemolysis (breaking open of red blood cells)
- Supplements do not prevent or cure muscular dystrophy.
- Fibrocystic breast disease responds to vitamin E treatment.
- Intermittent claudication responds to vitamin E treatment.

VITAMIN E

- Vitamin E Toxicity
  - Rare and the least toxic of the fat-soluble vitamins
  - Upper level for adults: 1000 mg/day
  - May augment the effects of anticlotting medication
- Vitamin E Recommendations (2000 RDA)
  - RDA adults: 15 mg/day

VITAMIN E DEFICIENCY AND IMMUNE RESPONSE QUALITY IN MEN

Immune response	Results
Mitogenesis of T-cells	Decreased
Production of IL-2	Decreased
Fagocytosis of PMNs	Decreased
Chemotaxis of PMNs	Decreased

VITAMIN E AND HEALTH

- α-Tocopherol is a required nutrient that functions as a peroxyl radical scavenger. If the diet contains inadequate amounts of vitamin E, then insufficient amounts are absorbed and the erythrocyte is a key target tissue susceptible to oxidative damage, which leads to anemia. In contrast, if α-TTP is lacking or non-functional, then the dietary α-tocopherol is absorbed, erythrocytes can acquire α-tocopherol and are protected, but the body does not retain α-tocopherol, leading to its depletion in tissues. In this latter case, the most susceptible tissues are the large-caliber sensory neurons in the peripheral nerves.
- Ultimately, all tissues become depleted and signs of deficiency are severe due to free-radical damage. Although vitamin E-specific pathways and molecular targets have been sought in a variety of studies, the most likely explanation as to why humans require α-tocopherol is that it is a fat-soluble antioxidant.

„ORPHAN" NUCLEAR RECEPTORS

- "Orphan" nuclear receptors include receptors for fatty acids (peroxisome-proliferator activated receptors (PPARs)), bile acids (farnesoid X receptor), oxysterols (liver X receptors), as well as lipophilic xenobiotics (PXR) and constitutive androstane receptor (CAR).

VITAMIN E AND ATHEROSCLEROSIS PREVENTION

Target	Function
LDL	Antioxidant
Endothelial and other cells	Potentiates arachidonate release and affects prostane production and activity
Endothelium	Inhibits cell adhesion
Endothelium	Protects nitric oxide and endothelial cell dependent vasoactivity
Smooth muscle cell	Inhibits proliferation
Platelet	Inhibits adhesion and aggregation
Neutrophils	Reduces leukotriene synthesis
Blood cells	Reduces leukotriene urinary excretion
Monocytes	Reduced adhesion, decreased production of oxidants, and altered cytokine expression

VITAMIN K

- Also known as phylloquinone, menaquinone, menadione, and naphthoquinone
- Vitamin K is unique in that half of human needs are met through the action of intestinal bacteria.
- **Vitamin K is essential in blood clotting.**
- deficiency can cause uncontrolled bleeding.
- Deficiencies can occur in newborn infants and people taking antibiotics.

VITAMIN K

- Vitamin K is a fat-soluble vitamin, which is involved in blood coagulation mediated by maintaining the activity of coagulation factors in the liver.
- Vitamin K also has extrahepatic actions and has been shown to prevent bone fractures in clinical studies.
- Lack of vitamin K is associated with several geriatric diseases, including osteoporosis, osteoarthritis, dementia and arteriosclerosis.
- Vitamin K contributes to the prevention and treatment of some kinds of malignancies.
- In addition to its established roles as a cofactor of γ-glutamyl carboxylase (GGCX) in mediating post-transcriptional modifications, vitamin K has a different mode of action mediated by transcriptional regulation of SXR/PXR target genes.

VITAMIN K

- Two forms: fylochinone and menachinone. Fylochinone (vitamin K1) is contained in green vegetables and in some plant oils. Menachinone (vitamin K2) is of animal and bacterial origin

- Vitamin K2 is a transcriptional regulator of genes specific for bone. Its effect is realized by SXR (steroid and xenobiotic receptor) which supports osteoblastic markers expressions.

SXR AND NECHANISM OF ITS EFFECT

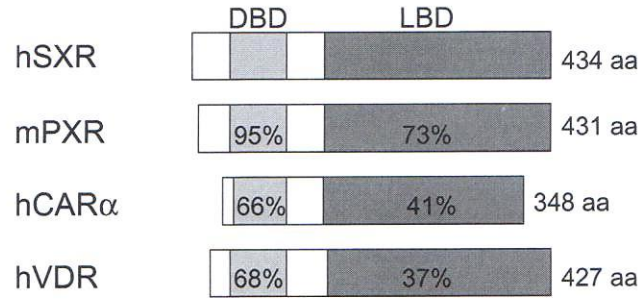


Fig. 1. Schematic comparisons among the nuclear receptor steroid and xenobiotic receptor (SXR) and its related receptors. All the receptors belong to nuclear receptor subfamily 1, group I (NR1I), and form heterodimers with their common partner retinoid X receptor (RXR). The similarity between SXR and other receptors is expressed as percent amino acid identity [1]. *DBD*, DNA-binding domain; *LBD*, ligand-binding domain; *hSXR*, human SXR; *mPXR*, mouse pregnane X receptor; *hCARα*, human constitutive androstane receptor-α; *hVDR*, human vitamin D receptor

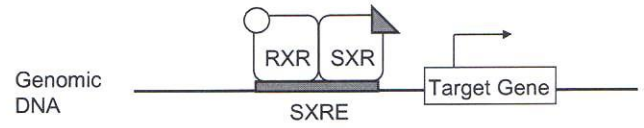


Fig. 2. Transcriptional regulatory mechanism of SXR. The ligand-activated SXR forms heterodimers with RXR and regulates the transcription of adjacent target genes by binding to SXR response elements (SXREs) in the genome

Inoue KH a Inoue S: J Bone Miner Meat (2008) 26: 9-12

SXR AND VITAMIN K

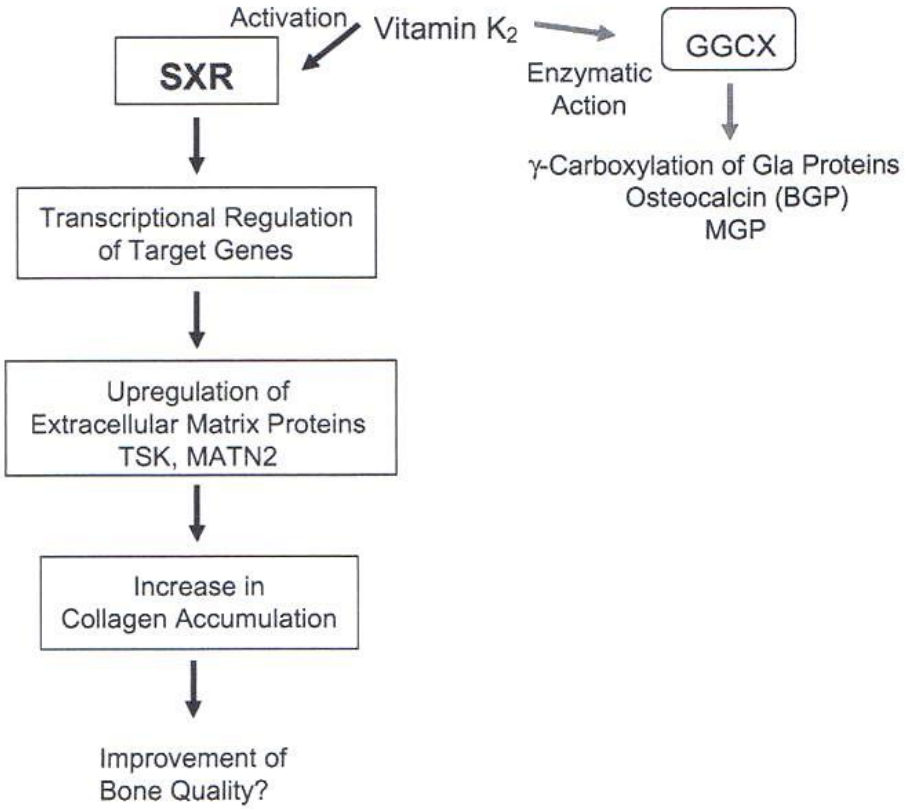


Fig. 3. SXR- and vitamin K_2-dependent regulatory mechanisms of bone metabolism in osteoblastic cells. SXR promotes collagen accumulation in osteoblastic cells by regulating the transcription of its target genes including those encode extracellular matrix proteins. Vitamin K_2 plays a role in the posttranslational modification of Gla proteins by functioning as a coenzyme of γ-glutamyl carboxylase (GGCX) and also acts as a potent SXR ligand in bone metabolism

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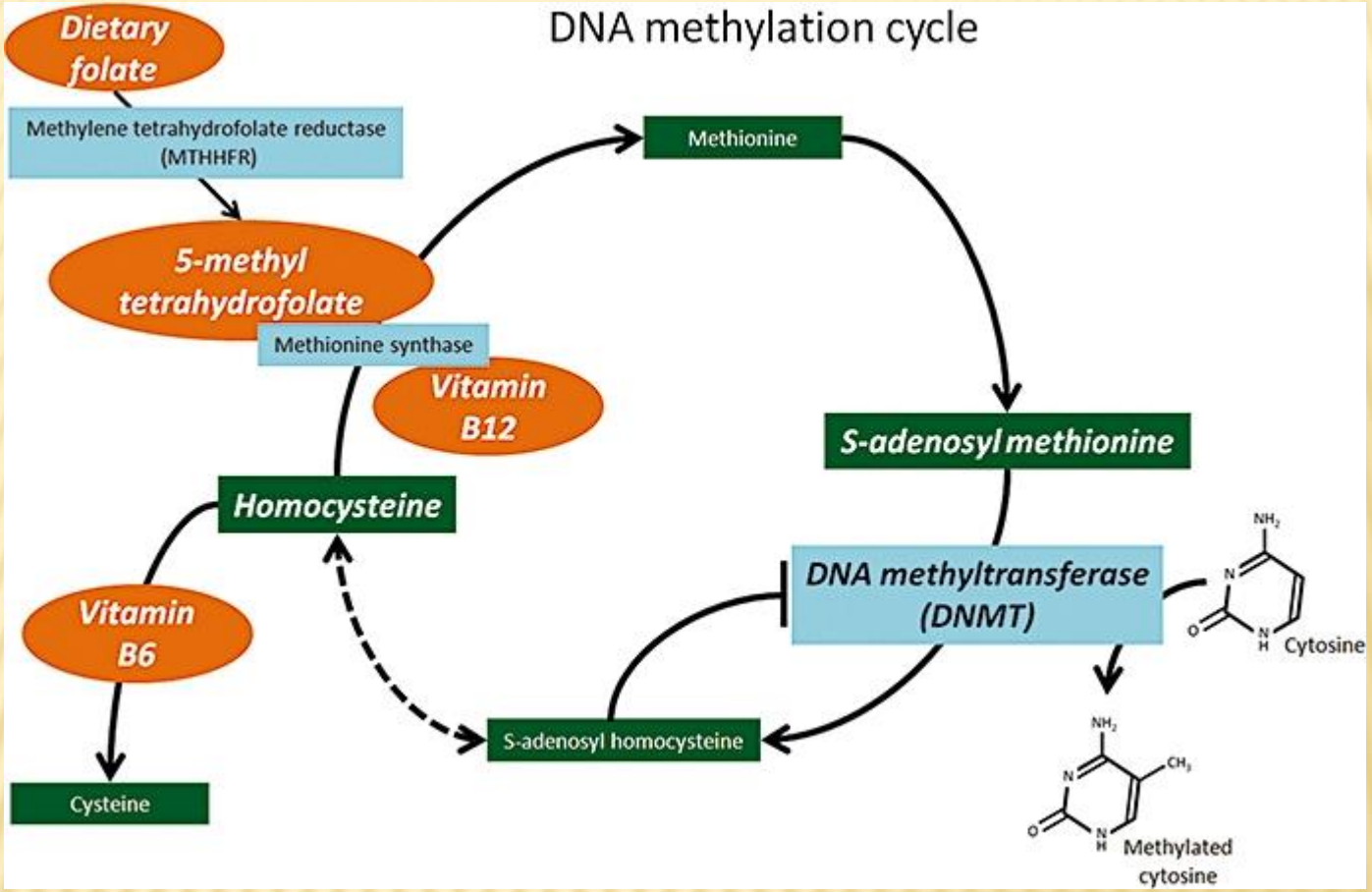


Dietary components that can alter epigenetics. The enzymes involved in the DNA methylation cycle are dependent on the availability of essential cofactors: folate, and vitamins B12 and B6. In their abundance, DNA methyl transferases (DNMTs) readily transfer methyl groups to cytosine residues; however, in the absence of appropriate cofactors, methionine is converted back to its precursors, homocysteine and *S*-adenosyl homocysteine. Excess *S*-adenosyl homocysteine levels inhibit DNMT activity, thus they can reduce/prevent DNA methylation and compromise gene silencing. The cycle can be potentially rescued by supplementation with these essential vitamins, to clear elevated homocysteine levels and restore DNA methylation processes

Br J Pharmacol. 2010 Jan; 159(2): 285–303.

REDUCTIVE AND OXIDATIVE STRESS

- Reductive stress (RS) is the counterpart oxidative stress (OS), and can occur in response to conditions that shift the redox balance of important biological redox couples, such as the NAD^+/NADH, $NADP^+$/NADPH, and GSH/GSSG, to a more reducing state.
- Overexpression of antioxidant enzymatic systems leads to excess reducing equivalents that can deplete reactive oxidative species, driving the cells to RS.

Int J Mol Sci. 2017 Oct; 18(10): 2098.

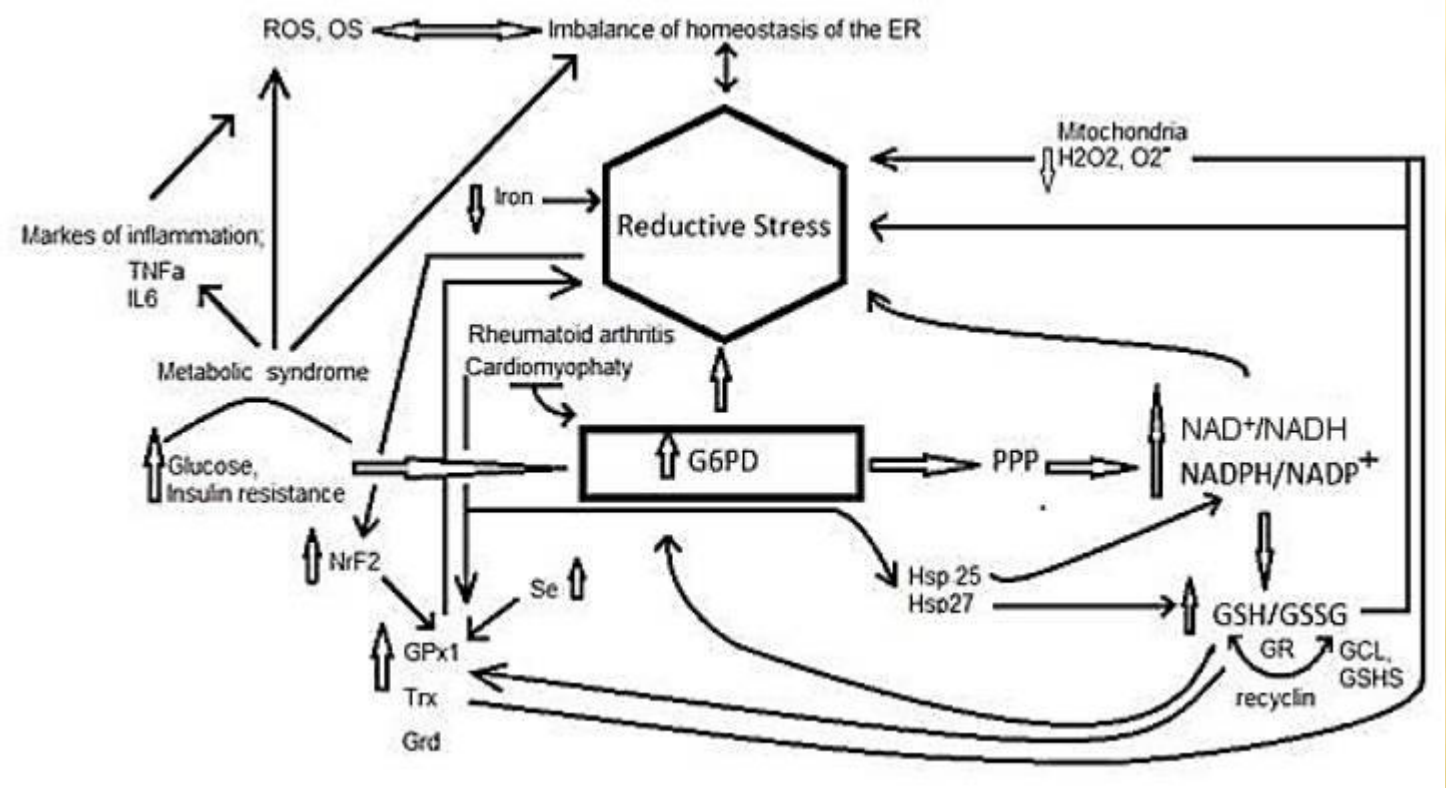
REDUKČNÍ A OXIDAČNÍ STRES

- A feedback regulation is established in which chronic RS induces OS, which in turn, stimulates again RS. Excess reducing equivalents may regulate cellular signaling pathways, modify transcriptional activity, induce alterations in the formation of disulfide bonds in proteins, reduce mitochondrial function, decrease cellular metabolism, and thus, contribute to the development of some diseases in which NF-κB, a redox-sensitive transcription factor, participates.
- Diseases: cardiomyopathy, hypertrophic cardiomyopathy, muscular dystrophy, pulmonary hypertension, rheumatoid arthritis, Alzheimer's disease, and metabolic syndrome, among others.
- Chronic consumption of antioxidant supplements, such as vitamins and/or flavonoids, may have pro-oxidant effects that may alter the redox cellular equilibrium and contribute to RS, even diminishing life expectancy.

Int J Mol Sci. 2017 Oct; 18(10): 2098.

REDUCTIVE STRESS

- RS is characterized by an excess of reducing equivalents. It leads to a decrease of ROS production through antioxidant enzyme overexpression that may cause an alteration in the redox state of intracellular higher NAD^+/NADPH, and GSH/GSSG ratio.
- A balance in Se and iron levels is needed for several biological functions in the human body, and its excess and/or insufficient intake can result in adverse health effects and contribute to RS.
- RS alters the mitochondrial function, causes misfolding of proteins, and may participate in several inflammation-associated diseases.
- Hyperglycemic conditions induce RS through inhibition of the insulin receptor by selenium-GPx-1 overexpression.
- .

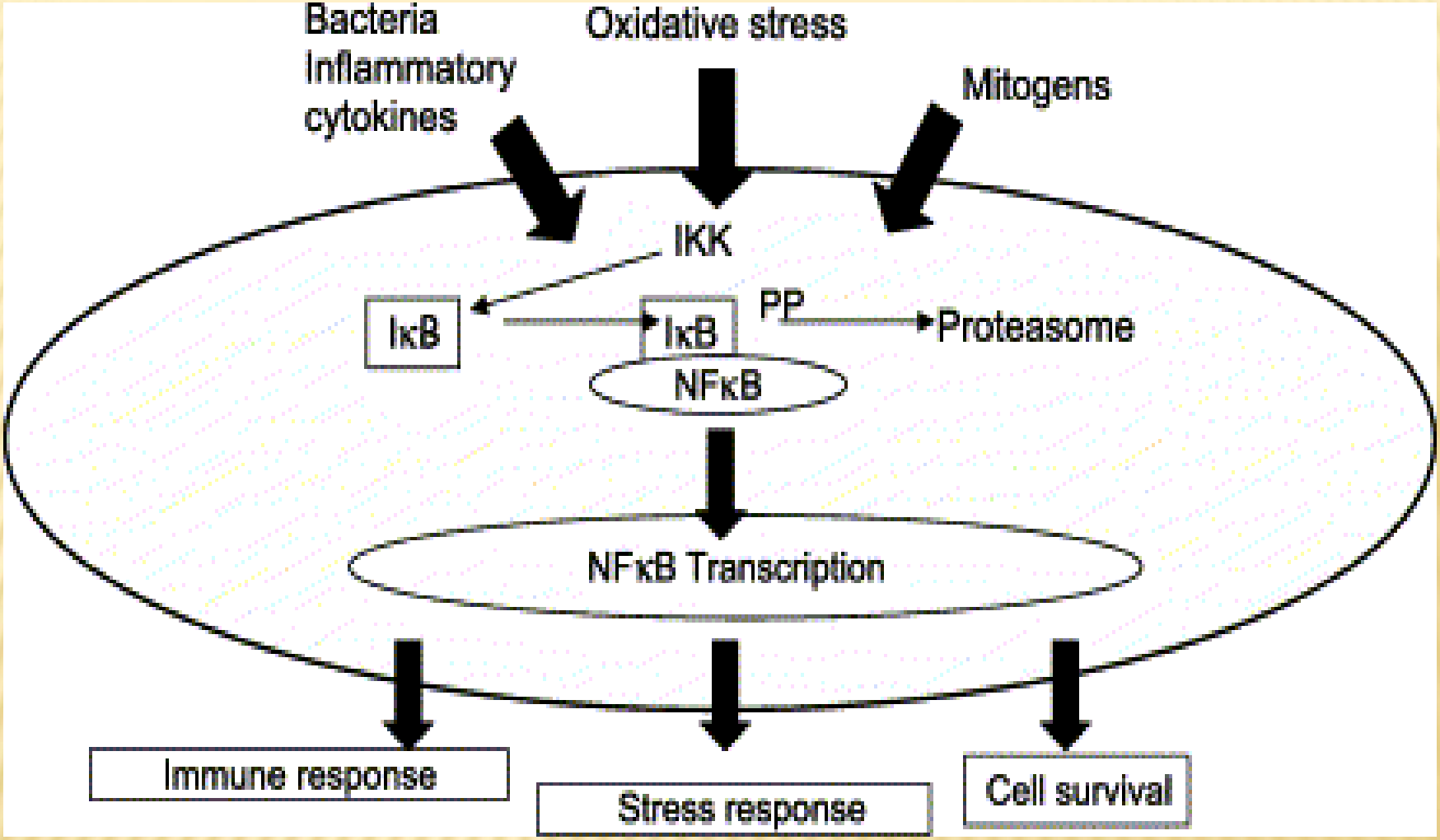


Int J Mol Sci. 2017 Oct; 18(10): 2098

Participation of several agents such as the reducing equivalents, antioxidant enzymes and pathologies in reductive stress. Abbreviations: G6PD = glucose 6 phosphate dehydrogenase, NAD = nicotinamide adenine dinucleotide, NAD^+ = nicotinamide adenine dinucleotide oxidized, NADH = nicotinamide adenine dinucleotide reduced, NADPH = nicotinamide adenine dinucleotide phosphate reduced, GSH = glutathione, GSSG = glutathione disulfide, PPP = pentose phosphate pathway, γ-glutamyl-cysteine synthase, GSHS = glutathione synthetase, GPx = Glutathione peroxidase, Trx = thioredoxin, Grd = glutaredoxin, TNFα = tumor necrosis factor alpha, NrF2 = erythroid related factor 2, IL6 = interleukin 6, ROS = reactive oxidative species, OS = oxidative stress, ER = endoplasmic reticulum, Se = selenium, Hsp = heat shock protein, GR = glutathione reductase.

Oxidační stres

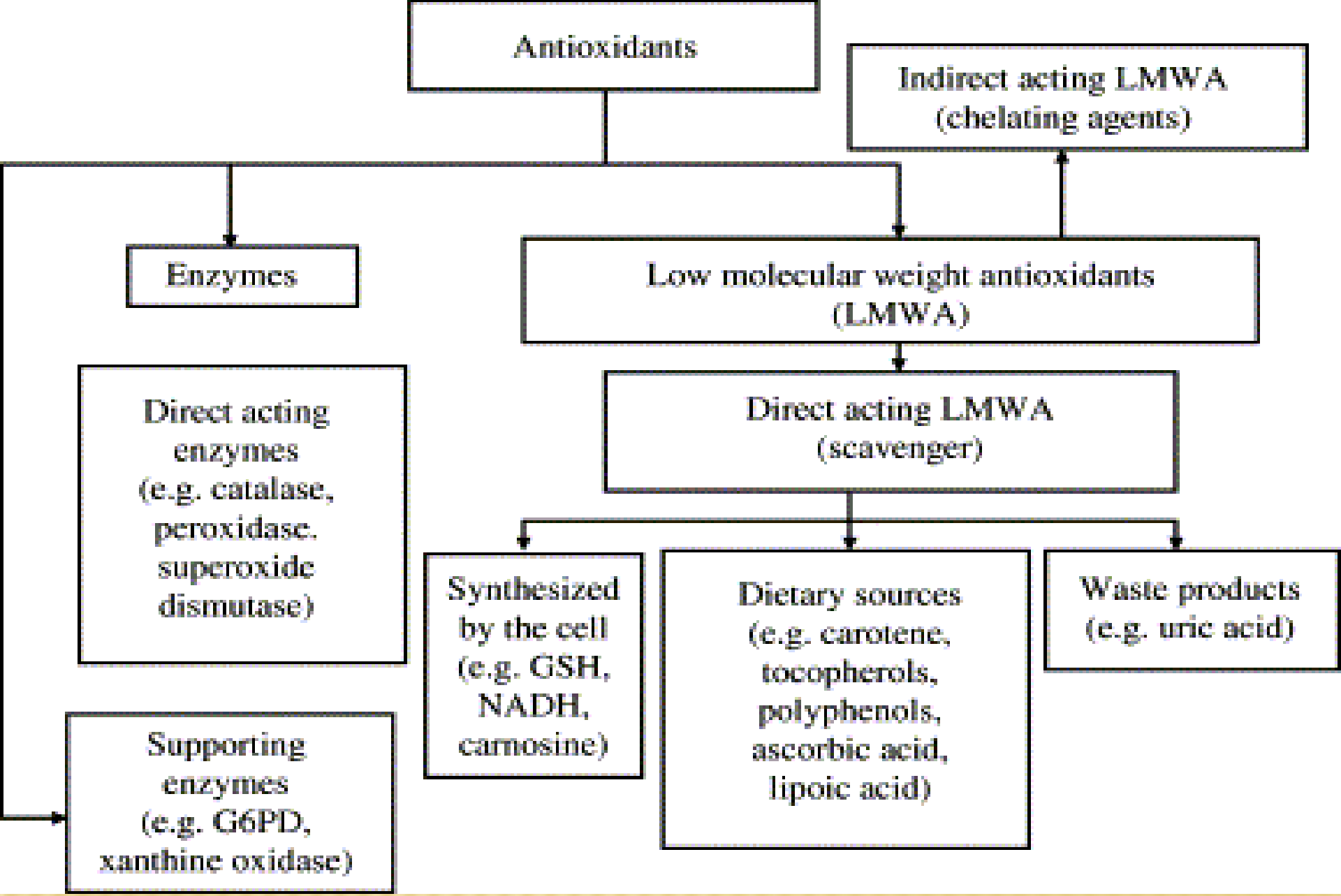
- je spjat se zmenšením počtu antioxidačních molekul, jako alfa-tokoferol.
- Alfa-tokoferol specificky snižuje proliferaci buněk hladké svaloviny cév v závislosti na koncentraci. Snižuje přitom aktivitu protein kinázy C zvýšením aktivity protein fosfatázy 2A1, který defosforyluje PKC-alfa, což vede ke změnám složení a vazby transkripčního faktoru pro AP-1 na DNA.
- několik genů v buňkách hladké svaloviny cév mění svou transkripci pod vlivem alfa-tokoferolu. Zvyšuje se transkripce i translace alfa-tropomyosinu, ale jen pod vlivem alfa-tokoferolu, nikoliv beta-tokoferolu
- PKC-alfa se v průběhu života zvyšuje 8x, podobně jako MMP-1, která degraduje kolagen. Alfa-tokoferol snižuje expresi MMP, aniž ovlivňuje aktivitu TIMP-1.
- Antioxidační vitamíny, poylfenoly a estrogeny konzumované ve vysokých koncentracích mohou navodit prooxidační stnt stav.



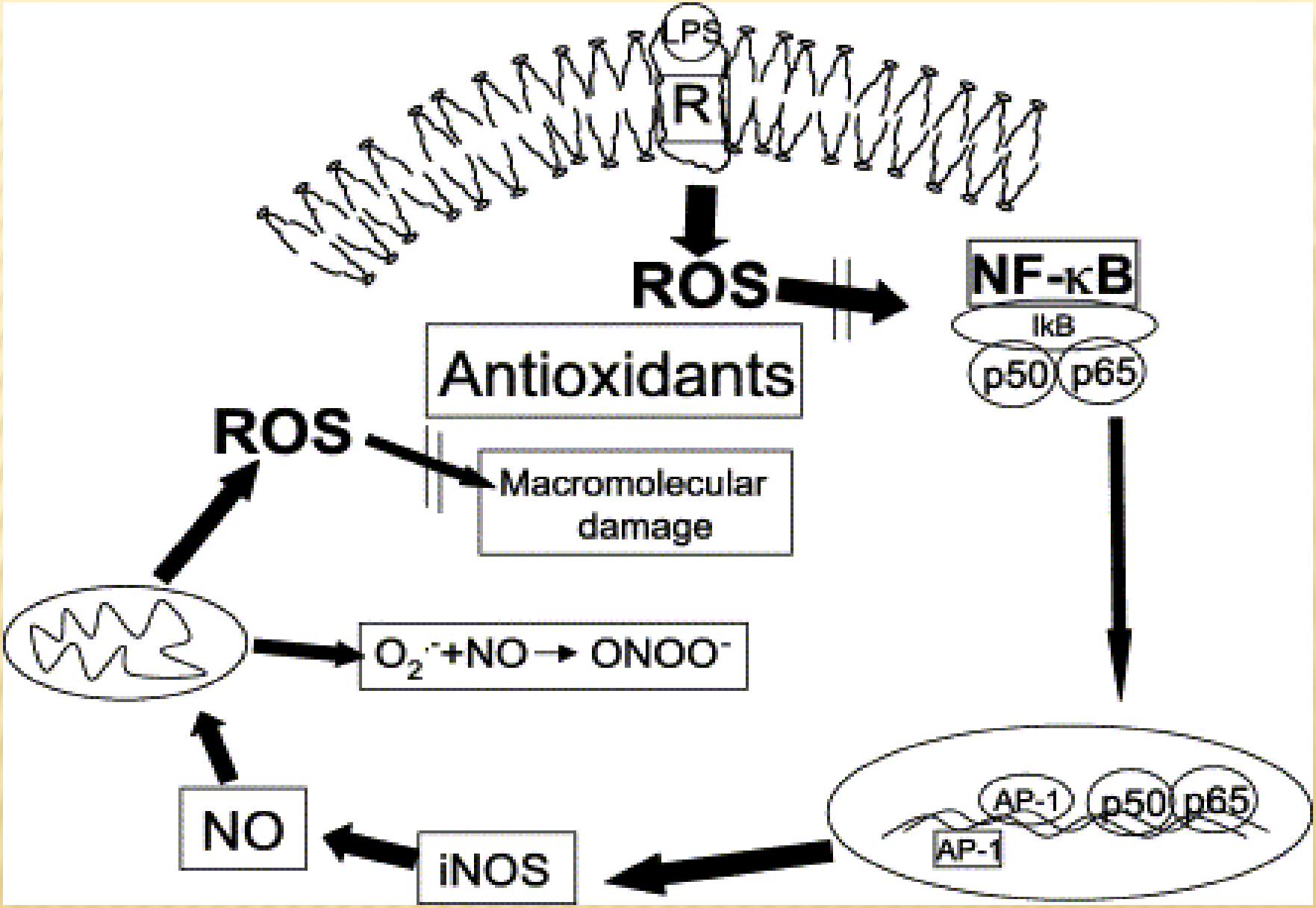
Signalizace oxidačního stresu. Cytokiny a ROS indukují aktivaci NF-κB. Tato aktivace zabraňuje apoptóze buněk navozované TNF upregulací antiapoptotických genů

Oxidační stres

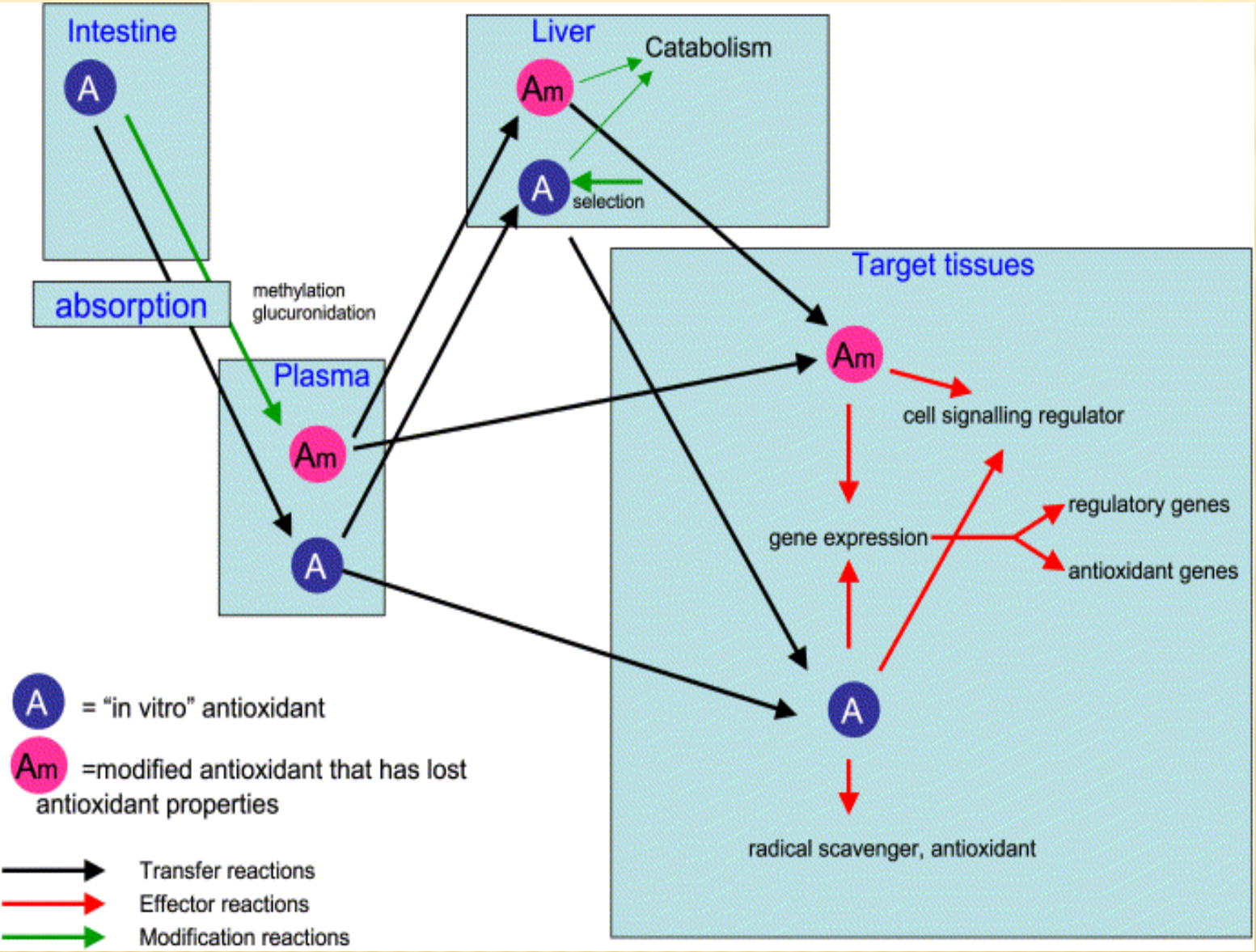
- nezávisle na doprovodných proměnných, jako je tkáňová reakce, moduluje expresi genů pro kolagen in vivo.
- Rovnováha v oxidačním-antioxidačním stavu je důležitou determinantou pro funkci imunocytů.
- Zajišťuje:
- udržování integrity a funkčního stavu membránových lipidů, celulárních proteinů a NK
- kontrolu signální transdukce buněk imunitního systému
- kontrolu genové exprese buněk imunitního systému



Antioxidační obranný systém

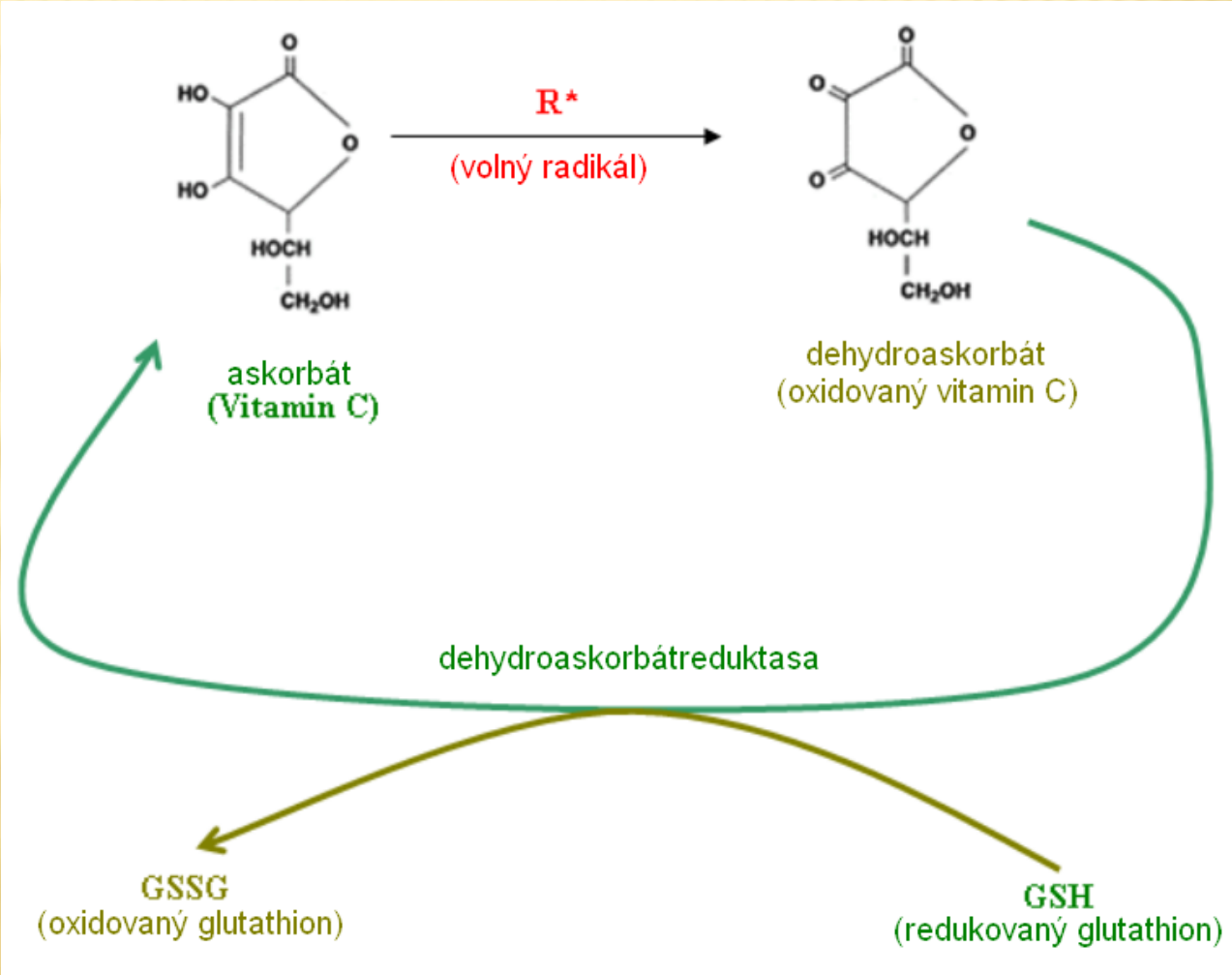


Možná místa působení antioxidant.

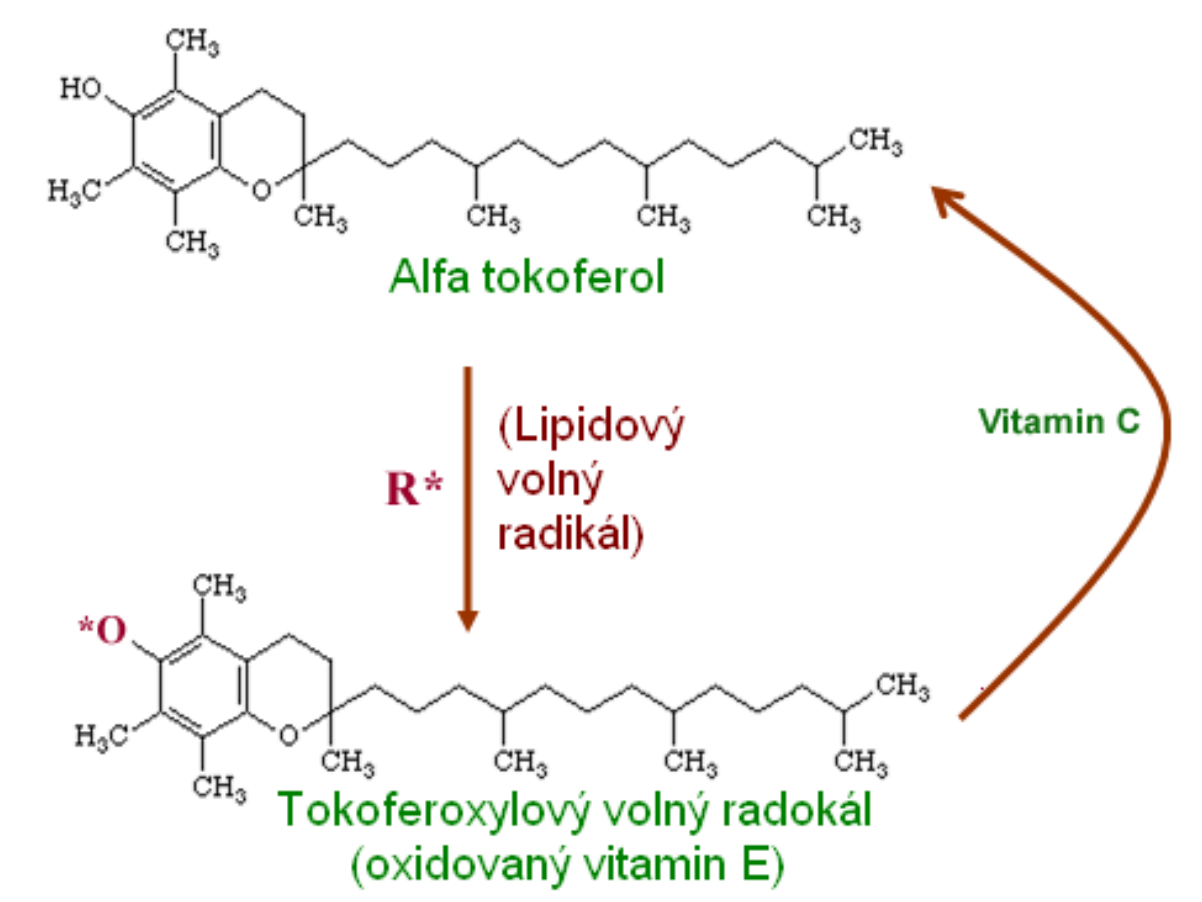


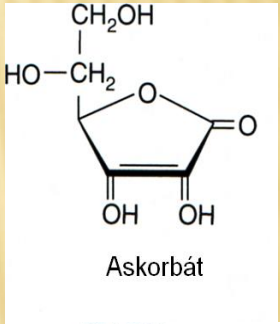
Absorbce, modifikace, distribuce a účinky molekul s antioxidačními účinky *in vitro*

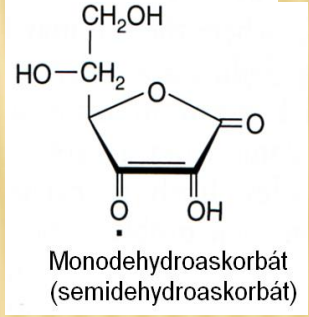
Vitamin C – antioxidant

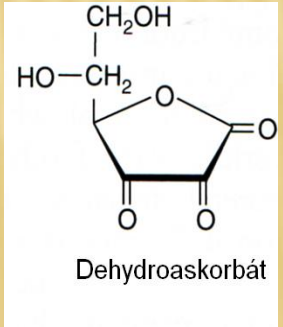


Vitamin C – antioxidant





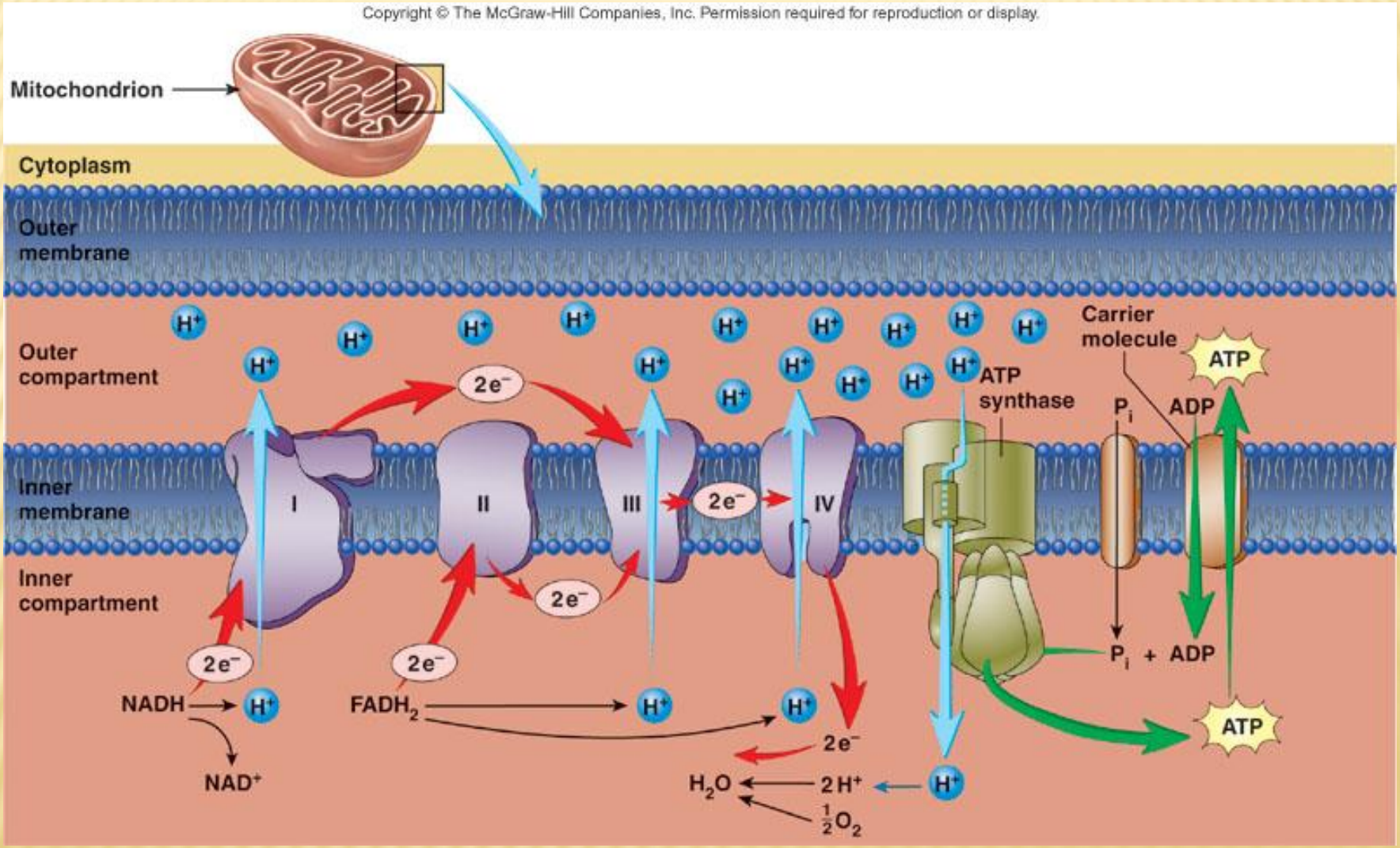


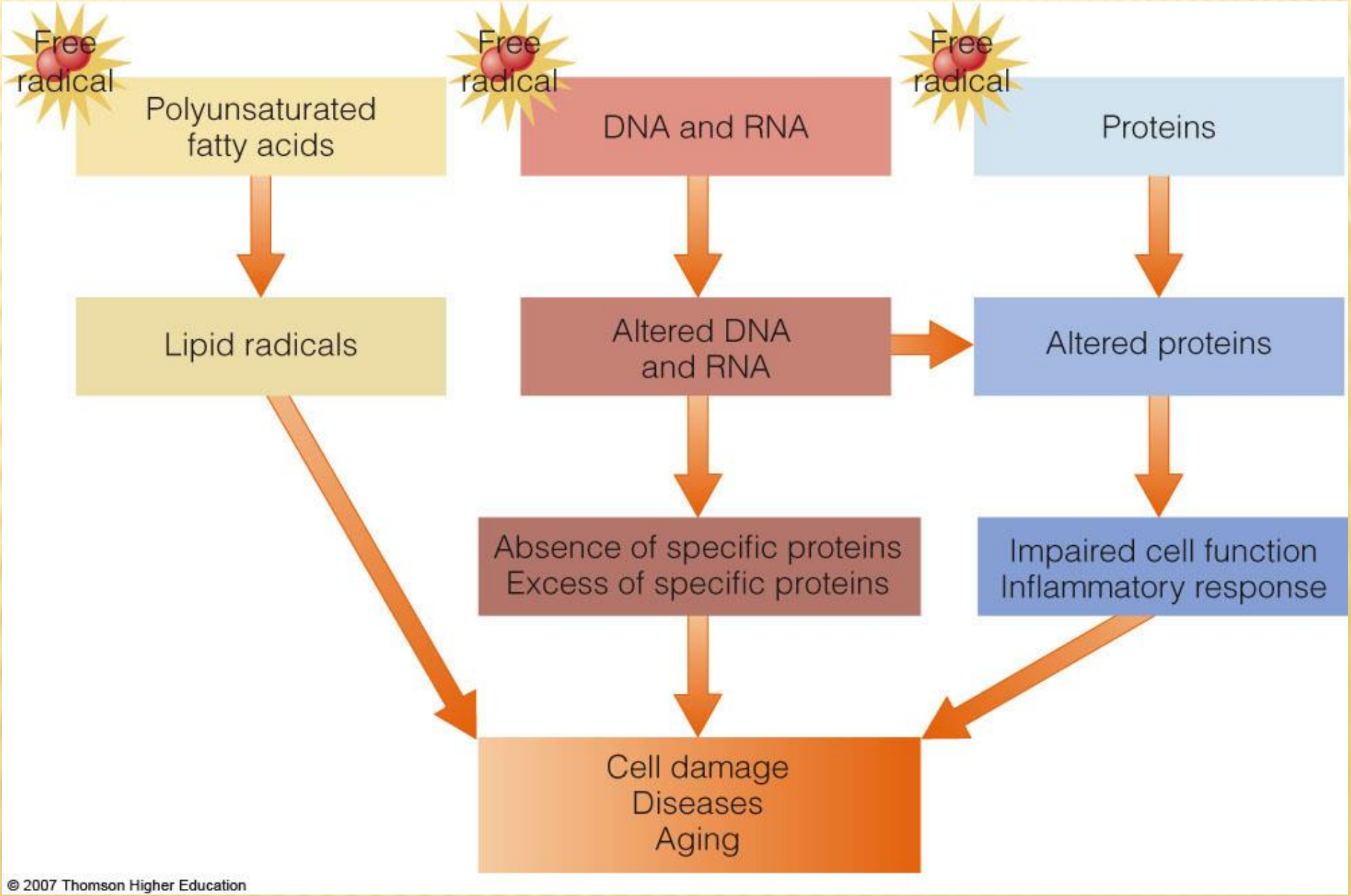


OXIDATIVE STRESS

- Is defined as disequilibrium between oxidants and antioxidants which potentially can lead to damage of cells and/ or of cellular structures.

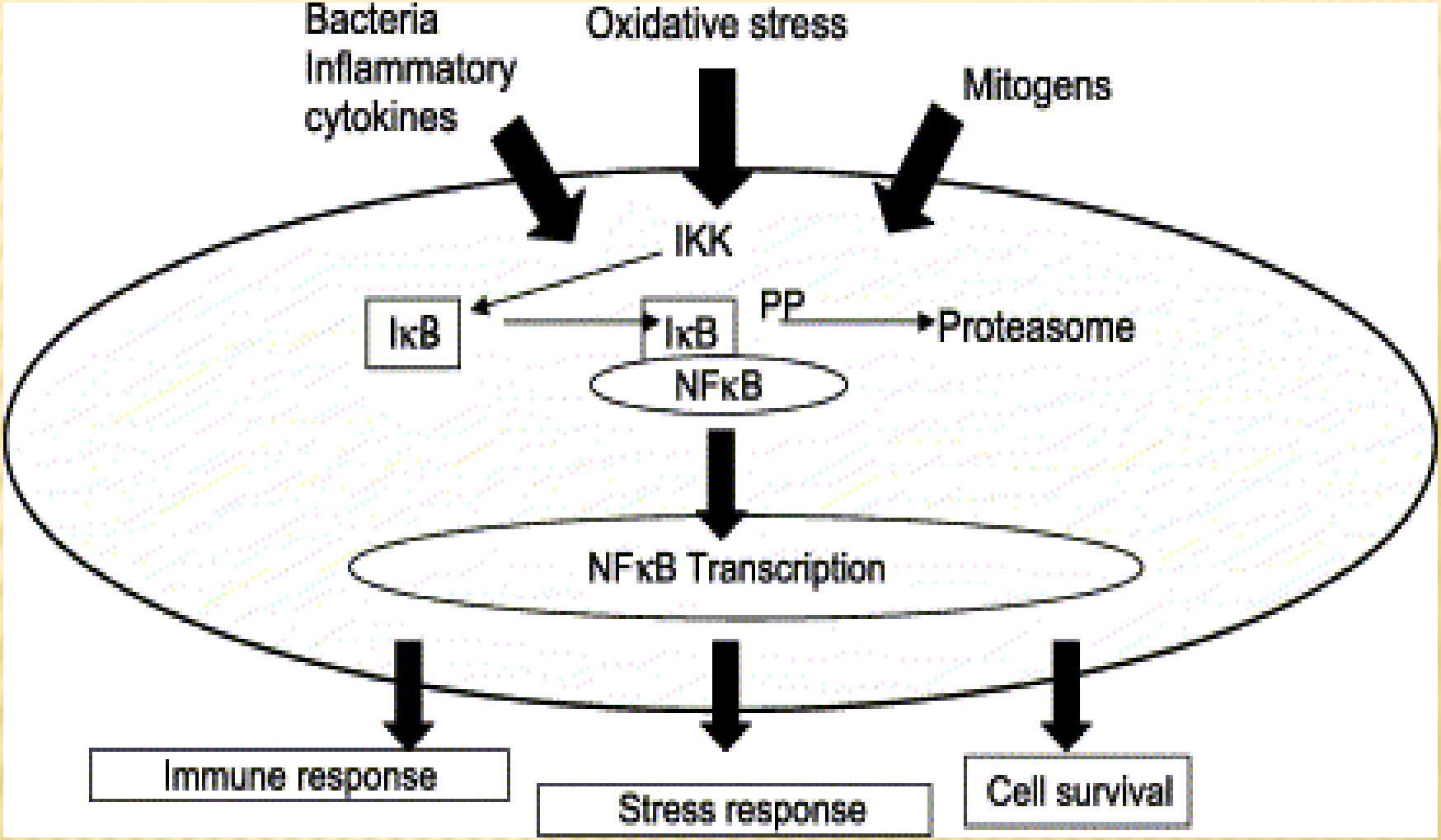
CHAIN TRANSPORTING ELECTRONS



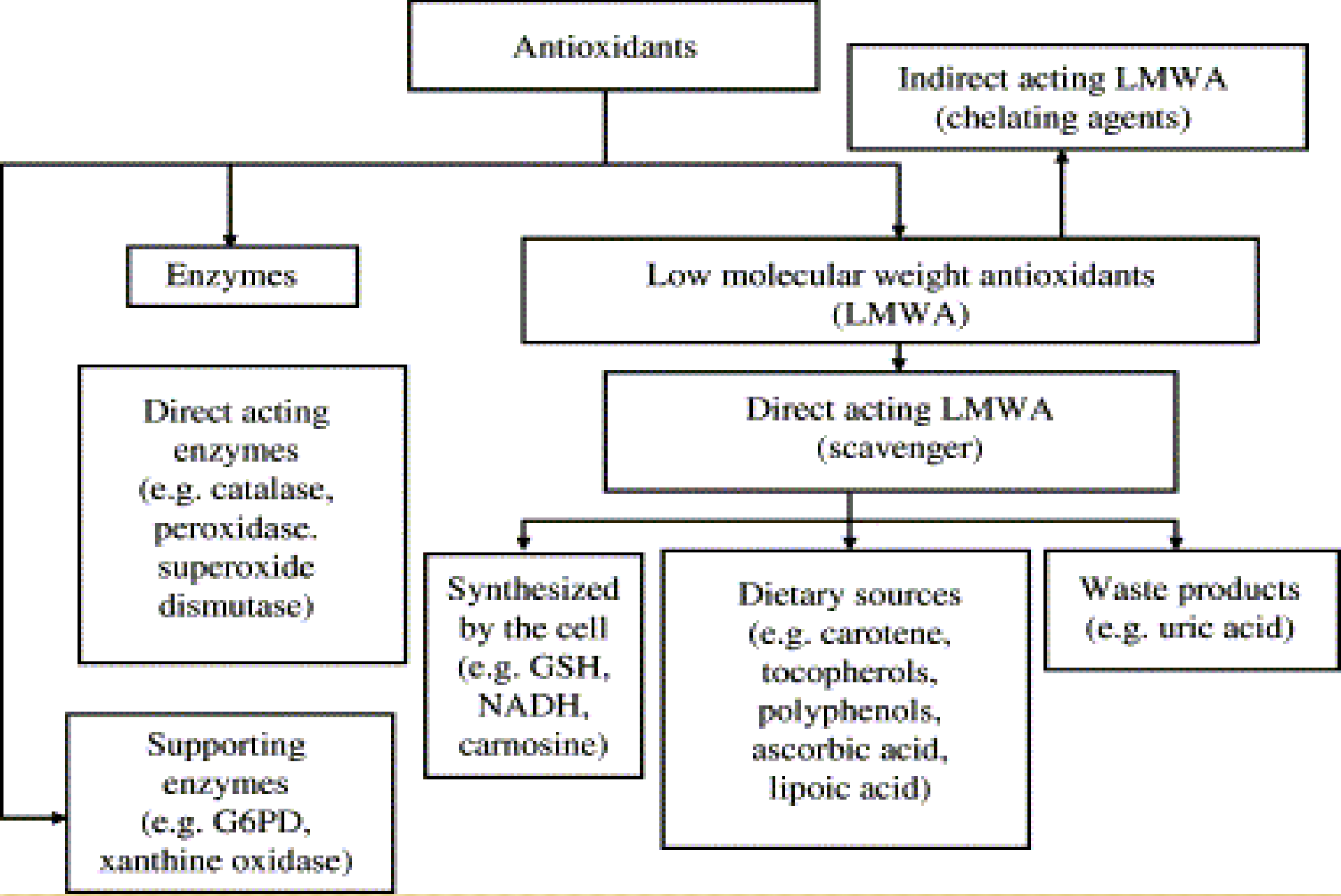


DEFENDING AGAINST FREE RADICALS

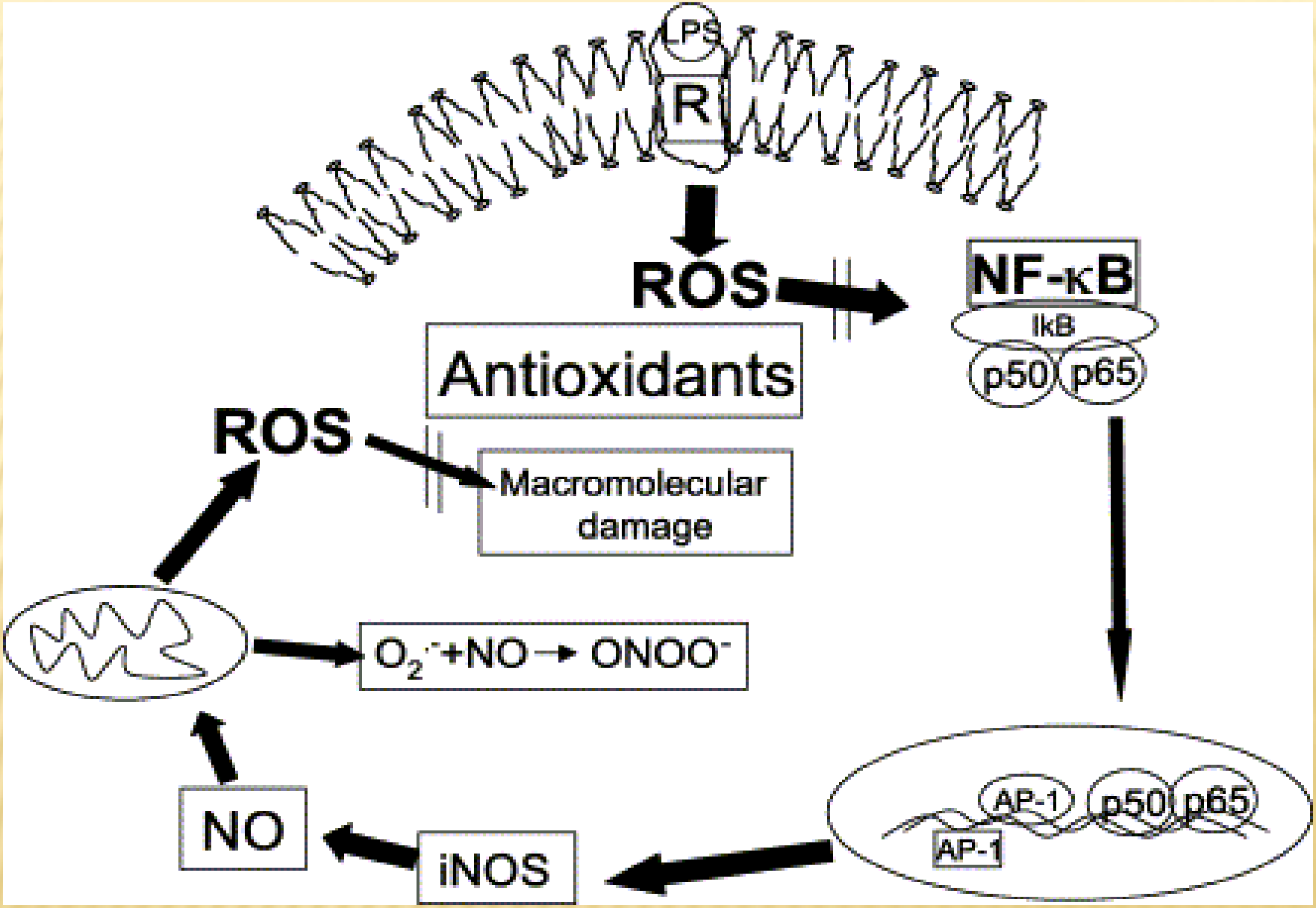
- Limiting free radical formation
- Destroying free radicals or their precursors
- Stimulating antioxidant enzyme activity
- Repairing oxidative damage
- Stimulating repair enzyme activity



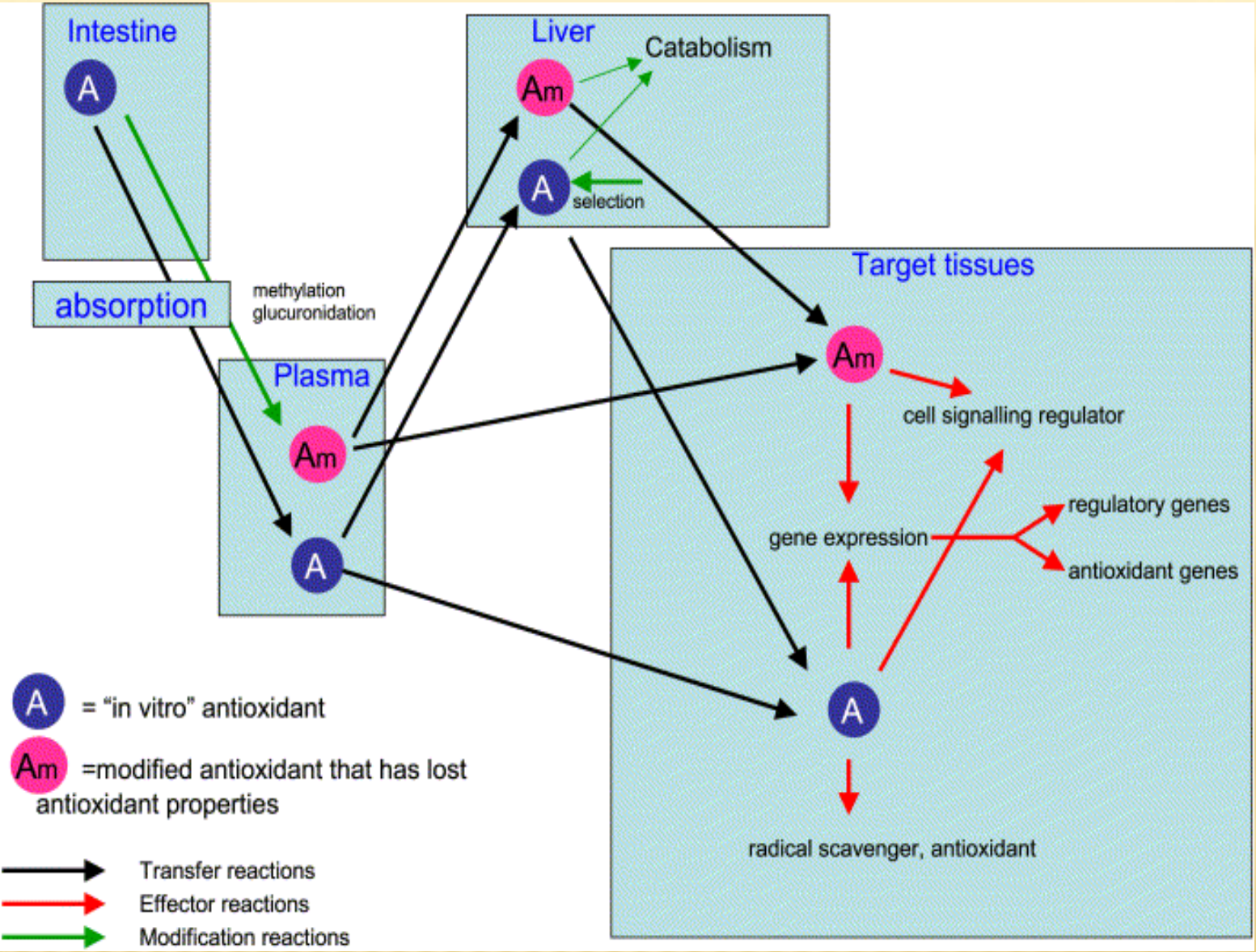
Signaling of oxidative stress



Antioxidative defence system



Možná místa působení antioxidant.



Absorption, modification, distribution and effects of molecules with antioxidation effects *in vitro*

VITAMIN C AND EPIGENETIC REGULATION

- Vitamin C is an essential nutrient for those mammals that cannot biosynthesize it, including primates, guinea pigs and certain species of bats.
- Deficiency in the vitamin leads to scurvy, through disruption of the extracellular matrix secondary to loss of proline hydroxylase activity and consequent interruption of collagen biosynthesis.

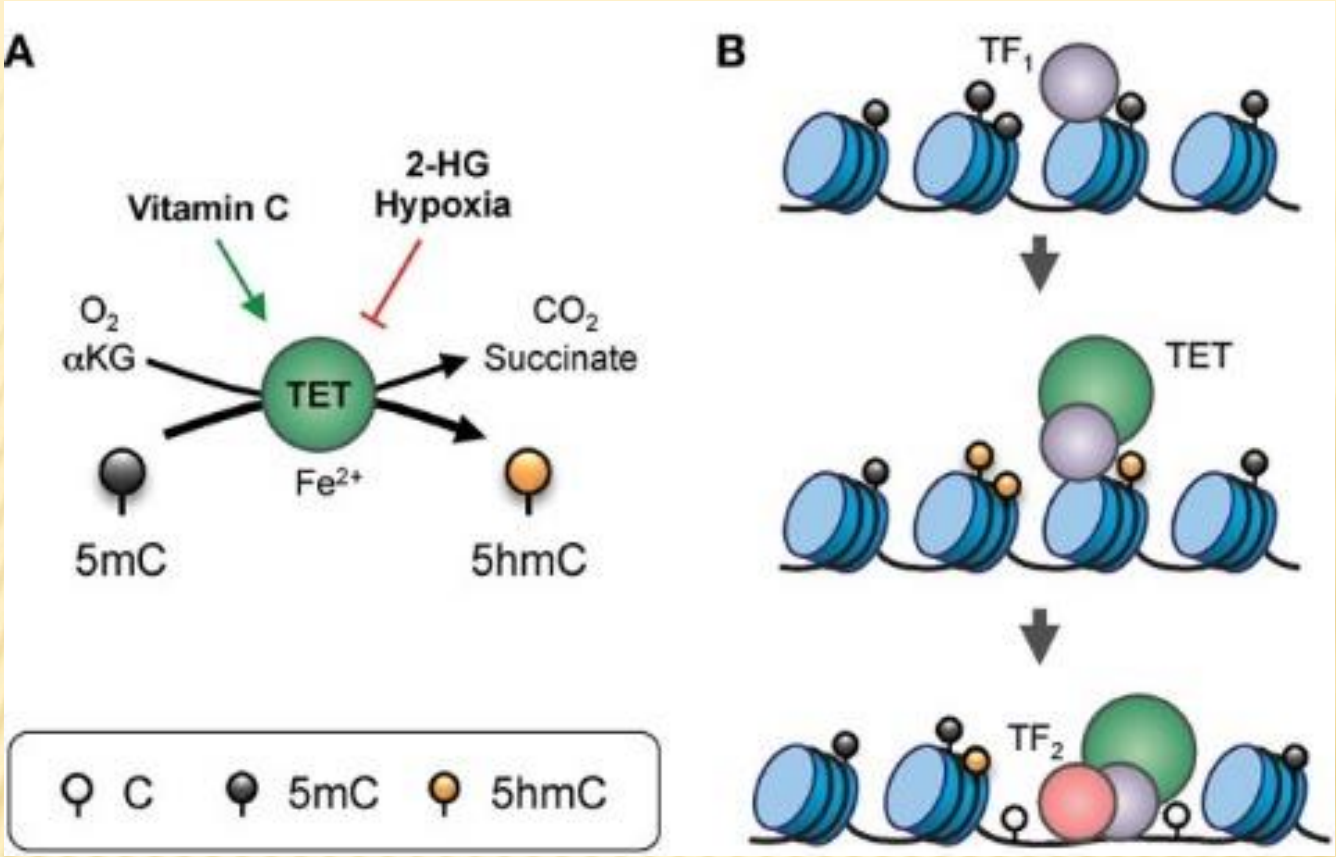
- Vitamin C can cause genome-wide changes in epigenetic marks on DNA and can accelerate cell state transitions along the pathway of reprogramming of somatic cells to pluripotency. These actions of vitamin C relate not to its antioxidant activity but to its role as a cofactor and electron donor for iron-dependent oxidoreductases.

VITAMIN C AND EPIGENETIC REGULATION

- In 2010, two independent studies showed that the addition of vitamin C to the medium used to culture human pluripotent stem cells resulted in genome-wide demethylation in these cells and that this addition of vitamin C could enhance reprogramming of mouse and human cells to pluripotency.

TET

- Members of this important class of enzymes include ten-eleven translocation (TET) enzymes, which can convert 5-methylcytosine to 5-hydroxymethylcytosine (5hmC) in DNA, a process hypothesized to be critical to active DNA demethylation.
- DNA demethylation is an integral part of the epigenetic remodeling that occurs during reprogramming; thus, TET activity might be critical for the reprogramming process.

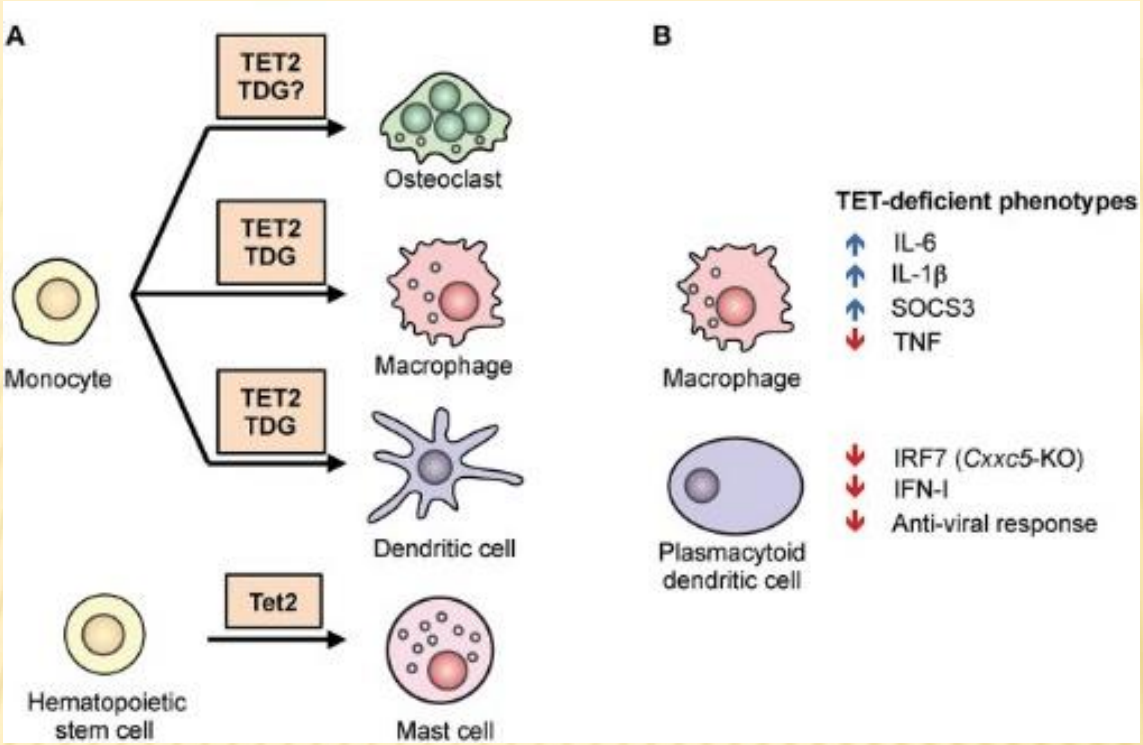


Front Immunol. 2019; 10: 210

Gene regulation by TET proteins. **(A)** Enzymatic activity of TET. TET proteins, with the co-factors Fe^{2+} and α-ketoglutarate (αKG), use oxygen to oxidize 5mC into 5hmC, generating CO_2 and succinate as by-products. The enzymatic activity of TET can be modulated by additional factors. For instance, vitamin C (ascorbate) can enhance TET activity, potentially via reduction of the iron ion. On the other hand, the "oncometabolite" 2-hydroxyglutarate (2-HG), generated in acute myeloid leukemia and glioblastoma by recurrent dominant-active mutants of isocitrate dehydrogenase 1 or 2 (IDH1/2), inhibits TET activity. Furthermore, lack of oxygen in hypoxia also inhibits TET function. **(B)** Model of TET-mediated enhancer regulation. Prior to the commissioning of an enhancer, pioneer transcription factor (indicated as TF_1) binds to nucleosomal DNA and recruits TET which oxidizes the surrounding 5mC into 5hmC (and/or other oxi-mCs), facilitating DNA demethylation. TET proteins and, TF_1 promote enhancer accessibility by recruiting nucleosome remodeling complexes, thus allowing binding of secondary transcription factors (indicated here as TF_2) that are otherwise inhibited by DNA methylation or the presence of nucleosomes.

TET

- In the presence of vitamin C, cells lacking TET1 undergo reprogramming more efficiently and this effect is related to the levels of 5hmC at loci involved in a key early step of reprogramming, the mesenchymal-to-epithelial transition (MET).



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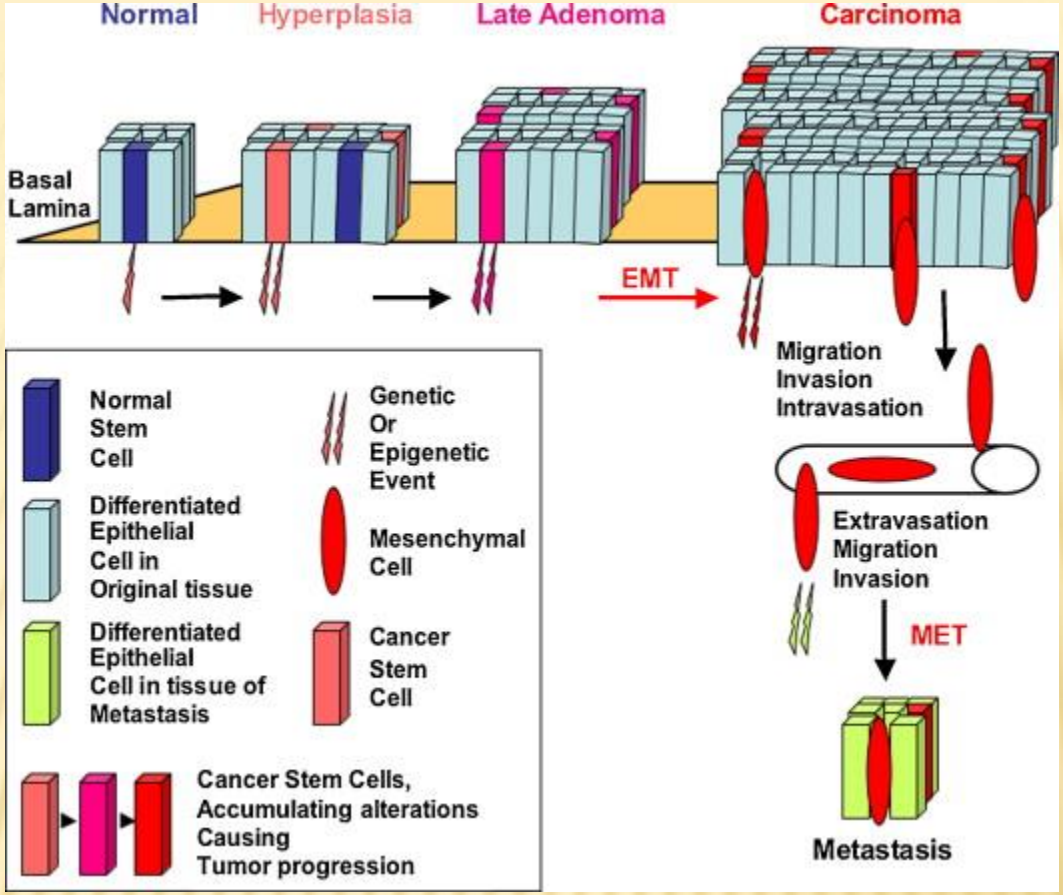
The role of TET2 in myeloid differentiation and function

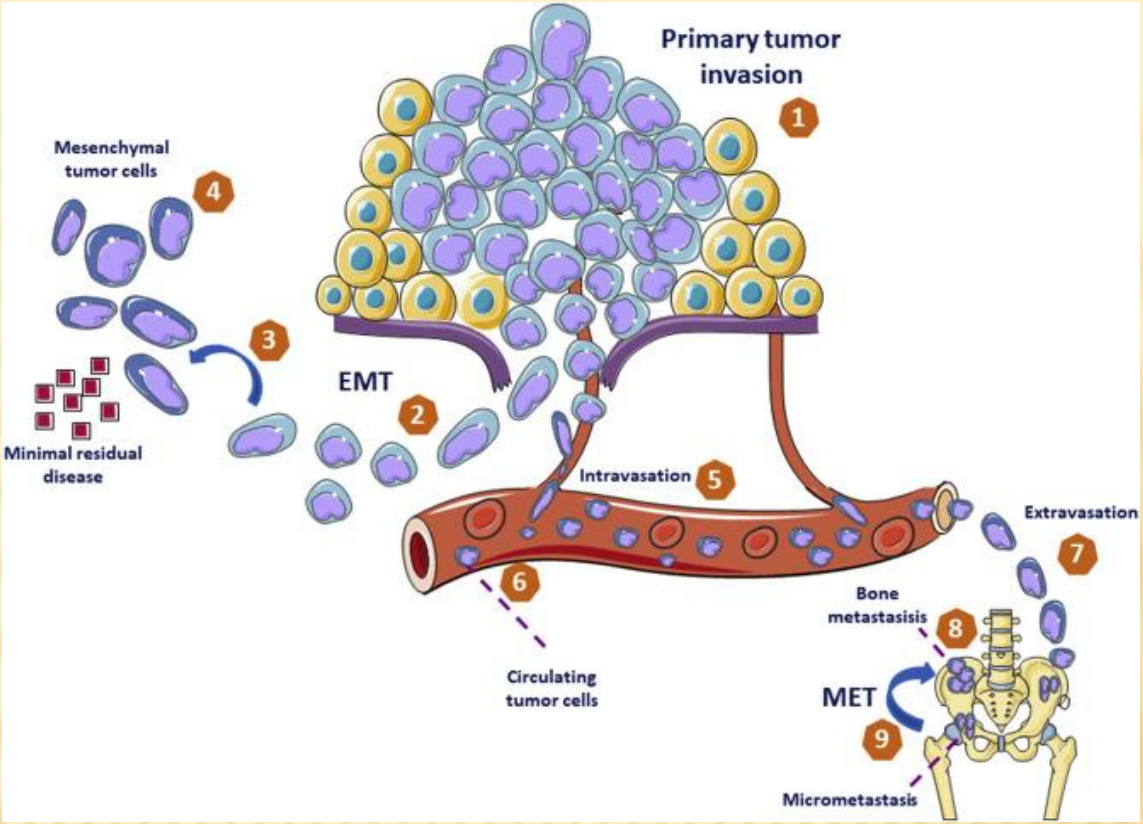
(A)TET2 regulates myeloid cell differentiation. TET2, together with the thymine DNA glycosylase (TDG), facilitate active DNA demethylation and promotes lineage-specific gene expression during the differentiation of osteoclasts, macrophages, and dendritic cells from human monocytes.

(B)TET2 regulates the function of myeloid cells. In mouse and human macrophages, TET2 repressed expression of the pro-inflammatory cytokines IL-1β and IL-6. In plasmacytoid dendritic cells, CXXC5 recruited TET2 to an intragenic CpG island in *Irf7 (interferon regulatory factor 7)*, facilitating the demethylation and maintaining basal expression. As a result, loss of *Cxxc5*, and to a lesser extent *Tet2*, resulted in decreased levels of IRF7, decreased type I interferon (IFN-I) production, and decreased anti-viral responses.

EMT = mesenchymal –epithelial transition



The role of cancer stem cells and EMT in homeostasis and carcinogenesis. Normal stem cells in epithelial tissues play an essential role in homeostasis. However, since they are long-term residents, they are able to accumulate sufficient genetic or epigenetic alterations to give rise to cancer stem cells that contribute to the etiology and progression of tumors. Because tumor progression is associated with the loss of epithelial characteristics, a motile phenotype, degradation of the basal lamina and ability to survive outside the epithelium, the normal cellular processes involved in EMT play a key role in the multi-stage evolution from a benign to an invasive, malignant tumor. In addition, the establishment of a distant metastasis can be seen as MET. EMT = epithelial–mesenchymal transition;



Tumor progression and the key events in the epithelial-mesenchymal (EMT) and the mesenchymal-epithelial (MET) transitions. (1,2) Epithelial carcinomas undergo the EMT to escape the tumor mass, resulting in (3) minimal residual disease. (4) Re-epithelialization is necessary to develop a new malignant process. (5,6) Cells that undergo the EMT are de-differentiated and well adapted to perform intravasation and maintain circulation. (7) This fact assists in the extravasation process. (8) In this de-differentiated stage, cells can remain as micro-metastases in the bone marrow. (9) Reversal of the epithelial phenotype through the MET may occur, promoting the formation of macro-metastases and the death of osteoblasts.

Nitric Oxide. 2019 Apr 19. pii: S1089-8603(18)30305-7. doi: 10.1016/j.niox.2019.04.009

Díky za pozornost