Metabolism of lipids VII:

Eicosanoids

Prof. Mamoun Ahram

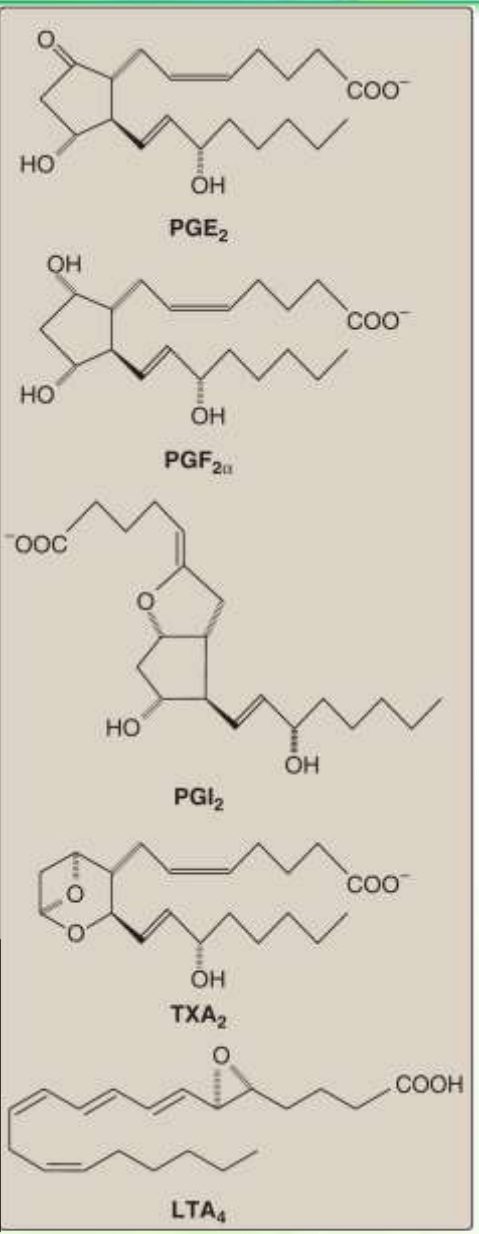
Resources

- This lecture
- Lippincott's Biochemistry, Ch. 17
- Eicosanoid Metabolism: Prostaglandins, Thromboxanes, Leukotrienes, and Lipoxins (https://themedicalbiochemistrypage.org/eicosanoid-metabolism-prostaglandins-thromboxanes-leukotrienes-and-lipoxins/)
- Bioactive Lipid Mediators of Inflammation (https://themedicalbiochemistrypage.org/bioactive-lipid-mediators-of-inflammation/)

Overview of eicosanoids

Do not memorize the structures

- Eicosanoids are classified into four groups: (1) Prostaglandins (PG) and prostacyclins (PGI), and (2) thromboxanes (TX); (3) the leukotrienes (LT) and (4) lipoxins (LX).
  - Prostaglandins, prostacyclins, and thromboxanes are known as prostanoids.
- They are produced from ω-3 and ω-6 polyunsaturated FA with 20 carbons (eicosa = 20).
- They elicit physiologic (inflammatory) and pathologic (hypersensitivity) responses:
  - Gastric integrity, renal function, smooth muscle contraction (intestine and uterus), blood vessel diameter, and platelet homeostasis.
- They are not stored.
- They have a short half-life.
- They are rapidly metabolized to inactive products.
- They are not hormones.



Reasons for naming

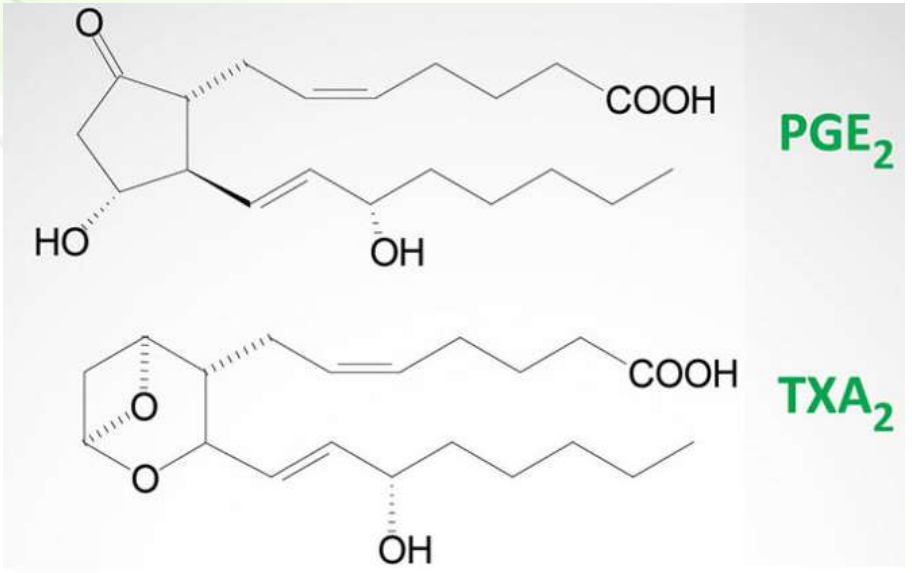
- Site of synthesis:
  - Prostaglandins were originally shown to originate from the prostate gland.
  - Thromboxanes from platelets (thrombocytes)
  - Leukotrienes from leukocytes.
  - Lipoxins are inflammation resolving eicosanoids synthesized through **lipox**ygenase **in**teractions.

Prostaglandins and thromboxanes

Do not memorize the table

TABLE 14.2: Salient features of prostaglandins

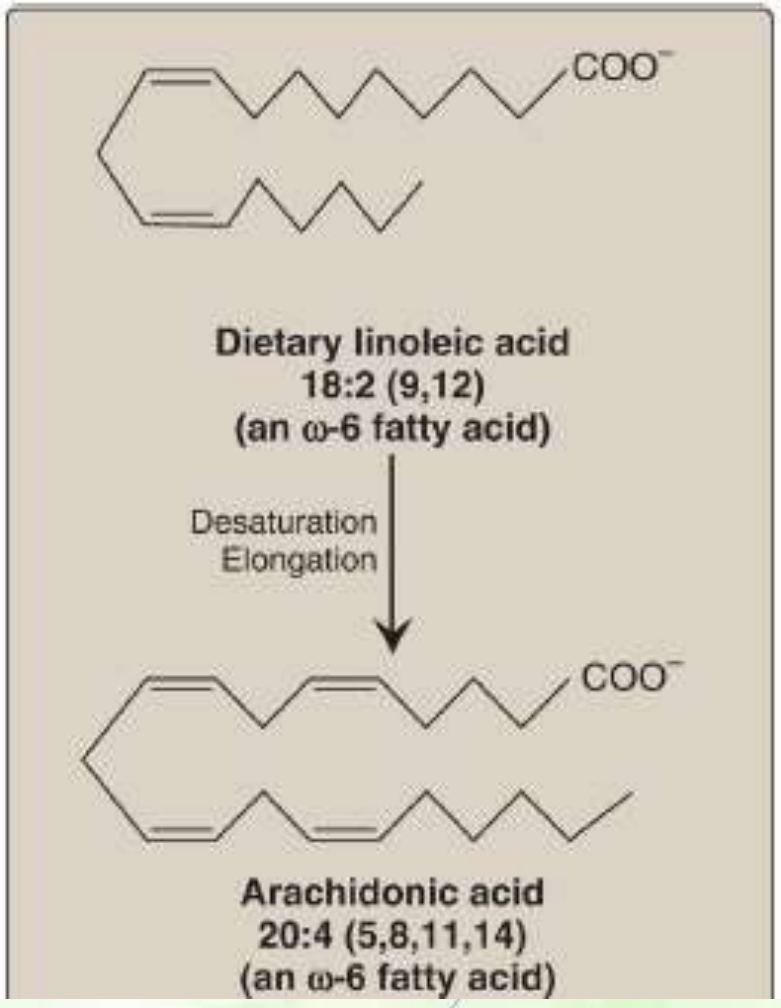
Name	*Substituent groups*
PGA	Keto group at C9; double bond C10 and 11
PGB	Keto group at C9; double bond C8 and 12
PGD	OH group at C9; keto group at C11
PGE	Keto group at C9; OH group at C11
PGF	OH groups at C9 and C11 (Fig.14.2)
PGG	Two oxygen atoms, interconnected to each other, and bonded at C9 and C11; hydroperoxide group at C15
PGH	Same ring as PGG; but C15 has OH group
PGI	Double ring. Oxygen attached to C6 and C9, to form another 5-membered ring. Hence called prostacyclin.



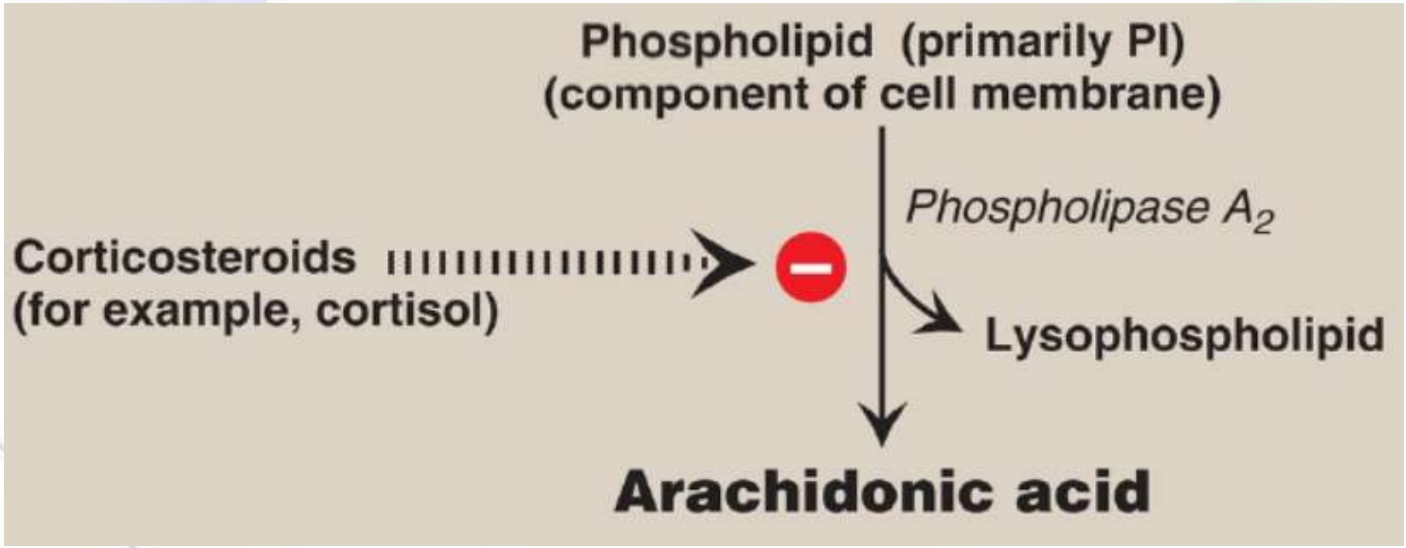
- Prostaglandins are produced by almost all nucleated cells in most tissues and organs.
- They have a cyclopentane ring.
- They are designated by a letter that describes the ring modification followed by a number that indicates the number of double bonds.
  - Series 1 PGs contain one double bond, series 2 has 2, and so on.
- Thromboxanes have a 6-membered ring.

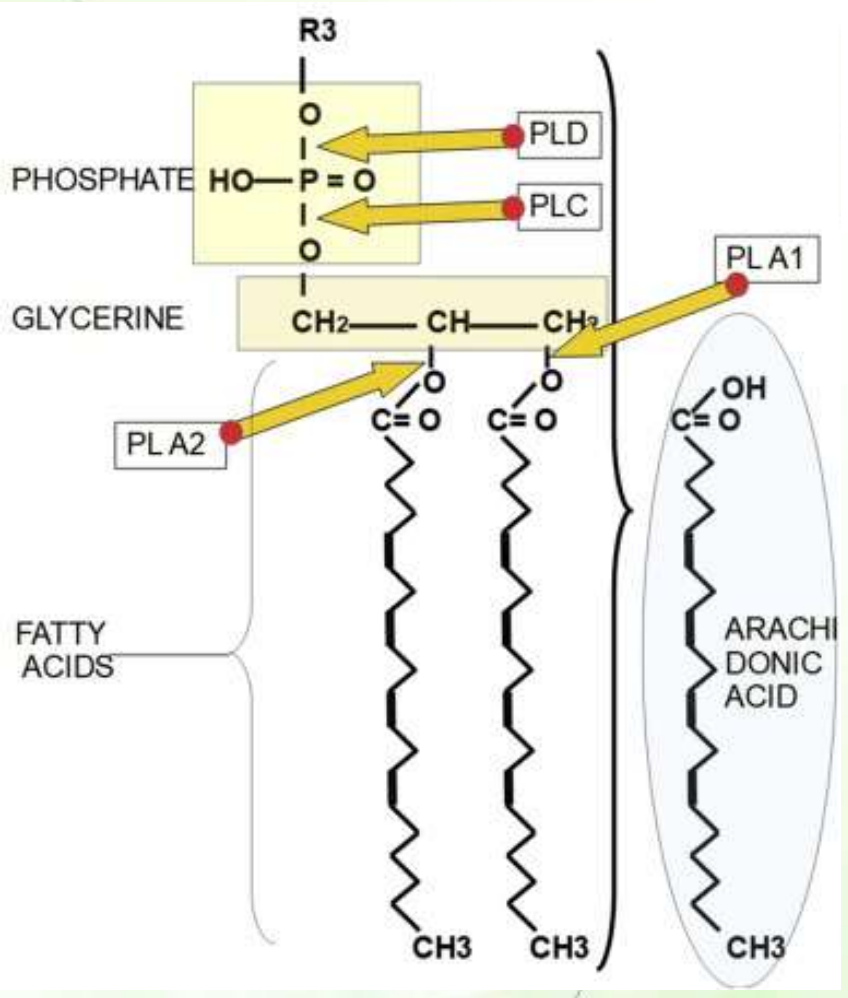
Synthesis from arachidonic acid

- Arachidonic acid (an eicosatetraenoic FA), is the immediate precursor of PG (AKA series 2 or those with two double bonds).
- Arachidonic acid is derived by the elongation and desaturation of the linoleic acid.
- Arachidonic acid is incorporated into membrane phospholipids (typically PI) at carbon 2 and released by *phospholipase A2.*



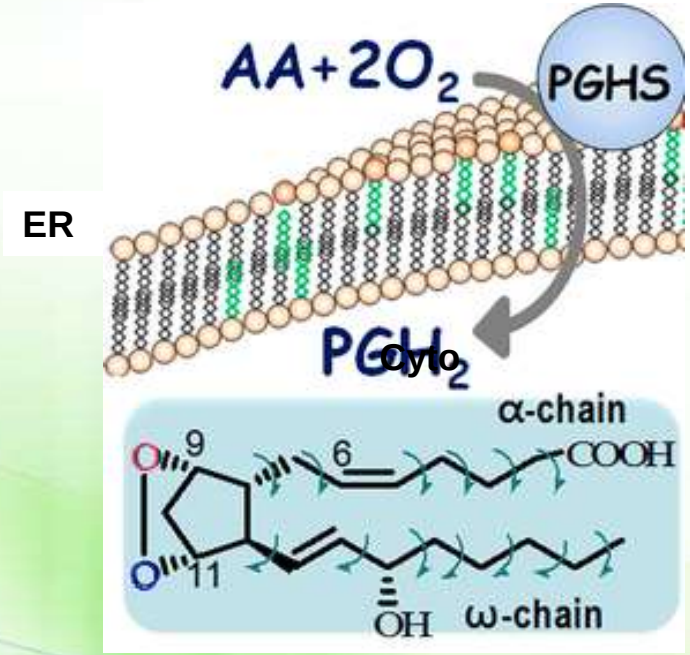
Before synthesis of PGs and TXs

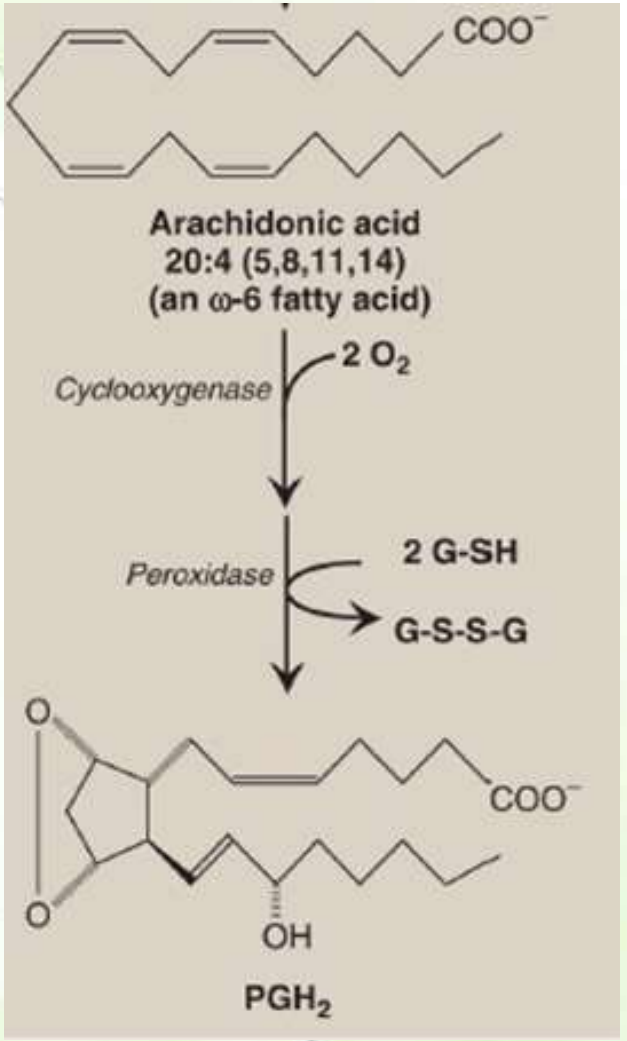




Prostaglandin H2 synthase

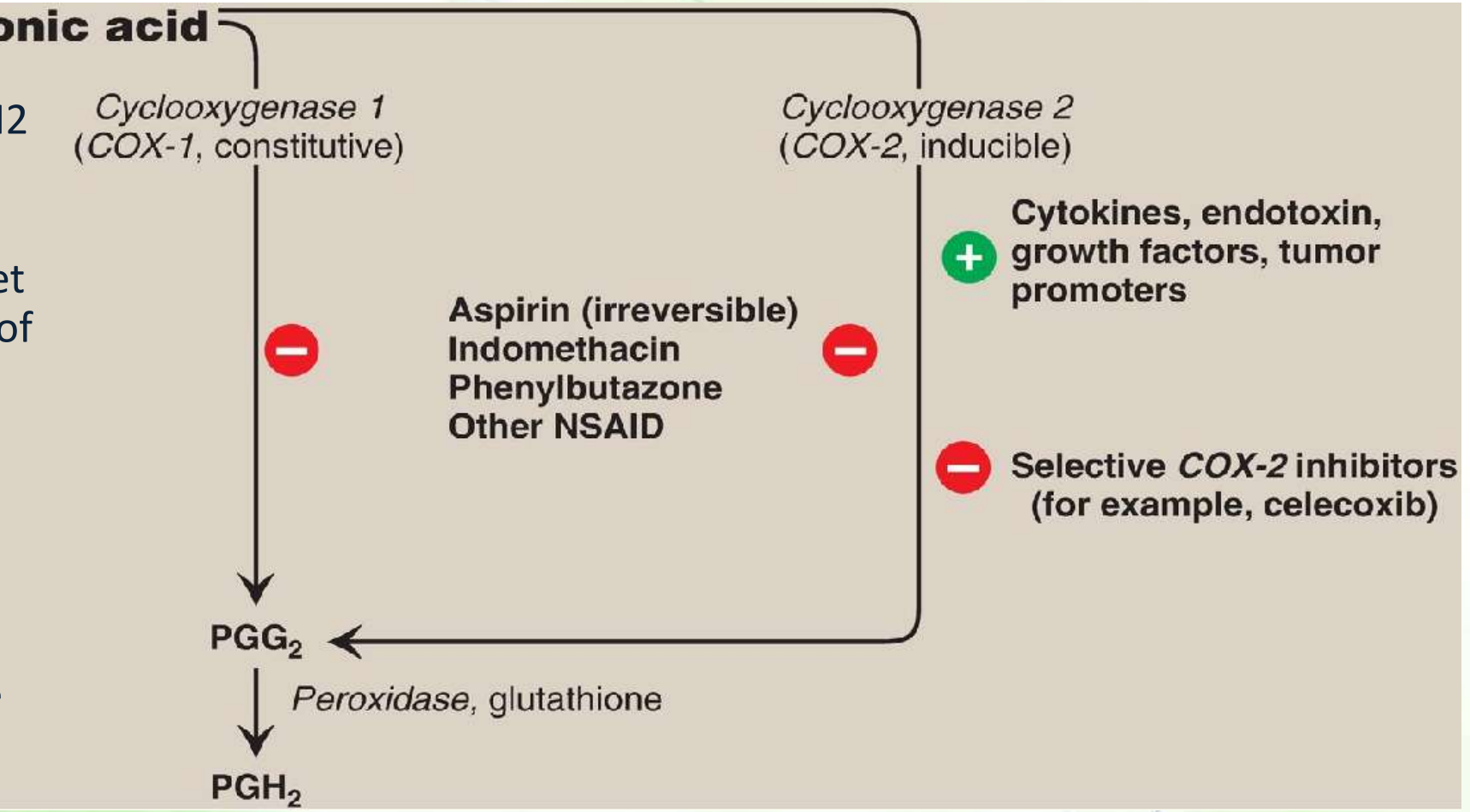
- Synthesis of PGs and TXs starts by oxidative cyclization of arachidonic acid to yield PGH2 by PGH2 synthase (or, prostaglandin endoperoxide synthase).
- PGH2 synthase has two catalytic activities: a fatty acid cyclooxygenase (COX) and a peroxidase, which requires reduced glutathione.



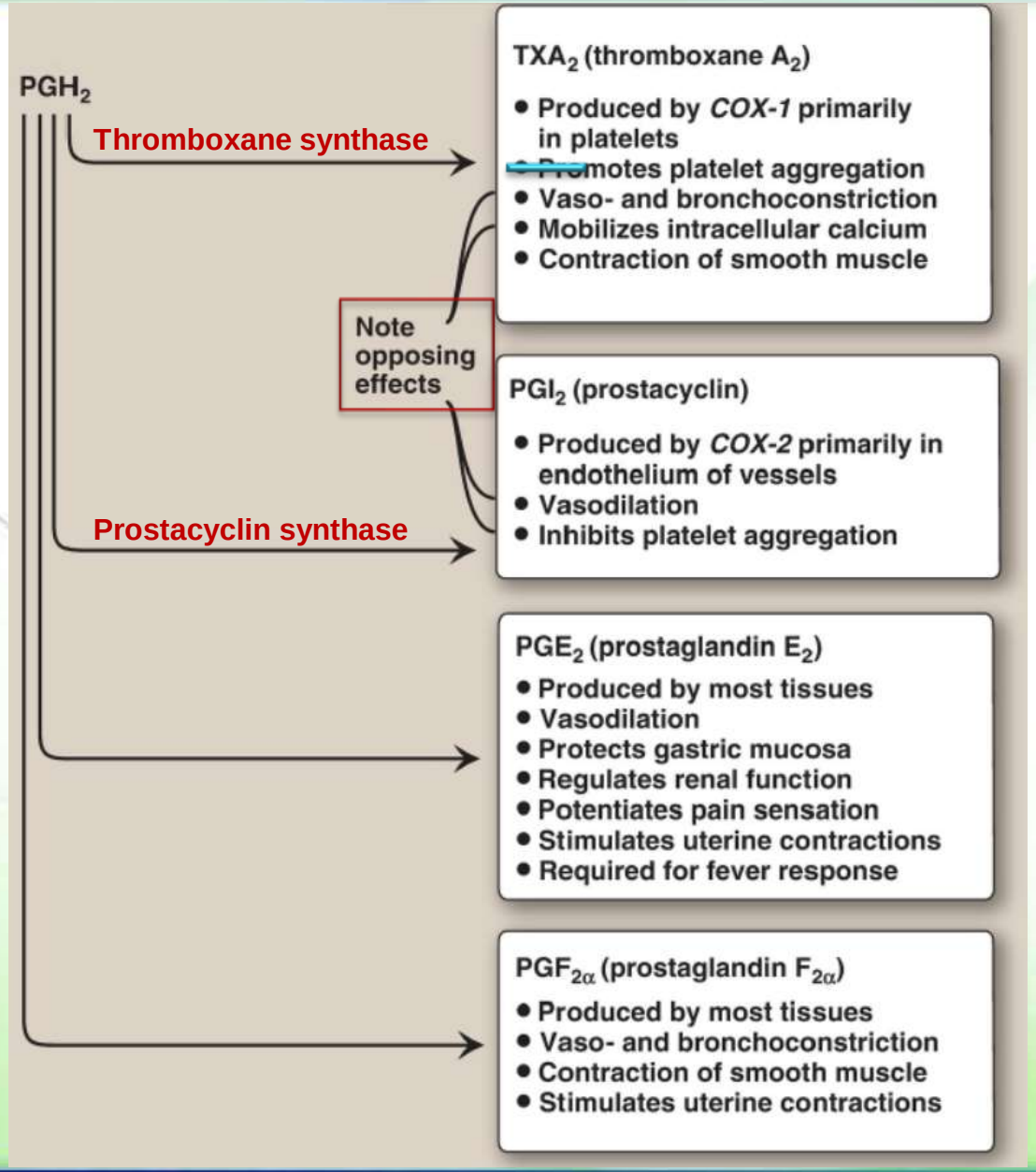


Cyclooxygenases

- There are two isozymes of PGH2 synthase: COX-1 and COX-2.
- COX-1 is made constitutively in most tissues and affects platelet aggregation and the functions of gastric renal tissues.
- COX-2 is inducible in specific tissues and mediates the pain, heat, redness, and swelling of inflammation and the fever of infection.
- Both COX-1 and COX-2 catalyze the two reactions.

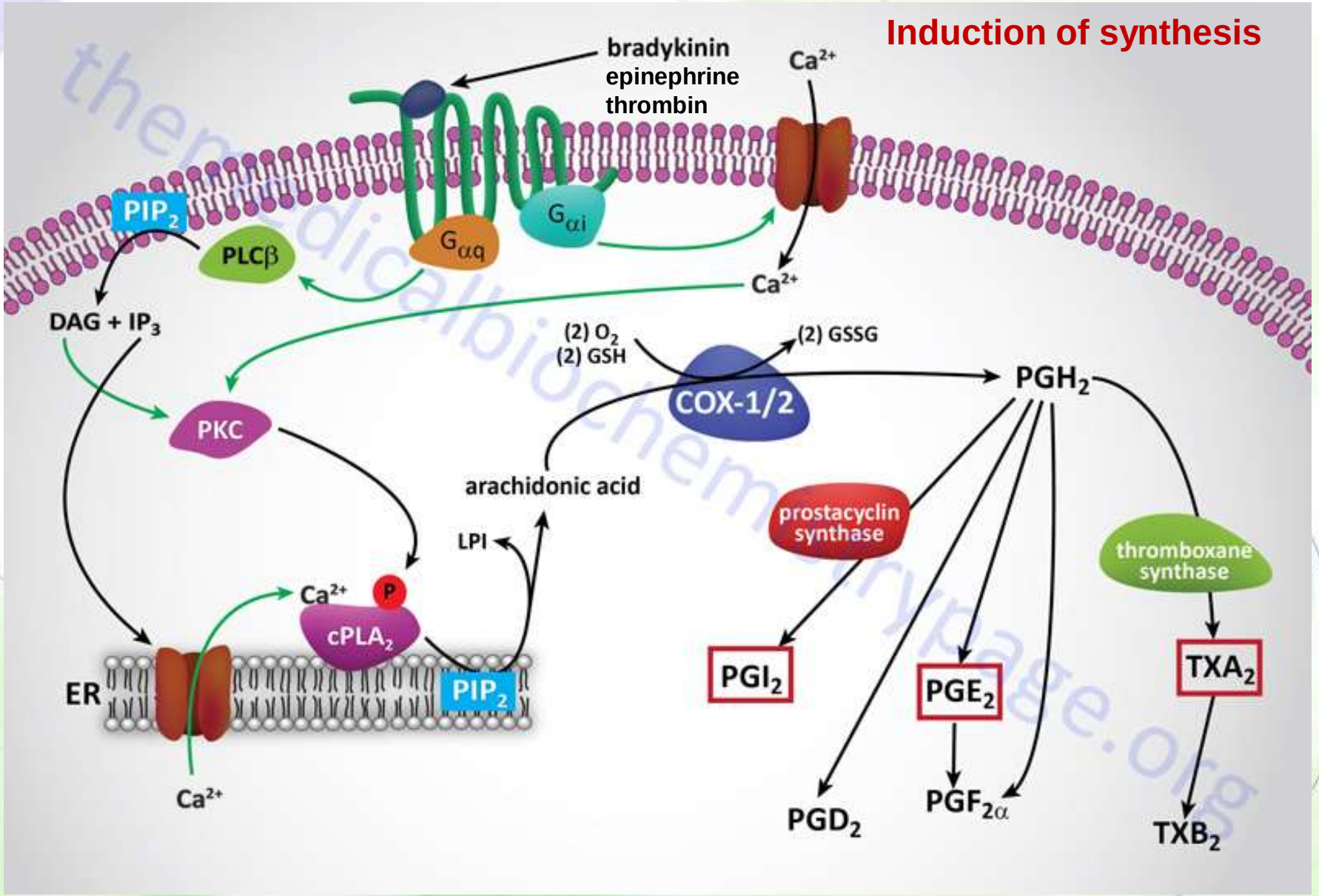


PGH2 is then converted to a variety of PG and TX

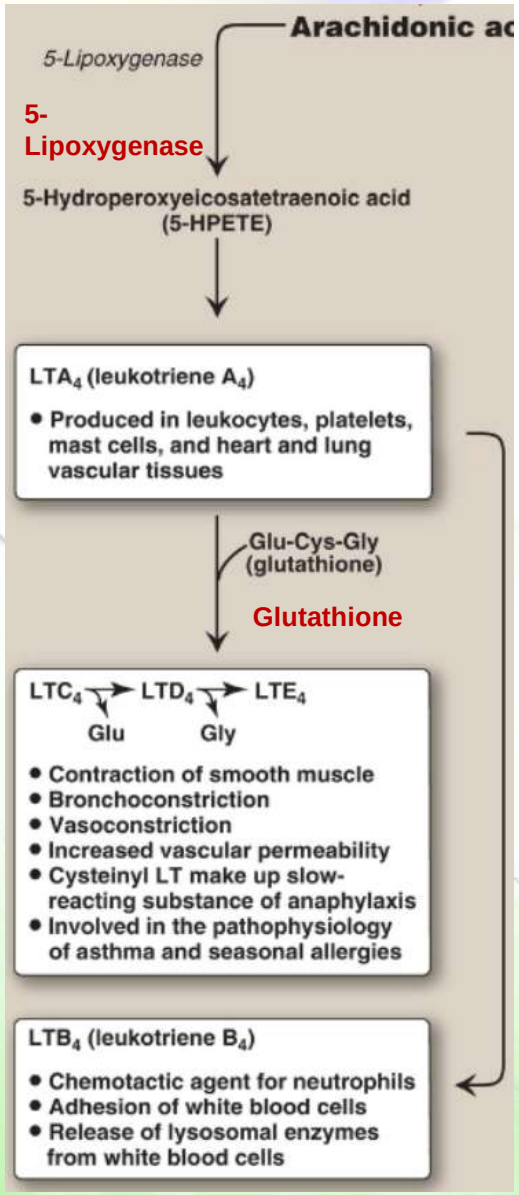


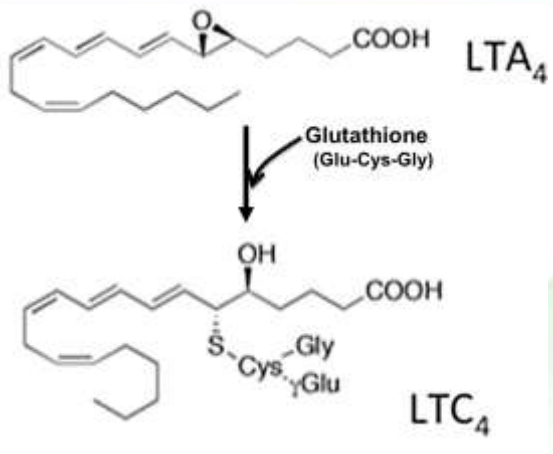
- The opposing effects of thromboxane A2 (TXA2) and prostacyclin (PGI2) limit thrombi formation to sites of vascular injury.
- Aspirin has an antithrombogenic effect. It inhibits TXA2 synthesis by COX-1 in platelets and PGI2 synthesis by COX-2 in endothelial cells
- COX-1 inhibition cannot be overcome in platelets because they cannot synthesize it anymore, but COX-2 inhibition can be overcome in endothelial cells.
- This is why low-dose aspirin is lowers the risk of stroke and heart attacks by decreasing the formation of thrombi.

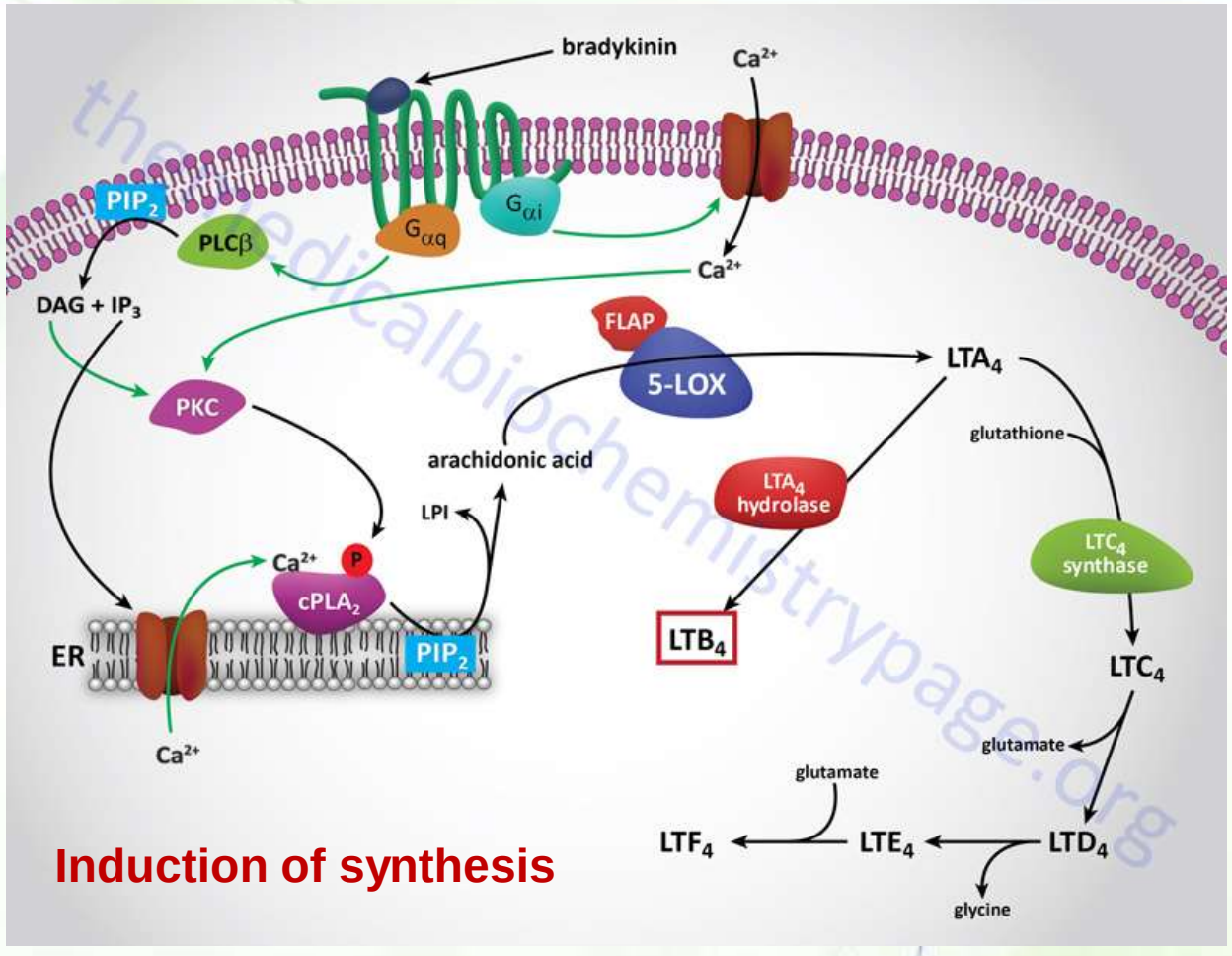
Signals leading to synthesis of eicosanoids



Leukotriene synthesis



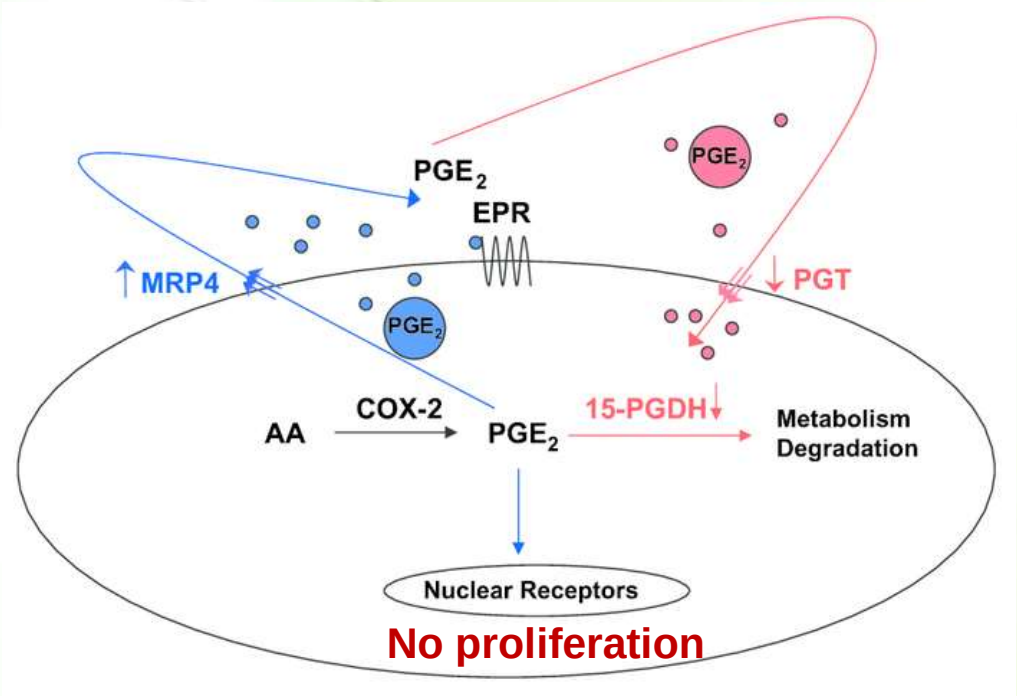




- LT are mediators of allergic response and inflammation.
- Inhibitors of 5-LOX and LT-receptor antagonists are used in the treatment of asthma.
- Note: LT synthesis is inhibited by cortisol and not by NSAID. Aspirin-exacerbated respiratory disease is a response to LT overproduction with NSAID use in ~10% of individuals with asthma.

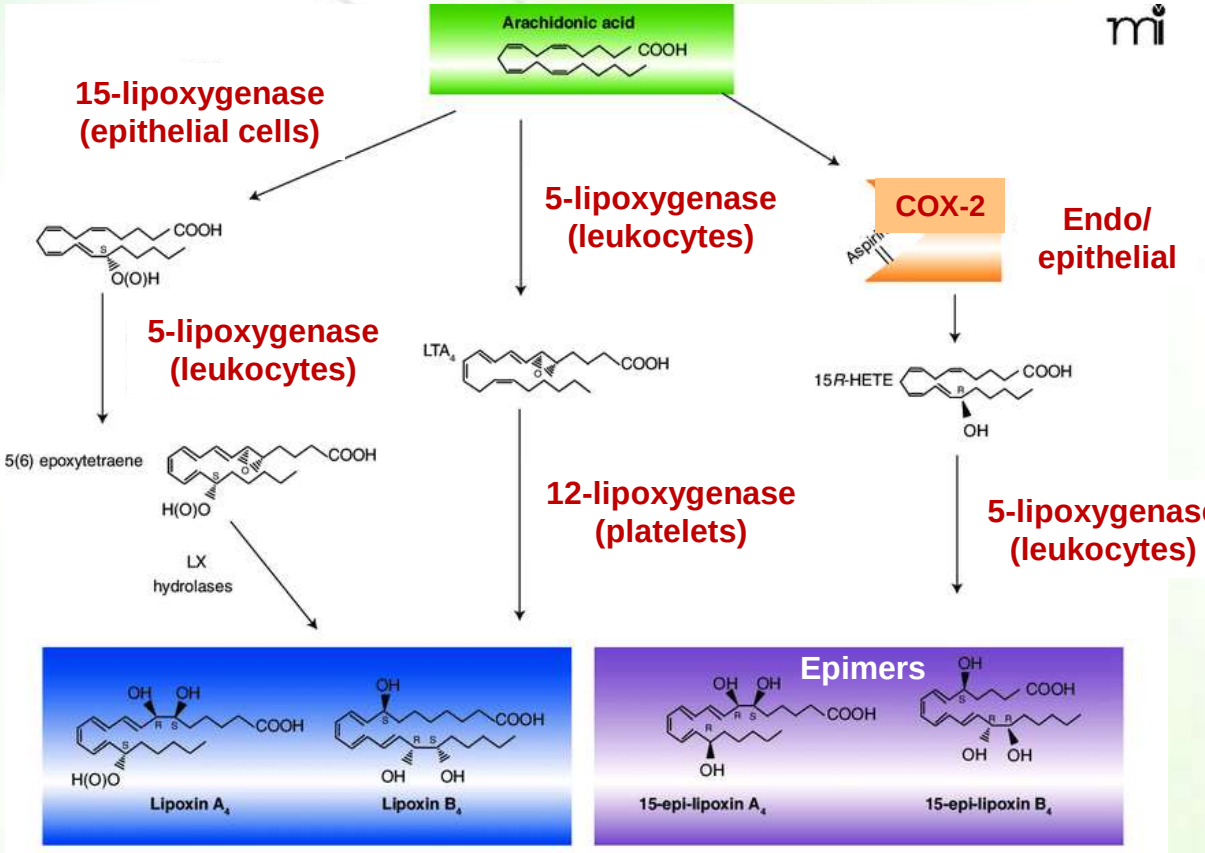
Catabolism of prostanoids

- Prostanoids are often deactivated quickly either spontaneously or enzymatically.
  - Half-lives of 30 seconds.
- Prostanoids are first transported from the extracellular fluid to the cytoplasm by the prostaglandin transport protein (PGT) where they are converted into products that are either inactive or can inhibit cell proliferation.
- They are eliminated via the kidney into the urine.



Synthesis of lipoxins

- The lipoxins are anti-inflammatory since they inhibit the actions of the leukotrienes.
- Synthetic pathways of lipoxins:
  - The “classic” pathway: 5-lipoxygenase (5-LOX) in leukocytes followed by 12-LOX in platelets.
  - 15-LOX in epithelial cell, such as airway cells, followed by 5-LOX action in leukocytes.
  - Aspirin-mediated acetylation of COX-2.
    - Aspirin-induced acetylation of COX-2 alters the enzyme such that it converts arachidonic acid to biologically active LXs in monocytes and leukocytes by 5-lipoxygenase (5-LOX).



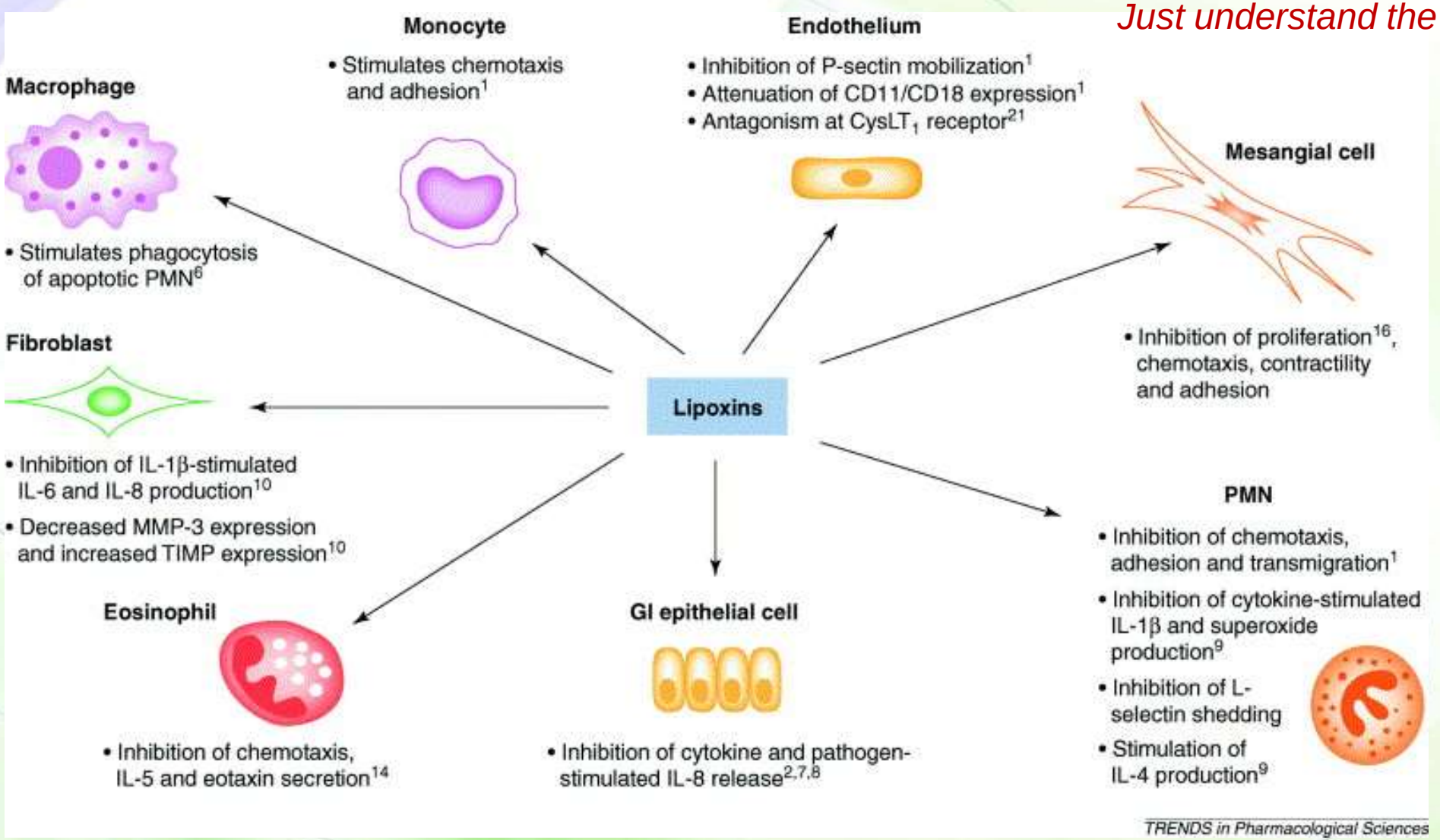
The functions of lipoxins

Do not memorize the points.
Just understand the concept

- The lipoxins LXA4 and 15 epi-LXA4 function through lipoxin A4 receptor (ALXR), a G protein-coupled receptor (GPCR) to:
  - Increase the production of prostacyclin (PGI_2) and nitric oxide (NO),
  - promote the relaxation of the vasculature,
  - inhibit polymorphonuclear leukocyte (PMN)-mediated increases in vasopermeability, and PMN chemotaxis, adhesion and migration through the endothelium,
  - stimulate phagocytosis of apoptotic PMNs by macrophages (the resolution phase of inflammatory events),
  - blocking the expression of the pro-inflammatory IL-8 by macrophages and endothelial,
  - regulate the actions of histamine leading to a reduction in edema.

The functions of lipoxins (in picture)

Do not memorize.
Just understand the concept



The specialized pro-resolving mediators (SPM)

- Resolvins (Rv), protectins (PD), and maresins (MaR) are anti-inflammatory lipids that are derived from the omega-3 EPA- and DHA by lipoxygenases.
- Aspirin triggers their synthesis.
- They stimulate the resolution of the inflammatory responses through G protein-coupled receptors via diverse action like:
  - limiting further neutrophil recruitment to the site of inflammation
  - promoting macrophage clearance of debris, apoptotic cells and bacteria.