Prof. Mamoun Ahram

Metabolism of lipids VII:

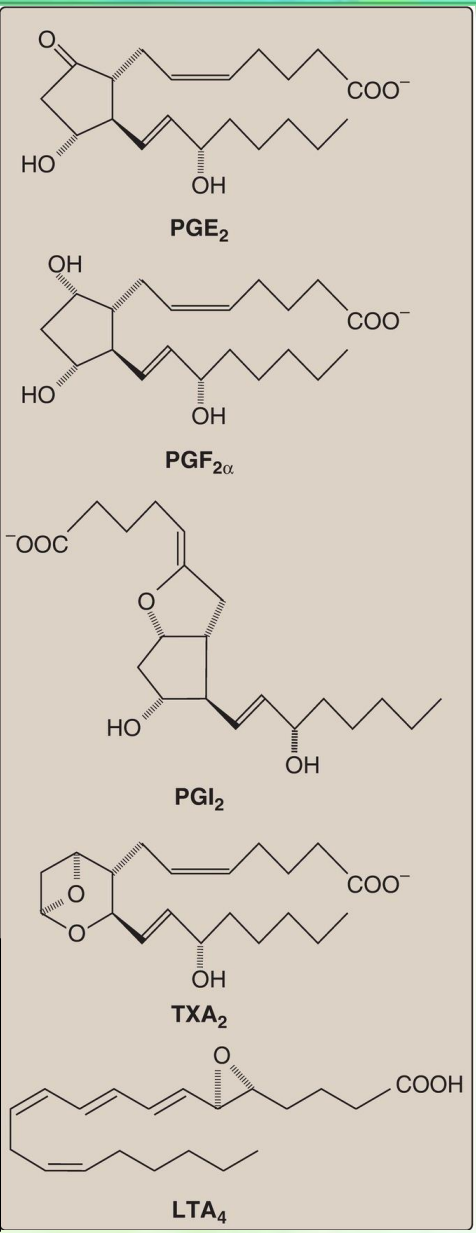
Eicosanoids

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

- Eicosanoids are classified into four groups: (1) Prostaglandins (PG) and prostacyclins (PGI), and (2) thromboxanes (TX); a third type is the leukotrienes (LT) and a fourth is and 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.

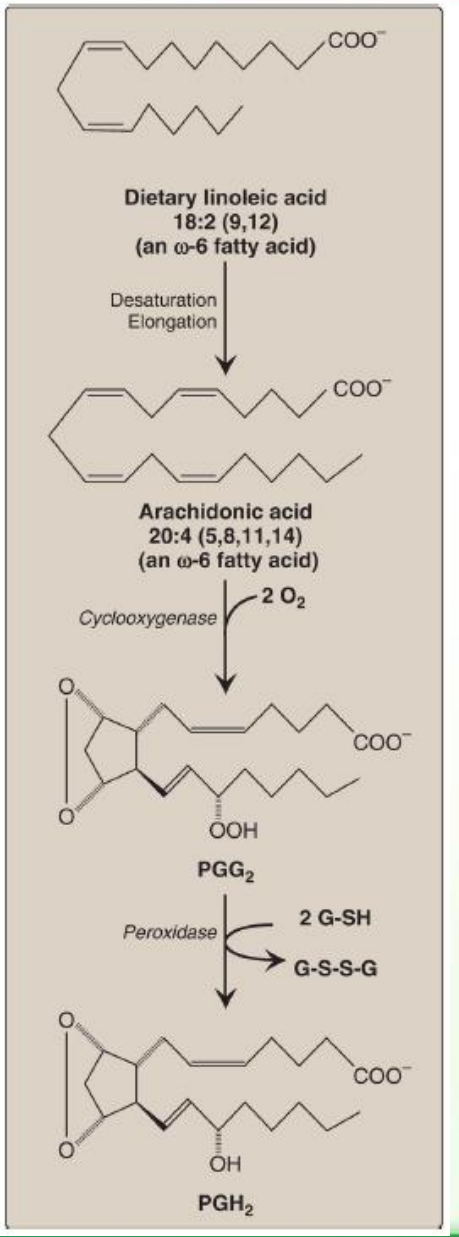


Reasons for naming

- 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.

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.*

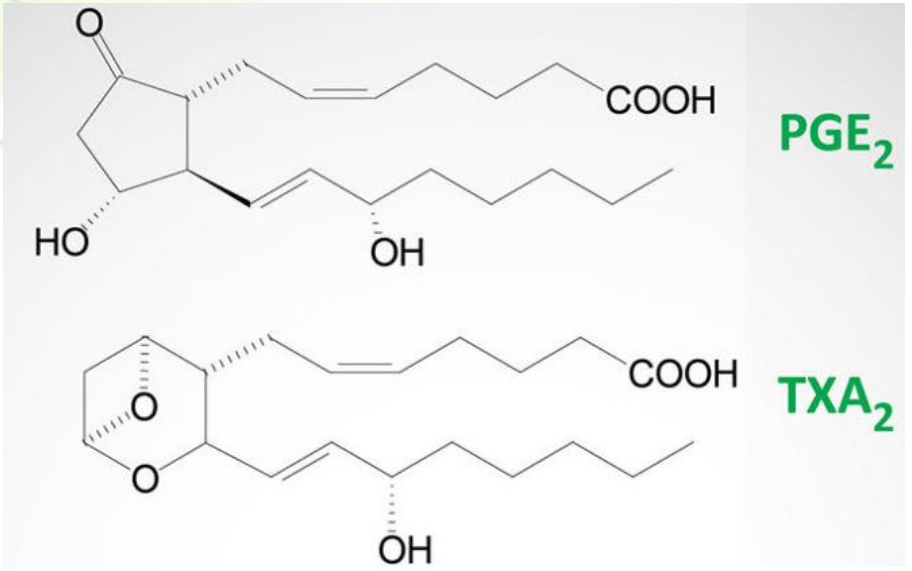


Prostaglandins and thromboxanes

Do not memorize the table

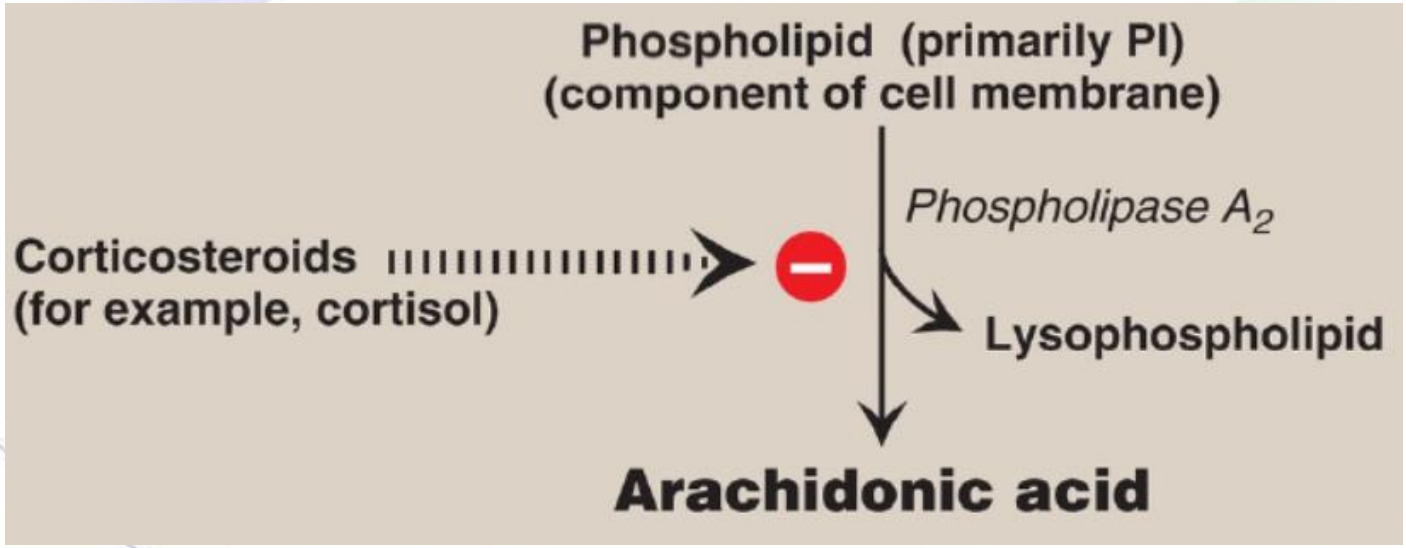
TABLE 14.2: Salient features of prostaglandins

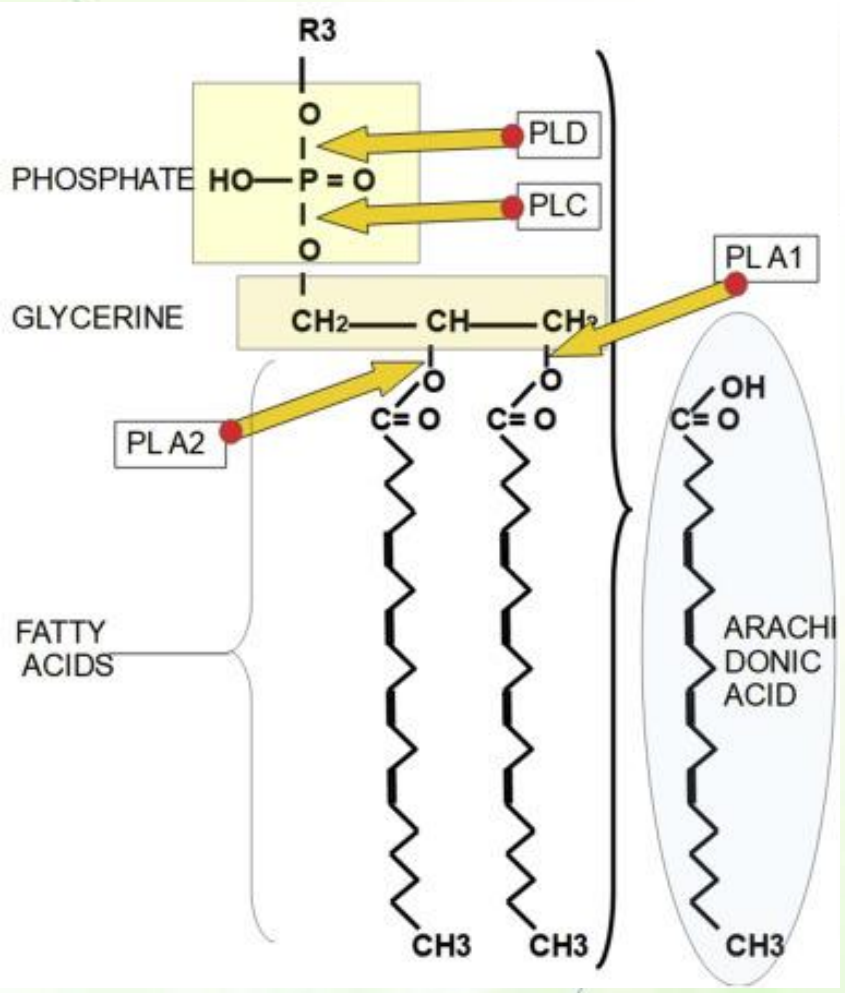
Name	*Substituent groups*
PGA	Keto group at C9; double bond C10 and 11
PGB	Keto group at C9; double bond C8 and 12
PGD	OH group at C9; keto group at C11
PGE	Keto group at C9; OH group at C11
PGF	OH groups at C9 and C11 (Fig.14.2)
PGG	Two oxygen atoms, interconnected to each other, and bonded at C9 and 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 found in most tissues and organs and are produced by almost all nucleated cells.
- 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.

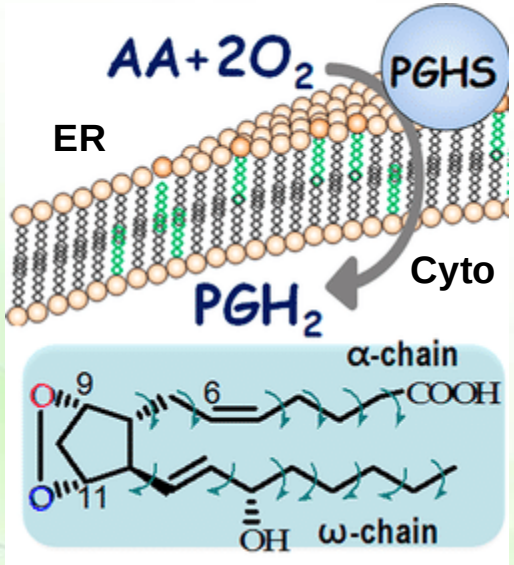
Before synthesis of PGs and TXs

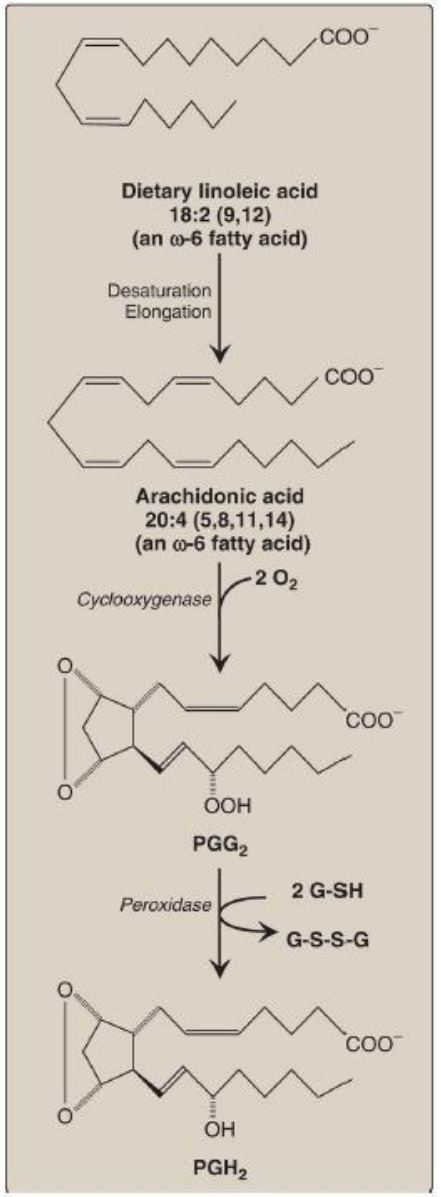




Prostaglandin H2 synthase

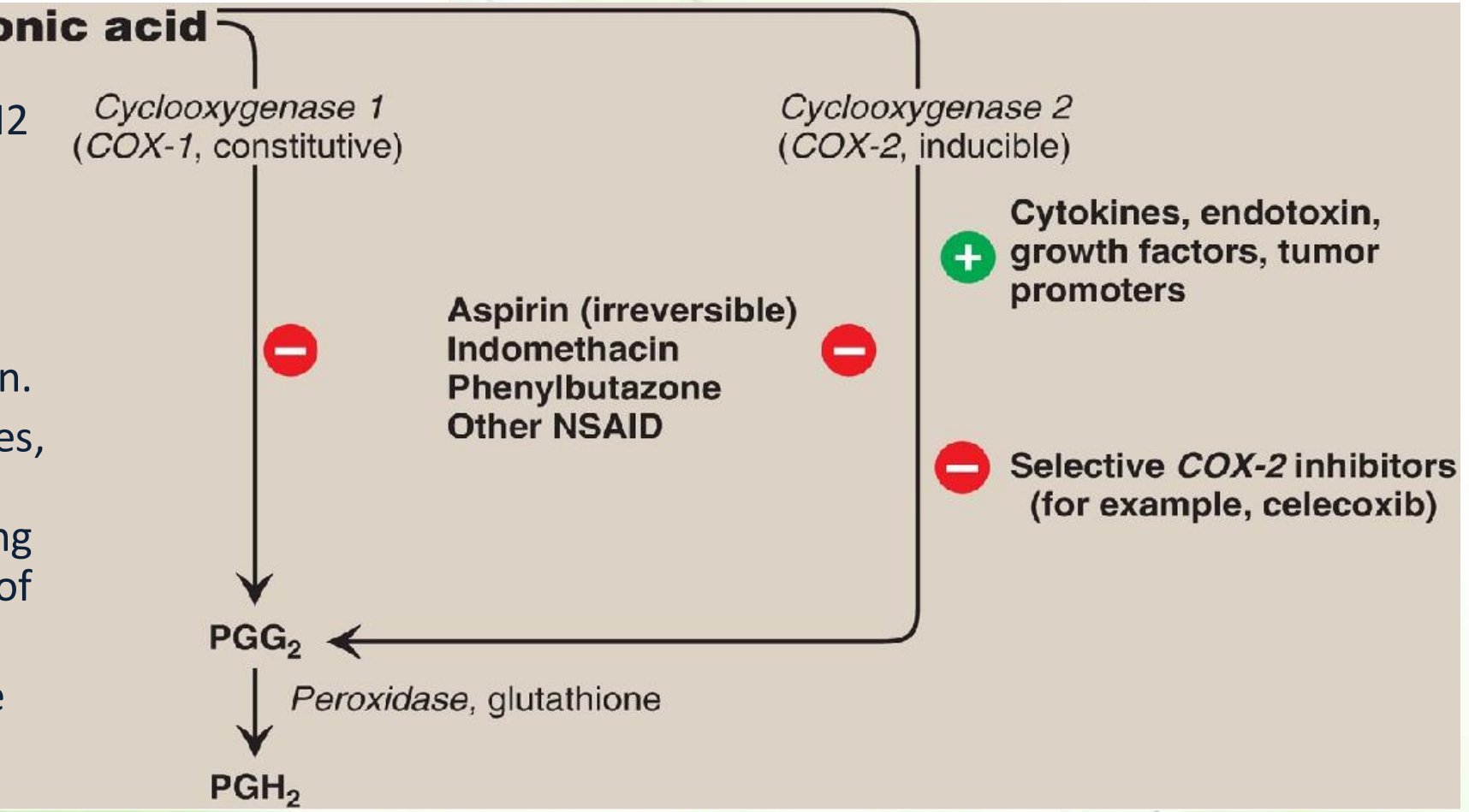
- Synthesis of PGs and TXs starts by oxidative cyclization of arachidonic acid to yield PGH2 by PGH2 synthase (or, prostaglandin endoperoxide synthase).
- PGH2 synthase is an ER membrane-bound protein and has two catalytic activities: a fatty acid cyclooxygenase (COX), which requires two molecules of O_2, and a peroxidase, which requires reduced glutathione.



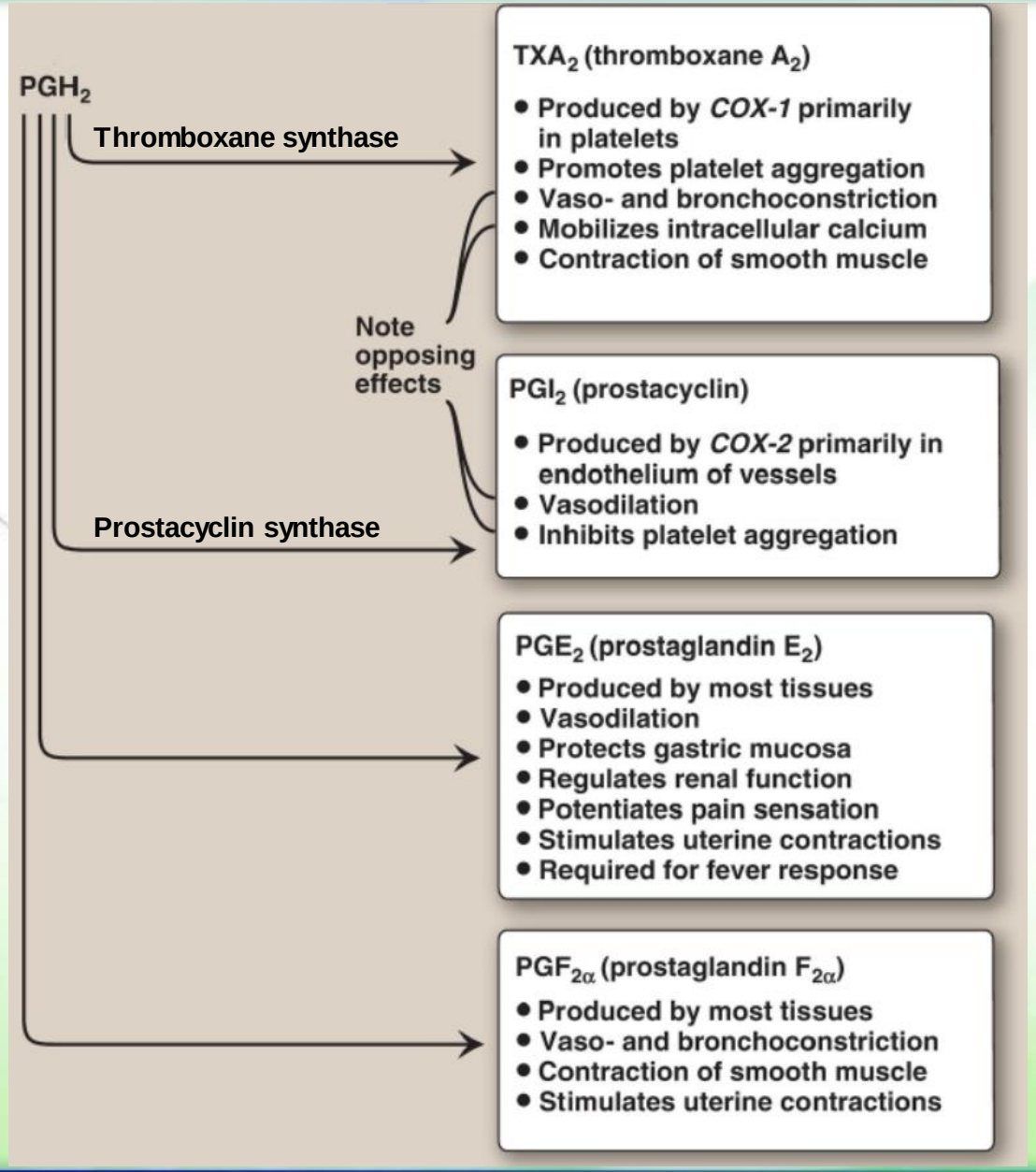


Cyclooxygenases

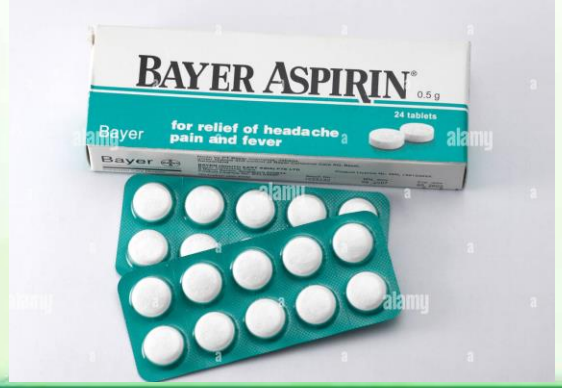
- There are two isozymes of PGH2 synthase: COX-1 and COX-2.
- COX-1 is made constitutively in most tissues and is involved in functions of gastric and renal tissues and platelet aggregation.
- COX-2 is found in specific tissues, is inducible, and mediates the pain, heat, redness, and swelling of inflammation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



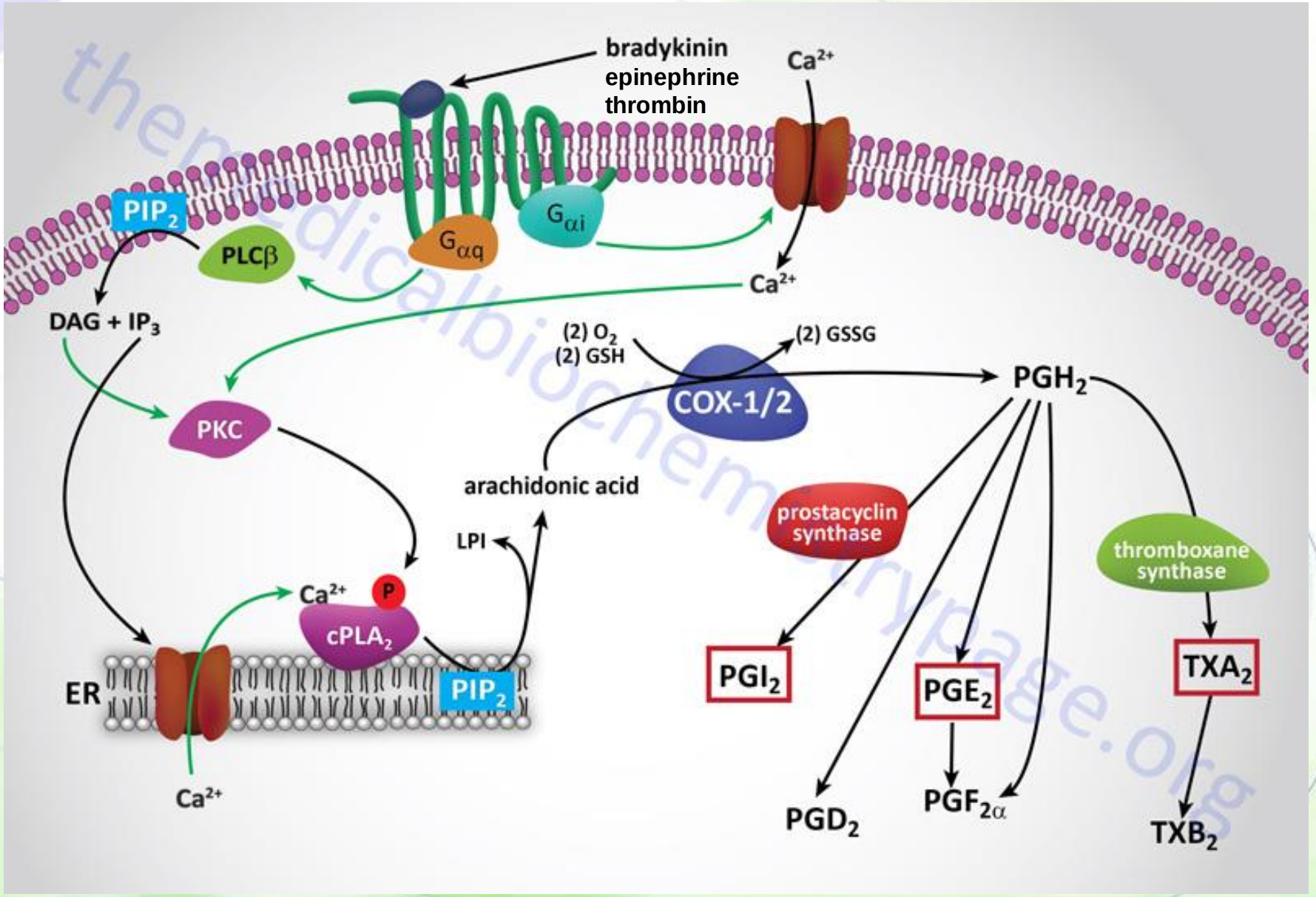
PGH2 is then converted to a variety of PG and TX



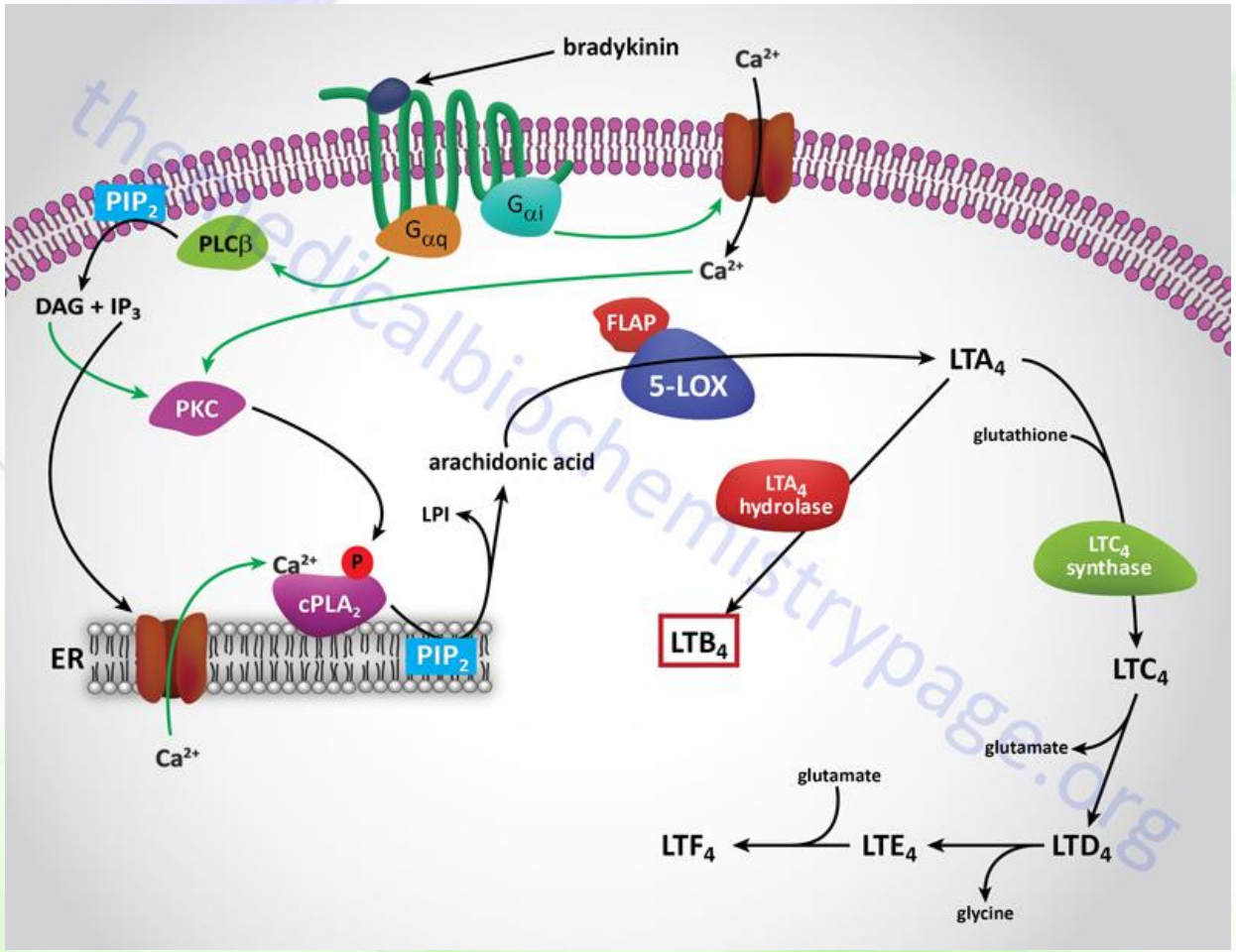
- The opposing effects of TXA2 and PGI2 limit thrombi formation to sites of vascular injury.
- Aspirin has an antithrombogenic effect. It inhibits TXA2 synthesis by COX-1 in platelets and PGI2 synthesis by COX-2 in endothelial cells
- COX-1 inhibition cannot be overcome in platelets because they cannot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

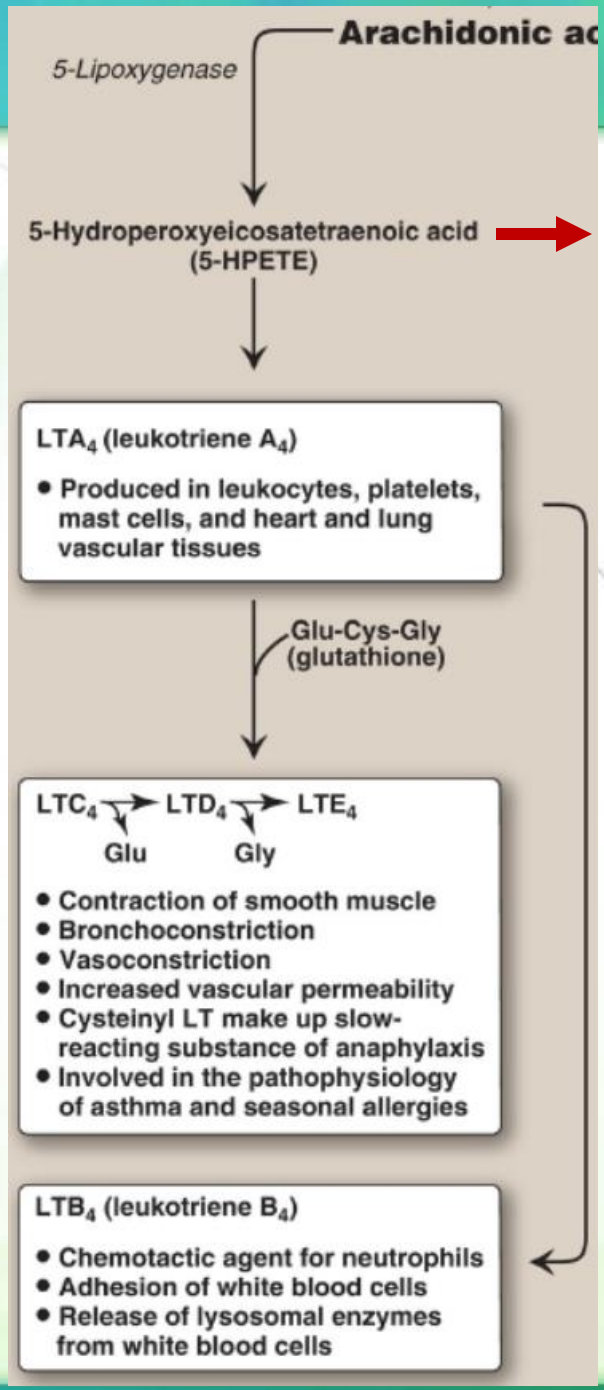


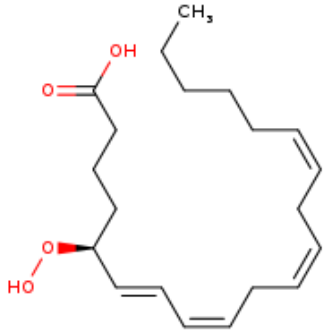
Signals leading to synthesis of eicosanoids

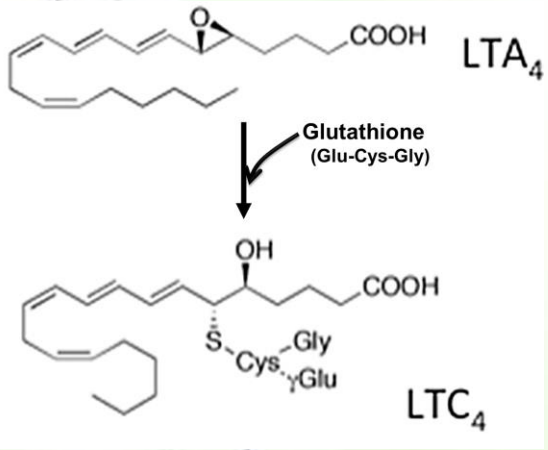


Leukotriene synthesis







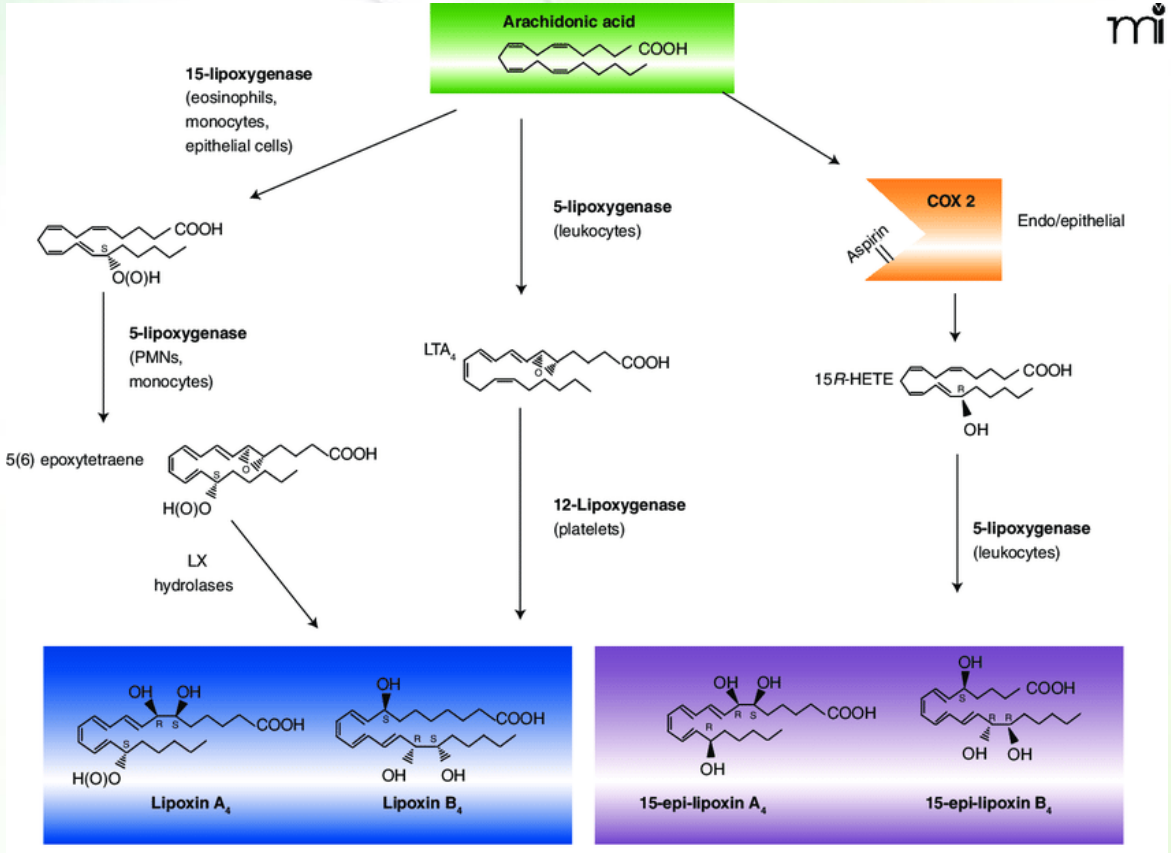


Catabolism of prostanoids

- 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

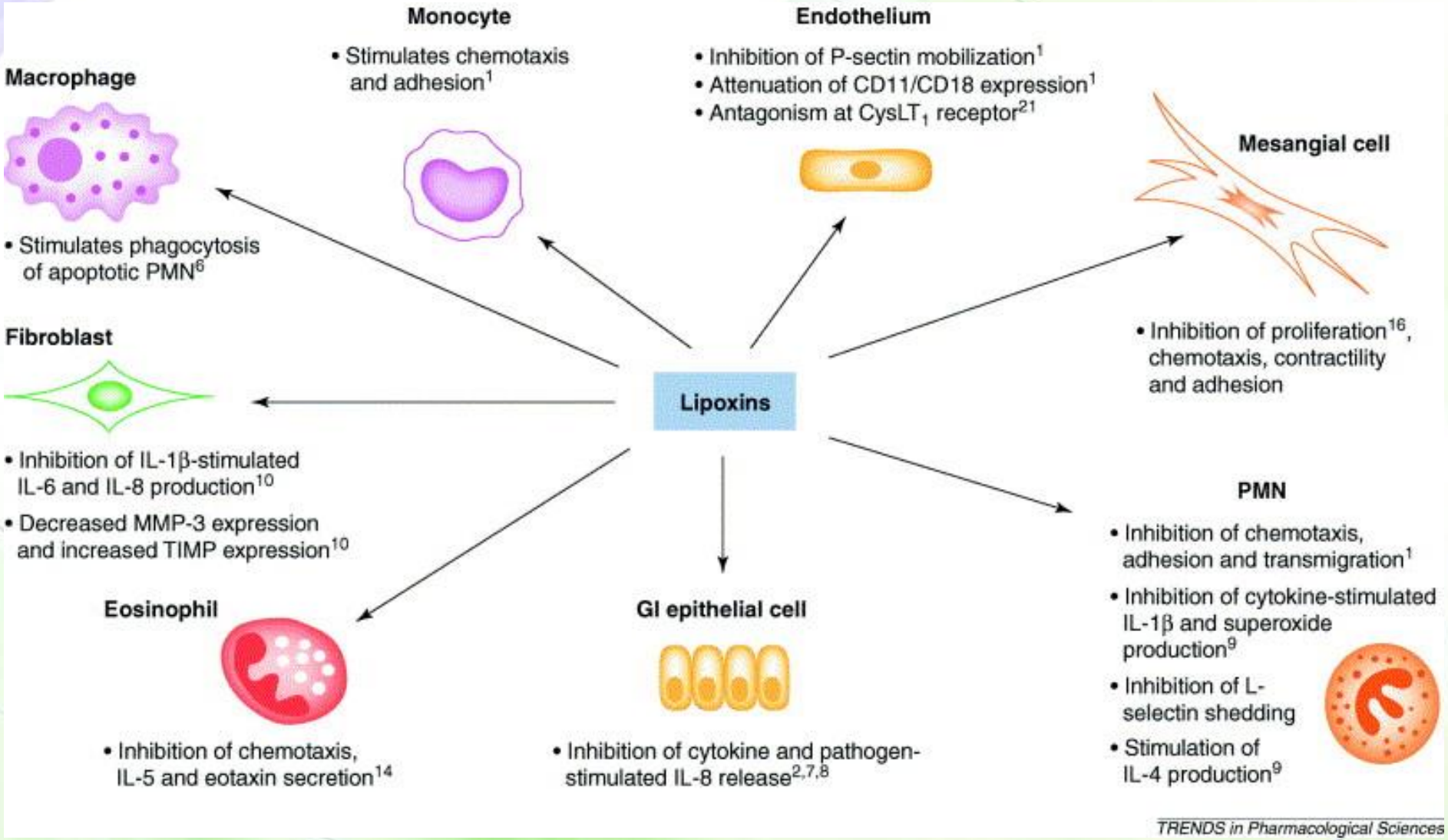
- The lipoxins are anti-inflammatory since they inhibit the actions of the leukotrienes.
- Synthetic pathways of lipoxins:
  - The “classic” pathway: 5-lipoxygenase (5-LOX) in leukocytes followed by 12-LOX in platelets.
  - 15-LOX in epithelial cell, such as airway cells, followed by 5-LOX action in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



The functions of lipoxins

- 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) chemotaxis, PMN-mediated increases in vasopermeability, and PMN adhesion and migration through the endothelium,
  - stimulate phagocytosis of apoptotic PMNs by macrophages (the resolution phase of inflammatory events),
  - blocking 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)



The specialized pro-resolving mediators (SPM)

- Resolvins (Rv), protectins (PD), and maresins (MaR) are EPA- and DHA-derived bioactive metabolites that are anti-inflammatory lipids.
- 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.
- They are synthesized by lipoxygenases.