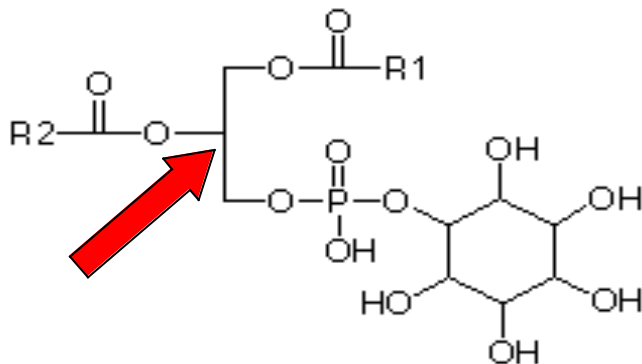


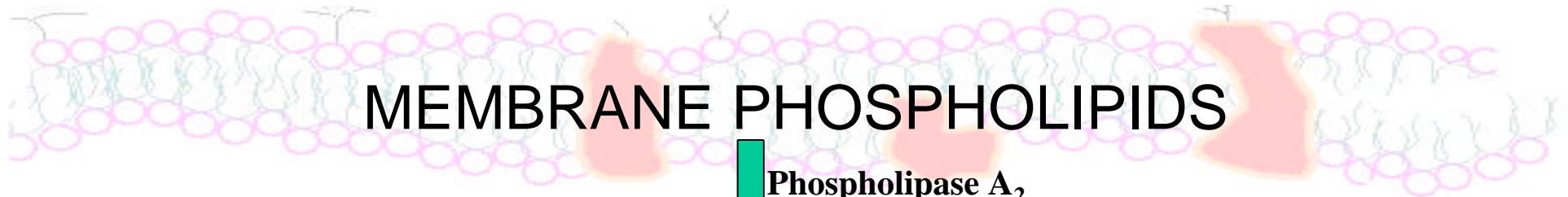
5,8,11,14-ICOSAPENTANOIC ACID

- CARBON-20 FATTY ACID WITH 4 CIS DOUBLE BONDS.
- ESSENTIAL DURING EARLY DEVELOPMENT
- STORED AS THE C-2 ESTER OF PHOSPHATIDYLINOSITOL
- METABOLIZED VIA CYCLOOXYGENASE TO EICOSANOIDS AND LIPOOXYGENASE TO LEUKOTREINES

PHOSPHATIDYLINOSITOL



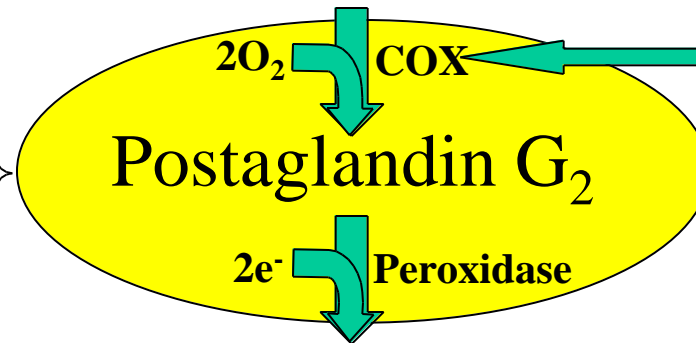
- Present in cell membranes
- Arachidonic acid is released through the action of phospholipase A₂ (PLA₂).



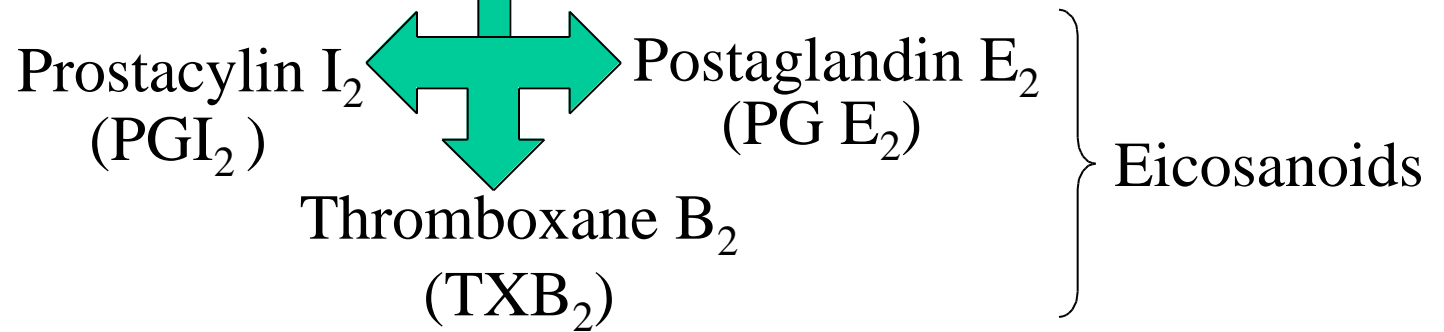
Arachidonic Acid

Vit. E & CLA

Prostaglandin
Endoperoxide
Synthase



Prostaglandin H₂



EICOSANOIDS

- Arachidonic acid metabolites that act as local intercellular messengers and are tissue specific.
- Act at low concentrations to mediate inflammatory responses and hypersensitivity reactions
- PGI₂, inhibits platelet adhesion to endothelium, and dilates blood vessels leading to thrombosis and edema
- TXB₂, stimulates platelet aggregation and constricts blood vessels
- PGE₂, Inhibits apoptosis, and decreases T-cell function

LEUKOTRIENES

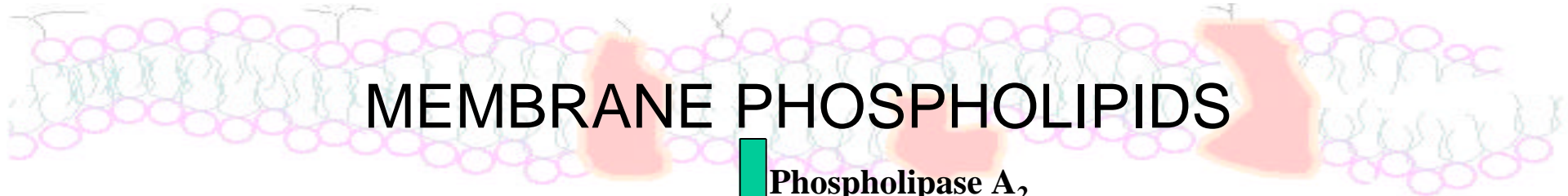
- 5- HPETE, induce inflammation and asthmatic constriction of the bronchioles. Asthma medications include inhibitors of 5-Lipoxygenase
- 12-HPETE, induction and regulation of anaphylaxis

ARTERIOSCLEROSIS

- A cardiovascular disease associated with unstable plaque formation on endothelium. Essentially an inflammatory disease. Plaque rupture, and thrombosis leading to myocardial infarction, is a result of increased inflammation within the plaque, and decreased plaque stability.
- Macrophage produced eicosanoids participate in pathogenesis of arteriosclerosis through their ability to induce inflammation, stimulate platelet aggregation, and decrease collagen secretion.
- Aging results in the altered expression of prostaglandin endoperoxide synthase, a dual function enzyme that acts as cyclooxygenase (COX) and peroxidase. COX-2, the inducible form of the enzyme, increases in areas of vascular damage.
- COX-2 expression has been shown to be increased by benzo(a)pyrene, a major component of tobacco smoke and tar.
- High levels of COX-2 expression in epithelial cells is associated with inhibited apoptosis, cancer, and decreased T-cell function.

PROSTAGLANDIN ENDOPEROXIDE SYNTHASE

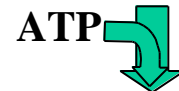
- PGHS is a homodimer of 70 kD subunits, composed of three domains, a membrane binding domain, a dimerization domain, and a catalytic domain. PGHS is bound to the inner membrane of the endoplasmic reticulum. The enzyme functions as a cyclooxygenase and a peroxidase in a heme dependant free radical mechanism. Arachidonate is bound in an L-shaped channel within the active site.
- The COX active site is composed of five functional regions: 1) residues directly in hydrogen abstraction from C-13 (Tyr-385); 2) residues essential for positioning C-13 for H-abstraction (Gly-533, and Tyr-348); 3) residues for high affinity AA binding (Arg-120); 4) residues critical for H-abstraction leading to proper products (Val-349, Trp-387, and Leu-534).



Arachidonic Acid



12(s) HETE & 12(s) HPETE (?)

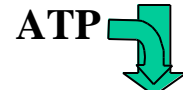


p38~P_i

Drug Target

A red arrow points from the text "Drug Target" to the p38~P_i molecule, indicating that p38~P_i is the target of the drug.

MAPKAP II



HSP27 (?)

Altered adhesion receptor conformation (?)

Altered metastasis and invasiveness of breast cancer (?)

STERIODOGENESIS

- The steroidogenic acute regulatory protein (StAR) plays a critical role in trophic-hormone stimulated steroid biosynthesis by facilitating the transfer of cholesterol to the inner mitochondrial membrane. Arachidonate stimulates steroid production through its regulation of StAR protein expression by 5-HPETE
- 5-HPETE may regulate StAR protein by regulating transcription factors necessary for its production. The mechanism may involve the signal transduction pathway from trophic hormones to the nucleus.

CELL ADHESION AND TUMOR FORMATION

- Arachidonate stimulates the adhesion of metastatic mammary carcinoma cells to basement membrane collagen type IV during cancerous tumor growth. This may be mediated by: 1) 12(s)-HPETE and 12(s)-HETE through their phosphorylation of p38, a mitogen-activated protein kinase type protein (MAP); 2) the activation of MAP-kinase-activated protein kinase 2 (MAP KAPK2); and 3) phosphorylation and overexpression of heat shock protein 27 (HS27).