

# Cell-Derived Inflammatory Mediators



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# Introduction about chemical mediators in inflammation

- Mediators may be  cell-produced or cell-secreted
-  derived from circulating inactive precursors, which are typically synthesized by the liver

e.g., complement proteins & kinins

- Cellular mediators  sequestered in secretory granules and secreted upon activation (e.g., histamine in mast cells)

Activated by proteolytic cleavage

 synthesized de novo in response to stimulus (e.g., prostaglandins & cytokines)

# Cell-Derived Mediators

- **Vasoactive amines:**
  - Histamine
  - Serotonin
- **Arachidonic acid metabolites:**
  - Prostaglandins & thromboxanes
  - Leukotrienes
  - Lipoxins
- **Platelet activating factor**
- **Cytokines**
- **Reactive oxygen species**
- **Nitric oxide**
- **Lysosomal enzymes of leukocytes**
- **Neuropeptides**

# Vasoactive amines: Histamine and serotonin

...stored as preformed molecules in mast cells and other cells  
...released early in the acute inflammation


## \*\*Histamine:

-released by mast cell, basophil and platelet


-stimuli for its release:

- physical (trauma, heat...etc)
- binding of IgE to Fc receptors on mast cells
- C3a & C5a (anaphylatoxins)
- leukocyte-derived histamine-releasing proteins
- neuropeptides (e.g., substance P)
- certain cytokines (e.g., IL-1, IL-8)

Inactivated by  
histaminase



Arteriolar  
dilation and  
venular  
endothelial cell  
contraction ( ↑  
permeability)



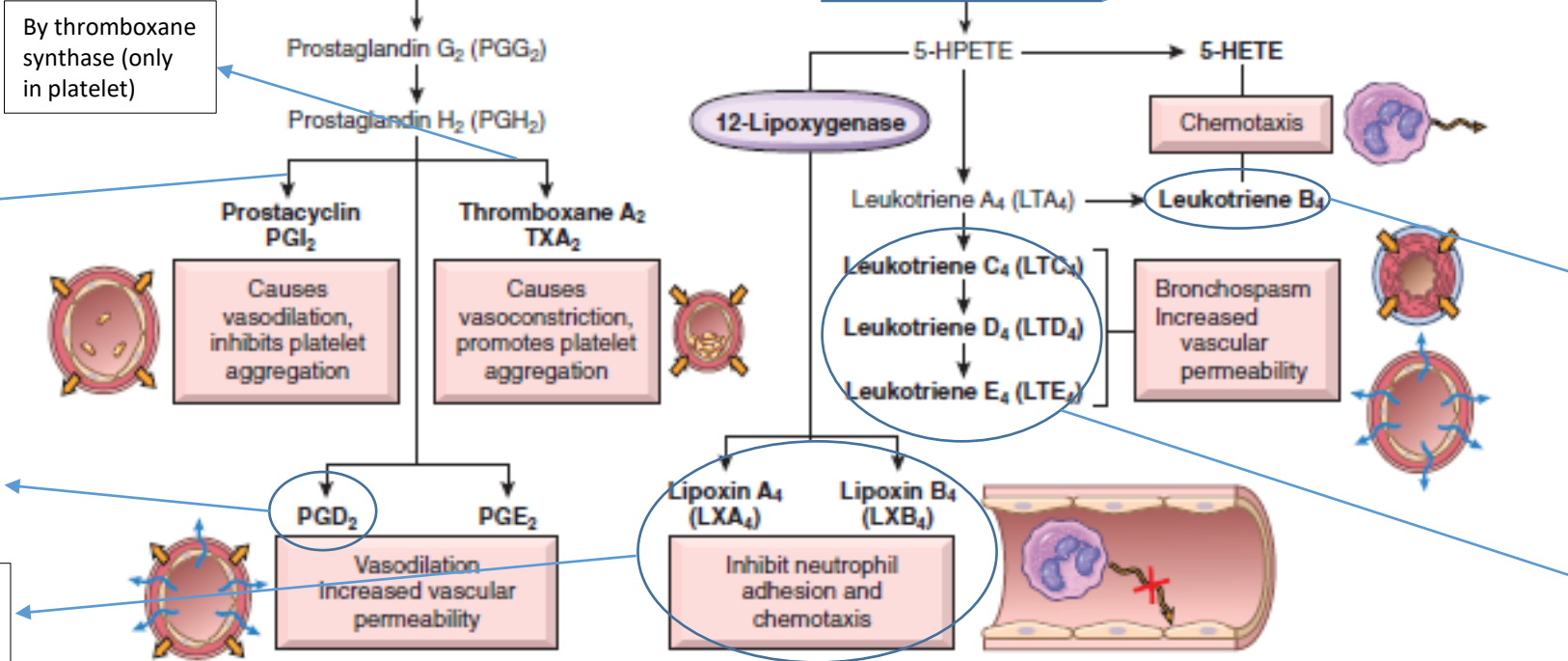
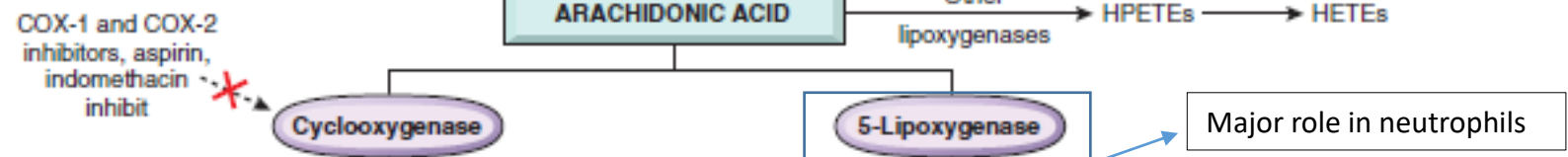
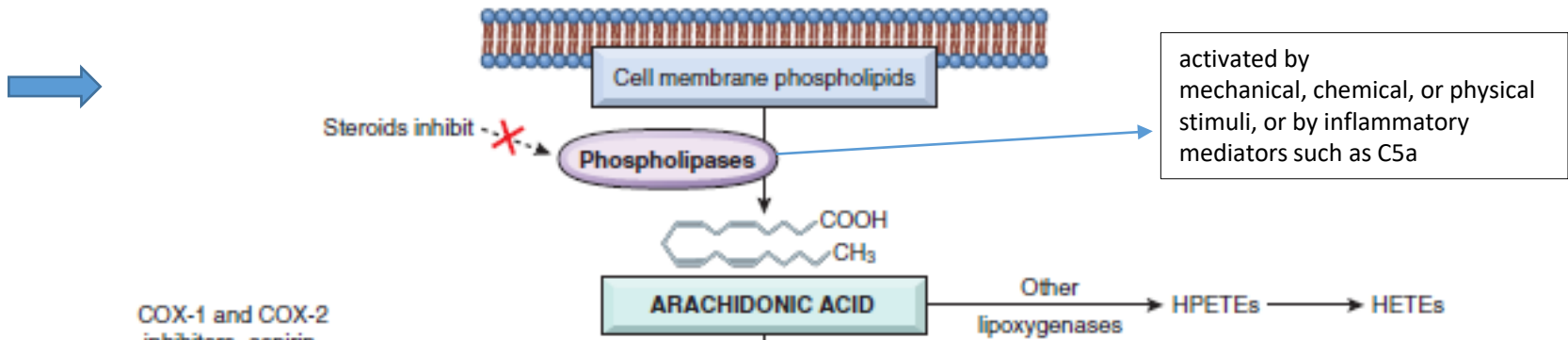
# Vasoactive amines: Histamine and serotonin, cont'd

\*\* Serotonin (5-hydroxytryptamine):

- within platelet granules...released during platelet aggregation
- induces vasoconstriction
- produced in some neurons and enterochromaffin cells  
...neurotransmitter → (for GI motility)

# Arachidonic acid metabolites (eicosanoids)

- Mast cells
- Other WBCs
- Endothelial cells
- Platelets





Prostaglandins: pain and fever

-especially produced by neutrophils and macrophages  
-especially chemotactic for neutrophils

Mainly in mast cells

-Produced by neutrophils  
-also by platelets but need intermediates from neutrophils

# COX-1 & COX-2

- COX-1 is produced in response to inflammatory stimuli  
...and also constitutively expressed in most tissues for the production of prostaglandins that are useful for:
  - fluid and electrolyte balance in the kidneys
  - cytoprotection in the gastrointestinal tract
- COX-2  only in inflammation  
...not in normal tissues  
...COX-2 inhibitors do not affect the kidney and GIT but   
cardiovascular & cerebrovascular events...Why???



# Platelet-Activating Factor

Acts through G  
protein-coupled  
receptor

- A phospholipid-derived mediator
- Induces platelet aggregation and degranulation
- generated from the membrane phospholipids of
  - neutrophils
  - monocytes
  - basophils
  - endothelial cells
  - platelets
  - others cells



By phospholipase A2

-bronchoconstriction  
-vasodilation  
-increased vascular permeability  
-induces synthesis of  
inflammatory mediators like  
eicosanoids and cytokines



# Cytokines

- IL-1, IL-6, TNF and chemokines: in acute inflammation
- IFN-alpha and IL-12: in chronic inflammation
- IL-17: recruits neutrophils

# Cytokines, cont'd

- IL-1 & TNF...mainly by macrophages (and many other cell types)
  - ...- ↑ adhesion molecules on endothelial cells
  - induce production of other cytokines and eicosanoids
- \*TNF ↑ thrombogenicity of endothelium
- \*IL-1 ↑ ECM production (by activating fibroblasts)

# Cytokines, cont'd

- IL-1 & TNF may enter the circulation, and by this they will induce:
  - liver production of acute phase reactants...also induced by IL-6
  - fever and lethargy
  - cachexia (metabolic wasting)
  - neutrophil release into the circulation
  - fall in blood pressure

# Cytokines, cont'd

- Chemokines:
  - act by binding to specific G protein–coupled receptors on target cells

...examples of these receptors: CXCR4 and CCR5

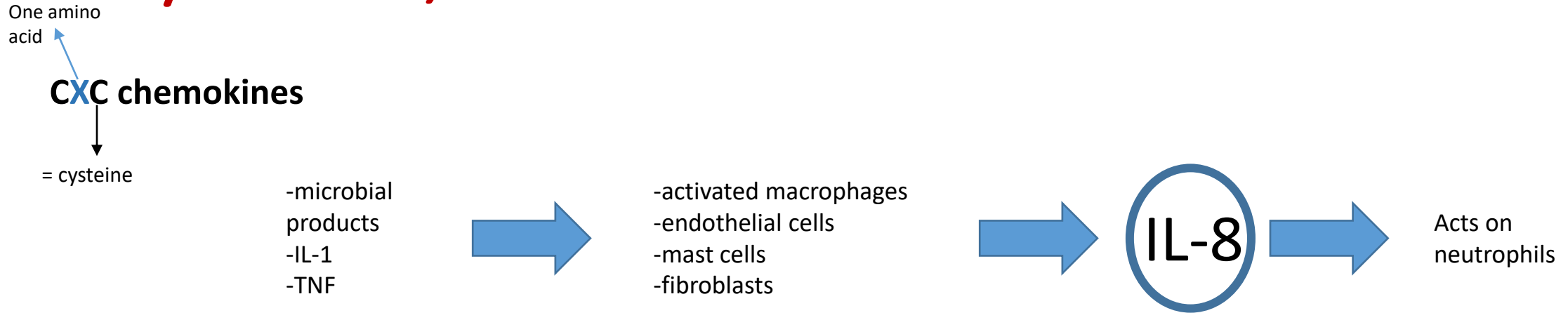


used by HIV to enter lymphocytes

\*\*4 groups, the major 2 of which are:

- CXC chemokines...see next slide
- CC chemokines...see next slide

# Cytokines, cont'd



## CC chemokines

- Monocyte chemoattractant protein-1 (MCP-1)...chemotactic for monocytes
- Macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ )...chemotactic for monocytes
- RANTES (*regulated on activation, normal T cell-expressed and secreted*)...chemotactic for memory CD4+ T cells and monocytes
- Eotaxin...chemotactic for eosinophils

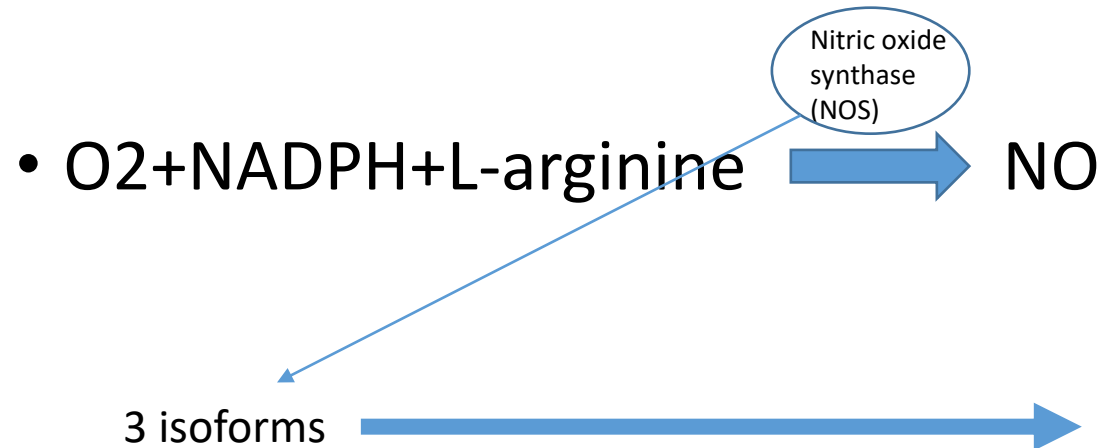
# Reactive oxygen species

- Discussed before
- ROS can increase chemokine, cytokine, and adhesion molecule expression
- Protective mechanisms: -superoxide dismutase  
-catalase  
-glutathione

# Nitric oxide

- Short-lived
- Soluble
- Free radical
- Different producers and different functions:
  - CNS...affects neurotransmitter release and blood flow
  - in macrophages...destroy microbes
  - by endothelial cells...vascular S.M. relaxation & vasodilation

# NO, cont'd



<b>Type I NOS</b> = <b>nNOS</b> = <b>neuronal NOS</b>	Insignificant in inflammation
<b>Type II NOS</b> = <b>iNOS</b> = <b>inducible NOS</b>	*induced in macrophage and endothelial cell due to: -IL-1 -TNF -IFN- $\gamma$ -bacterial endotoxin *also present in respiratory epithelial cells, cardiac myocytes, and hepatocytes
<b>Type III NOS</b> = <b>eNOS</b> = <b>endothelial NOS</b>	Mainly but not exclusively in endothelial cells



# Functions of NO

- Microbicidal (cytotoxic) in activated macrophages
- Vasodilation
- Antagonism of platelet
  - adhesion
  - aggregation
  - degranulation

# Lysosomal enzymes of leukocytes

- Acid proteases...act only inside phagolysosome

- Neutral proteases...active in extracellular locations → -elastase  
-collagenase  
-cathepsin



They also cleave:

-C3 → C3a

-C5 → C5a

-kininogen → bradykinin-like peptides



These are called:



# Inhibitors of lysosomal enzymes

- Antiproteases:

- $\alpha$ 1-antitrypsin...the major inhibitor of neutrophil elastase

- $\alpha$ 2-macroglobulin

Its deficiency will  
cause:



# Neuropeptides

- Small proteins
- Substance P...the typical example
- Transmit pain signals
- Regulate vessel tone
- Modulate vascular permeability
- Especially from nerve fibers in GIT and lung

Thank You