

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)



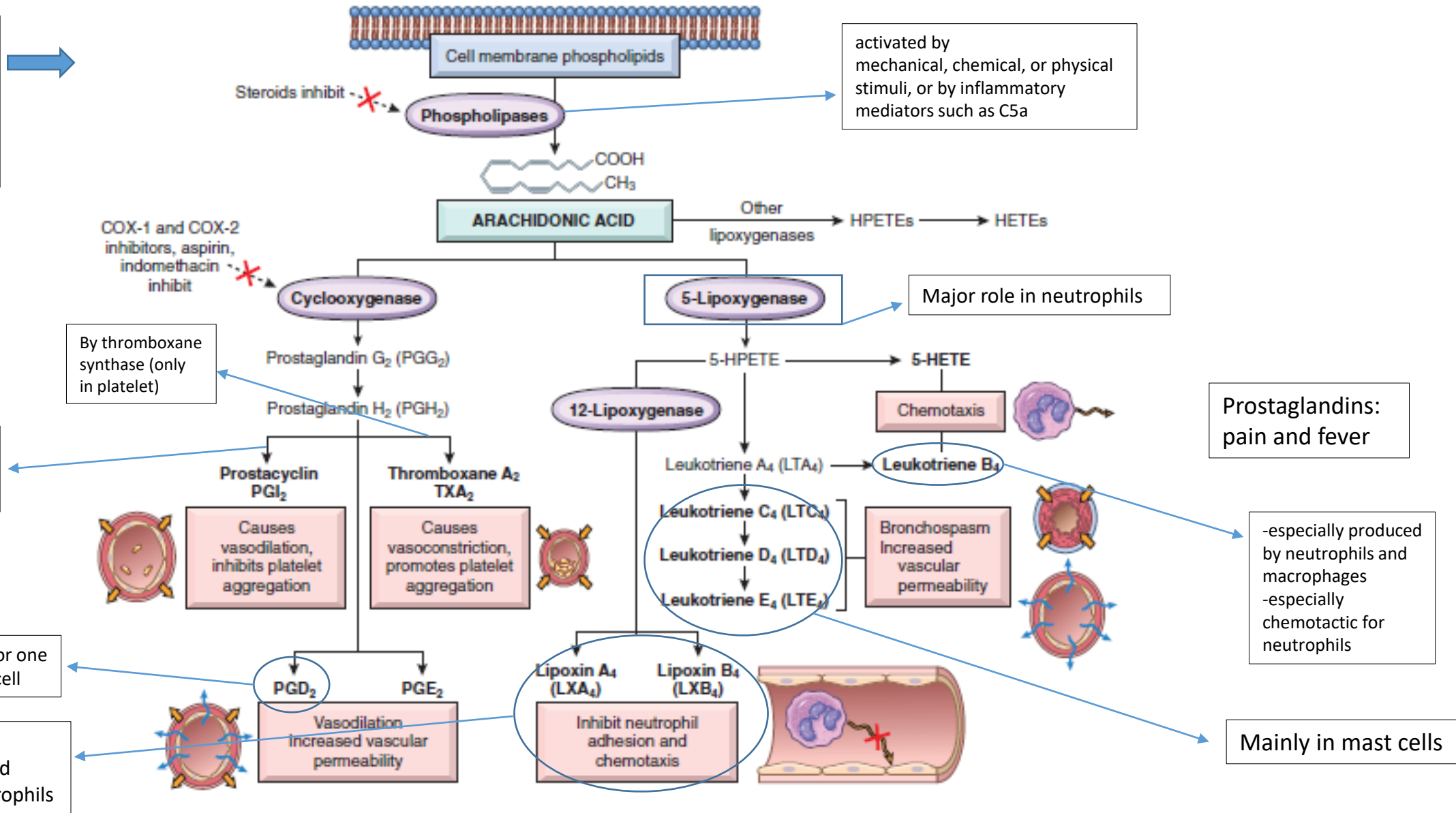
Vasoactive amines: Histamine and serotonin, cont'd

** 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



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

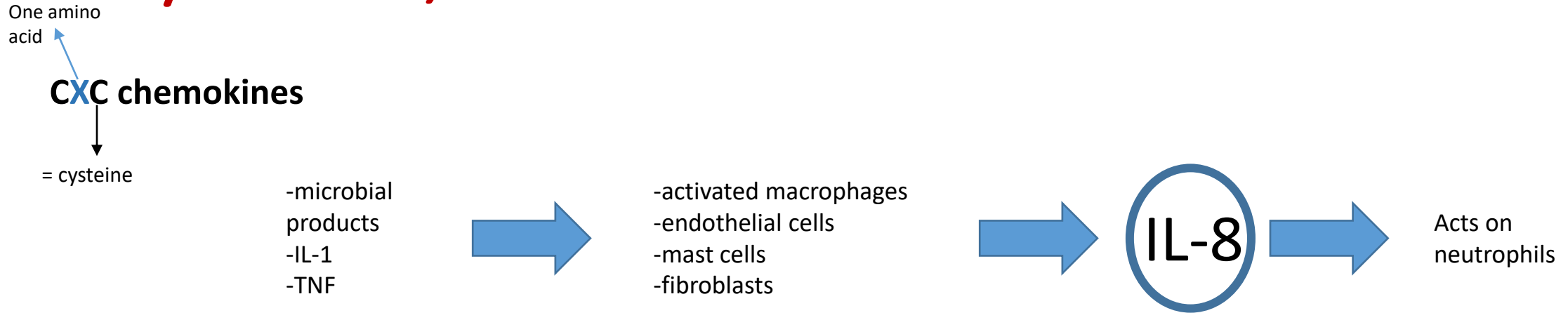


used by HIV to enter lymphocytes

**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 α (MIP-1 α)...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

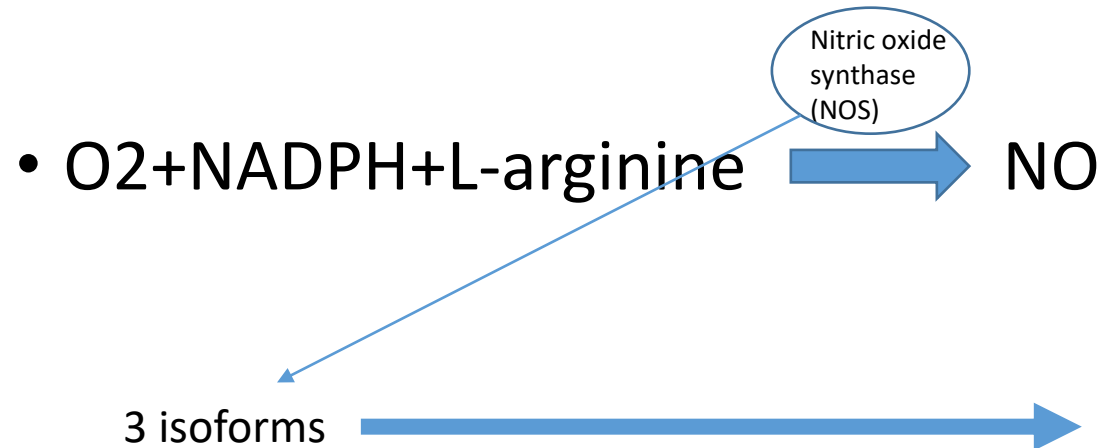
Reactive oxygen species

- 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



Type I NOS = nNOS = neuronal NOS	Insignificant in inflammation
Type II NOS = iNOS = inducible NOS	*induced in macrophage and endothelial cell due to: -IL-1 -TNF -IFN- γ -bacterial endotoxin *also present in respiratory epithelial cells, cardiac myocytes, and hepatocytes
Type III NOS = eNOS = endothelial NOS	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:

- α 1-antitrypsin...the major inhibitor of neutrophil elastase

- α 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