

INFLAMMATION

L-26 CHEMICAL MEDIATORS

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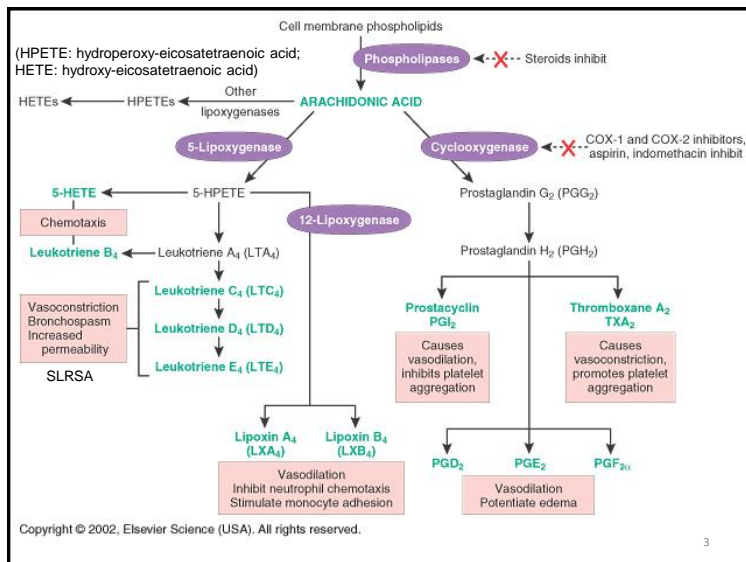
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ARACHIDONIC ACID METABOLITES

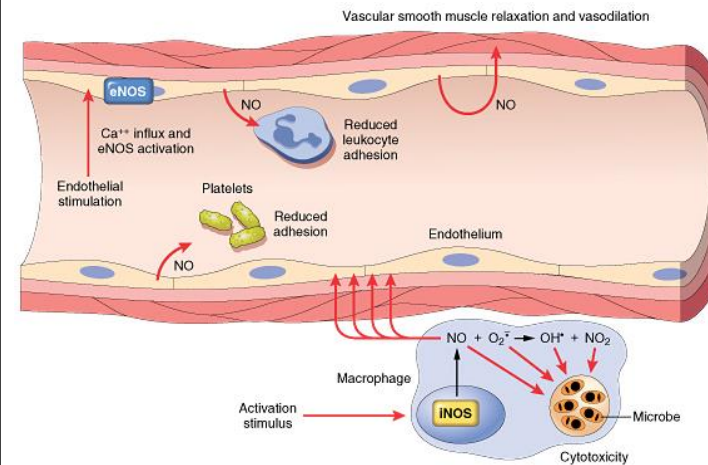
- Arachidonic acid (AA) is a **20-C polyunsaturated fatty acid** released from membrane phospholipids by **phospholipase A2**
- **Mechanical, chemical, physical stimuli** can activate phospholipase A2.
- Metabolites of AA are called **ECOSINOIDS**, and are generated by **cyclooxygenases** and **lipoxygenases**.
- **Cyclooxygenases** synthesize **PGs, PGI, TXA**.
- **Lipoxygenases** synthesize **LT and Lipoxins**.

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NITRIC OXIDE (NO) short-acting soluble free-radical gas



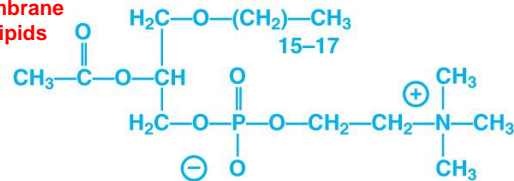
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PAF (Glycero-phospholipid)

SOURCES

Mast cells/basophils
Neutrophils
Monocytes/macrophages
Endothelium
Platelets
Others

Derived from
Cell membrane
Phospholipids



PLATELET-ACTIVATING FACTOR

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MAJOR INFLAMMATORY ACTIONS

Increased vascular permeability
Leukocyte aggregation
Leukocyte adhesion
Leukocyte priming/chemotaxis
Platelet activation
Stimulation of other mediators (LT, O₂⁻)

LYMPHOKINES

- Lymphokines are **non-antibody**, hormone like proteins or glycoproteins produced by **lymphocytes**.
- Some lymphokines participate in **immune reactions**, while others participate in **inflammatory reactions**.
- Lymphokines are **produced locally** and have short half life.
- Lymphokines act on **leukocytes, endothelial cells** and **fibroblasts**.
- Lymphokines attract, accumulate, activate and localize several types of leukocytes at inflammatory sites.

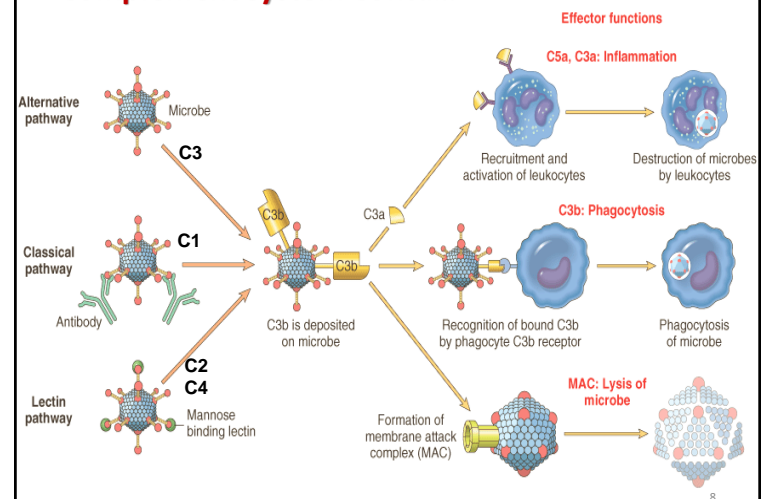
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COMPLEMENT SYSTEM

- More than **30** Plasma Proteins (inactive form)
- Components C1-C9 present in inactive form
- Activated via classic (C1), alternative (C3) or lectin pathways to generate MAC (**C5 – C9**) that punch holes in microbe membranes
- In acute inflammation
 - Vasodilatation, vascular permeability, mast cell degranulation (C3a, C5a)
 - Leukocyte chemotaxis, increases integrin avidity (C5a)
 - As an opsonin, increases phagocytosis (C3b)
 - Neutrophils
 - Release of Enzymes, Generation of FR, Arachidonic Acid Metabolism

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Complement System Contd...

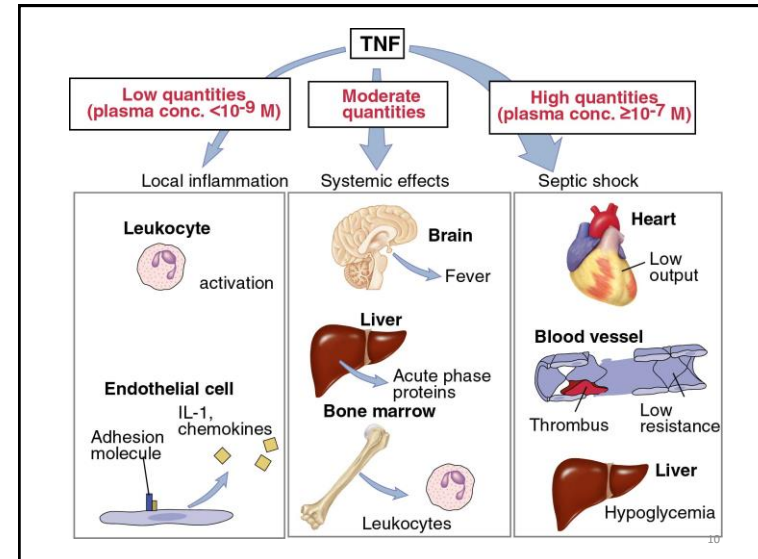


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TUMOUR NECROSIS FACTOR (TNF α)

- Major cellular **source**: **macrophage**, T-cells, NK cells, **Mast cells**
- Major **stimulus** for production: (LPS, **endotoxin**)
- Major **protective functions**: Increases vascular **endothelial adhesiveness** for leukocytes and increases vascular wall **permeability** for plasma proteins
- The TNF is a 17 kD proteolytic fragments of membrane TNF, generated by a membrane-bound metalloproteinase.

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INTERLEUKIN (~36 Identified)

IL1

- Major cellular **source**: **macrophage**, also by keratinocytes, endothelial cells, T & B Lymphocytes, other cell types
- Major stimulus for production: bacterial products (**LPS**, endotoxin), and TNF (cytokine cascade)
- Major functions: Increases leukocyte **adhesion** to endothelium, and increases vascular **permeability**; induces **acute phase response**
- **Fever** through **PGE2** – endothelial cells in brain
- Two different membrane receptors for IL-1, both Ig super-family members.

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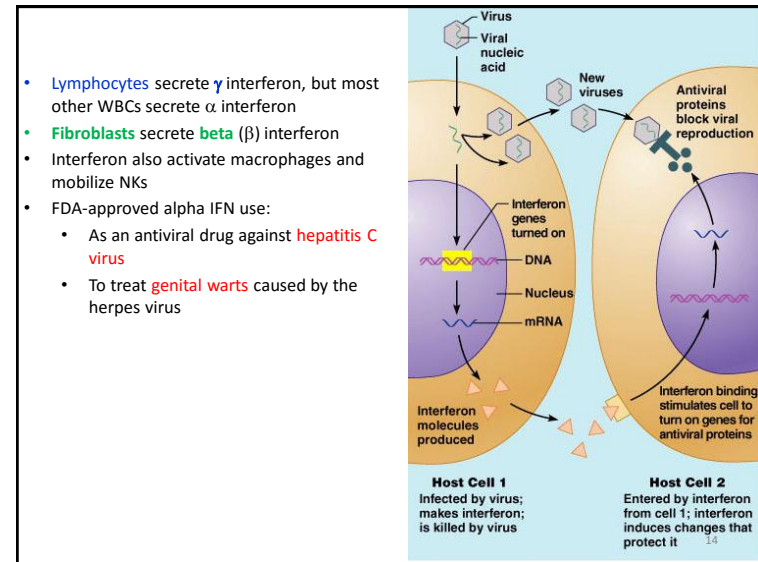
- **IL-5** has an effect on proliferation, chemotaxis, and activation of **eosinophils**,
- **IL-6**. The major biological activities of IL-6 include: stimulate both B and T cell proliferation. “Master cytokine” similar to IL-1 and TNF.
- **IL-8** is a powerful chemoattractant and activator of **neutrophils** and to lesser degree monocytes and eosinophils

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INTERFERON (IFN)

- Genes that synthesize IFN are activated when a host cell is invaded by a **virus**
- Interferon molecules leave the infected cell and enter neighboring cells
- Interferon stimulates the neighboring cells to activate genes for **PKR** (an antiviral protein)
- PKR nonspecifically **blocks viral reproduction** in the neighboring cell
- Interferon are a family of related proteins each with slightly different physiological effects

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EOTAXIN

- Eotaxin is a specific chemoattractant for **eosinophils**.
- It is produced by cytokine-stimulated **epithelial** and **endothelial** cells as well as IL-3-stimulated **eosinophils**.
- Eotaxin is implicated in inflammatory bowel disease, especially in **ulcerative colitis**.

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PRODUCTS OF BLOOD COAGULATION

- **Fibrino-peptides** are also found responsible for increase in vascular **permeability** and leukocyte **chemotaxis**.
- The fibrinopeptides are formed in the process of conversion of **fibrinogen to fibrin**, a component of many inflammatory reactions, e.g., fibrinous peritonitis, fibrinous pneumonia.
- Similarly, fibrin degradation products (**FDPs**) are produced by **plasmin** (proteolytic enzyme) by its action on fibrin clots.
 - **FDPs** causes increase in capillary **permeability** and induce **chemotaxis of granulocytes**.

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TO BE CONTINUED