Chemical Mediators of Inflammation

Types:

1- Cellular mediators

-Produced **locally by cell** at the site of **inflammation.**

-Types:

1.Preformed in **intracellular granule**, **rapidly** secreted upon cellular **activation (e.g. histamine in mast cells).**

2.**Newly synthesized** in response to **a stimulus (e.g. PGs & cytokines).**

2- Plasma Proteins

-Typically **synthesized by the liver** as **inactive precursors** that are **activated at the site of inflammation** (e.g**. Complement proteins & kinins**)

- ✓ Most mediators act **on target cells** by binding to **specific receptors on target cells.**
- ✓ may act **on only one or a very few targets** .
- ✓ may have **wide-spread action** with **different outcomes** depending on target cell
- ✓ have **direct enzymatic** &/or **toxic activities** (e.g. Lysosomal proteases & ROS).
- ✓ may **stimulate target cell** to **release 2ry effectors molecules** ➔ **amplify the response** or **cause –ve control on the response**.

The actions of most mediators are tightly REGULATED DUE TO :

1.Quick decay (arachidonic acid metabolites)

2.Inactivation by Enzymes (Kininase → inactivates bradykinin)

3.Elimination (e.g. antioxidants → ROS)

4.Inhibition (e.g. complement inhibitory proteins)

Most likely Mediators in inflammation:

- ❑ **Vasodilation**
  - Histamine ,Prostaglandins, Nitric oxide
- ❑ **Increased vascular permeability**
  - -Vasoactive amines, C3a & C5a (by liberating vasoactive amines), Bradykinin, leukotrienes C4,D4, E4, Platelet-activating factor(PAF), substance P.
- ❑ **Chemotaxis, Leukocyte activation**

- TNF, IL-1, C5a, C3a, leukotriene B4, Bacterial products, Chemokines (e.g. IL-8)

- ❑ **Fever**
  - IL-1, TNF, Prostaglandins
- ❑ **Pain**
  - **P**rostaglandins, **B**radykinines, neuro**P**eptides.
- ❑ **Tissue damage**
  - Neutrophil & macrophage lysosomal enzymes, ROS, Nitric Oxide

A.VASOACTIVE AMINES

- **Histamine** & **Serotonin**
- Preformed molecules in **mast cells**, **basophils**, **platelets**.

1- Histamine is released in response to:

1.Physical injury as trauma or heat.
2.Hypersensitivity reaction (IgE binding to mast cell)
3.Anaphylatoxins (C3a & C5a)
4.Leukocyte-derived histamine-releasing proteins
5.Neuropeptides(e.g. substance P)
6.Certain cytokines (e.g. IL-1, IL-8)

- Soon after histamine is released, it is inactivated by histaminase.

•Function

1.Arteriolar dilation 2.Increase vascular permeability (Immediate phase mediator)

2- Serotonin found in platelets dense body granules.

- Serotonin is released during platelets aggregation.

B.Arachidonic Acid Metabolites (Eicosanoids)

- **Prostaglandins, Leukotrines, Lipoxins.**
- **Short-lived** locally acting hormones.
- **Source:**

1-Leukocytes, 2-Mast cells, 3-Endothelial cells, 4-Platelets

- **Synthesis Of Eicosanoids:**

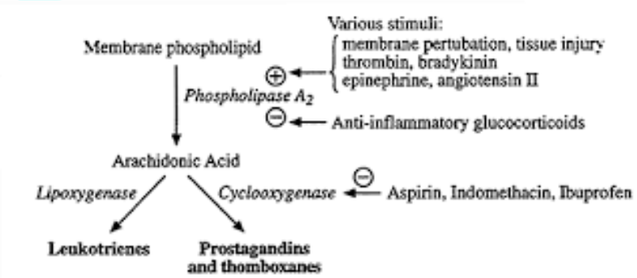
-arachidonic acid is a component of cell membrane phospholipids.

-it is released by the action of **PHOSPHOLIPASE** which can be activated by **C5a.**

-AA metabolism occurs through 2 pathways:

1.**Cyclooxygenase Pathway** PGs and Thromboxanes.

2.**Lipoxygenase pathway** leukotrienes and lipoxins.



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•Actions Of Eicosanoids:

1-Vasodilatation

PGI2,PGE2, PGF2α, PGD2

2-Vasoconstriction

thromboxane A2 , leukotrienes C4 ,D4 ,E4

3-Increased vascular permeability

leukotriene C4 ,D4,E4

4-Chemotaxis, leukocyte adhesion

leukotriene B4

5-Pain & Fever : PGE2

• Types:

1.Thromboxane A2 (Platelets)

Plat. Aggregation & Vasoconstriction

2.PGI2 (Endothelial Cells)

Vasodilation

Plat. Aggregation inhibitor

Pain and fever.

3. PGD2 (Mast Cells) vasoDilatation

4. Leukotrienes (Neutrophils)

LTB4 (produced by neutrophils & macrophages) ----- chemotatic for neutrophils)

LTA4 → LTB4 , LTC4

LTC4 → LTD4 & LTE4

(mast cells)

Vasoconstriction

Bronchospasm

Increased vascular permeability

5. Lipoxins

- Once **Neutrophils** enter the tissue they start to produce lipoxins.
- **Functions :**

Inhibitors of inflammation (Neg. stimuli on **neutrophil** chemotaxis & adhesion)

- Source: Neutrophils / Platelets.

Clinical applications

1-**Aspirin** and **NSAIDs** as **Ibuprofen**

inhibit cyclooxygenase activity inhibition of PGs synthesis → ⇩⇩⇩ **Pain & Fever**.

- **Cyclooxygenase Enzymes COX-1 & COX-2**

2- In **Gastric Mucosa** only **COX-1 is present** generating PGs that **protect the mucosa against acid-induced damage.**

- **Aspirin** & **NSAIDs** inhibit COX-1 & COX□2→ **Gastric Ulceration.**
- **Highly selective COX-2 inhibitors** are used (induce prothrombotic state)

3- **Glucocorticoids (anti-inflammatory agents)** act by inhibiting the **activity of phospholipase A2** inhibiting the release of AA metabolites.

C. Platelets Activating Factor

-Source: it is generated from the membrane phospholipids of neutrophils, monocytes, basophils, endothelial cells, and platelets (and other cells) by the action of phospholipase A2.

□ Function:

1.**Plat. Aggregation**

2.**Brochoconstriction**

3.**Increase vascular permeability**

4.Enhances **leukocyte adhesion**, **chemotaxis** and **degranulation**.

5.**Positive stimuli** on the synthesis of other mediator **esp. eicosanoids**.

D.Cytokines

The major cytokines in **Acute Inflammation** are:

1-Interleukins

2-TNF

3-Chemokines

4-Others (**Interferon – gamma, IL-12**) chronic inflammation.

a. Tumor necrosis factor (TNF) & interleukin-1(IL-1)

Source:

1. Activated macrophages 2. Mast cells 3. Endothelial cells.

Stimuli

1.Microbial products 2.Immune complexes 3.Products of T-lymphocytes 4.Toxins, Physical injury

Function

1. Endothelial **activation**

TNF & IL-1 simulate adhesion molecule on endothelial cell → ⇧⇧leuk. Binding.

2. Enhance the production of other cytokines **(chemokines & eicosanoids).**

3. TNF ⇧⇧ the **thrombogenicity** of endothelium.

4. TNF causes **aggregation & activation of neutrophils.**
5. IL-1 activates tissue **fibroblasts** with → ⇧ proliferation & production of ECM.
6. Systemic acute phase reaction as **fever, lethargy, cachexia, increase neurtrophil in blood, increase hepatic synthesis of various acute-phase proteins**, & **release of corticosteroids.**
7. **Septic shock** : DIC , hypoglycemia , hypotension.

b. Chemokines

-**Chemoattractant** for leukocytes.

-Classification:

1. **CXC chemokines**	2. **CC chemokines**
-Acts on neutrophils.	-Acts on monocytes.
-E.g **IL-8,** produced by activated macrophages, endothelial cells, mast cells, fibroblasts.	**- 4-RANTES** (regulated on activation normal T expressed and secreted) -chemotactic for memory CD4+ T cells and monocytes **- 5-eotaxin** (chemotactic for eosinophils).

E. Reactive O2 species (ROS)

-Released from activated neutrophils & macrophages.

-**ROS at low levels:**

⇧⇧ chemokines, cytokines & adhesion molecules.

-ROS at high level:

Induce tissue injury by several ways:

1.**Endothelial damage** with thrombosis & increase permeability.
2.Protease activation & anti-protease inactivation →increase **breakdown of ECM**
3.**Direct injury to other cell types**.

F. Nitric oxide (NO)

-**Short lived** soluble **free radical gas.**
-Produced by many cell types.

Function:

1-In **CNS**, it regulates **neurotransmitters release** & **blood flow.**
2- **Cytotoxic** metabolite for killing microbes.
3- Smooth muscle **relaxation** & vasodilation.

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4-**Antagonise ALL** stages of Platelets Activation. (Adhesion, aggregation, degranulation)
5- **⇩⇩ leukocyte recruitment** at inflammatory sites.
6-**Cytotoxic agent** in activated macrophages.

G. Lysosomal Enzymes

- **Acid proteases:**

Active within Phagolysosomes

- **Neutral proteases (active in ECM)**

Elastase, collagenase, cathepsin.

- **Function:**

1.**Destruction of ECM**.
2.**Cleavage of complement system** C3 & C5 to generate C3a & C5a(vasoactive mediators).
3.Generation of **bradykinin** - like peptide from kininogen.

- **Antiproteases**
- **e.g α-1-antitrypsin (inhibitor of neutrophil elastase)**

Plasma Protein Derived Mediators

- Circulating proteins are of 3 types:

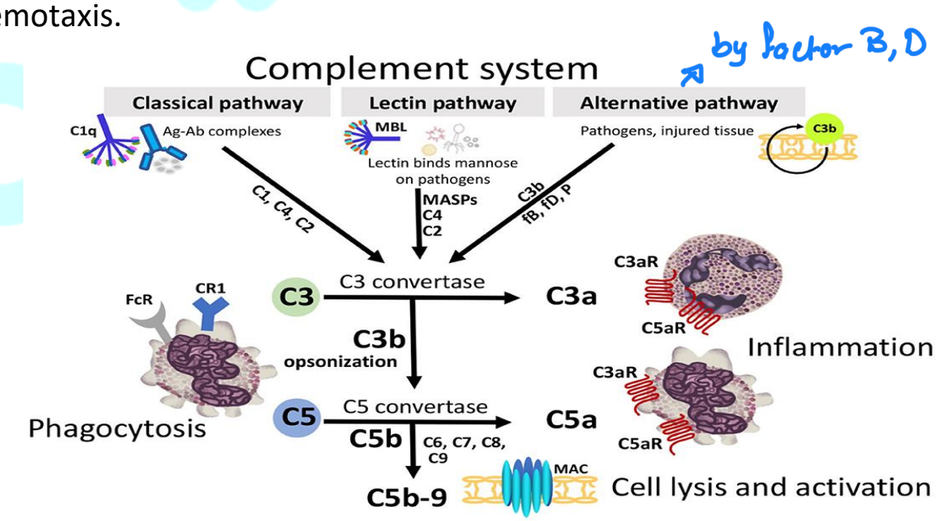
1- Complement system 2- Kinin system 3- Coagulation system

A. Complement system

-**Plasma proteins** that play an important role **in host defense** & **inflammation**.
-**Function**:

1. Opsonization
2. Increase vascular permeability
3. Leukocyte chemotaxis.

- **C1-C9**
- The critical step in biologically active components is the **activation of C3 by cleavage.**



- C3 cleavage occurs via **3 pathways:**

A. Classical pathway

Triggered by **fixation of C1 to Ag-Ab complexes**.

B. Alternative pathway

Triggered by **endotoxins, microbial cell wall** involving other plasma proteins as **properdin** and **factor B &D** .

C. Lectin pathway

Plasma lectin binds **mannose residue on microbes** → activates **C1** in **the absence of Abs.**

✓ **C3 convertase** → **C3a & C3b**

a. C3b has the following effects :

1- C3b → **opsonization** → phagocytosis of M.O

2- C5 convertease → C5a & C5b

3- Formation of **Membrane Attack Complex** that generates holes in the membranes
of invading M.O

b. C3a has the following effects :

1- recruitment and activation of leukocytes

2- increase vascular **permeability** (C5a also)

3- **vasodilatation** by inducing mast cells to release histamine (C5a)

4- activation of LOX pathway of AA metabolism in neutrophils & macrophages

5- chemotaxis

Functions of Complements

1. Vascular effect

C3a & C5a → Vasodilatation & increase permeability by inducing histamine release

2. C5a activate lipoxygenase pathway of AA metabolism in neutrophils & macrophages causing release of inflammatory mediators.

3. Leukocyte activation adhesion & chemotaxis

C5a potent **chemotactic** agent for neutrophils, monocytes, eosinophil & basophils

4. Phagocytosis

C3b Acts as **opsonin**

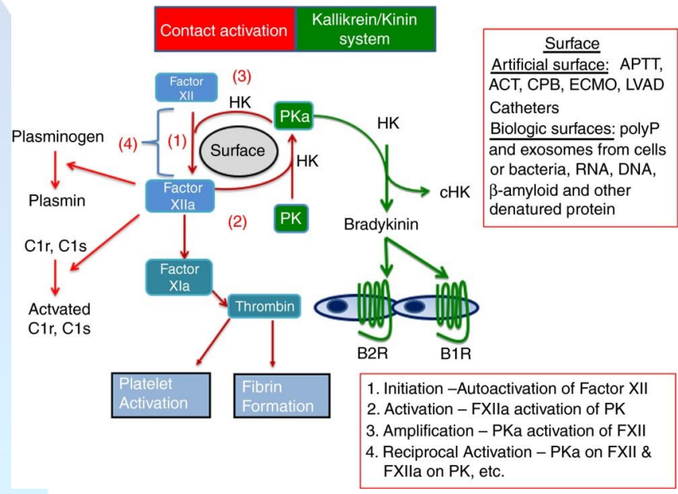
- Activation of complement is controlled by **regulatory protiens.**

B. Coagulations System

Activation of **Factor XII (hageman factor)** initiates **4 systems** involved in **inflammatory response:**

1. **Kinin System** → Vasoactive Kinins.
2. **Clotting system** → postive stimuli on Thrombin, Fibrinopeptide & Factor X.
3. **Fibrinolytic System** → plasmin & inactivating thrombin.
4. The **Complement System** and **formation of anaphylatoxins** C3a & C5a.

- Factor XII is a protein synthesized by **liver** and **activated by collagen, B.M** or **activated platelets** along with **HMWK** cofactor.
- Factor XIIa → cleavage of several proteins of **Kinin** & **coagulation** systems
- In clotting system factor XIIa
→activation of thrombin →
1- cleavage of **fibrinogen into fibrin** → fibrin clot.
2- increase leukocyte adhesion.
3- generation of **fibrinopeptides** that increase vascular permeability & chemotaxis.



- Factor XIIa also **activates fibrinolytic system** to limit clotting by cleaving fibrin.
- **Plasminogen activator** released from endothelium & leukocytes cleaves plasminogen to produce plasmin that acts as protease & cleaves fibrin.
- Plasmin also **activates C3 & produce C3a .**

C. Kinin system

- Result in formation **bradykinin**
- Bradykinin causes:
  1. Increase vascular **permeability**
  2. Arteriolar **vasodilation**
  3. Bronchial **smooth muscle contraction.**
  4. **Pain**
  5. **Activation of Hageman factor (Factor 12).**