Lec 4

• **Terminating the Inflammatory Reaction**:(R4+R5)
The inflammatory response is terminated through seven key mechanisms:

1. Mediators are produced rapid burst , activating one another.
2. The response depend on the stimulus.
3. Mediators have short half-lives.
4. Enzymes degrade mediators post-release.
5. Neutrophils have a short half lives
6. Releasing (TGF,IL10) stop signaling (inhibit earlier mediators)
7. Releasing Cholinergic neural inhibitors that inhibit TNF production.

• **Mediators** are derived from cells, can be stored in granules and secreted or synthesized when the offending agent is detected. They are **four main types**:

1. **Vasoactive Amines**: Histamine and serotonin.
2. **Lipid Products**: **Prostaglandins** and **leukotrienes**, → (phospholipase(which inhibited by steroids)) metabolize the cell membrane producing arachidonic acid. The pathways include:
   - **Lipoxygenase Pathway**: Produces leukotrienes (e.g., leukotriene B4, a potent chemoattractant).
   - **Cyclooxygenase Pathway**: Produces prostaglandins (e.g., PGE2 causes pain and fever, PGI2 promotes vasodilation and inhibits platelet aggregation,TXA2 promotes vasoconstriction and platelet aggregation so PGI2 and TXA2 impalance leads to (IHD,CVA)deseases and PG(C4,D4,E4) promotes smooth muscle contraction.
3. **Cytokines**: (TNF,IL,Chemokines) Proteins that regulate the inflammatory response and can have local or systemic effects, including protective (e.g., in the brain and liver)(its effects help in inflamation detection)and pathological (e.g., heart failure and thrombosis).

Chemokines:(chemoattractants) its function is :1.inf.rxn 2. Conserve the tissue architicsture

Its mechanisism by G-protien coupled receptor

4. **Complement System**: inactive innate immune plasma proteins (C1 to C9) with C3 as the central activator (fix the comp.system). Functions include:
   - Increasing vascular permeability in early inflamation by C5a (anaphylatoxin)
   - Promoting chemotaxis by C5a,C3a • Opsonization (coating microbes) by C3b

(the activasion of the C5,6,7,8,9 cascade activate MAC which pierce the microbial membrane

Regulatory proteins of the complement system include:

- C1 Inhibitor: Deficiency can lead to hereditary angioedema.
- DAF and Factor H: Inhibit C3 convertase; deficiencies lead to hemolytic uremic syndrome.
- CD59: Inhibits the membrane attack complex MAC; its deficiency can cause (PNH).

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, and activation
Cytokines (e.g., TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain