Foundation block

Natural Defense Mechanisms

2nd lecture

- Objectives:

- ☑ First (non-specific immunity) and second (adaptive immunity) lines of defense.

- ☑ Complement activation provides protection by killing pathogens.

- ☑ Accumulation of inflammatory cells important for clearance of infection.

- ☑ Cytokines as mediators regulate inflammation.

Key words:

Mannan: any of a group of polysaccharides that yield mannose upon hydrolysis.
Lectin: any of a group of proteins that bind to particular carbohydrates in the manner of an antibody.
Anaphylatoxin: a substance that may cause the release of histamine and other compounds that causes hypersensitivity.
Diapedesis: the passage of blood cells, especially leukocytes, through the unruptured walls of the capillaries into the tissues.

Opsonization: to increase the susceptibility of (bacteria) to ingestion by phagocytes.

Note:
Black: Slides
Orange: Explanation
Purple: Extra
Red: Important

- The main function of the immune system is to protect us from infections.

- First and second lines of defense:

First Line of defense (none specific defense mechanism) (Innate immunity)	Second Line of Defense (specific defense mechanism) (Stronger)
Skin – mucous membranes – phagocytic WBC – antimicrobial protein – the inflammatory response	**Lymphocytes - antibodies**

(1st and 2nd line of defense do NOT work independently; they complete each other and at certain points they also may overlap at the same time)

First line of defense (Natural Immunity)

Physical	Mechanical	Biochemical barriers
• Skin → impermeable to microbes. • Mucous membranes → lining the gastrointestinal, genitourinary and respiratory tracts.	**Protective mechanisms :** • Coughing and sneezing. • Flushing of urine. • Vomiting. • Mucus and cilia in respiratory tract.	• Body secretions contain toxic substances to pathogens e.g.; saliva, tears and sweat. (In sweat we have high PH and some bacteria can't survive in high PH) • Antimicrobial peptides e.g.; defensins, hepcidins • Normal bacterial flora : (Compete with pathogenic bacteria for nutrients)

Inflammation

What is it?	How does it begin?	Goals
• It's the first response of the immune system to infection or irritation. • It consists of a series of vascular & cellular changes that occur in response to various stimuli. → e.g. : infections, injury, radiation , etc.	Microbial infections initiate inflammation ; As bacteria possess an array of pro-inflammatory molecules : → e.g.: Lipopolysaccharides (LPS) Found in the cell wall.	1) Prevent and limit infection and further damage. 2) Interact with adaptive immune system ; (For example : Monocytes / Macrophages serve as a link between the adaptive and innate immunity by antigen presentation) 3) Prepare the area of injury for healing.

The complement system

- **Consist of a group of small proteins serum proteins (proteins + glycoprotoens) circulate in inactive form.**

(Once they become activated, they produce important biological effects that start inflammation).

- **This system plays an important role in both Innate & Adaptive immunity.**
- **There are three types to activate The Complement System:**

Type of pathway :	Classical	Lectin	Alternative
Activated by :	**Antigen-antibody binding**	**The binding between "Mannan Binding Protein" and "manose groups of bacterial carbohydrates"**	**bacterial products**

Its components:	C1, C4, C2, C3, C5, C6, C7, C8, C9	-C4, C2, C3, C5, C6, C7, C8, C9	-C3, C5, C6, C7, C8, C9

In order to perform their functions, they have to split into **"Cn a" and "Cn b" .**
For example: "C2a" and "C2b" Also as you can see they are not in numerical order (ordered according to activation).

- C_1 ⟶ C_2 ⟶ C_3 ⟶ C_4 ⟶ C_5 ⟶ C_6 the line of activation is in order first C_1 is activated then C_2 ..... till C_9

-The difference between the classical pathway and the other two is that the classical has C_1

-The activation of complement is split into 2 parts (a & b)

- **Lytic Pathway Assembly of The Lytic Complex:**

-First assembly on the surface of cells [$C_{4b} + C_{2a} + C_{3b}$] activate ⇨ C_5 .
then C_{5b} + C_6 + C_7 + C_8 assemble to form multiple C_9 .
- This sequence (cascade) all will be activated which will rupture the bacteria.
-[$C_{4b} + C_{2a} + C_{3b}$] is the pre-requisite
- Multiple C_9 will make a hole in the bacteria cell wall and rupture it.

- **When they are activated, there are Biological effects of complement activation:**

1. **Anaphylatoxin (C3a, C5a)**
   - **stimulate histamine to release from mast cells.**
   - **release chemotactic agents.**

2. **Opsonization: (opsonin, C3b)**
   - **Coating of bacteria enhances phagocytosis**

3. **Cause direct cell lysis**
   - **Destruction of bacteria.**

- **Types of Cells attracted to site of infection that mediate inflammation:**
  1. **Monocytes : Become Macrophages when they leave the blood and enter the tissues.**
  2. **Neutrophils: (Phagocytic cells)**
  3. **Eosinophils: (Allergy and Parasitic infections)**
  4. **Natural Killer (NK) cells: (Kill tumor cells and virus infected cells) (Cytotoxic cells work as natural killer)**

cytokines

They are Soluble molecules, produced by different cells, that control cell functions **e.g. activation or inhibition.**

- **Control and regulate the immune system**
- **Mediators between cells**
- **Any cytokine will be activated when bonded to its specific receptors (excrete its biological action)**

Interleukins	Interferons	Tumor Necrosis Factor (TNF)
• Produced primarily by macrophages and lymphocytes in response to a pathogen. • There are many types, for example : IL-1, IL-2, IL-3…	• Protects against viral infections. • Produced and released by virally infected cells in response to viral infections.	• Secreted by macrophages. Induces fever by acting as an endogenous pyrogen (a substance released from inside the body that produces fever). Increases synthesis of inflammatory serum proteins (For example, RF factor and C reactive)