Lec.2: Innate Immunity

Immune response

The immune system is the collection of cells, tissues and molecules that functions to defend us against infectious microbes. The coordinated reaction of the immune system against infections (and other foreign substances) is known as the **immune response**. Abnormalities of the immune system that result in defective immune responses make individuals susceptible to infections by viruses, bacteria, fungi and parasites. This anti-microbial defense function of the immune system is essential for the ability to survive in an environment that is teeming with potentially deadly microbes. However, immune responses are also capable of causing damage. Many common diseases are caused by uncontrolled or excessive immune responses (examples include rheumatic fever, asthma and glomerulonephritis; inflammatory bowel disease and autoimmune thyroiditis and multiple sclerosis).

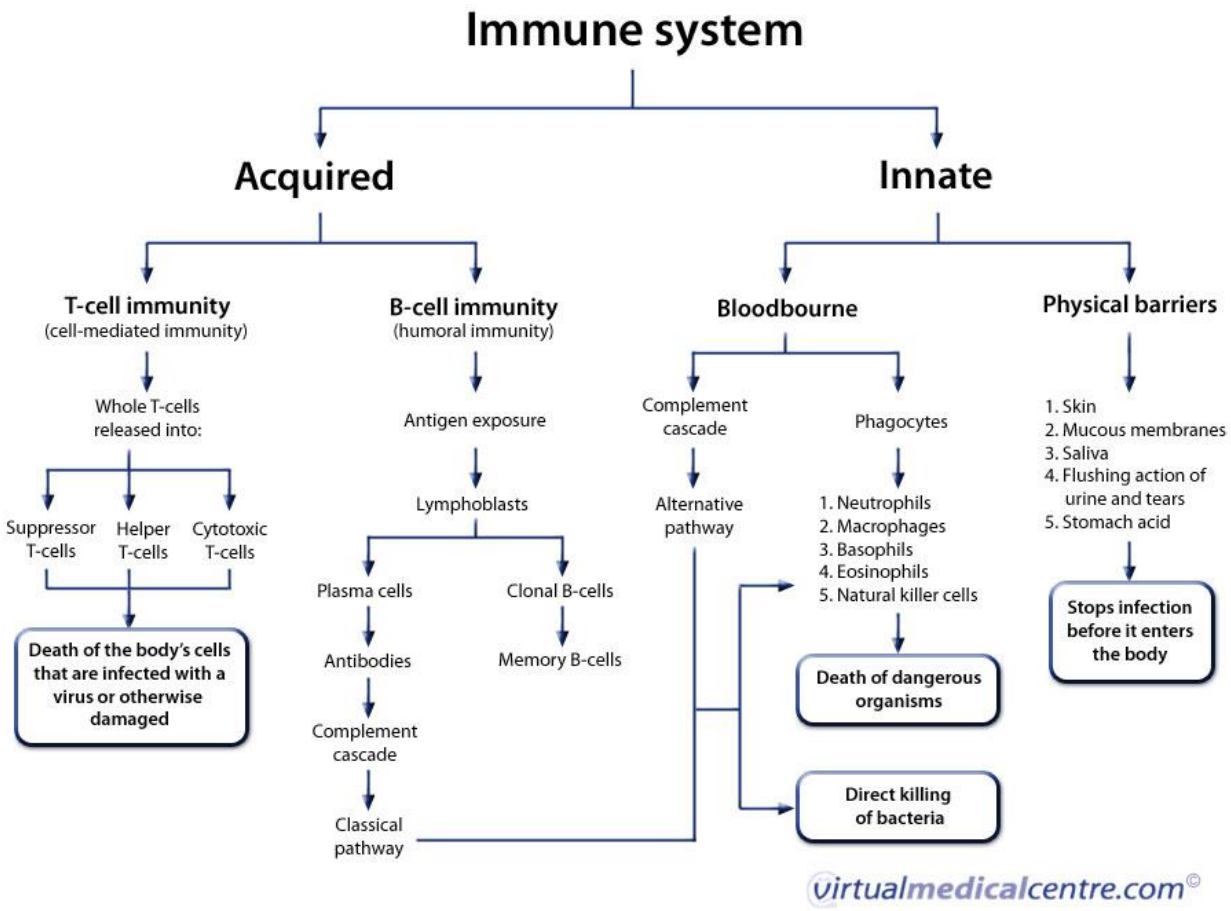
Immunity involves both specific and nonspecific components. The nonspecific components act either as barriers or as eliminators of wide range of pathogens irrespective of antigenic specificity. Other components of the immune system adapt themselves to each new disease encountered and are able to generate pathogen-specific immunity.

The basic premise for the division of the immune system into innate and adaptive components .

Innate immunity

Innate immunity, or nonspecific immunity, is the natural resistances with which a person is born. It provides resistances through several physical, chemical ,biological and cellular approaches. Microbes first encounter the epithelial layers, physical barriers that line skin and mucous membranes. Subsequent general defenses include secreted chemical signals (cytokines), antimicrobial substances, fever, and phagocytic activity associated with the inflammatory responses. The phagocytes express cell surface receptors that can bind and respond to common molecular patterns expressed on the surface of invading microbes. Through these

approaches, innate immunity can prevent the colonization, entry and spread of microbes.



Innate Immunity Barriers to Infection

1- Physical/anatomic barriers

- Skin: effective if intact
- Mucus traps pathogens. Respiratory, gastrointestinal, and genitourinary tracts:
- mucosal cell layer continuous with skin.
- Blood clotting - post injury

2- Physiological/chemical

defenses present in body cavities and fluids.

- tearing, coughing, sneezing, vomiting

- low pH in skin , fatty acids, hydrolytic enzymes,anti-microbial peptides
- acidic secretions, degradative enzymes,
- soluble proteins such as the complement system, cytokines, acute phase proteins.

3-Biological barriers such as normal flora .

4- Cellular barriers (Killing of pathogens & infected cells) cellular components of the immune system (both innate and acquired) .

Innate immunity defense mechanisms :

Several plasma protein and cellular systems contribute to non-adaptive immunity:

Plasma protein systems:

- complement system

Many very complex actions
- Innate response is recognition of micro-organisms
- Lysis of invading micro-organisms
- Also reinforces other inflammatory responses .

- coagulation system and fibrinolytic system
- kinin system

Cellular systems:

- polymorphonuclear granulocytes (PMN)
- mast cells
- platelets (thrombocytes)
- endothelial cells
- macrophages and dendritic cells
- NK (natural killer) cells

- Attack virus-infected cells.
- Cause lysis

Several of these cell types share molecular systems that are necessary for their defense functions. Collectively, these are designated "mediators of inflammation". They are either preformed or newly synthesized on demand. While these molecules in fact cause inflammation, their ultimate goal is of course not inflammation, but defense. Inflammation is a transitory state that makes it easier to combat infectious agents.

Cellular subsystems contributing to defense/ inflammation mediators:

Preformed molecules are stored in granules and released when necessary:

- vasoactive amines: histamine, serotonin
- lysosomal proteins

Newly synthesized molecules:

- prostaglandins and leukotrienes
- platelet activating factor (PAF)
- reactive oxygen species (ROS)
- NO
- cytokines
- Interferons

-Released by virus-attacked cells
- Protects other cells from any virus
-Anti-cancer effect
- Slows cell division
-Enhances action of NK cells and cytotoxic T cells (qv)

Cells of Innate Immunity

- **Granulocytes**: These are the major populations of blood leukocytes, the circulating white blood cells. They are called granulocytes because they contain cytoplasmic granules that are visible under the light microscope. They have nuclei that possess two or more lobes, and are thus also called polymorphonuclear leukocytes to distinguish them from monocytes and lymphocytes, the mononuclear leukocytes, which do not have lobulated nuclei and no granules in their cytoplasm . Granulocytes are divided into

three groups derived from a common precursor: neutrophils, which are abundant in blood and are a very important type of phagocyte; the rarer eosinophils, and the basophils that are somewhat related to mast cells in function. A crucial feature of granulocytes is that they normally circulate in the blood but can be recruited selectively into inflammatory sites in response to different types of infection. (Note that although mast cells also contain granules, they do not circulate in the blood in a mature form and are therefore by definition not included in the term granulocyte; they may also originate from a distinct progenitor.)

- **Properties of Neutrophils**

- Neutrophils have their origin in multi-potential stem cells in the bone marrow. They differentiate in the marrow and are released in a mature form, containing a full complement of bactericidal agents.
- They are short-lived cells which constitute 30-70% of the circulating white blood cells (leukocytes).
- During differentiation in the marrow (2-3 days) the nucleus of the cell becomes multilobed (hence the name polymorphonuclear leukocyte), cell division ceases, and mitochondria and endoplasmic reticulum disappear from the cytoplasm. At the same time the cell becomes motile and actively phagocytic.
- Cytoplasmic granules are formed from the Golgi apparatus. These membranous granules are called lysosomes and contain the various bactericidal and digestive enzymes which can destroy bacterial cells after engulfment. The contents of lysosomes include lysozyme, cationic proteins, acid hydrolases, proteases, peroxidase and lactoferrin. Neutrophils also contain large store of glycogen; since they derive most of their metabolic energy from glycolysis, they can function efficiently in anaerobic environments.
- Only half the neutrophils in human circulation are detectable in the blood; the rest adhere to vessel walls.
- For every circulating neutrophil, approximately 100 near mature cells are held in reserve in the bone marrow pool.
- Once a neutrophil enters the tissues, intestinal tract or respiratory tract, it never returns to the circulation.

- **Macrophages** :These are divided into two main types:

- Resident macrophages are present in steady-state tissues (before infection occurs) and can detect the presence of microbes. In turn they can help to trigger inflammation.

-Recruited (or elicited) macrophages are not tissue-resident cells, but they develop from circulating precursors called monocytes that can be recruited into sites of infection. After development into macrophages they can act as effector cells to help eliminate the infection.

Macrophages are one of the two main types of specialized phagocyte that can engulf and internalize (phagocytose), and subsequently kill microbes such as bacteria.

Properties of Macrophages

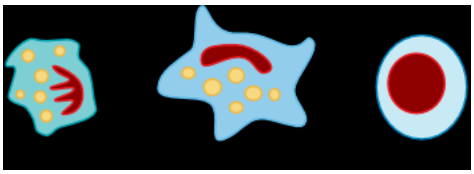
- **Macrophages** (also called **mononuclear phagocytes**) also arise from bone marrow stem cells which give rise to promonocytes which develop into **monocytes** that are released into the blood stream.
- Monocytes make up 3-7% of the circulating white blood cells. The monocyte is actively phagocytic and and bactericidal.
- Within 2 days or so, the blood stream monocytes (sometimes called wondering macrophages) emigrate into the tissues where they settle down, enlarge and become fixed macrophages (tissue histiocytes), which also have phagocytic potential.
- Macrophages are more active in phagocytosis than monocytes and develop many more granules containing hydrolytic enzymes. New macrophages can develop by cell division under inflammatory stimuli, but most macrophages are matured blood monocytes.
- The total pool of macrophages is referred to as the **system of mononuclear phagocytes**. The system is scattered throughout connective tissue, basement membranes of small blood vessels, liver sinusoids, the spleen, lung, bone marrow and lymph nodes. Monocytes from the blood migrate into virtually

every organ in the body where they mature into fixed macrophages. In the lymph nodes, they function as scavengers to remove foreign material from the circulation.

- macrophages have another indispensable function in host defense: they "process" the antigenic components of infective agents and present them to lymphocytes, a process that is usually required for the initiation of the adaptive immune responses of the host. For this activity, macrophages are known as **antigen-presenting cells** or **APC's** and they are an important bridge between the innate defenses and the adaptive immune response.
- Compared to neutrophils, macrophages are long-lived cells. As phagocytes, neutrophils play a more important role in the acute stages of an infection, while macrophages are principally involved in chronic types of infections. Neutrophils circulate in the blood stream, and during an acute inflammatory response they migrate through the endothelial cell junctions as part of the inflammatory exudate. They migrate to the focus of the infection and ingest or "phagocytose" the foreign agents. Neutrophils which have become engorged with bacteria usually die and largely make up the material of pus. Macrophages, which are also attracted to the area during an inflammatory response, are slower to arrive and become increasingly involved in chronic infections. They, too, are actively phagocytic and will engulf and destroy foreign particles such as bacteria.

- **Mast Cells** :These cells also reside in steady-state tissues and can detect the presence of microbes. Mast cells contain granules that are discharged when they are stimulated, and the granule contents can contribute to triggering of local inflammation.

- **Natural Killer Cells NK**: NK cells are developmentally related to lymphocytes, but differ in many aspects from them. NK cells are present in tissues as resident cells and can also be recruited to sites of inflammation. They can kill other cells, such as virally infected cells (i.e. they have cell-killing (cytotoxic) activity) and they also regulate immune responses.



Factors affecting innate immunity

A host's innate immunity depends , in part , on some predisposing factors of disease resistance that are inherent in each host and in the host's environment .

1.Nutrition

Poor nutrition contributes to greater disease incidence. A diet containing the required amounts of proteins and vitamins is directly related to protection from microbial disease. Dietary proteins are used to make healthy tissues and serum proteins .Vitamins promote efficient metabolism and maintain integrity of skin and membrane surfaces .

2.Species

Resistance to infection varies with the species of animal or plant . and this may be explained by the basic physiological and anatomical characteristics of a species which can determined whether a microorganism can be pathogenic for that species . for example , because of the differences in normal body temperature , many diseases of mammals do not affect fish or reptiles .

3.Genetic factors

make certain races of people more susceptible or more resistant than other races to a particular infection . the likely basis for these susceptibility differences probably relates to differences in major histocompatibility complex (MHC) gene composition .

4.Age

Age of the host also plays a role in disease susceptibility, with the very young and the very old having the highest risk of infection . In a young child the immune system is less developed or experienced whereas in an elderly persons it is no longer as efficient .

5.Physical and emotional stresses

Such as sleep deprivation ,fatigue, anxiety and depression – make a person more vulnerable to disease .In the stressed condition , there is enhanced production of adrenaline accompanied by altered levels of adrenal corticoid hormones ; this suppresses the function of many groups of defensive cells and depresses a wide range of defense mechanisms used by the body .