TOPIC: Innate (Nonspecific) Immune Response Lecture #1

OBJECTIVES:

1. To recognize the significance of the immune system
2. To distinguish between the innate (nonspecific) and adaptive (specific) immune systems
3. To understand the mechanisms of combating infection/disease (killing pathogens)
4. To know the humoral and cellular components of the innate immune response
5. To recognize the mechanisms of action of the components of the innate immune response

INNATE (NONSPECIFIC) IMMUNE RESPONSE

We are constantly being exposed to infectious agents and yet, in most cases, we are able to resist these infections. It is our immune system that enables us to resist infections. The immune system is composed of two major subdivisions, the innate or non-specific immune system and the adaptive or specific immune system (Figure 1). The innate immune system is our **first line** of defense against invading organisms while the adaptive immune system acts as a second line of defense and also affords protection against re- exposure to the same pathogen. Each of the major subdivisions of the immune system has both **cellular and humoral components** by which they carry out their protective function (Figure 1). In addition, the innate immune system also has anatomical features that function as barriers to infection. Although these **two arms of the immune system** have distinct functions, there is interplay between these systems (i.e., components of the innate immune system influence the adaptive immune system and vice versa).

There are two phases to the immune response: **pathogen recognition and pathogen removal.** Although the innate and adaptive immune systems both function to protect against invading organisms, they differ in a number of ways.

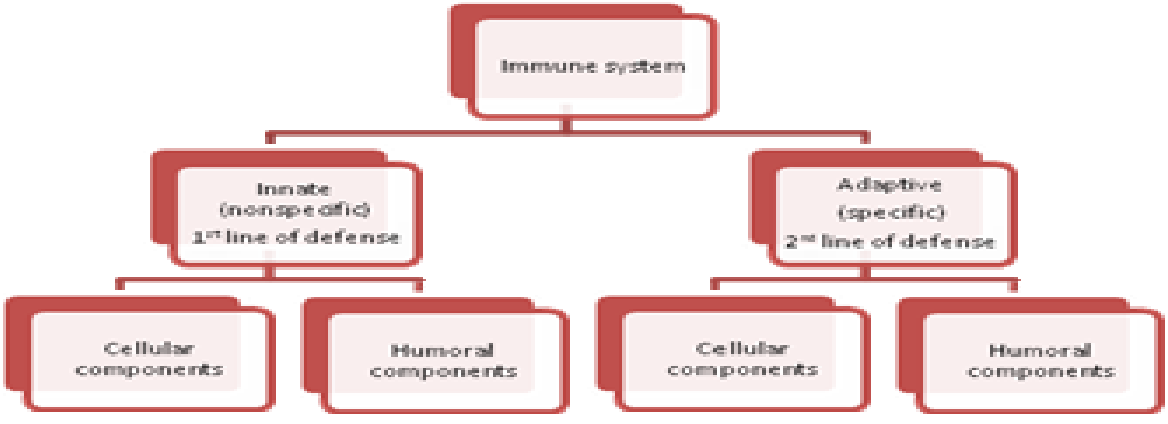

Fig.1

All cells of the immune system have their origin in the bone marrow. They include myeloid (neutrophils, basophils, eosinophils, macrophages, and dendritic cells) and lymphoid cells (B lymphocytes, T lymphocytes, and natural killer cells) (Figure 2).

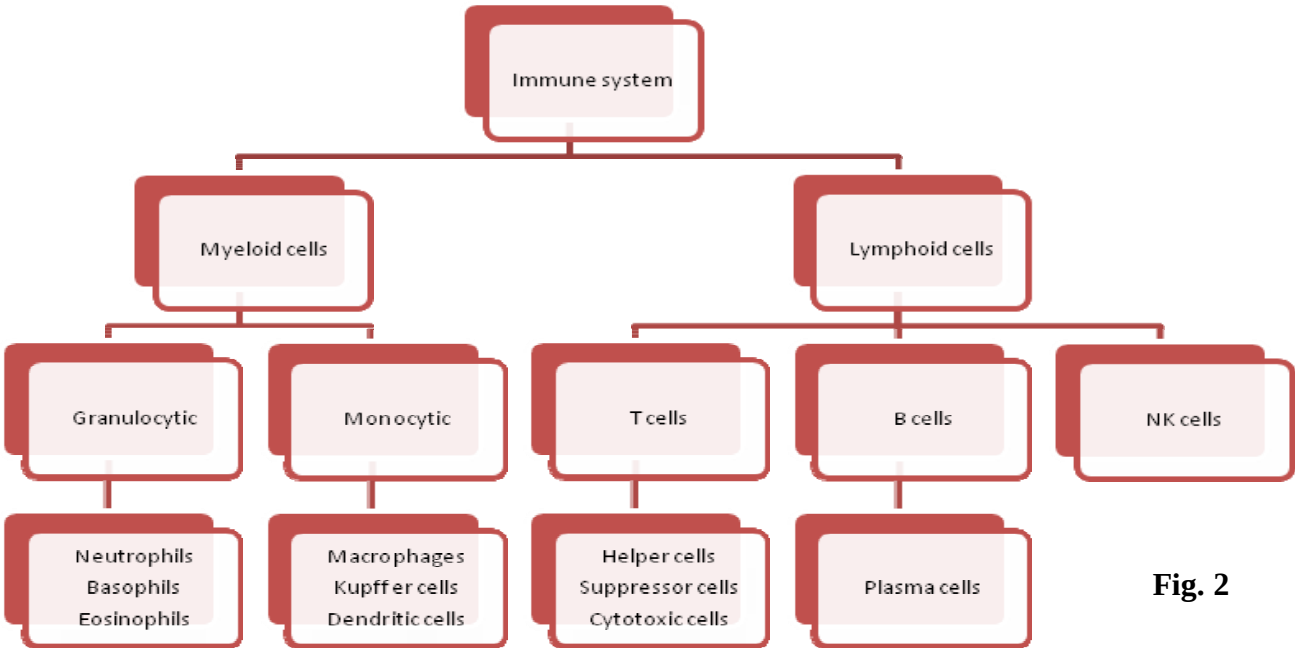

Fig. 2

The main function of the immune system is

- self/non-self discrimination. This ability to distinguish between self and non-self is necessary to protect the organism from invading pathogens and to eliminate modified or altered cells (e.g. malignant cells). Since pathogens may replicate intracellularly (viruses and some bacteria and parasites) or extracellularly (most bacteria, fungi and parasites), different components of the immune system have evolved to protect against these different types of pathogens.
- It is important to remember that infection with an organism does not necessarily mean diseases, since in most cases the immune system will be able to eliminate the infection before disease occurs.
- Disease occurs only when the bolus of infection is high, when the virulence of the invading organism is great or when immunity is compromised. Although the immune system, for the most part, has beneficial effects, there can be detrimental effects as well. During inflammation, which is the response to an invading organism, there may be local discomfort and collateral damage to healthy tissue as a result of the toxic products produced by the immune response.
- In addition, in some cases the immune response can be directed toward self tissues resulting in autoimmune disease.

Innate host defenses (barriers) against infection:

1. Anatomical barriers

- **Mechanical factors:** epithelial surfaces form a physical barrier that is very impermeable to most infectious agents. Thus, the skin acts as our first line of defense against invading organisms. The desquamation of skin epithelium also helps remove bacteria and other infectious agents that have adhered to the epithelial surfaces. Movement due to cilia or peristalsis helps to keep air passages and the gastrointestinal tract free from microorganisms. The flushing action of tears and saliva helps prevent infection of the eyes and mouth. The trapping effect of mucus that lines the respiratory and gastrointestinal tract helps protect the lungs and digestive systems from infection.

- **Chemical factors:** fatty acids in sweat inhibit the growth of bacteria. **Lysozyme** and **phospholipase** found in tears, saliva and nasal secretions can breakdown the cell wall of bacteria and destabilize bacterial membranes. The low pH of sweat and gastric secretions prevents growth of bacteria. **Defensins** (low molecular weight proteins) found in the lung and gastrointestinal tract have antimicrobial activity. Surfactants in the lung act as **opsonins** (substances that promote phagocytosis of particles by phagocytic cells).

- **Biological factors:** the normal flora of the skin and in the gastrointestinal tract can prevent the colonization of pathogenic bacteria by secreting toxic substances or by competing with pathogenic bacteria for nutrients or attachment to cell surfaces.

2. Humoral barriers

- Anatomical barriers are very effective in preventing colonization of tissues by microorganisms. However, when there is damage to tissues the anatomical barriers are breached and infection may occur. Once infectious agents have penetrated tissues, another innate defense mechanism comes into play, namely acute inflammation. Humoral factors play an important role in inflammation, which is characterized by edema and the recruitment of phagocytic cells. These humoral factors are found in serum or they are formed at the site of infection.

- The **complement system** is the major humoral non-specific defense mechanism. Once activated complement can lead to increased vascular permeability, recruitment of phagocytic cells, and lysis and opsonization of bacteria.

- Depending on the severity of the tissue injury, the **coagulation system** may or may not be activated. Some products of the coagulation system can contribute to the non-specific defenses because of their ability to increase vascular permeability and act as chemotactic agents for phagocytic cells. In addition, some of the products of the coagulation system are directly antimicrobial. For example, beta-lysin, a protein produced by platelets during coagulation can lyse many Gram positive bacteria by acting as a cationic detergent.

- By binding iron, an essential nutrient for bacteria, **lactoferrin and transferrin** limit bacterial growth.

- **Lysozyme** breaks down the cell wall of bacteria.

- **Cytokines** have various effects depending on the balance. Interferons are proteins that can limit virus replication in cells. Some interleukins induce fever and the production of acute phase proteins, some of which are antimicrobial because they can opsonize bacteria.

3. Cellular barriers

- Part of the inflammatory response is the recruitment of polymorphonuclear eosinophils and macrophages to sites of infection. These cells are the main line of defense in the non-specific immune system.

- **Neutrophils**, Polymorphonuclear cells (PMNs), are recruited to the site of infection where they phagocytose invading organisms and kill them intracellularly. In addition, PMNs contribute to collateral tissue damage that occurs during inflammation.

- Tissue **macrophages** and newly recruited **monocytes**, which differentiate into macrophages, also function in phagocytosis and intracellular killing of microorganisms. In addition, macrophages are capable of extracellular killing of infected or altered self target cells. Furthermore, macrophages contribute to tissue repair and act as antigen- presenting cells, which are required for the induction of specific immune responses.

- **Natural killer** (NK) and lymphokine activated killer (LAK) cells can nonspecifically kill virus infected and tumor cells. These cells are not part of the inflammatory response but they are important in nonspecific immunity to viral

infections and tumor surveillance.

- **Eosinophils** have proteins in granules that are effective in killing certain parasites.

Determinants recognized by the innate immune response

- Determinants recognized by components of the innate (nonspecific) immune system differ from those recognized by the adaptive (specific) immune system. Antibodies, and the B and T cell receptors recognize discrete determinants and demonstrate a high degree of specificity, enabling the adaptive immune system to recognize and react to a particular pathogen. In contrast, components of the innate immune system recognize broad molecular patterns found in pathogens but not in the host. Thus, they lack a high degree of specificity seen in the adaptive immune system. The broad molecular patterns recognized by the innate immune system have been called PAMPS (pathogen associated molecular patterns) and the receptors for PAMPS are called PRRs (pattern recognition receptors). A particular PRR can recognize a molecular pattern that may be present on a number of different pathogens enabling the receptor to recognize a variety of different pathogens. Examples of some PAMPs and PRRs are illustrated in Figure 3.

PRRs include:

- ❖ Toll-like receptors (TLRs), which signals the synthesis and secretion of cytokines to promote inflammation by recruiting cells.
- ❖ Scavenger receptors that are involved in internalization of bacteria and phagocytosis of host cells that are undergoing apoptosis.
- ❖ Opsonins, the molecules (C3a, IgM), which bind to microbes to facilitate their phagocytosis.

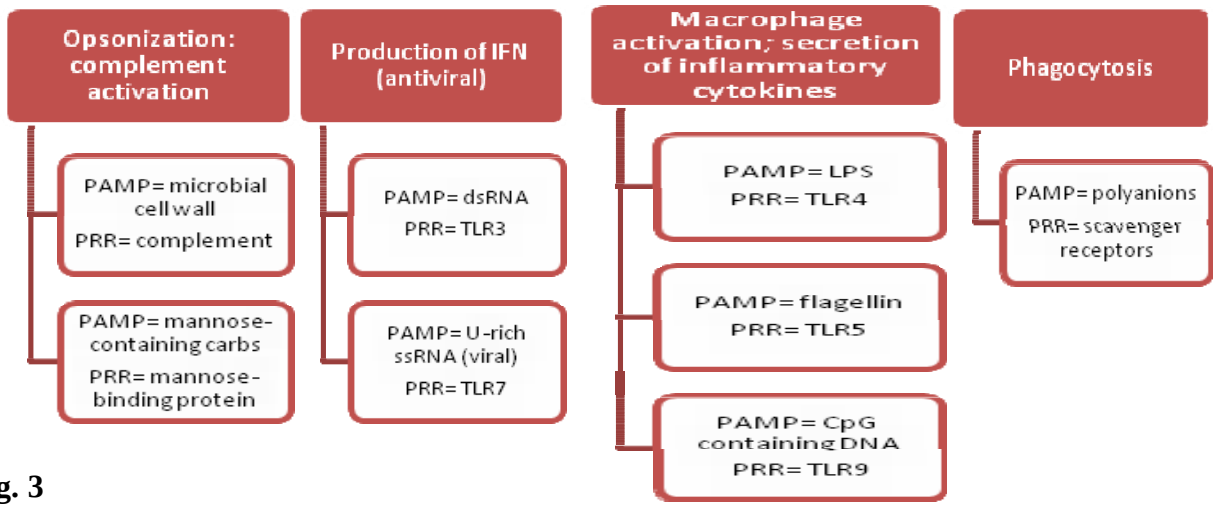

Fig. 3