Lec.3: Inflammatory Response

Inflammatory Response

The inflammatory response (Inflammation) is a series of local cellular and vascular responses which are triggered when the body is injured, or invaded by antigen. For instance, when you nick your skin, get a foreign object in your eye, or are stung by a bee, reactions occur in order to protect you.

The purpose of inflammation is:

1- to eliminate the initial cause of cell injury.
2- clear out necrotic cells and tissues damaged from the original insult and the inflammatory process.
3-to initiate tissue repair.

The classical signs of acute inflammation are:

1- pain 2-heat 3-redness 4-swelling 5- loss of function.

Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity.

Inflammatory Response steps:

1. Bacteria enter tissue/damage

2. Release of histamine

– Increased blood flow

– Increased vascular permeability

3. Increased leucocytes at site

Results

– Destroy or inactivate invaders

- Remove debris

- Prepare for healing & repair.

The Phagocytic Response

Phagocytic Defenses

When invading an pathogen penetrates the tissues, the inflammatory response is immediately brought into play. Part of this response leads to the recruitment of phagocytes at the site of inflammation.

Phagocytes are a class of white blood cells which are capable of ingestion (engulfment) and destruction of microorganisms and viruses that are responsible for inciting the inflammatory response. First to accumulate around the invaders and initiate the phagocytic process are **neutrophils**. Later, local and blood-borne **macrophages** also migrate to the tissue site and initiate phagocytosis. Neutrophils (also known as polymorphonuclear leucocytes or PMNs) and macrophages are sometimes referred to as **professional phagocytes** for their roles in this process.

Phagocytes of humans and other animals are called "**professional" or "non-professional"** depending on how effective they are at phagocytosis.[9] The professional phagocytes include many types of white blood cells (such as **neutrophils, monocytes and eosinophil** in blood **and macrophages , and dendritic cells** in tissue). The main difference between professional and non-professional phagocytes is that the professional phagocytes have molecules called receptors on their surfaces that can detect harmful objects, such as bacteria, that are not normally found in the body.

- **Non-Professional Phagocytes**

Dying cells and foreign organisms are consumed by cells other than the "professional" phagocytes. These cells include epithelial cells, endothelial cells,

fibroblasts, and mesenchymal cells. They are called non-professional phagocytes, to emphasize that, in contrast to professional phagocytes, phagocytosis is not their principal function. Fibroblasts, for example, which can phagocytose collagen in the process of remolding scars, will also make some attempt to ingest foreign particles. Non-professional phagocytes are more limited than professional phagocytes in the type of particles they can take up. This is due to their lack of efficient phagocytic receptors, particularly opsonins. Additionally, most nonprofessional phagocytes do not produce ROS in response to phagocytosis.

The Phagocytic Process

Phagocytosis and destruction of engulfed bacteria involves the following sequence of events:

1. **Delivery** of phagocytic cells to the site of infection

2. **Phagocytic adherence** to the target

3. **Ingestion** or engulfment of the target particle

4. **Phagosome formation**

5. **Phagolysosome formation**

6. **Intracellular killing**

7. **Intracellular digestion** (and egestion, in the case of macrophages)

These **steps involved in the phagocytic process** in macrophages are illustrated below.

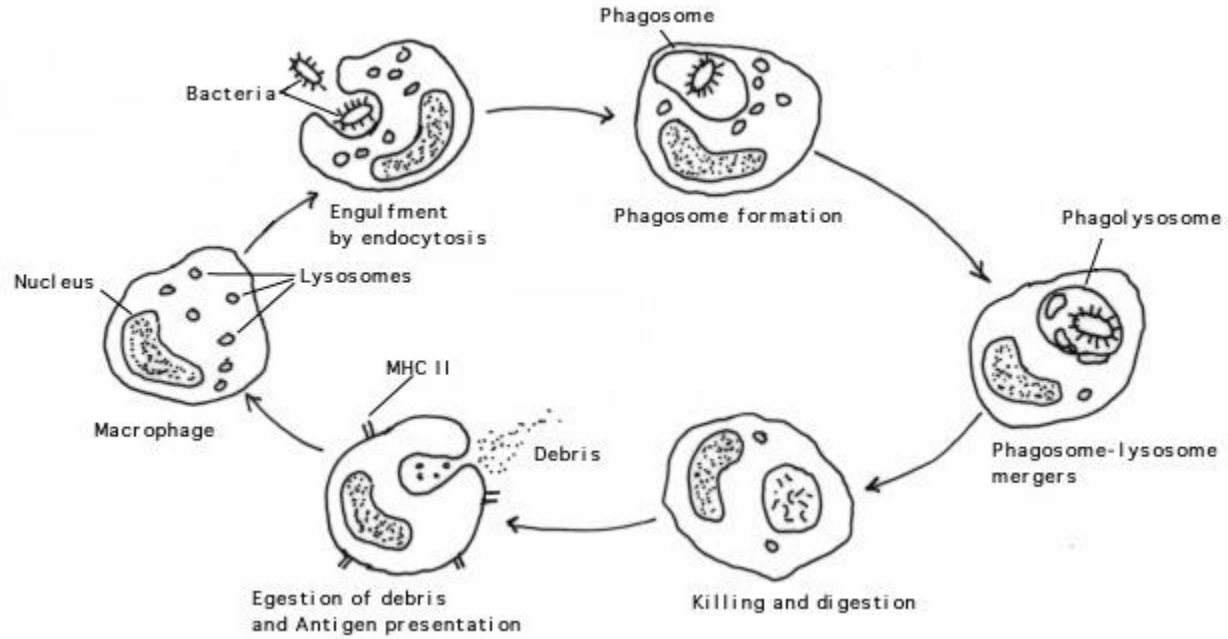
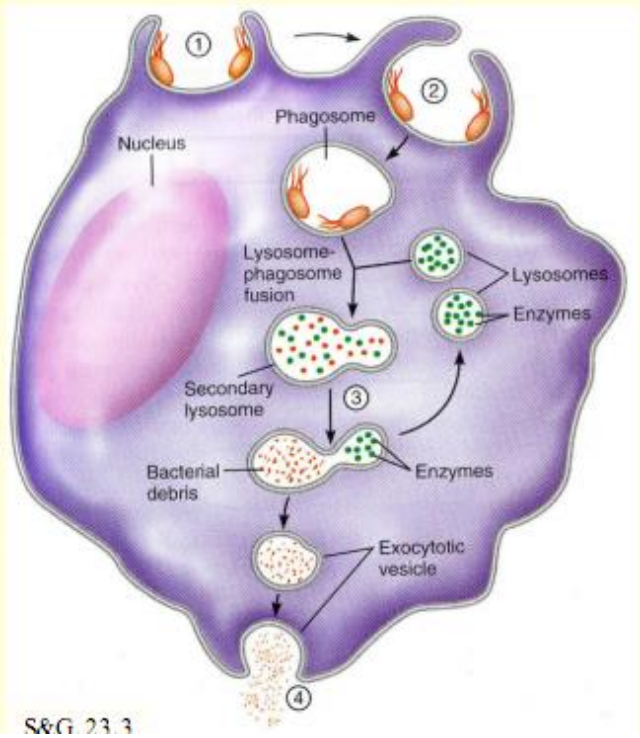


Figure: Phagocytosis by a Macrophage. A bacterium, which may or may not be opsonized, is engulfed by the process of endocytosis. The bacterium is ingested in a membranous vesicle called the phagosome. Digestive granules (lysosomes) merge with phagosome, release their contents, and form a structure called the phagolysosome. The killing and digestion of the bacterial cell takes place in the phagolysosome. The macrophage egests debris while processing the antigenic components of the bacterium, which it returns to its surface in association with MHC II for antigen presentation to T cells.



- **Delivery of phagocytic cells to the site of infection**

The **delivery** of phagocytic cells, monocytes or neutrophils, to the site of microbial infection involves two processes:

Diapedisis: the migration of cells across vascular walls which is initiated by the mediators of inflammation (kinins, histamine, prostaglandins, etc.)

Chemotaxis. Phagocytes are motile by ameboid action. Chemotaxis is movement of the cells in response to a chemical stimulus. The eventual concentration of phagocytes at a site of injury results from chemotactic response by the phagocytes which is analogous to bacterial chemotaxis. A number of chemotactic factors (attractants) have been identified, both for neutrophils and monocytes. These include bacterial products, cell and tissue debris, and components of the inflammatory exudate such as peptides derived from complement.

- **Phagocytic adherence**

Phagocytosis is initiated by adherence of a particle to the surface of the plasma membrane of a phagocyte. This step usually involves several types of surface receptors on the phagocyte membrane. Three major receptors on phagocytes recognize the Fc portion of IgG antibody molecules: one is for monomeric IgG and the others are for antigen-crosslinked IgGs. Another receptor binds a complement factor, C3b. Other phagocyte receptors bind fibronectin and mannose-terminated oligosaccharides. Under certain circumstances of infection, bacteria or viruses may become coated or otherwise display on their surfaces one or another of these substances (i.e., IgG, C3b, fibronectin or mannose). Such microbes are said to be **opsonized** and such substances as IgG or complement C3b bound to the surface of microbes are called **opsonins**. (Opsonin comes from a Greek word meaning "sauce" or "seasoning": they make the bacterium or virus more palatable and more easily ingested by the phagocyte.) Opsonins provide extrinsic ligands for specific receptors on the phagocyte membrane, which dramatically increases the rate of

adherence and ingestion of the pathogen. Opsonized bacteria can be cleared from the blood by phagocytes; many types of non opsonized bacteria cannot be cleared.

Less firm attachments of a phagocyte to a particle can take place in the absence of opsonization. This can be thought of as **nonspecific attachment** which might be due to net surface charge on the phagocyte or particle and/or hydrophobicity of the particle.

Also, a phenomenon called **surface phagocytosis** exists: a phagocyte can simply trap an organism against a surface and initiate ingestion. Surface phagocytosis may be an important pre-antibody defense mechanism which may determine whether an infection will become a disease and how severe the disease will become.

- **Ingestion**

After attachment of the phagocyte to its target, some sort of signal generation, which is poorly understood, results in physical or chemical changes in the cell that triggers ingestion. Ingestion is an engulfment process that involves infolding or invagination of the cell membrane enclosing the particle and ultimately releasing it into the cytoplasm of the cell within a membrane vesicle. The end result of ingestion is entry of the particle enclosed in a vesicle derived from the plasma membrane of the cell. This structure is called the **phagosome**.

- **Formation of the phagolysosome**

The phagosome migrates into the cytoplasm and collides with lysosomal granules which explosively discharge their contents into the membrane-enclosed vesicle (phagosome). Membranes of the phagosome and lysosome actually fuse resulting in a digestive vacuole called the **phagolysosome**. Other lysosomes will fuse with the phagolysosome. It is within the phagolysosome that killing and digestion of the engulfed microbe takes place. Some of the microbicidal constituents of the lysosomes of neutrophils and macrophages include lysozyme, cationic proteins, various proteases and hydrolyases and peroxidases. The killing processes are confined to the membranous organelles of the phagocytes (the phagolysosome) such that none of the toxic substances and lethal activities of the phagocytes are turned against themselves.

- **Intracellular killing of organisms**

After phagolysosome formation the first detectable effect on bacterial physiology, occurring within a few minutes after engulfment, is loss of viability (ability to reproduce). The exact mechanism is unknown. Inhibition of macromolecular synthesis occurs later. By 10 to 30 minutes after ingestion many pathogenic and nonpathogenic bacteria are killed followed by lysis and digestion of the bacteria by lysosomal enzymes. The microbicidal activities of phagocytes are complex and multifarious. Metabolic products, as well as lysosomal constituents, are responsible. These activities differ to some extent in neutrophils, monocytes and macrophages.

The microbicidal activities of phagocytes are usually divided into **oxygen-dependent** and **oxygen-independent** events.

- **Oxygen-independent activity**

Lysosomal granules contain a variety of extremely basic proteins that strongly inhibit bacteria, yeasts and even some viruses. A few molecules of any one of these cationic proteins appear able to inactivate a bacterial cell by damage to their permeability barriers, but their exact modes of action are not known. The lysosomal granules of neutrophils contain lactoferrin, an extremely powerful iron-chelating agent, which withholds potential iron needed for bacterial growth. The pH of the phagolysosome may be as low as 4.0 due to accumulation of lactic acid, which is sufficiently acidic to prevent the growth of most pathogens. This acidic environment apparently optimizes the activity of many degradative lysosomal enzymes including lysozyme, glycosylases, phospholipases, and nucleases.

- **Oxygen-dependent activity**

Liganding of Fc receptors (on neutrophils, monocytes or macrophages) and mannose receptors (on macrophages) increases their O_2 uptake, called the **respiratory burst** or "oxygen burst". These receptors activate a membrane-bound **NADPH oxidase** that reduces O_2 to O_2^- (superoxide). Superoxide can be reduced to $OH^\cdot$ (hydroxyl radical) or dismutated to H_2O_2 (hydrogen peroxide) by superoxide dismutase. O_2^-, $OH^\cdot$, and $H_2O_2$are activated oxygen species that are

potent oxidizing agents in biological systems which adversely affect a number of cellular structures including membranes and nucleic acids. Furthermore, at least in the case of neutrophils, these reactive oxygen intermediates can act in concert with a lysosomal enzyme called **myeloperoxidase** to function as the myeloperoxidase system, or MPO.

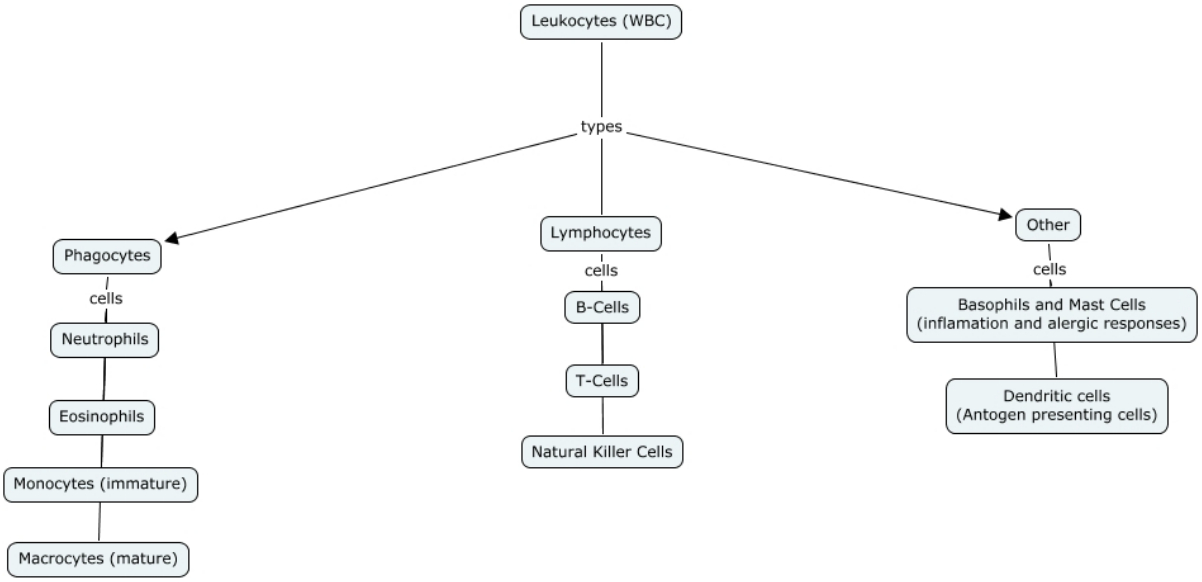
Myeloperoxidase is one of the lysosomal enzymes of neutrophils which is released into the phagocytic vacuole during fusion to form the phagolysosome. Myeloperoxidase uses H_2O_2 generated during the respiratory burst to catalyze halogenation (mainly chlorination) of microbes contained within the phagolysosome. Such halogenations are a potent mechanism for killing cells.

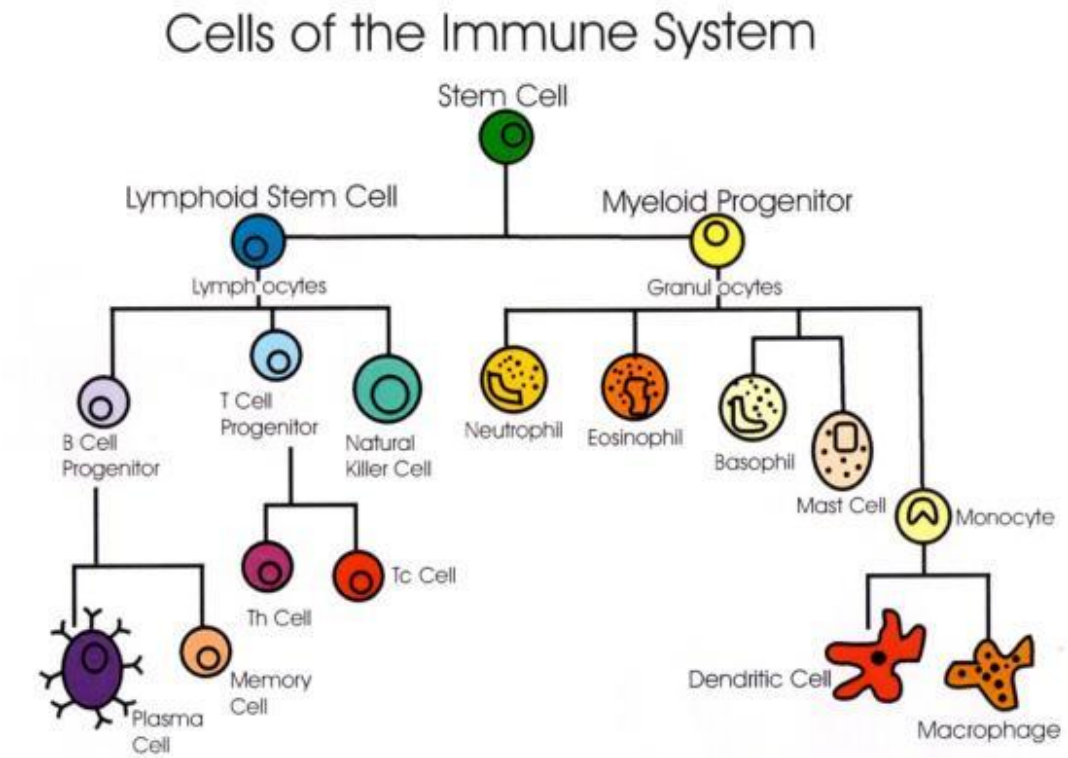
When the NADPH oxidase and myeloperoxidase systems are operating in concert, a series of reactions leading to lethal oxygenation and halogenation of engulfed microbes occurs.

- **Intracellular digestion**

Dead microbes are rapidly degraded in phagolysosomes to low molecular-weight components. Various hydrolytic enzymes are involved including lysozyme, proteases, lipases, nucleases, and glycosylases. Neutrophils die and lyse after extended phagocytosis, killing, and digestion of bacterial cells. This makes up the characteristic properties of pus.

Macrophages egest digested debris and allow insertion of microbial antigenic components into the plasma membrane for presentation to lymphocytes in the immunological response.


Leukocytes (WBC)
types
Phagocytes
cells
Neutrophils
Eosinophils
Monocytes (immature)
Macrocytes (mature)
Lymphocytes
cells
B-Cells
T-Cells
Natural Killer Cells
Other
cells
Basophils and Mast Cells
(inflamation and alergic responses)
Dendritic cells
(Antogen presenting cells)


Cells of the Immune System
Stem Cell
Lymphoid Stem Cell
Myeloid Progenitor
Lymphocytes
Granulocytes
B Cell Progenitor
T Cell Progenitor
Natural Killer Cell
Neutrophil
Eosinophil
Basophil
Mast Cell
Monocyte
Tc Cell
Th Cell
Memory Cell
Plasma Cell
Dendritic Cell
Macrophage