Macrophage

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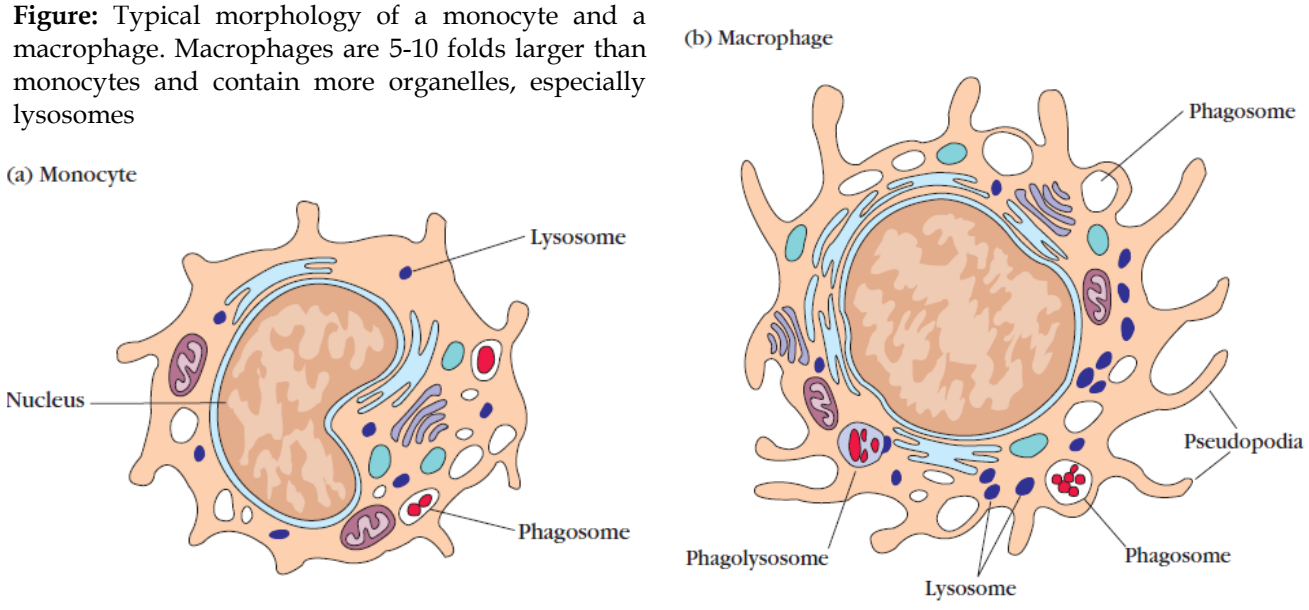
Origin:

- Macrophage is an important innate immune cell that has potent phagocytic function.
- The mononuclear phagocytic system consists of **monocytes** circulating in the blood and **macrophages** in the tissues.
- During hematopoiesis in the bone marrow, granulocyte-monocyte progenitor cells differentiate into promonocytes, which leave the bone marrow and enter the blood, where they further differentiate into mature monocytes.
- Monocytes circulate in the bloodstream for about 8 h, during which they enlarge; they then migrate into the tissues and differentiate into specific tissue macrophages or, into dendritic cells.
- Differentiation of a monocyte into a tissue macrophage involves a number of changes:
    a) the cell enlarges five- to tenfold;
    b) its intracellular organelles increase in both number and complexity;
    c) it acquires increased phagocytic ability, produces higher levels of hydrolytic enzymes,
    d) it begins to secrete a variety of soluble factors.

Macrophages are dispersed throughout the body. Some take up residence in particular tissues, becoming fixed macrophages, whereas others remain motile and are called free, or wandering, macrophages. Free macrophages travel by amoeboid movement throughout the tissues. Macrophage-like cells serve different functions in different tissues and are named according to their tissue location:

1. **Alveolar macrophages** in the lung
2. **Histiocytes** in connective tissues
3. **Kupffer cells** in the liver
4. **Mesangial cells** in the kidney
5. **Microglial cells** in the brain
6. **Osteoclasts** in bone

Figure: Typical morphology of a monocyte and a macrophage. Macrophages are 5-10 folds larger than monocytes and contain more organelles, especially lysosomes



Activation:

Although normally in a resting state, macrophages are activated by a variety of stimuli in the course of an immune response.

- Phagocytosis of particulate antigens serves as an initial activating stimulus.
- However, macrophage activity can be further enhanced by cytokines secreted by activated T_H cells, by mediators of the inflammatory response, and by components of bacterial cell walls.
- One of the most potent activators of macrophages is interferon gamma (IFN- γ) secreted by activated T_H cells.

Function:

- Activated macrophages exhibit greater phagocytic activity, an increased ability to kill ingested microbes, increased secretion of inflammatory mediators, and an increased ability to activate T cells.
- Activated macrophages secrete various cytotoxic proteins that help them eliminate a broad range of pathogens, including virus-infected cells, tumor cells, and intracellular bacteria.
- Activated macrophages also express higher levels of class II MHC molecules, allowing them to function more effectively as antigen-presenting cells.
- Thus, macrophages and T_H cells facilitate each other's activation during the immune response.

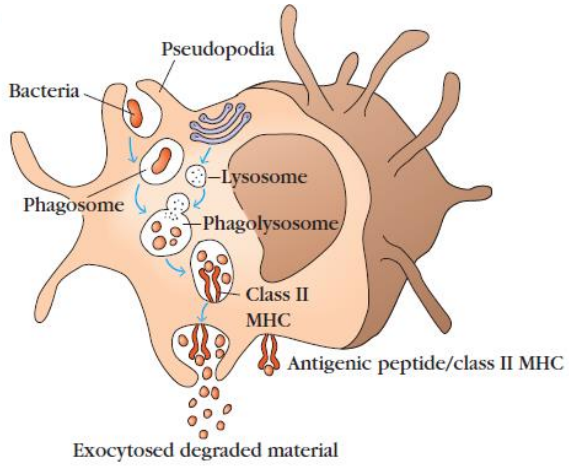


Figure: The figure demonstrates the typical functions of an activated macrophage.

Phagocytosis

- Macrophages are capable of ingesting and digesting exogenous antigens, such as whole microorganisms and insoluble particles, and endogenous matter, such as injured or dead host cells, cellular debris, and activated clotting factors.
- In the first step in phagocytosis, macrophages are attracted by and move toward a variety of substances generated in an immune response; this process is called **chemotaxis.**
- The next step in phagocytosis is adherence of the antigen to the macrophage cell membrane. Complex antigens, such as whole bacterial cells or viral particles, tend to adhere well and are readily phagocytosed; isolated proteins and encapsulated bacteria tend to adhere poorly and are less readily phagocytosed.
- Adherence induces membrane protrusions, called **pseudopodia,** to extend around the attached material .
- Fusion of the pseudopodia encloses the material within a membrane-bounded structure called a **phagosome,** which then enters the endocytic processing pathway. In this pathway, a phagosome moves toward the cell interior, where it fuses with a **lysosome** to form a **phagolysosome.** Lysosomes contain lysozyme and a variety of other hydrolytic enzymes that digest the ingested material.
- The digested contents of the phagolysosome are then eliminated in a process called **exocytosis**.

Opsonization:

- The macrophage membrane has receptors for certain classes of antibody.
- If an antigen (e.g., a bacterium) is coated with the appropriate antibody, the complex of antigen and antibody binds to antibody receptors on the macrophage membrane more readily than antigen alone and phagocytosis is enhanced.
- The rate of phagocytosis of an antigen may be 4000-fold higher in the presence of specific antibody to the antigen than in its absence.
- Thus, antibody functions as an **opsonin,** a molecule that binds to both antigen and macrophage and enhances phagocytosis.
- The process by which particulate antigens are rendered more susceptible to phagocytosis is called **opsonization.**

Secretion of factors

- A number of important proteins central to development of immune responses are secreted by activated macrophages.
- These include a collection of cytokines, such as **interleukin 1 (IL-1),** TNF- α and **interleukin 6 (IL-6),** that promote inflammatory responses.
- Typically, each of these agents has a variety of effects: IL-1 activates lymphocytes; and IL-1, IL-6, and TNF- α promote fever by affecting the thermoregulatory center in the hypothalamus.

Antimicrobial and cytotoxic activities

A number of antimicrobial and cytotoxic substances produced by activated macrophages can destroy phagocytosed microorganisms. Many of the mediators of cytotoxicity are reactive forms of oxygen.

OXYGEN-DEPENDENT KILLING MECHANISMS

- Activated phagocytes produce a number of **reactive oxygen intermediates (ROIs)** and **reactive nitrogen intermediates** that have potent antimicrobial activity.
- During phagocytosis, a metabolic process known as the **respiratory burst** occurs in activated macrophages.
- This process results in the activation of a membrane-bound oxidase that catalyzes the reduction of oxygen to superoxide anion, a reactive oxygen intermediate that is extremely toxic to ingested microorganisms.
- The superoxide anion also generates other powerful oxidizing agents, including hydroxyl radicals and hydrogen peroxide.
- As the lysosome fuses with the phagosome, the activity of yeloperoxidase produces hypochlorite from hydrogen peroxide and chloride ions. Hypochlorite is toxic to ingested microbes.
- When acrophages are activated with bacterial cell-wall components such as lipopolysaccharide (LPS) or, in the case of mycobacteria, muramyl dipeptide (MDP), together with a T-cell–derived cytokine (IFN-γ), they begin to express high levels of nitric oxide synthetase (NOS), an enzyme that oxidizes L-arginine to yield L-citrulline and nitric oxide (NO), a gas:

$$\textbf{L-arginine} + O_2 + \textbf{NADPH} \rightarrow \textbf{NO} + \textbf{L-citrulline} + \textbf{NADP}$$

- Nitric oxide has potent antimicrobial activity; it also can combine with the superoxide anion to yield even more potent antimicrobial substances.
- Recent evidence suggests that much of the antimicrobial activity of macrophages against bacteria, fungi, parasitic worms, and protozoa is due to nitric oxide and substances derived from it.

OXYGEN-INDEPENDENT KILLING MECHANISMS

- Activated macrophages also synthesize **lysozyme** and various hydrolytic enzymes whose degradative activities do not require oxygen.
- In addition, activated macrophages produce a group of antimicrobial and cytotoxic peptides, commonly known as **defensins.**
- These molecules are cysteine-rich cationic peptides containing 29–35 amino-acid residues. Each peptide, which contains six invariant cysteines, forms a circular molecule that is stabilized by intramolecular disulfide bonds.
- These circularized defensin peptides have been shown to form ion-permeable channels in bacterial cell membranes.
- Defensins can kill a variety of bacteria, including *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Pseudomonas aeruginosa,* and *Haemophilus influenzae.*
- Activated macrophages also secrete tumor necrosis factor alpha **(TNF- α),** a cytokine that has a variety of effects and is cytotoxic for some tumor cells.

Oxygen-dependent killing	Oxygen-independent killing
Reactive oxygen intermediates	Defensins
$O^{\bullet}_2{}^{-}$ (superoxide anion)	Tumor necrosis factor α
$OH^{\bullet}$ (hydroxyl radicals)	(macrophage only)
H_2O_2 (hydrogen peroxide)	Lysozyme
ClO^{-} (hypochlorite anion)	Hydrolytic enzymes
Reactive nitrogen intermediates	
NO (nitric oxide)	
NO_2 (nitrogen dioxide)	
HNO_2 (nitrous acid)	
Others	
NH_2CL (monochloramine)	

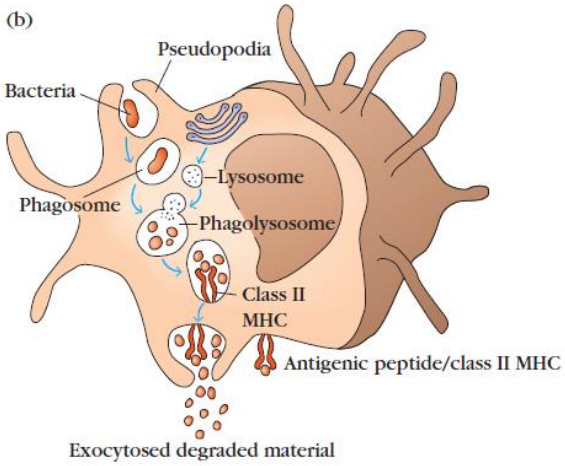


Figure: (a) Mediators of cytotoxic response in macrophage (b) process of antigen processing and presentation

Antigen processing and presentation

- Although most of the antigen ingested by macrophages is degraded and eliminated, experiments with radiolabeled antigens have demonstrated the presence of antigen peptides on the macrophage membrane.
- Phagocytosed antigen is digested within the endocytic processing pathway into peptides that associate with class II MHC molecules; these peptide–class II MHC complexes then move to the macrophage membrane.
- Activation of macrophages induces increased expression of both class II MHC molecules and the co-stimulatory B7 family of membrane molecules, thereby rendering the macrophages more effective in activating T_H cells.
- This processing and presentation of antigen, are critical to T_H-cell activation, a central event in the development of both humoral and cell-mediated immune responses.

Reference: Immunology by J. Kuby