Principles of Innate and Adaptive Immunity

Cells and molecules of the innate and adaptive immune responses work as an integrated host defense system to eliminate the infectious agent and provide long lasting protective immunity.

Most of the microorganisms encountered daily in life of a normal healthy individual are detected and destroyed within hours by defense mechanisms that are not antigen specific and do not require a prolonged period of induction. These are the mechanisms of **innate immunity**.

Only if an infectious organism can breach these early lines of defense will and **adaptive immune response** ensue, with the generation of antigen specific cells that prevent subsequent infection with the same microorganism.

Summary of features of innate and adaptive immunity is given in Table 7.

	Innate	**Adaptive**
Physicochemical barriers	Skin, mucous membranes	cutaneous and mucosal immune systems; antibody in mucosal secretions
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes
Soluble mediators active on other cells	Macrophage-derived cytokines, e.g. α and β interferon, tumor necrosis factor	Lymphocyte-derived cytokines, e.g. interferon γ

Table 7: Features of innate and adaptive immunity.

Principles of Innate immune

Natural barriers

The skin and mucus membranes make up a natural barrier to infection. Our body surfaces are defended by **epithelia,** which provide a physical barrier between the internal milieu and the external world containing pathogens. They also produce chemical substances that are microbicidal or inhibit microbial growth.

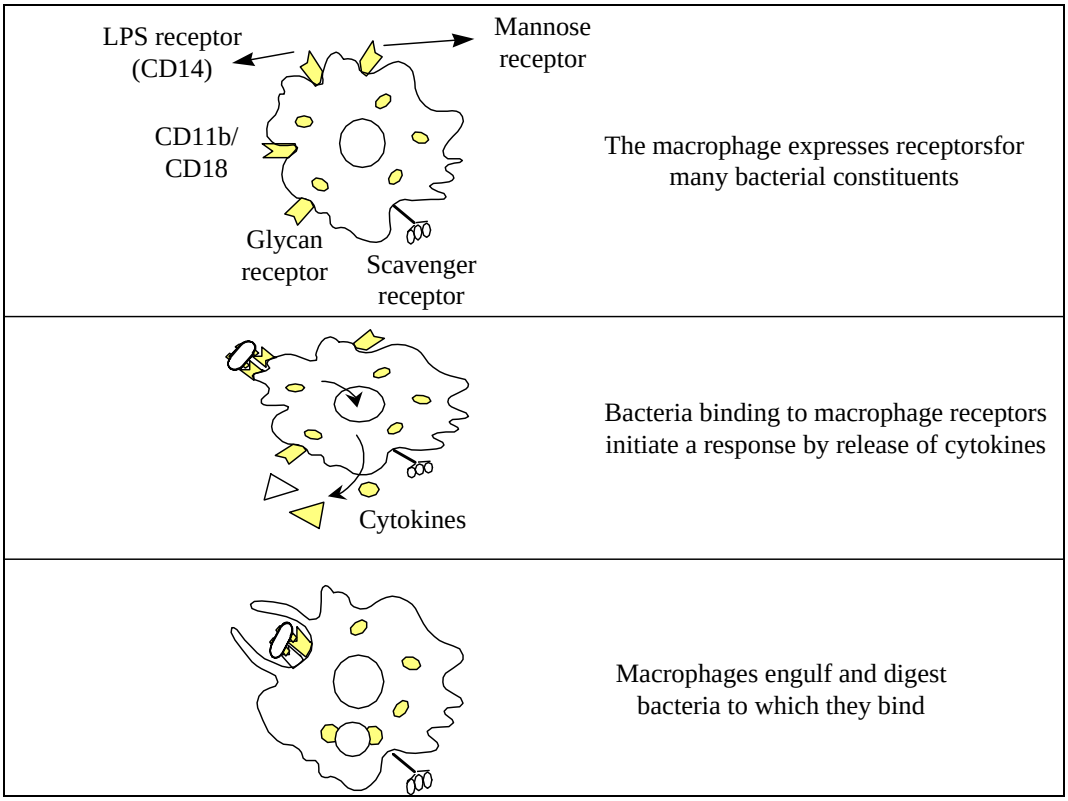

Figure 22: Macrophages bear several different receptors that recognize microbial components and induce phagocytosis and release of cytokines.

Furthermore, most epithelia are associated with a normal flora of non pathogenic bacteria that compete with pathogens for attachment sites and nutrients, helping to prevent infection.

Epithelial barriers to infection	
Mechanical	Epithelial cells joined by tight junctions Longitudinal flow of air or fluid across epithelium
Chemical	Fatty acids (skin) Enzymes : lysozyme (saliva, sweat, tears), pepsin (gut) low pH (stomach) Antibacterial peptides (intestine)
Microbiological	Normal flora competes for nutrients and attachment to epithelium and can produce antibacterial substances.

Table 8: Surface epithelia comprise a mechanical, chemical and microbiological barrier to infection.

Cellular defenses

Macrophages provide innate cellular immunity in tissues and initiate host defense responses. In addition to the Fc receptors, macrophages have on their surface several receptors for various microbial constituents. These receptors include the macrophage mannose receptor, the "scavenger" receptor and CD14, a molecule that binds bacterial lipopolysaccharide (LPS), Figure 22. The leukocyte integrin CD11b/CD18, also known as Mac-1, is also able to recognize a number of microbial substances, including LPS. When pathogens cross an epithelial barrier they are recognized by phagocytes in the sub-epithelial connective tissues with **three important consequences**.

- The **first** is the trapping, engulfment, and destruction of the pathogen by tissue macrophages.
- The **second** important effect of the interaction of macrophages with pathogens is the secretion of the **cytokines** by the phagocytes.
- The **third** effect of the interaction of macrophages with antigen is that they take up antigens, process them by denaturation or by partial digestion, and present them on their surfaces to specific T cells. Thus macrophages function also as **antigen presenting cells.**

Cytokine production and inflammation

The innate immune response produces cytokines and other mediators that recruit new phagocytic cells to local sites of infection. One important function of the innate immune response is to recruit more phagocytic cells and effector molecules to the site of infection through the release of cytokines and other inflammatory mediators. Cytokines (**monokines**) whose synthesis is stimulated when macrophages recognize microbial constituents include interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), and tumor necrosis factor-α (TNF-α). All have important local and systemic effects which are summarized in Figure 23.

The other mediators released by macrophages in response to infectious agents comprise a large number of molecules, including **prostaglandin and nitrous oxide (NO).**

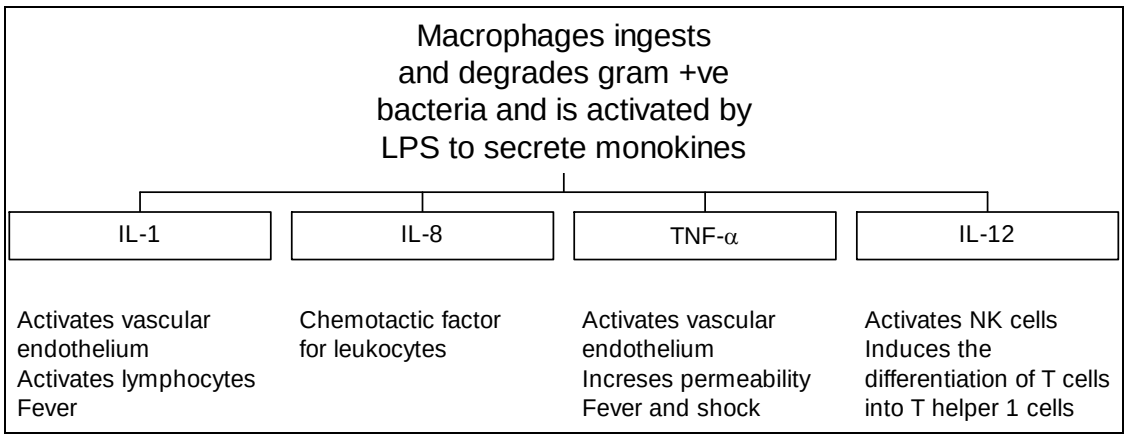

Figure 23: Important cytokines secreted by macrophages in response to bacterial products include IL-1, IL-6, IL-8, IL-12 and TNF-α.

The combined local effects of these mediators contribute to local reactions to infection in the form of an **inflammatory response**, which are clinically characterized by pain, redness, heat and swelling at the site of an infection. Figure 24.

The **second** effect of these cytokines on endothelium is to induce the expression of **adhesion molecules** that bind to the surface of circulating monocytes and polymorphonuclear leukocytes and greatly enhanced the rate by which these phagocytic cells migrate across local small blood vessel walls into the tissues. The migration of leukocytes out of blood vessels, a process known as **extravasation**, Figure 24.

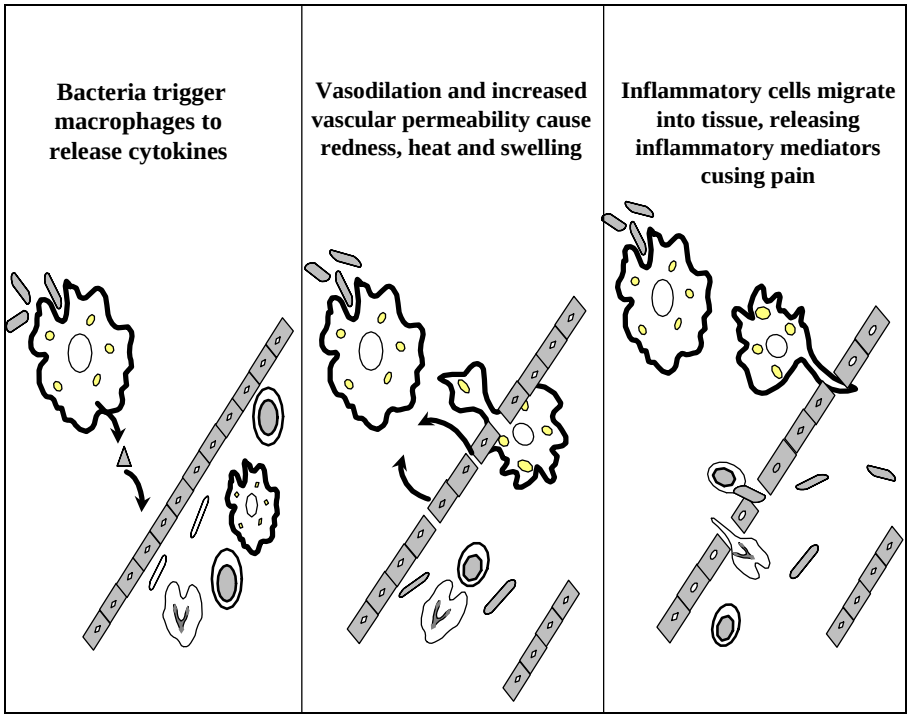

Figure 24: Bacterial infection triggers and inflammatory response.

Acute phase proteins

Cytokines released by macrophages also activate the acute phase response. Acute phase proteins are produced by liver in response to IL-6 released by macrophages in the presence of bacteria. They include C-reactive proteins (CRP), fibrinogen and mannose binding protein (MBP). Both proteins bind to the bacterial surfaces and activate complement to lyse bacteria and directly opsonize bacterial.

Interferons

Interferons inhibit viral replication and activate certain host defense responses. Infection of cells with viruses induces the production of proteins known as interferons because they were found to interfere with viral replication in previously uninfected cells. These interferons, called interferon-α (IFN-α) and interferon-β (IFN-β) are quite distinct from interferon-α (IFN-α) which is produced chiefly by T cells. The function of α and β interferons are shown in fig (2.4).

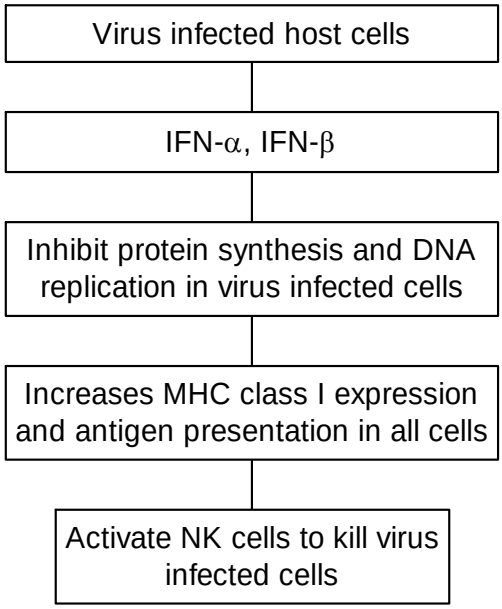

Figure 25: Interferons are anti-viral proteins produced by cells in responses to viral infection.

Role of natural killer cells

Natural killer cells serve as early defense against certain intracellular infections and cancer. Natural killer cells or **NK cells** can recognize unique structure on the membrane of virus infected cells. Killing is achieved by the release of various cytotoxic molecules. Some of these molecules cause the formation of pores in the membrane of target cell leading to its lysis.

Other molecules enter the target cell and cause **apoptosis** (a form of **programmed cell death**) of the target cell by enhanced fragmentation of its nuclear DNA.

γδ T cells

T cells bearing αδ T cell receptors are found in most epithelia and may contribute to host defense of the body surfaces. γδ T cells are lymphocytes with receptors of limited diversity that seem to provide early protection from a limited range of pathogens but do not generate lasting immunity.

Principles of adaptive immunity

Features of adaptive immunity

The adaptive immune response is characterized by:

1- **Specificity**: The ability to discriminate between different antigenic epitopes, and respond only to those that necessitate a response rather than making a random response.

2- **Memory**: The ability to recall (remember) previous contact with a particular antigen, such that subsequent exposure leads to a more rapid and larger immune response.

3- **Adaptiveness**: The ability to respond to previously unseen antigens, which may never have existed before on earth.

4- **Discrimination between "self" and "nonself"**: The ability to respond to those antigens that are not "self" and to avoid making responses to those antigens that are part of "self".

The most widely accepted theory that best explains these features is the **clonal selection theory**. The essential features of the clonal selection theory may be summarized as follows:

1- B and T lymphocytes of all antigenic specificities exist **prior** to contact with antigen.

2- Each lymphocyte carries immunoglobulin or T cell receptor molecules of only a **single** specificity on its surface.

3- Lymphocytes can be stimulated by antigen under appropriate conditions to give rise to progeny with **identical** antigenic specificity. In case of B cells, but not T cells, the antigen-specific receptor - immunoglobulin - is secreted as a consequence of stimulation.

4- Lymphocytes potentially reactive with "self" are **deleted** or in some way **inactivated**. This ensures that no immune response is mounted against self components.

Antigen receptors

Both T and B lymphocytes bear on their surface highly diverse receptors, each of which is specific for a particular antigen and which together are capable of recognizing a wide diversity of antigens.

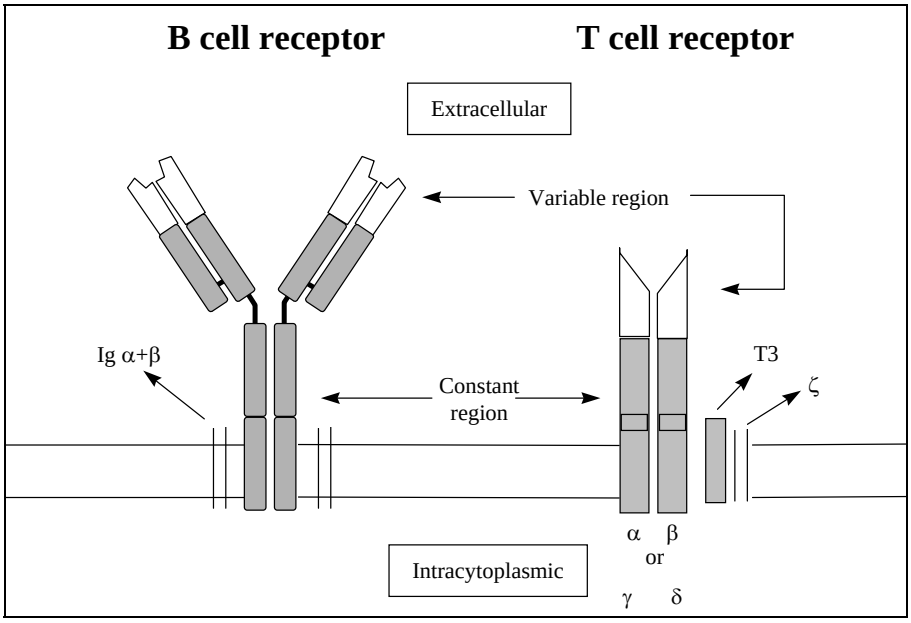

Figure 26: The antigen receptor of T cells show many similarities with the B cell antigen receptor.

The antigen receptor of B lymphocytes (**BcR**) is a membrane-bound form of the antibody **(surface immunoglobulin)**, while the antigen receptor of T lymphocytes (**TcR**) is composed of an **αβ (or γδ) chains**, each with a variable and a constant domains.

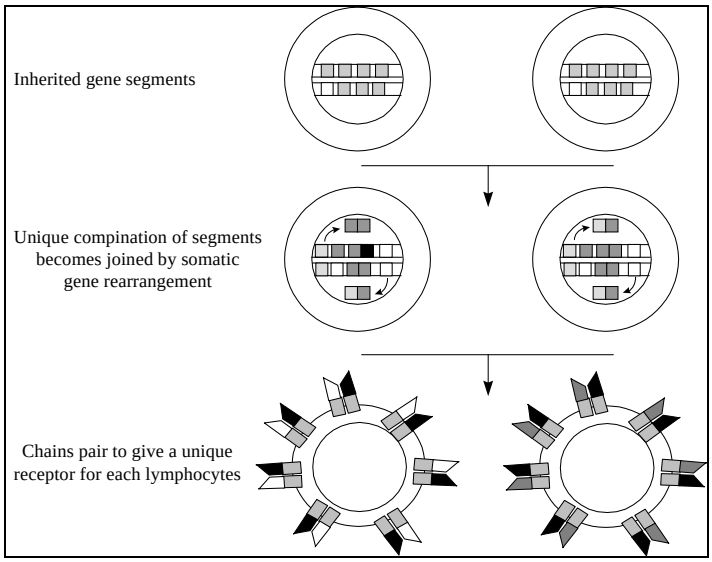

Figure 27: The diversity of lymphocyte receptors generated by somatic gene rearrangement.

The diversity of lymphocyte receptor is made by pairing two different variable chains, each encoded by distinct sets of gene segments. A thousand different chains of each type could generate 10^6 distinct antigen receptor through this combinatorial diversity.

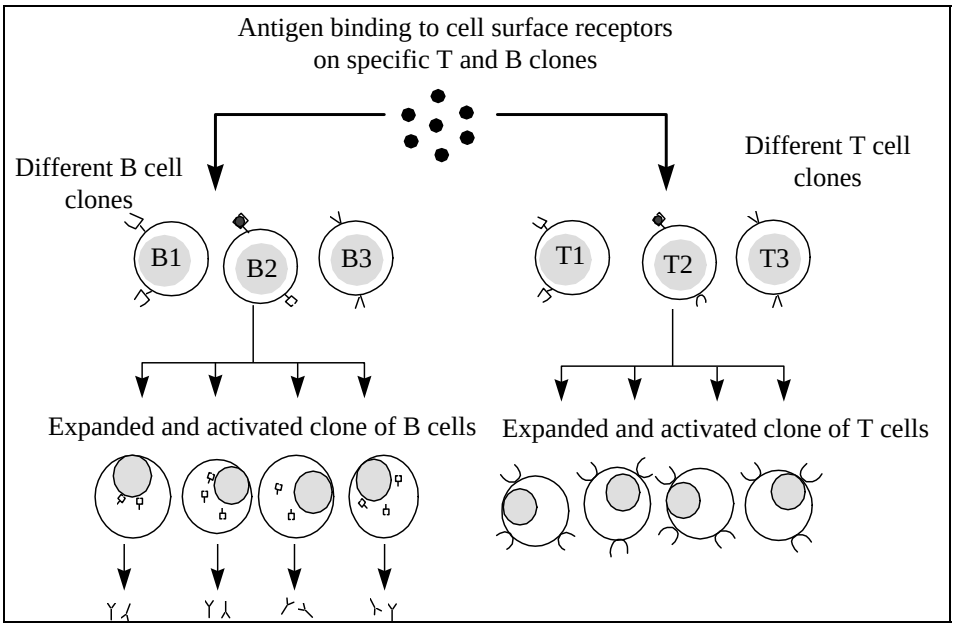

Figure 28: Clonal selection theory.

Clonal selection and clonal expansion

Interaction between a foreign antigen and a lymphocyte receptor leads to lymphocytes activation of the cell that is capable of binding this antigen. The differentiated effector cells from an activated lymphocyte will bear receptors of identical specificity to those of the parental cell from which that lymphocyte was derived, Figure 28.

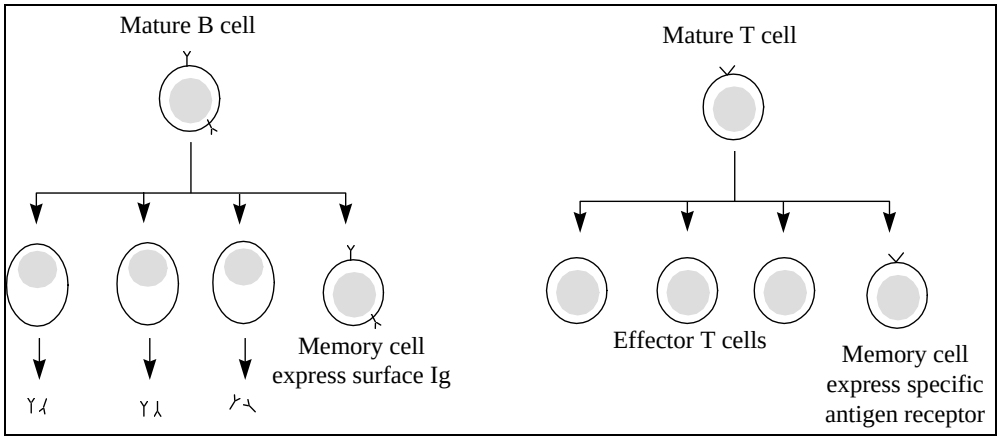

Figure 29: Antigen dependent mature lymphocytes differentiation into effector and memory cells.

Immunological memory

Immunological memory is one of the important features of the immune response. Subsequent exposure leads to a more rabid and larger immune response mediated by memory cells.

Interrelationship between innate and acquired immunity

The innate and acquired arms of the immune system have developed a beautiful interrelationship. The intricate and ingenious communication system through the various cytokines and cell adhesion molecules allows components of innate and acquired immunity to interact, send each other signals, activate each other, and work in concert toward the final goal of destroying and eliminating the invading microorganism and its products.