The Adaptive Immune Responses

The two arms of the immune responses are; 1) the **cell mediated**, and 2) the **humoral responses.** In this chapter we will discuss the two responses in detail and we will start with the first one.

The cell mediated immune response

The cell mediated immune response can be divided into **two phases**;

- The activation of naive CD4+ and CD8+T cells and their differentiation into effector T cells.
- The effector phase whereby the effector CD4+ and CD8+ T cells eliminate infection.

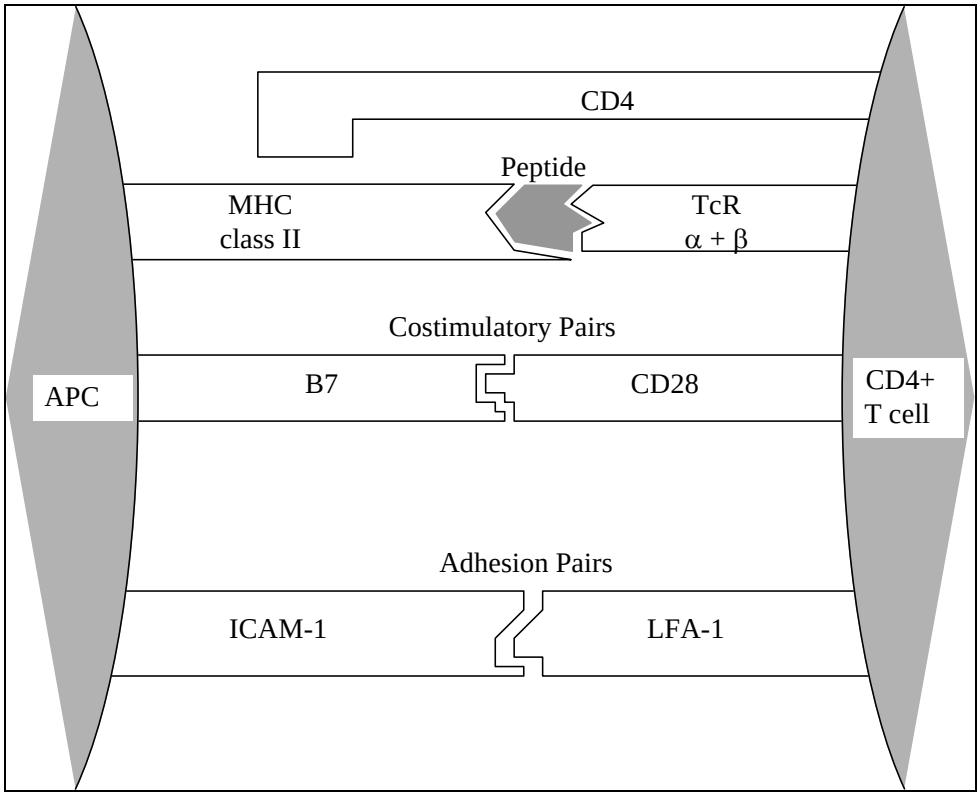

Figure 30: Interaction between T and Antigen Presenting Cell (APC).

The activation and differentiation phase is carried out in three steps; 1) activation, 2) proliferation, and 3) differentiation.

Activation

Activation of naïve CD4+ cells requires binding of MHC class II plus peptide to the T cell receptor TcR of the CD4+ T cell, in conjunction with the interaction of co-stimulatory and adhesion pairs of molecules on the surface of antigen presenting cell (APC) and the T cell leads to T cell activation, Figure 30.

Activation of naïve CD8+ cell requires binding of MHC class I plus peptide to the T cell receptor TcR of the CD8+ T cell, in conjunction with high levels of co-stimulatory molecules.

Thus, activation of both CD4+ and CD8+ naive T cells requires **two** independent signals; (1) the binding of the peptide MHC complex by the T cell receptor; and (2) a co-stimulatory signal delivered by the co-stimulatory molecules such as the CD4 co-receptor. This co-stimulatory signal (signal 2) is delivered by the same antigen presenting cell, Figure 31.

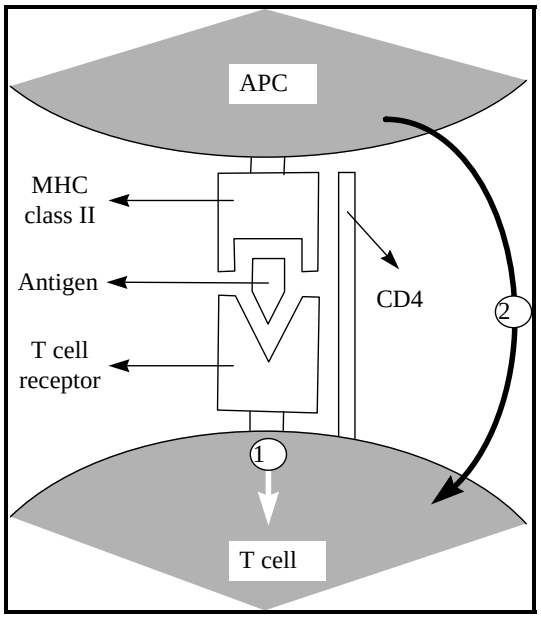

Figure 31: Activation of naive T cells requires two independent signals.

Proliferation

Naive T cells can live for many years without dividing. On activation, these small resting lymphocytes divide rapidly to provide large number of progeny (**clonal expansion**) that will differentiate into effector T cells. Their proliferation and differentiation depends on **cytokines** such as the T cell growth factor Interleukin-2 (IL-2).

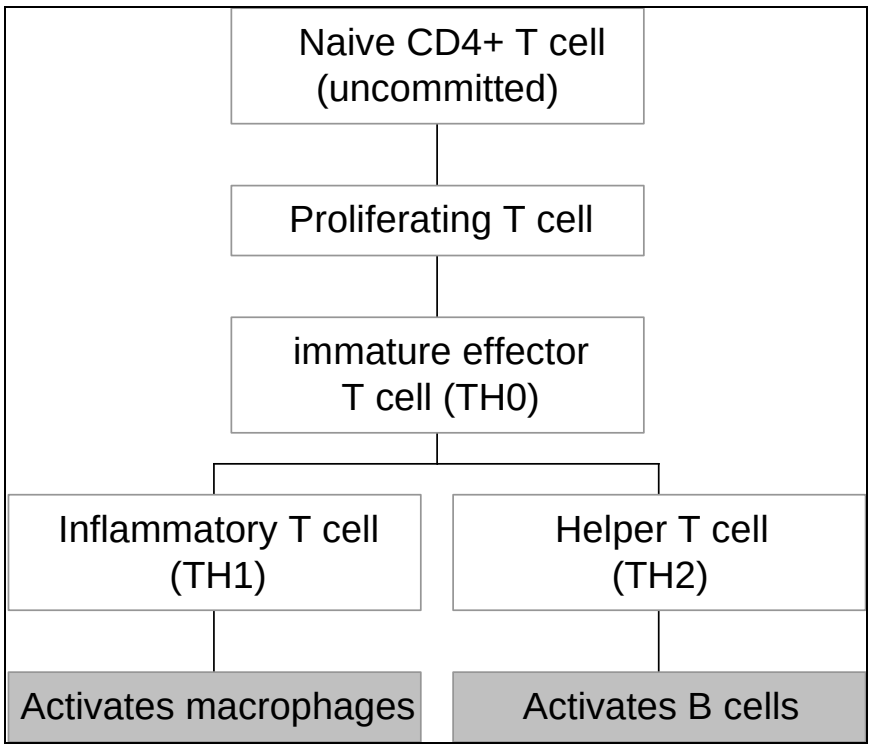

Figure 32: The stages of activation of CD4+ cells.

Differentiation

Following activation and proliferation, CD4+ cells differentiate into two distinct types of effector cells; 1) the Inflammatory T cell (TH1) and 2) the helper T cell (TH2), Figure 32. On the other hand activated CD8+ cells differentiate into one type of cytotoxic T cell (Tc).

Role of cytokines in differentiation

Differentiation of naïve CD4+ cells into effector cell types is influenced by cytokines elicited by activated macrophage. Many pathogens specially

intracellular bacteria and viruses activate macrophages and NK cells to produce IL-12 and INF-γ which act on proliferating CD4 T cells causing them to differentiate into inflammatory T cells (TH1), Figure 33.

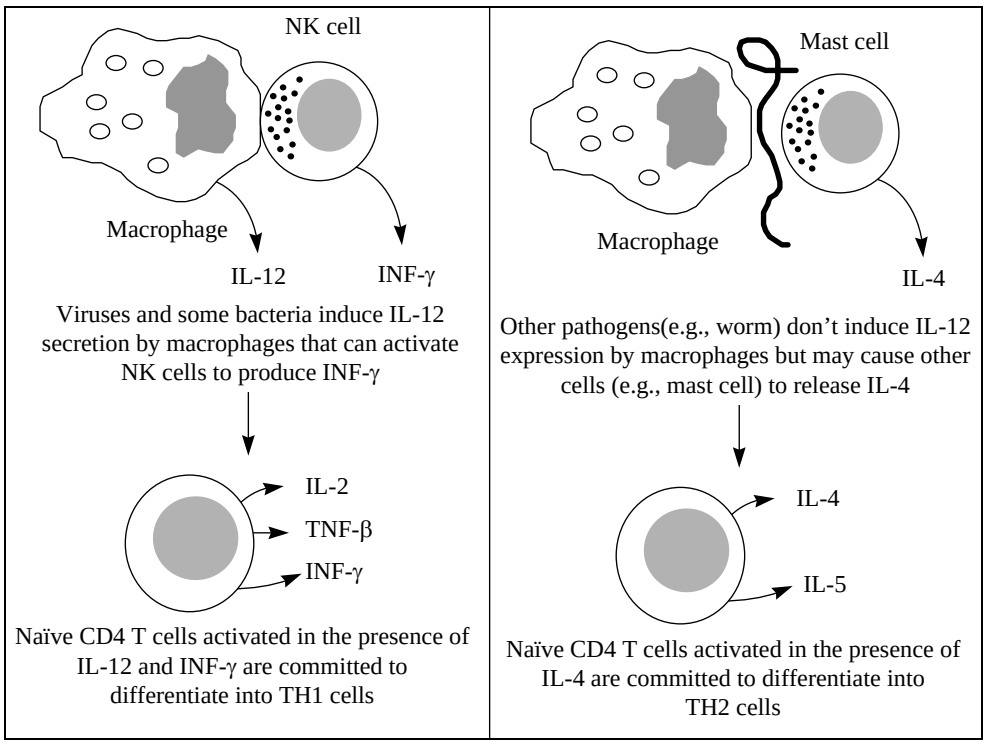

Figure 33: The differentiation of naïve CD4 cells into effector cell types is influenced by cytokines elicited by activated macrophage.

The end result of the above described activation and differentiation phase is the production of three distinct effector cells each with distinct function and ready to start the effector phase of the immune response. The functions of the three effector T cells are illustrated in fig. (9.6). These functions are:

- Killing target cells (e.g., virus infected cells and tumor cells) → mediated by cytotoxic T cell (TC).
- Activation of macrophages → mediated by inflammatory T cell (TH1).
- Activation of B cell → mediated by T helper cell (TH2).

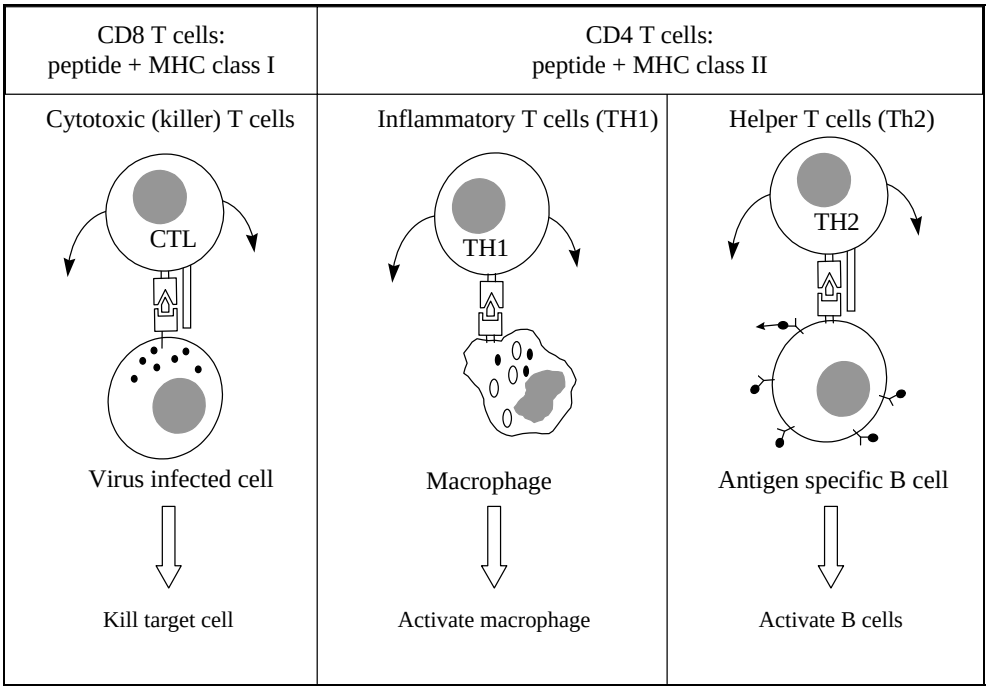

Figure 34: Functions of the three main types of effector T cell.

Granuloma formation:

When microbes such as mycobacteria resists the effects of macrophage activation, a characteristic localized inflammatory response called a granuloma develops. It consists of a central core of infected macrophages. The core may include multinucleated giant cells, which are fused macrophages, surrounded by large macrophages often called epithelioid cells. Mycobacteria can persist in the cells of the granuloma. The central core is surrounded by T cells, many of which are CD4 positive, Figure 35.

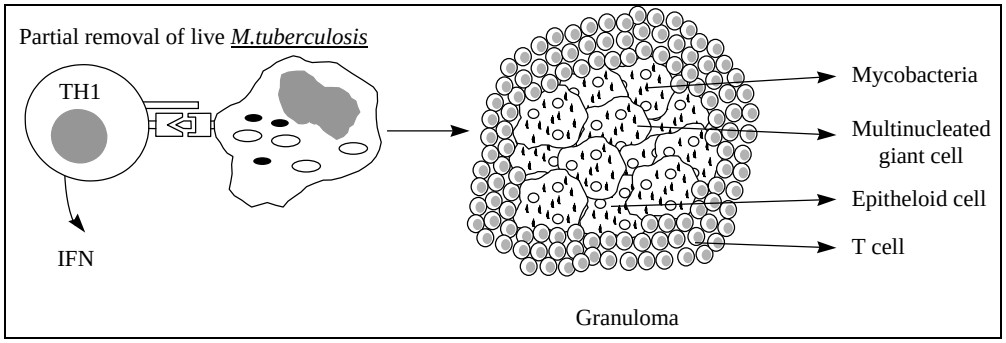

Figure 35: Granulomas form when an intracellular pathogen or its constituents cannot be totally eliminated.

The humoral immune response

One of the functions of effector CD4+ T cells is to cooperate with B cells in the production of antibodies to the major class of antigens referred to as **thymus dependent** (TD) antigens. For this reason a set of CD4+ T cells is referred to as T helper (TH2).

As with cell mediated response, the humoral response can be divided into **two** phases:

- The activation of B cells and their differentiation into antibody secreting plasma cell.
- The effector phase whereby antibodies eliminate infections.

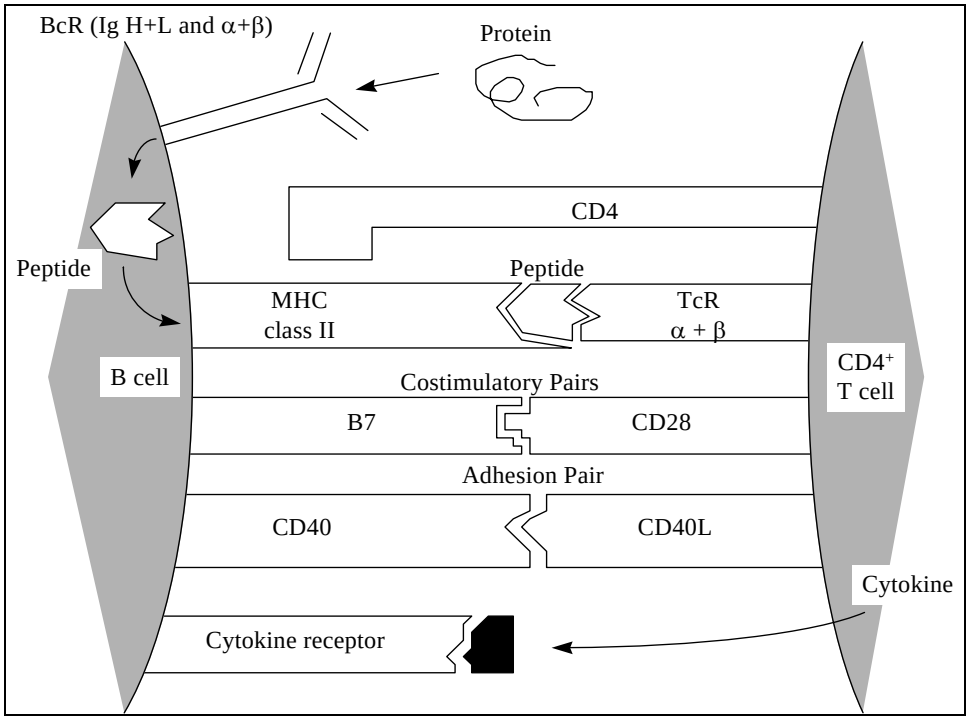

Figure 36: Interaction between T and B cells.

Activation of B cells and their differentiation into plasma cells

The B cell receptor (BcR) plays two roles in their activation. **First**, like the antigen receptor on T cells, when it binds antigen it directly transmits a signal to the cells' interior. **Second**, it delivers the antigen to intracellular sites where it is degraded and from which it is returned to the B cell surface as peptide bound to MHC class II molecules.

The specific interaction of an antigen-binding B cell with an effector helper cell leads to the expression of the B cell stimulatory molecules **CD40 Ligand (CD40-L)** on the helper T cell surface and the secretion of the B cell stimulatory cytokines, **IL-4, IL-5 and IL-6**, which drive the proliferation and differentiation of the B cell into antibody-secreting plasma cell, Figure 37.

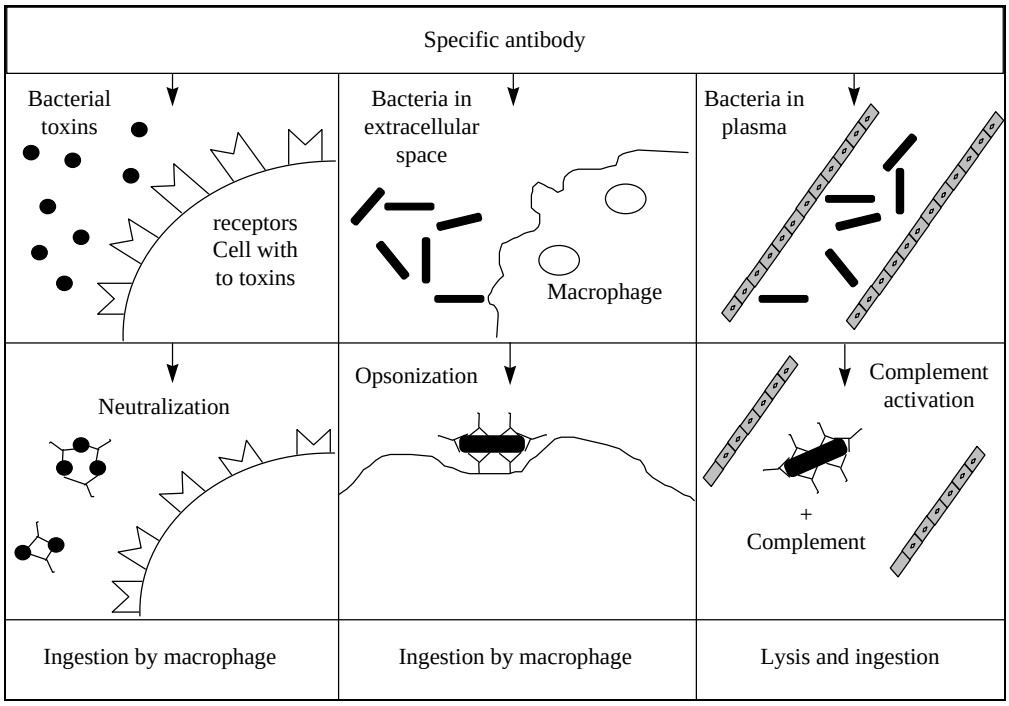

Figure 37: Three main ways in which the antibodies protect the host from infection.

Isotype switching of antibody

The early stages of the antibody response are dominated by IgM antibodies. Later, IgG, IgA are the predominant isotypes, with IgE, contributing small part of the response. These changes do not occur in individuals who make a defective CD40 Ligand, which is necessary for isotype switching; such individual makes only IgM. **Cytokines** also play a role in regulating antibody isotype expression. They can induce or inhibit production of certain isotypes. Examples of these cytokines are IL-4, IFN-γ and TGF-β.

The effector phase: Functions of these antibodies

Many of the pathogenic bacteria multiply in the extracellular spaces of the body, and most intracellular pathogens must spread by moving from cell to cell through the extracellular fluids. **The humoral immune response leads to the destruction of extracellular microorganisms and prevents spread of intracellular infections**. This is achieved by antibodies secreted by B lymphocytes.

There are **two main ways** in which the antibodies protect the host from infection:

- They may inhibit the toxic effects or infectivity of pathogens by binding to them. This is termed **neutralization**.
- They can coat the pathogens, they may enable accessory cells that recognize the Fc part of antibody to ingest and kill the pathogen, a process called **opsonization**.