

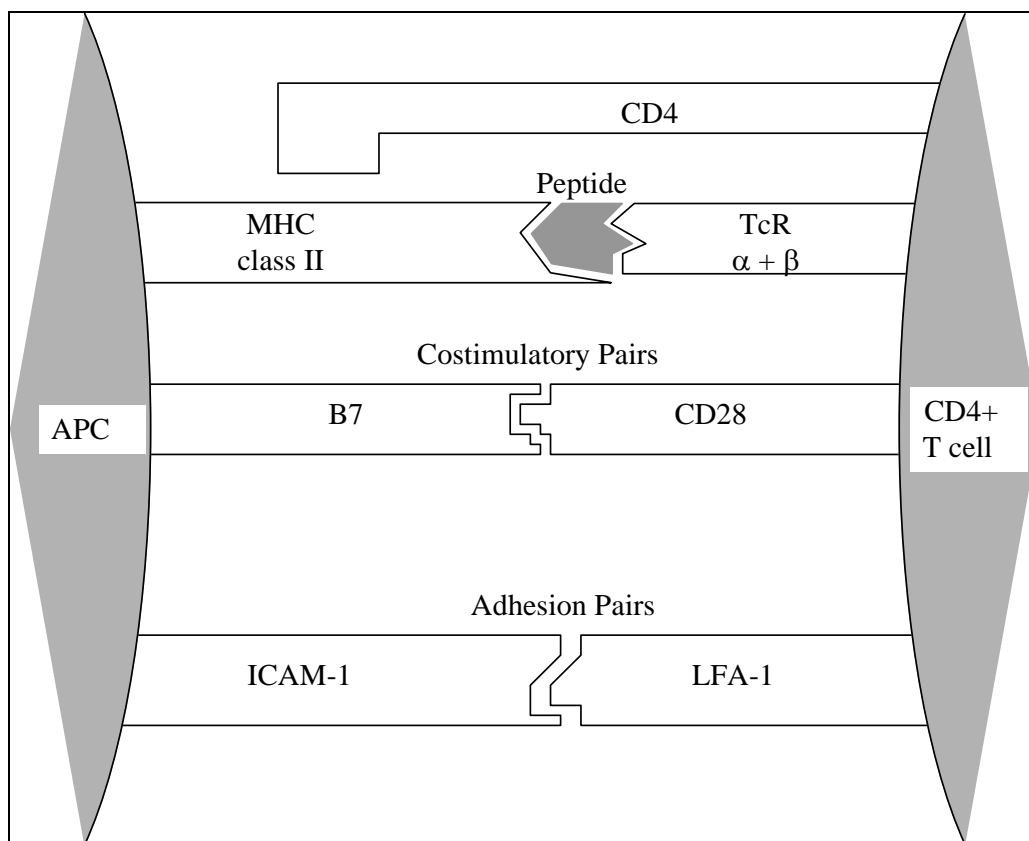
## The Adaptive Immune Responses

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).**

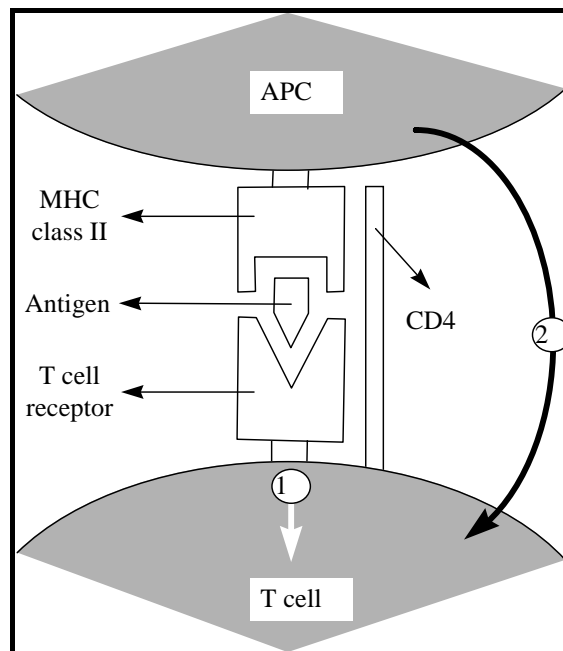
The activation and differentiation phase is carried out in three steps; 1) activation, 2) proliferation, and 3) differentiation.

### Activation

Activation of naïve CD4<sup>+</sup> cells requires binding of MHC class II plus peptide to the T cell receptor TcR of the CD4<sup>+</sup> 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<sup>+</sup> cell requires binding of MHC class I plus peptide to the T cell receptor TcR of the CD8<sup>+</sup> T cell, in conjunction with high levels of co-stimulatory molecules.

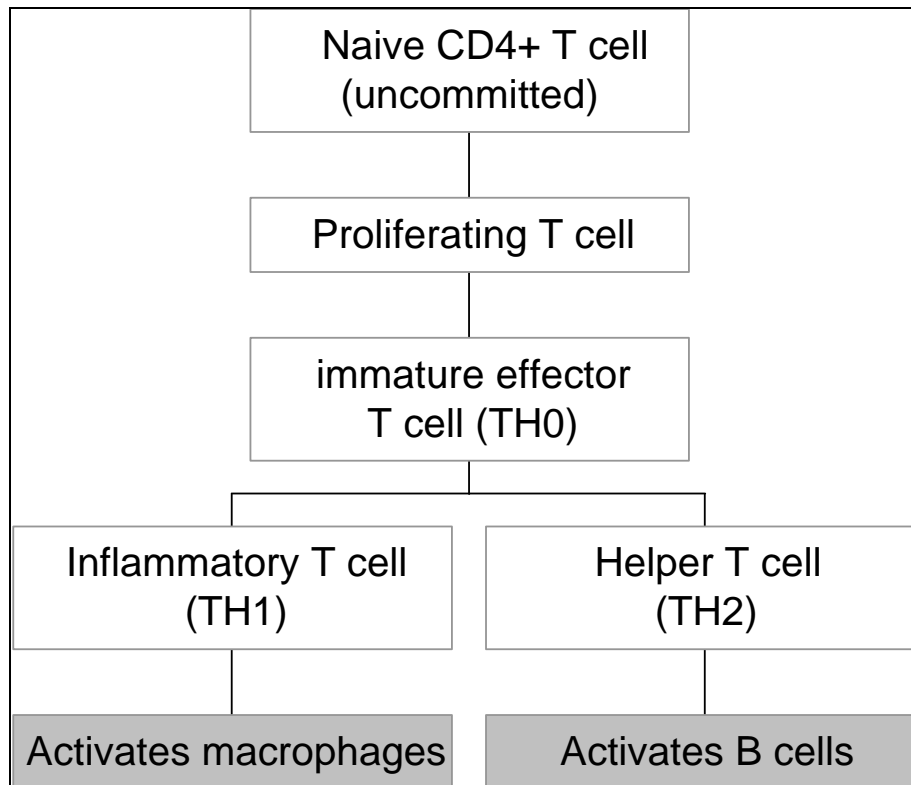
Thus, activation of both CD4<sup>+</sup> and CD8<sup>+</sup> naïve T cells requires **two** independent signals; (1) the binding of the peptide MHC complex by the T cell receptor; and (2) a co-stimulatory signal delivered by the co-stimulatory molecules such as the CD4 co-receptor. This co-stimulatory 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.**

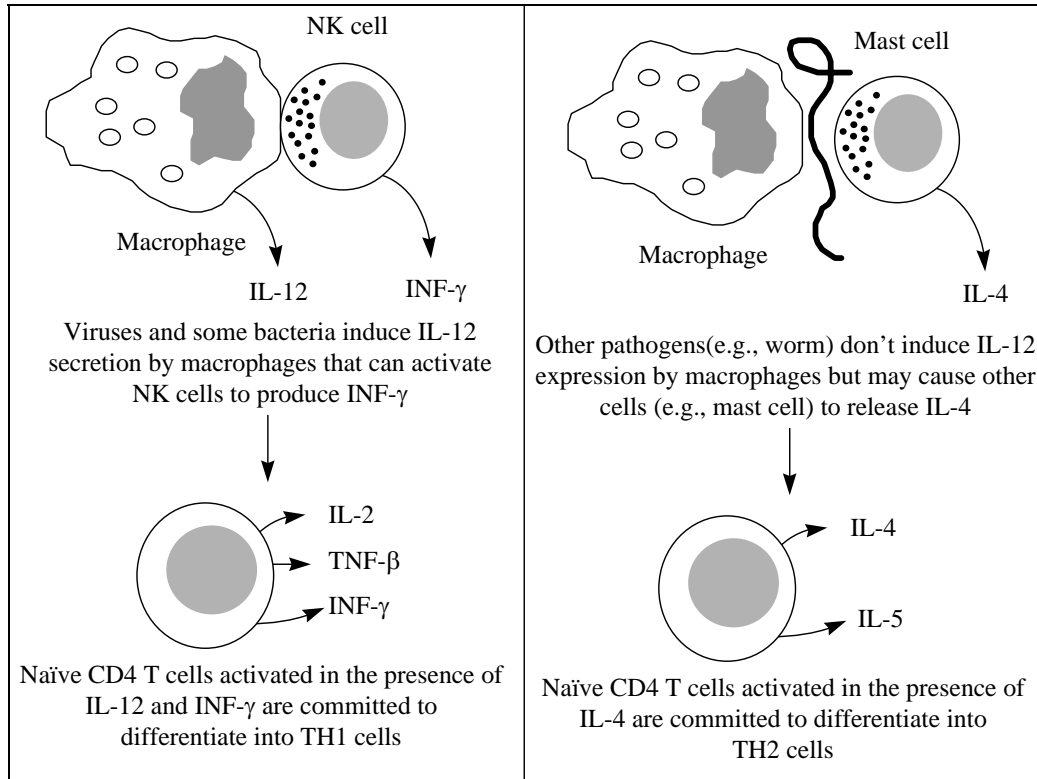
## Differentiation

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

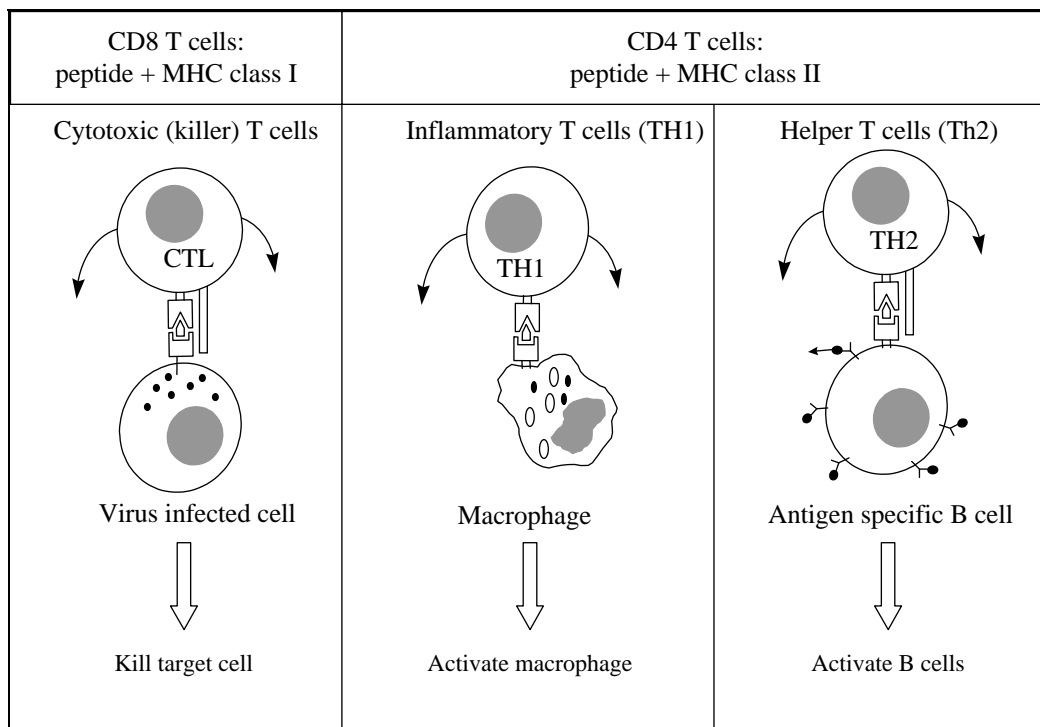
intracellular bacteria and viruses activate macrophages and NK cells to produce IL-12 and INF- $\gamma$  which act on proliferating CD4 T cells causing them to differentiate into inflammatory T cells (TH1), Figure 33.



**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:

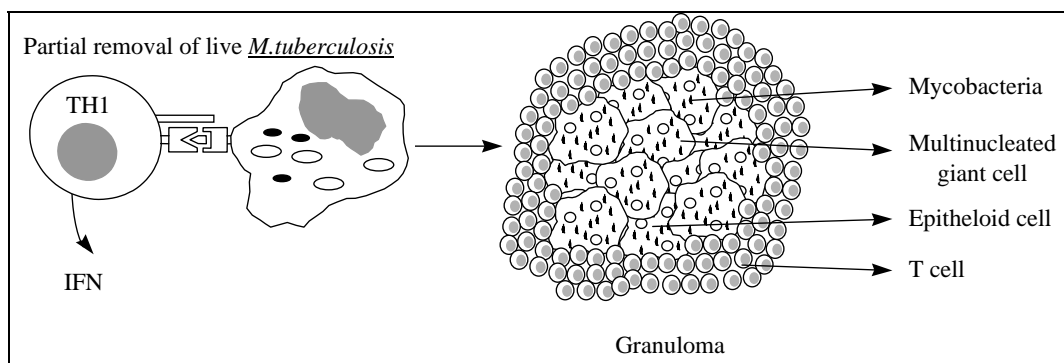
- Killing target cells (e.g., virus infected cells and tumor cells) → mediated by cytotoxic T cell ( TC).
- Activation of macrophages → mediated by inflammatory T cell (TH1).
- Activation of B cell → mediated by T helper cell ( TH2).



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

### Granuloma formation:

When microbes such as mycobacteria resist 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.



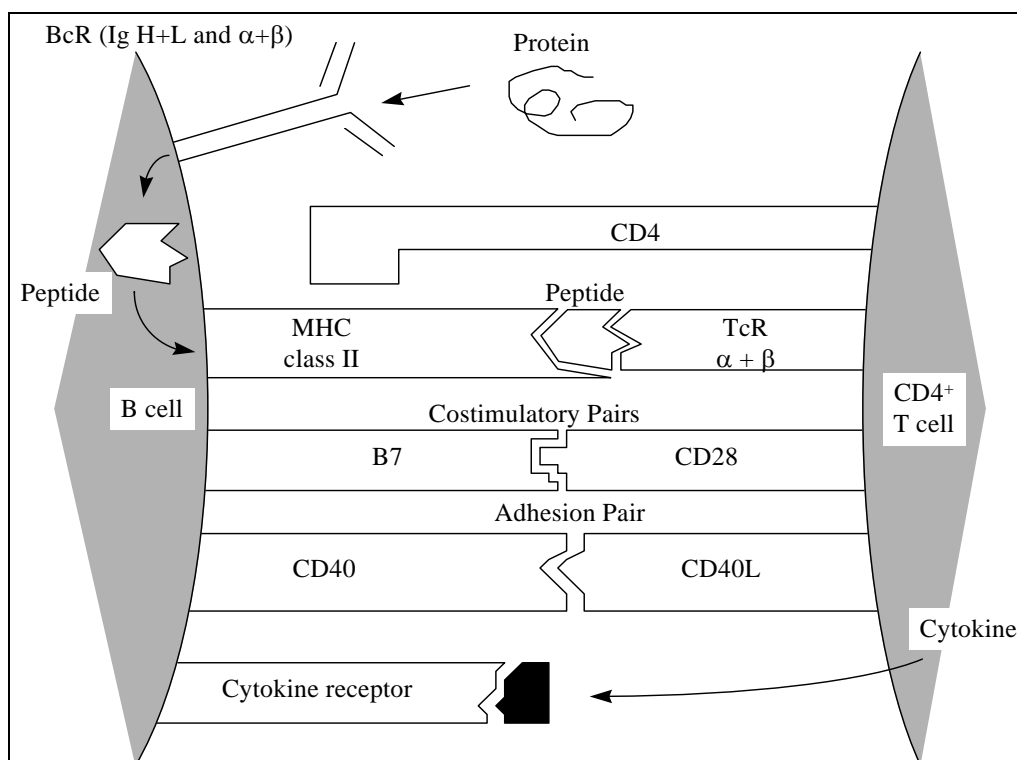
**Figure 35: Granulomas form when an intracellular pathogen or its constituents cannot be totally eliminated.**

## The humoral immune response

One of the functions of effector CD4<sup>+</sup> 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<sup>+</sup> 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.

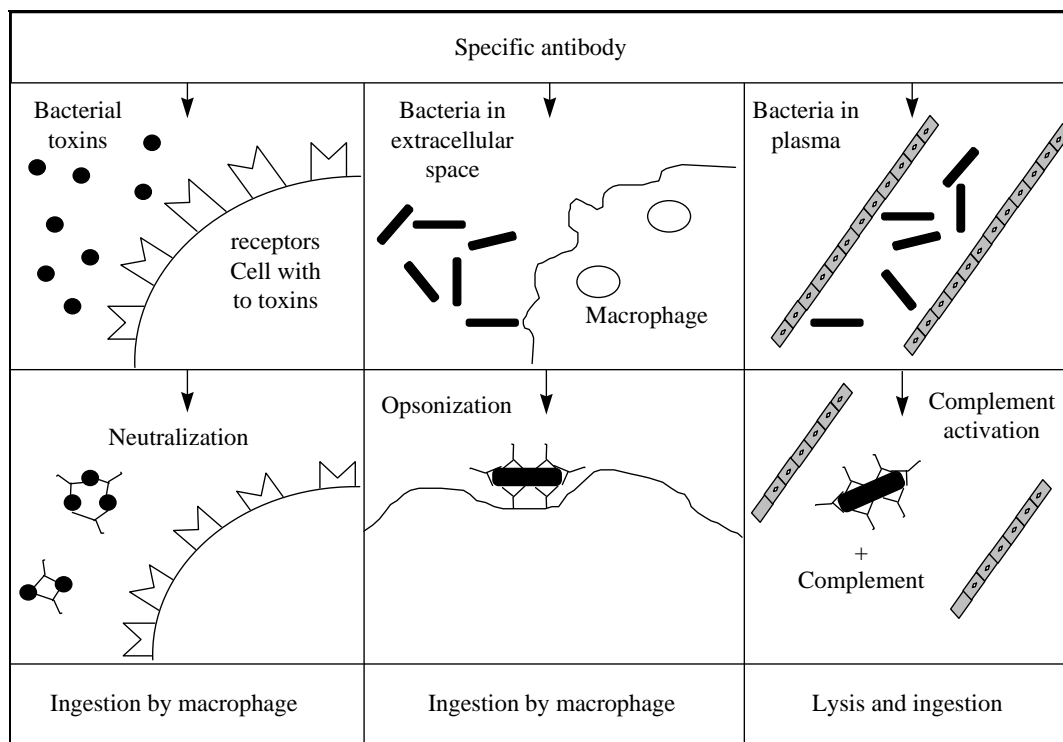


**Figure 36: Interaction between T and B cells.**

### 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- $\gamma$  and TGF- $\beta$ .

### 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**.

## Control and Manipulation of The Immune Response

### Introduction

An understanding of the immune response as a complete physiologic system requires, in addition to understanding of the “**on**” signals described in previous chapters, some understanding of the “**off**” signals.

In a system as complex as one that produces an immune response, multiple levels of control exist. Basically, there are two major aspects to regulation of the immune response.

**One** occurs in the developmental pathways of immunocompetence by induction of tolerance to self antigens; the **other** concerns the regulation of the response of mature lymphocytes to antigens.

Breakdown of control mechanisms may lead to autoimmunity and autoimmune disease.

### Tolerance to self antigens

**Tolerance** is the state of unresponsiveness to a particular antigenic epitope. It occurs when the interaction of antigen with antigen specific lymphocyte results in inactivation “**turnoff**”, rather than activation “turn-on”.

Only cells with antigen specific receptors, that is lymphocytes can be tolerized and this state of tolerance can be achieved anytime in the ontogeny “i.e. development” of the cell, provided that it expresses a receptor for the antigen.

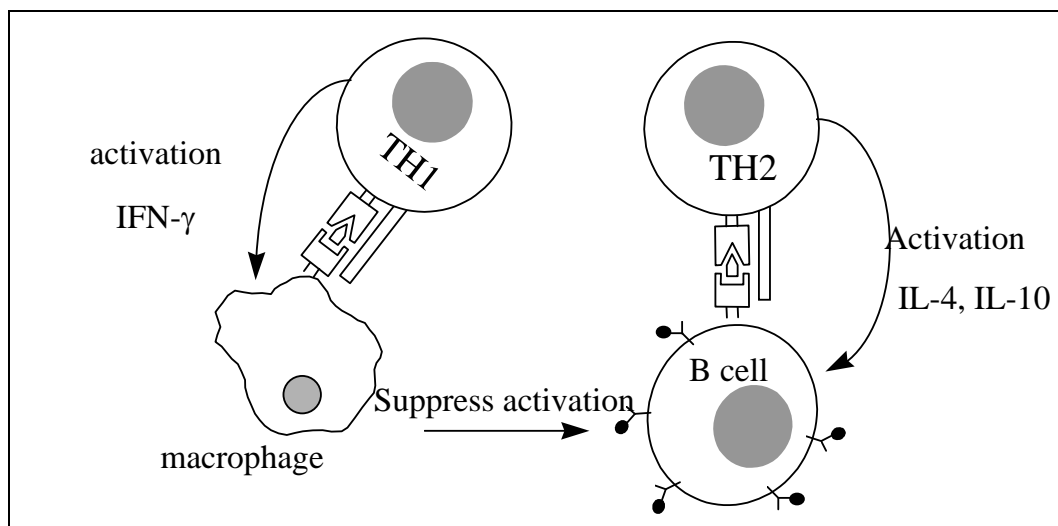
As a consequence of inactivation by antigen the lymphocyte may be **deleted** or alternatively, becomes **anergic** (i.e. unresponsive).

## Up-regulation of the response of mature lymphocytes

### Up-regulation effect of Cytokines

We have learned that T cell activation and proliferation are dependent on signals from cytokines. Within the population of CD4<sup>+</sup> T cells, there are subsets that produce distinct cytokines with different functions. Thus TH1 cells produce IFN- $\gamma$ , a potent activator of macrophages, and TNF- $\beta$ , a lymphotoxin.

On the other hand, TH2 cells secrete IL-4, IL-6 and IL-10, all of which are involved in B cell activation and differentiation, Figure 38.



**Figure 38: Inflammatory T cells (TH1) can suppress the activation of B cells by helper T cells (TH2).**

## Down-regulation of the response of mature lymphocytes

### Active suppression via T cells

The production of **suppressor T cells** may play a major role in inhibiting immune response to foreign antigen. **One mechanism to explain suppression is that suppressor cells produce inhibitory cytokines that act on other cells.** An example is IFN- $\alpha$  which may prevent IL-4 mediated switching of B cell. Also T cells produce **TGF- $\beta$** , a powerful suppressant of T and B cell proliferation. Thus, it is possible that a population of T cells may temporarily

function as a suppressor cell if they produce an appropriate cytokine, and there may not be a unique population of T cells whose sole function is to suppress immune responses.

**Another mechanism is that CD8+ cells may have cytotoxic activity** toward either T cells or B cells. They may recognize and lyse activated cells using mechanisms common to all cytotoxic CD8 T cells.

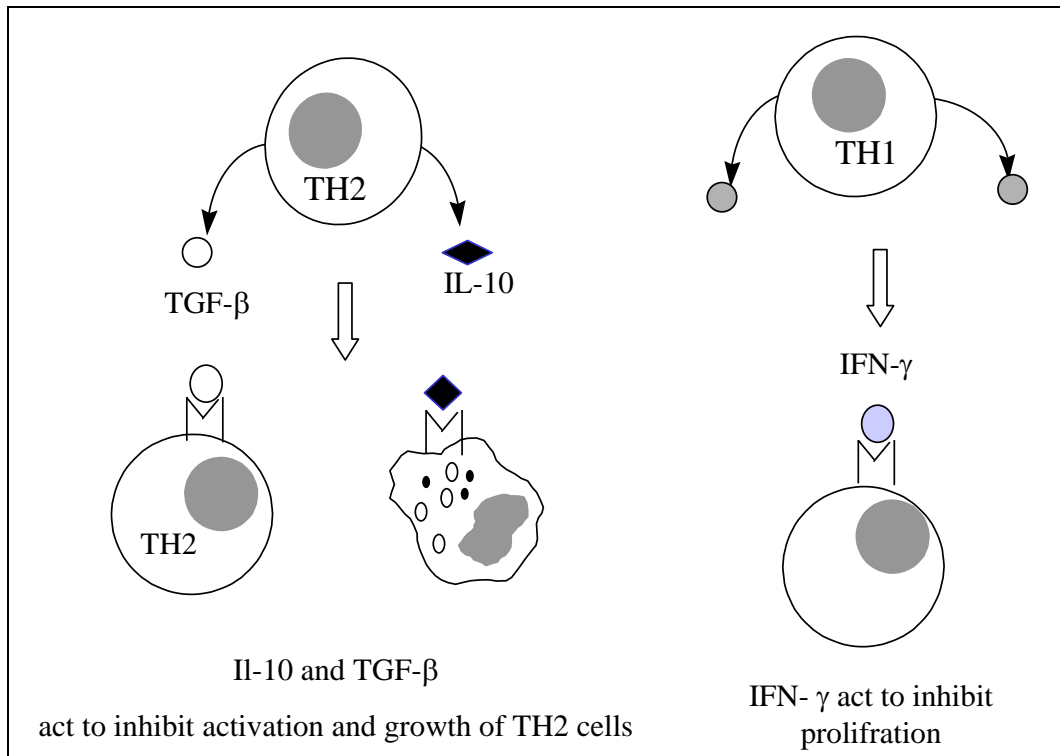
### **Inhibition of lymphocyte activation**

The production of peripherally acquired tolerance is now thought to be due to the **presentation of antigen to the T cell receptor in an incomplete or ineffectual way**. As we have learned, stimulation of T cell requires recognition by the T cell receptors of the antigen in the context of the proper MHC class II molecule, followed by secondary costimulatory signals. If the costimulatory molecule destroyed or absent, T cells fail to respond.

Similarly the B cell requires multiple signals to proliferate and differentiate into antibody secreting cells. Most of this signaling are engaged with antigen comes from T cell help in the form of **cytokines**. In the **absence of such cell help, B cell also undergoes negative signaling or down regulation**.

### **Feed back inhibition by antibody**

The production of antibody results in a **feedback inhibition** of further production of antibody and cell-mediated responses. For example, the appearance of IgG antibody results in a shutoff of synthesis of IgM antibody.



**Figure 39: The two subsets of CD4 T cells can negatively regulate the other subset.**

### Down regulation by cytokines

The two subsets of CD4<sup>+</sup> T cells (TH1 and TH2) can down regulate each other subsets through cytokines, Figure 39. For example INF- $\gamma$  released by TH1 act to inhibit proliferation of TH2, on the other hand TGF- $\beta$  and IL-10 produced TH2 act to inhibit proliferation of TH1. These last two cytokines can also inhibit macrophage activation, while IFN- $\gamma$  may prevent IL-4 mediated switching of B cells.

### Effects of antigen

Not every injection of an antigen results in an immune response. Generation of a response is a highly empirical process, depending on **dose, timing, and nature of the antigen** involved.