TOPIC: Immune Cells and Ag Recognition

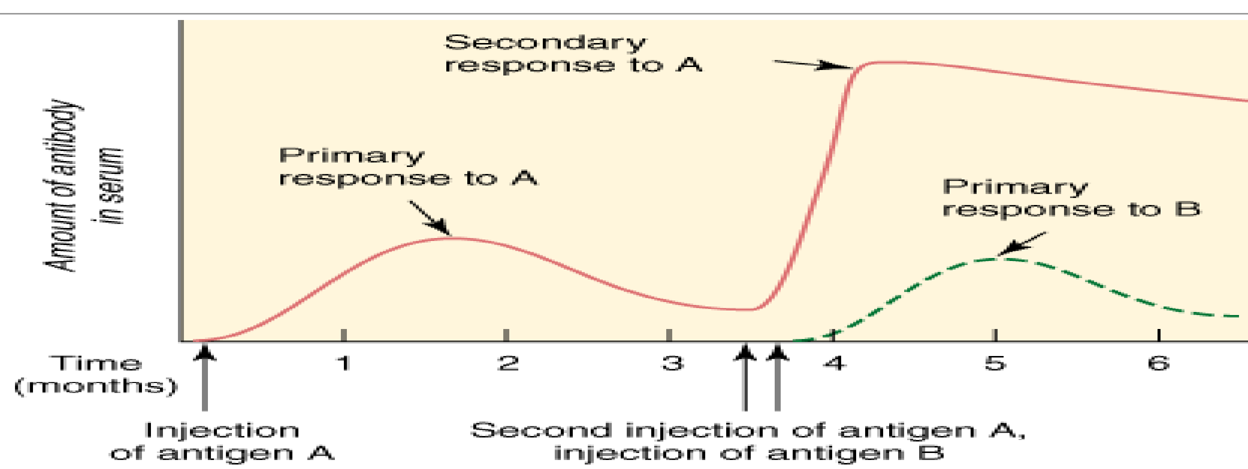
Antibody-Mediated (Humoral) Immunity

The Primary Response

- When an individual encounters an **antigen for the first time**, antibody to that **antigen is detectable in the serum within days or weeks** depending on the nature and dose of the antigen and the route of administration (eg, oral, parenteral).
- The serum antibody concentration continues to **rise for several weeks and then declines**; it may drop to very low levels. The first antibodies formed are IgM, followed by IgG, IgA, or both. IgM levels tend to decline sooner than IgG levels.

The Secondary Response

- In the event of a second **encounter with the same antigen** (or a closely related "cross-reacting" one) months or years after the primary response, the antibody response is more **rapid and rises to higher levels** than during the primary response.
- This change in response is attributed to the persistence of **antigen-sensitive "memory cells"** following the first immune response.
- In the secondary response, the amount **of IgM produced is qualitatively similar to that produced after the first contact** with the antigen; however, much more IgG is produced, and **the level of IgG tends to persist much longer than in the primary response**.
- Furthermore, such antibody tends to bind antigen **more firmly (ie, to have higher affinity)** and thus to dissociate less easily.



Cells of the immune system and antigen recognition

- The immune system has **developed to protect the host from pathogens** and other foreign substances.
- **Self/non-self-discrimination** is one of the hallmarks of the immune system. There are two mains sites where pathogens may reside:
- **Extracellularly** in tissue spaces or **intracellularly** within a host cell; and the immune system has different ways of dealing with pathogens at these sites.
- However, for any particular pathogen **an antibody or a cell-mediated response** may be more important for defense against the pathogen

A) Extracellular pathogens: antibodies are the primary defense against extracellular pathogens and they function in three major ways:

i) Neutralization and agglutination - by binding to the pathogen or foreign substance antibodies can block the association of the pathogen with their targets.

For example, antibodies to bacterial toxins can prevent the binding of the toxin to host cells thereby rendering the toxin ineffective. Similarly, antibody binding to a virus or bacterial pathogen can colonization.

ii) Opsonization - Antibody binding to a pathogen or foreign substance can opsonize the material and facilitate its uptake and destruction by phagocytic cells. The Fc region of **the antibody interacts with Fc receptors on phagocytic cells** rendering the pathogen more readily phagocytosed.

iii) Complement activation - Activation of the complement cascade by antibody can result in lysis of certain bacteria and viruses. In addition, some components of the complement cascade (*e.g.* **C3b) opsonize pathogens and facilitate their uptake via complement receptors on phagocytic cells**.

B:- Intracellular pathogens:

- Because antibodies do not get into host cells, they are ineffective against intracellular pathogens.
- **Cell-mediated responses** are the primary defense against intracellular pathogens and the approach is different depending upon where the pathogen resides in the host cell **(*i.e.*, in the cytosol or within vesicles).**
- For example, most viruses and some bacteria **reside in the cytoplasm of the host cell**, however, some bacteria and parasites actually live within **endosomes in the infected host cell.**
- The primary defense against pathogens in the cytosol is the **cytotoxic T lymphocyte (Tc or CTL).** In contrast, the primary defense against a pathogen within vesicles is a subset of **helper T lymphocytes (Th1).**
- **Cytotoxic T cells (CTL) -** CTLs are a subset of T lymphocytes that express a unique antigen on their **surface called CD8**. These cells recognize antigens from the pathogen that are displayed on the surface of the infected cell and kill the cell thereby preventing the spread of the infection to neighboring cells. **CTLs kill by inducing apoptosis in the infected cell.**
- **Th1 helper T cells -** Th cells are a subset of T cells that express a unique antigen on their **surface called CD4**. A subpopulation of Th cells, Th1 cells, is the primary defense against intracellular pathogens that **live within vesicles.**
- Th1 cells recognize antigen from the pathogen that are expressed on the surface of infected cells and **release cytokines that activate the infected cell.**
- Once activated, the infected cell can then kill the pathogen. For example, *Mycobacterium tuberculosis*, the causative agent of tuberculosis, infects macrophages but is not killed because it blocks the fusion of lysosomes with the endosomes in which it resides. Th1 cells that recognize *M. tuberculosis* antigens on the surface of an infected macrophage can secrete cytokines that activate macrophages. Once activated the lysosomes fuse with endosomes and the *M. tuberculosis* bacteria are killed.

The role of effector T cells in cell-medicated and humoral immune responses to representative pathogens

	Cell-mediated immunity		Humoral immunity
Typical pathogens	Vaccinia virus Influenza virus Rabies virus *Listeria*	*Mycobacterium tuberculosis* *Mycobacterium leprae* *Leishmania donovani* *Pneumocystis carinii*	*Clostridium tetani* *Staphylococcus aureus* *Streptococcus pneumoniae* Polio virus *Pneumocystis carinii* *Trichinella spiralis*
Location	Cytosol	Macrophage vesicles	Extracellular fluid
Effector T cell	Cytotoxic CD8 T cell	T_H1 cell	T_H1 and T_H2 cells
Antigen recognition	Peptide:MHC class I complex on infected cell	Peptide:MHC class II complex on infected macrophage	Peptide:MHC class II complex on antigen-specific B cell
Effector action	Killing of infected cell	Activation of infected macrophages	Activation of specific B cell to make antibody

Cells link the innate and adaptive immune systems antigen presenting cells (APCs).

- ❒ A specialized subset of cells called **antigen presenting cells (APCs)** are a heterogeneous population of leukocytes that play an important role in innate immunity and also **act as a link to the adaptive immune system by participating in the activation of helper T cells (Th cells).**
- ❒ These cells include **dendritic cells, macrophages**. A characteristic feature of APCs is the expression of a cell surface molecule encoded by genes in the **major histocompatibility complex, referred to as class II MHC molecules.**
- ❒ **B lymphocytes** also express class II MHC molecules and they also function as APCs, although they are not considered as part of the innate immune system.
- ❒ In addition, certain other cells **(*e.g.*, thymic epithelial cells)** can express class II MHC molecules and can function as APCs.

- Antigen processing and presentation are processes that occur within a cell that result in **fragmentation (proteolysis) of proteins**, association of the fragments with MHC molecules, and expression of the **peptide-MHC molecules** at the cell surface where they can be **recognized by the T cell receptor on a T cell**.
- **MHC class I molecules** present degradation products derived from **intracellular (endogenous) proteins in the cytosol**.
- **MHC class II molecules** present fragments derived from **extracellular (exogenous) proteins** that are located in an intracellular compartment.

Cells of the adaptive immune system:-

- Cells that make up the adaptive (specific) immune system **include the B and T lymphocytes.**
- After exposure to antigen, **B cells differentiate into plasma cells** whose primary function is the **production of antibodies.**
- Similarly, T cells can differentiate into either **cytotoxic (CTL) or T helper (Th) cells** of which there are two types **Th1 and Th2 cells**.
- There are a number of cell surface markers that are used in clinical laboratories to distinguish B cells, T cells and their subpopulations, Table 1.

Marker	B cell	CTL	T-helper
Antigen R	BCR (surface Ig)	TCR	TCR
CD3	--	+	+
CD4	--	--	+
CD8	--	+	--
CD19/ CD20	+	--	--
CD40	+	--	--

Comparison of BCR and TCR

B cells and T cells recognize different substances as antigens and in a different form. **Each B and T cell has a receptor** that is unique for a particular antigenic determinant and there are a vast array of different antigen receptors on both B and T cells.

- The B cell uses cell **surface-bound immunoglobulin** as a receptor and the specificity of that receptor is the same as the immunoglobulin that **it is able to secrete after activation.**
- **B cells recognize** the following antigens in soluble form: 1) proteins (both conformational determinants and determinants exposed by denaturation or proteolysis); 2) nucleic acids; 3) polysaccharides; 4) some lipids; 5) small chemicals (haptens).
- The TCR and BCR are similar in that each receptor is specific for one antigenic determinant but they differ in that **BCRs are divalent while TCRs are monovalent.**
- In contrast, the majority of **antigens for T cells are proteins**, and these must be fragmented and recognized in **association with MHC products expressed on the surface of nucleated cells**, not in soluble form.
- T cells are grouped functionally **according to the class of MHC molecules** that associate with the peptide fragments of protein: **helper T cells** recognize only those peptides associated with **class II MHC molecules**, and **cytotoxic T cells** recognize only those peptides associated with **class I MHC molecules**.

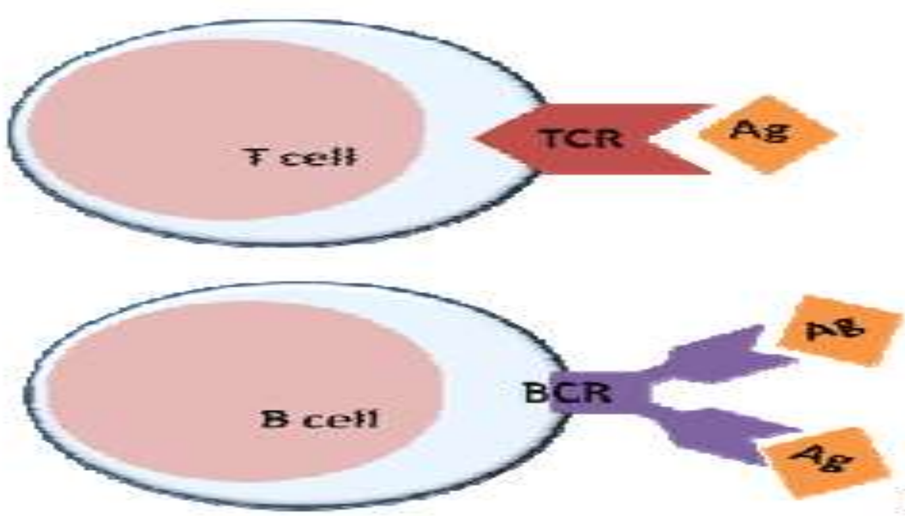


Figure 2.