Cell Mediated Immunity(CMI)&Humoral Immunity

The immune system assume different roles in protecting the host. The effectors of the humoral branch are secreted antibodies, highly specific molecules that can bind and neutralize antigens on the surface of cells and in the extracellular spaces. The primary domain of antibody protection lies outside the cell. While the principal role of cell-mediated immunity is to detect and eliminate cells that harbor intracellular pathogens. Cell-mediated immunity also can recognize and eliminate cells, such as tumorcells, that have undergone genetic modifications so that they express antigens not typical of normal cells.

❖ Cell mediated immunity

Both antigen-specific and -nonspecific cells can contribute to the cell-mediated immune response:

- **Specific cells** include CD8+cytotoxic T lymphocytes (TC cells or CTLs) and cytokine-secreting CD4+ TH cells that mediate delayed-type hypersensitivity (DTH).
- **Nonspecific cells** include NK cells and nonlymphoidcell types such as macrophages, neutrophils, and eosinophils.

The activity of both specific and nonspecific components usually depends on effective local concentrations of various cytokines.

Defects in CMI result in increased susceptibility to infections by viruses and intracellular bacteria. Cell-mediated immune reactions are also important in graft rejection and tumor immunity.

Types of cell mediated immunity:

o **CD4+ helper T cell** responses to microbes residing within the **phagosomes**of phagocytes

 T cell **cytokine and CD40-ligand expression, which activate the phagocytes** to kill the microbes and stimulate inflammation.

o **CD8+ cytolytic T lymphocyte** (CTL) responses to microbes (e.g. viruses) that infect and replicate in the cytosol of various cell types, including non-phagocytic cells

 CTL killing of the infected cells.

 CTL secretion of cytokines

- **CD4+ T cell mediated macrophage activation**: In CMI against phagocytosed microbes, the specificity of the response is due to T cells, the effector functions are provided by phagocytes, and the communications between lymphocytes and phagocytes are mediated mainly by cytokines and CD40 ligand:CD40 interactions. The steps in the process of CD4+ T cell and macrophage-mediated CMI include:

o **Induction of cell-mediated immunity**: Activation of CD4+ TH1 cells by microbes and protein antigens

 Antigen recognition by naïve T cells in lymph nodes.

 Requires costimulation by professional APCs.

 Clonal Expansion: driven by activated T cell IL-2 and IL-2 receptor production, leading to increase in numbers of T cells of a particular specificity, as much as 100-fold.

 Differentiation of CD4+ T Lymphocytes into effector cells

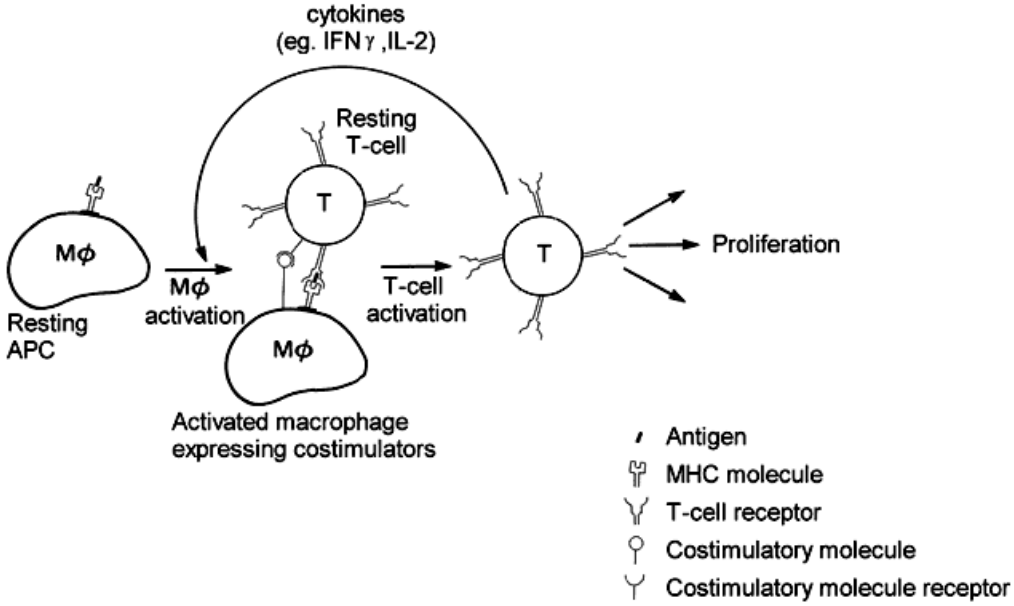
Th1 and **Th2** subsets of effector CD4+ T cells are defined by cytokines they produce.

• Th1 differentiation is stimulated by IL-12 produced by microbe-activated phagocytes
• Th2 differentiation stimulated by IL-4

 Th1 cells produce IFN-γ and are the effectors that activate macrophages in CMI.

 Th2 cells produce IL-4 and IL-5, which promote IgE and eosinophil-mediated anti-helminthic responses. Th2 responses may also down regulate Th1 responses.

 TH1 differentiation is stimulated by IL-12 produced by APCs

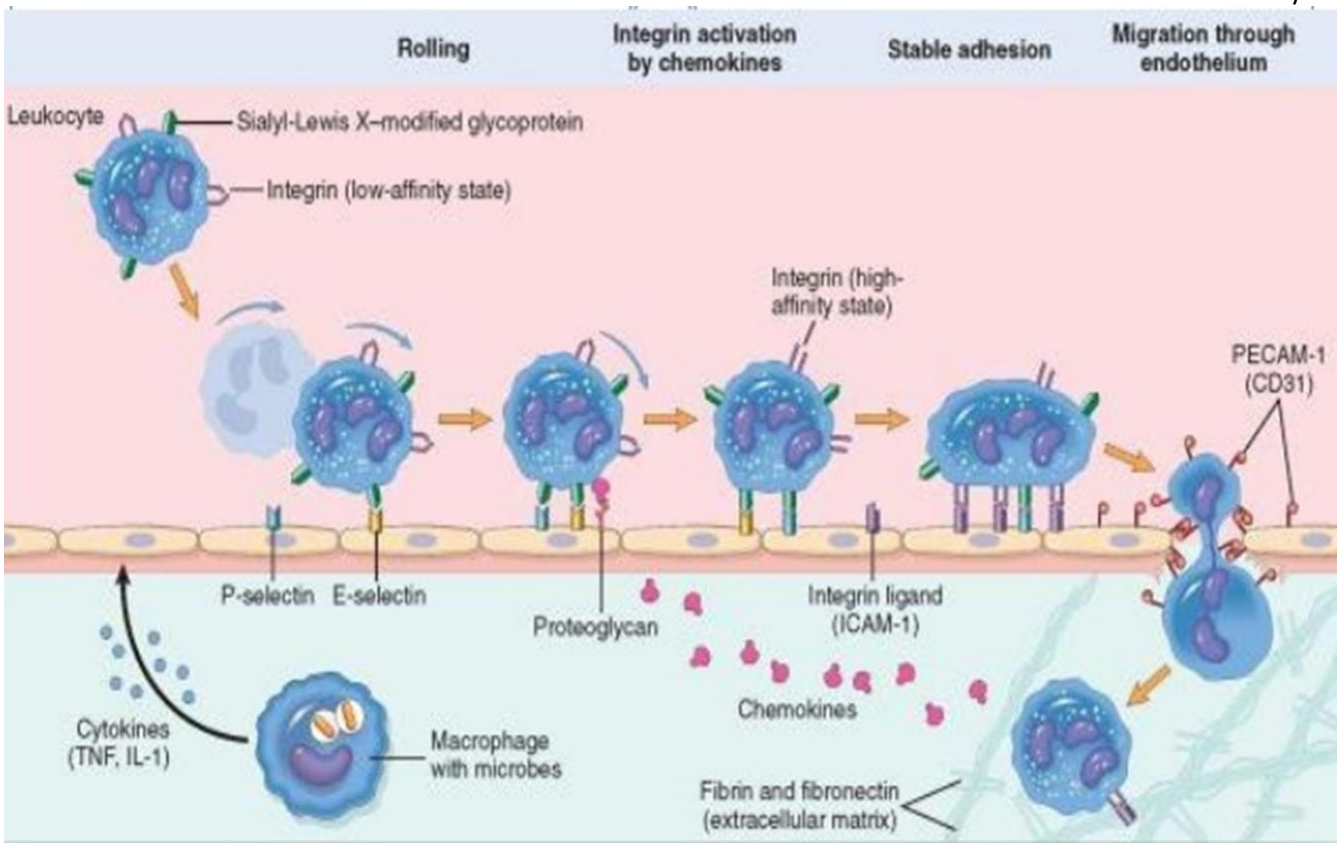


o **Migration of differentiated effector T cells and other leukocytes to site of antigen**.

 The migration of leukocytes to sites of infection is stimulated by cytokines, which induce the expression of adhesion molecules on endothelial cells and the chemotaxis of leukocytes.

 Effector and memory T lymphocytes express adhesion molecules (intergrins, selectin ligands) that promote their migration to sites of infection and inflammation.

 The migration of effector and memory T cells from the circulation to peripheral sites of infection is largely independent of antigen, but cells that recognize antigen inextravascular tissues are preferentially retained there



o **Activation of macrophages:** Activated macrophages are the effector cells of cell-mediated immunity that function to eliminate microbes and other sources of antigen.
 T cell stimuli for macrophage activation include **CD40 ligand** and **IFN-γ**

o **Functions of activated macrophages:**
 Killing phagocytosed and extracellular microbes, mainly by producing microbicidal reactive oxygen intermediates, nitric oxide, and lysosomal enzymes.
 Stimulate acute inflammation through secretion of cytokines, mainly TNF, IL-1 and chemokines, and short-lived lipid mediators, such as platelet-activating factor (PAF), prostaglandins, and leukotrienes.
 Remove dead tissues, facilitating repair after the infection is controlled.
 In addition to their effector functions, activated macrophages become more efficient APCs.

• **Delayed type hypersensitivity (DTH)** is injury (rather than protection) caused by a helper T cell mediated immune response. This happens if the activated macrophages fail to eradicate the infection; T cells and macrophages continue to produce cytokines and growth factors, and this leads to progressive modification of the local tissue environment, including fibrosis.

o **Granulomatous inflammation** is a form of chronic DTH with epithelioid macrophages, sometimes giant cells, and tissue fibrosis. Infection with Mycobacterium tuberculosis often leads to granuloma formation.

- **CD8+ T cells and cytolytic T lymphocyte (CTL) responses.** Cytolytic Tlymphocytes (CTLs) are effector T cells that recognize and kill target cells expressing foreign peptide antigens in association with class I MHC molecules.

o Most cell types may be infected with viruses, but most cell types also express class I MHC and can process proteins by the class I MHC pathway. Therefore most cells can be targets of CTL killing.

o Activation of naïve CD8+ T cells and development of effector CTLs

The differentiation of naive CD8+ T cells to functional CTLs requires the recognition of class I MHC-associated peptides ("signal 1") and costimulators and/or cytokines ("signal 2") normally only present on professional antigen presenting cells.

cross priming- a mechanism to ensure that naïve CD8+ T cells specific for the virus can be activated even when the primary infection is in cells that do not express costimulators, e.g. epithelial cells.

• Infected cells, debris form dying infected cells, or microbes released from the cells, are ingested by professional APCs.

• Microbial proteins leave the phagosomes/endosomes and enter the cytoplasm.

• The microbial proteins are processed and presented by the class I MHC pathway.

• Naïve CD8+ T cells specific for the peptide-MHC are activated by the professional APCs.

o Clonal expansion of CD8+ T cells in lymphoid tissues in response to viral infections often leads to as much as 50,000 to 100,000 fold increase in numbers of viral-specific CD8+ T cells.

o Peptide-MHC tetramers can be used as probes for expansion of viral peptide-specific T cells; this has been done with EBV and HIV infected patients.

o Differentiation of CD8+ T cells into effector T cells capable of cytolytic functions.

o Development of membrane-bound cytoplasmic granules that contain perforin and granzymes.

o Acquisition of the capacity to transcribe and secrete cytokines, mostly IFN-γ and TNF.

o Mechanisms of CTL-mediated cytolysis: Cell killing by CTLs is antigen-specific and contact-dependent. CTLs kill targets that express the same class I-associated antigen that triggered the proliferation and differentiation of naïve CD8+ precursor of the CTL.

 Recognition of antigen on the target cell and activation of CTLs (does not require costimualtion)

 Accessory molecule interactions, including CD2:LFA3(lymphocyte function-associated antigen) and LFA-1: ICAM-1 strengthen conjugate formation between CTL and target.

 Delivery of a "**lethal hit**" by the activated CTL to its target.

 Granule exocytosis releases:

• **Perforin** that forms pores in membrane of target cells.

• **Granzymes**(serine proteases) that enter the target cell through the perforin pore and activate cellular enzymes called caspases, which lead to target cell apoptosis.
• **Fas ligand** expressed on activated CTL may bind Fas on target cells and induce apoptosis.
 Cytokines (Th1-like) such as IFN-γ and TNF secreted by CTL promote inflammation.
 Release of the CTL: The CTL is not killed in the process, and can detach and find another target cell to kill.

• **Role of Th2 cells in cell mediated immunity**
o Suppression of Th1 mediated CMI by action of cytokines IL-4, IL-10, IL-13 which inhibit macrophage activation.
o Promote inflammatory reactions, by secretion of IL-4 and IL-5, that are dominated by eosinophils and mast cells for protection against helminthic infections.
 IL-4 stimulates the production of helminth-specific IgE antibodies, which opsonize the helminthes and bind to mast cells.
 IL-5 activates eosinophils, which bind to the IgE-coated helminths by virtue of Fc receptors specific for the ε heavy chain. Activated eosinophils release their granule contents, including major basic protein and major cationic protein, which are capable of destroying even the tough integuments of helminths.
• **Natural Killer (NK) cells.** NK cells are effector cells of the innate immune system that recognize and kill host cells which fail express some class I MHC molecules or kill host cells that express certain molecules indicative of intracellular infection or stress.
o Many viruses may interfere with class I MHC expression and class-I pathway antigen processing, thereby rendering their host cells invisible to CTL. NK cells, however, "recognize" the absence of class I MHC and/or recognize cell surface molecules only expressed on stressed (e.g. infected) cells infection.
o NK cells recognize" their target cells using both activating and inhibitory receptors.
 Activating receptors include CD16 (FcγR receptor), natural cytotoxicity receptors (unknown ligands), NKG2 (binds stress induced ligands)
 Inhibitory receptors include: CD94 and Killer Inhibitory Receptors (KIRs), which bind class I or class I-like molecules.
 Inhibitory receptor signals suppress signals from activating receptors.
o NK cells perform two major effector functions:
 Cytotoxicity: kill targets by same perforin/granzyme based mechanisms that CTLs use
 IFN-γ secretion-promote inflammation, and perhaps Th1 differentiation
o NK cells play important protective roles against viruses (e.g. EBV), and perhaps other intracellular microbes.
o Diseases characterized by lack of NK cells or NK function , such as X-linked lymphoproliferative disease (XLP) are associated with severe EBV infections and B cell neoplasm.

 XLP due to mutation sin gene encoding an adaptor protein in a signaling pathway and the NK-cell-activating

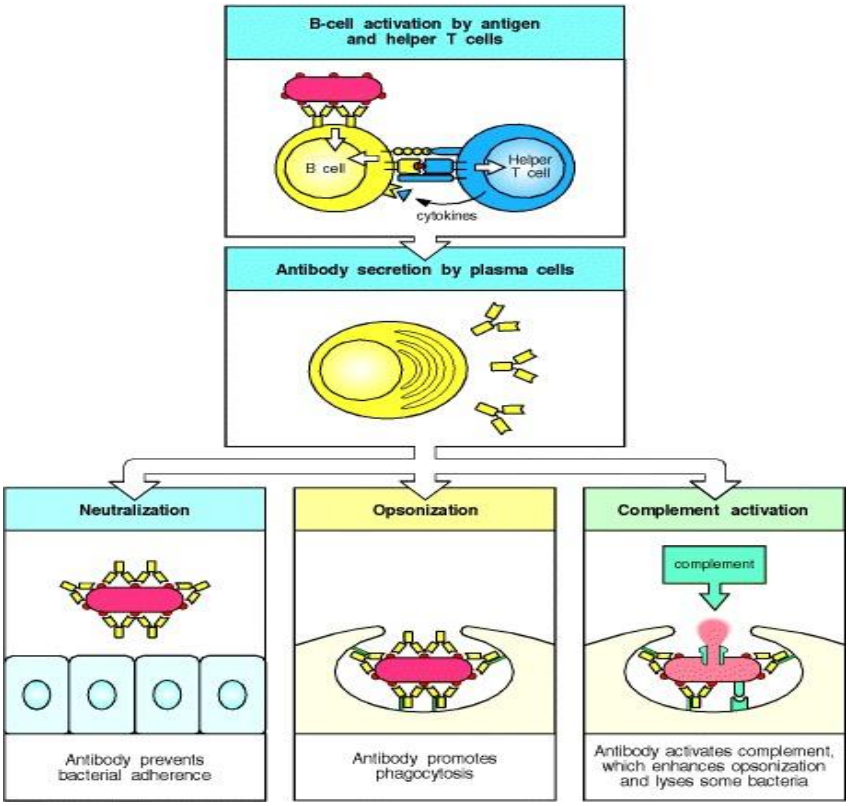
Humoral immunity

The term "humoral" refers to the liquid, noncellular components of the blood and other tissues, such as plasma and lymphatic fluid. The humoral immune response denotes immunologic responses that are mediated by antibodies. However, both B and T lymphocytes as well as dendritic cells and other antigen-presenting cells are necessary for the formation of antigen-specific antibody.

The extracellular spaces are protected by the **humoral immune response**, in which antibodies produced by B cells cause the destruction of extracellular microorganisms and prevent the spread of intracellular infections. The activation of B cells and their differentiation intoantibody-secreting plasma cells is triggered by antigen and usually requires helper T cells.

Antibodies contribute to immunity in three main ways .

1. **Neutralization**: To enter cells, viruses and intracellular bacteria bind to specific molecules on the target cell surface. Antibodies that bind to the pathogen can prevent this and are said to neutralize the pathogen. Neutralization by antibodies is also important in preventing bacterial toxins from entering cells
2. **Opsonization**: Antibodies protect against bacteria that multiply outside cells mainly by facilitating uptake of the pathogen by phagocytic cells that are specialized to destroy ingested bacteria.
3. **Complement activation**: antibodies binding to the surface of a pathogen can activate the proteins of the complement system, which results in complement proteins being bound to the pathogen surface, and these opsonize the pathogen by binding complement receptors on phagocytes.



There are two types of humoral immune response**: primary and secondary.**

The primaryresponse begins immediately after the inital contact with an antigen; the resultingantibody, predominantly IgM, appears 48 to 72 hours later.

The secondary response:occurs within 24 to 48 hours and produces large quantities of predominantly IgG. Thesecondary response persists much longer than the primary response and is the result ofrepeated contact with the antigens.

Antigen recognition and B cell activation

The IgD and monomeric IgM surface receptors of B cells binds to specific antigen and initiate the B cell activation. The B lymphocyte antigen receptor serves two roles in B cell activation.

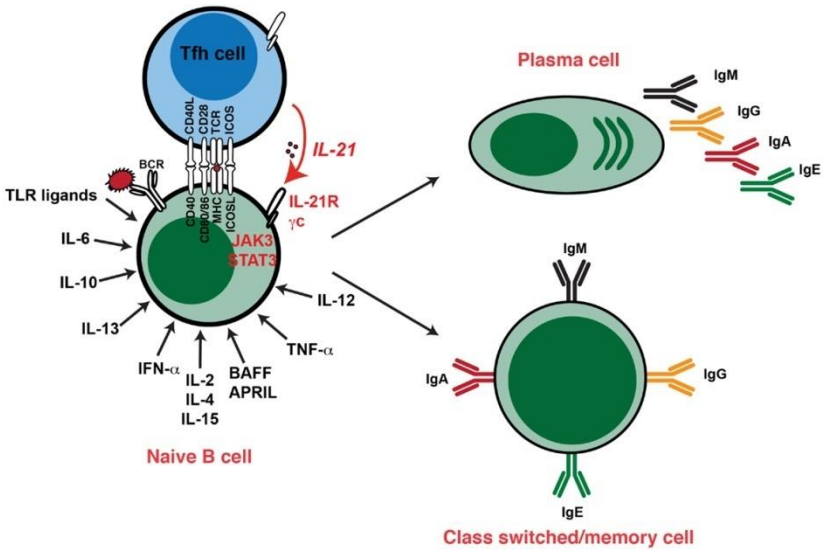
1. antigen-induced clustering of receptors delivers biochemical signals to the B cells that initiate the process of activation.
2. the receptor binds protein antigen and internalizes it into endosomal vesicles, which are processed and presented to helper T cells at the surface with MHC II molecules.

B cell activation varies with the nature of the antigen:

- **RESPONSE TO T-DEPENDENT ANTIGENS**

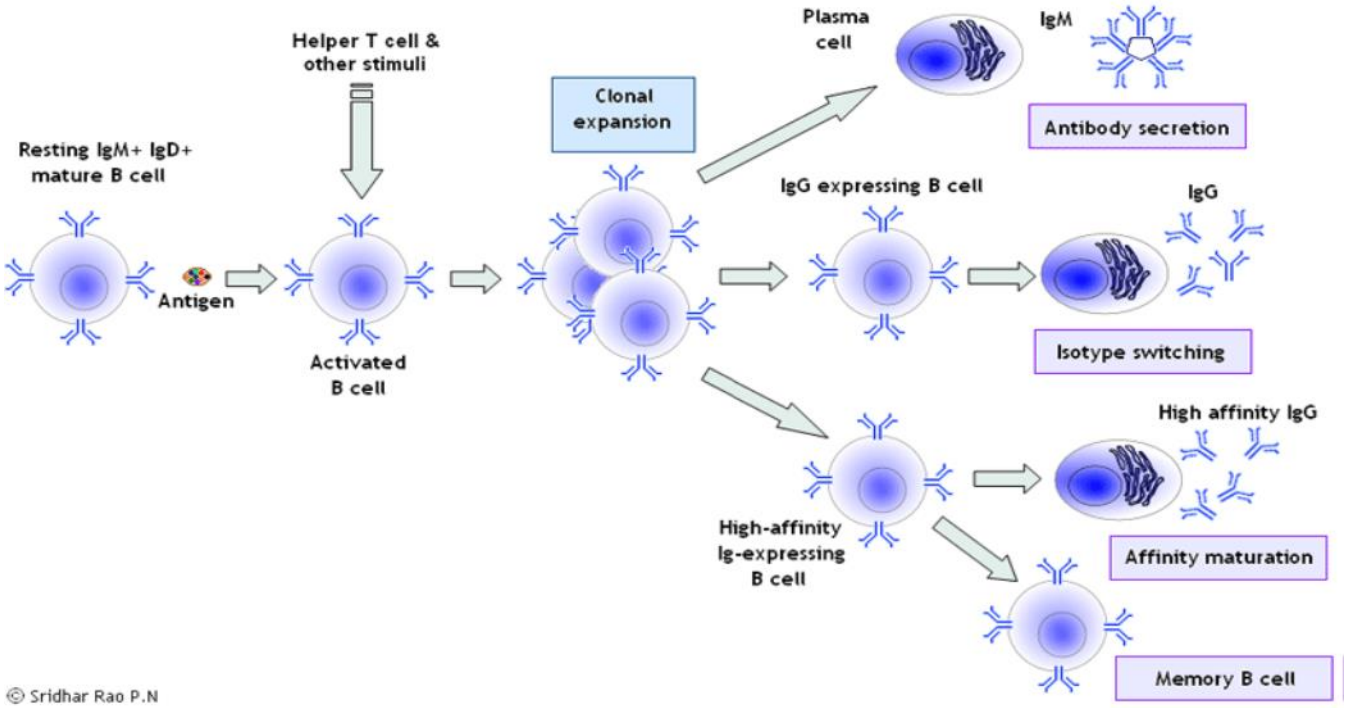
Antibody responses to protein antigens require recognition of antigen by the helper T cells and co-operationbetween the antigen-specific B cells and T lymphocytes. The

interaction between helper T cells and B cell sequentially involves antigen presentation by B cells to differentiated T cells, activation of helper T cells and expression of membrane and secreted molecules by the helper T cells that bind to and activate the B cells.The net result is the stimulation of B cell clonal expansion, isotype switching, affinity maturation and differentiation into memory cells.



- **RESPONSE TO T-INDEPENDENT ANTIGENS**

Many non-protein antigens such as polysaccharides and lipids stimulate antibody production in the absence of helper T cells, and these antigens are called T independent antigens. Important TI antigens include polysaccharides, glycolipids, and nucleic acids. These antigens are not processed and presented along withMHC proteins and hence cannot be recognized by helper T cell.


Helper T cell &
other stimuli
Plasma
cell
IgM
Clonal
expansion
Antibody secretion
Resting IgM+ IgD+
mature B cell
IgG expressing B cell
IgG
Antigen
Activated
B cell
Isotype switching
High affinity IgG
High-affinity
Ig-expressing
B cell
Affinity maturation
Memory B cell
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