T lymphocyte

T lymphocyte precursors, like those of B lymphocytes, originate in the bone marrow. Whereas B cells complete their maturation in the bone marrow, T lymphocyte precursors migrate to the thymus where they develop into mature T lymphocytes. The mature T lymphocytes then leave the thymus and circulate through the bloodstream and lymphoid tissue.

The two types of T cell are distinguishable phenotypically by the expression of mutually exclusive molecules on their cell surface. Helper T cells express a molecule called CD4 on their cell surface and are therefore called CD4 T cells (Th). Cells of the other T lymphocyte subset express a different molecule called CD8 on their cell surface and are called **CD8 T cells or Cytotoxic T Lymphocyte (CTL)**. T lymphocytes in the periphery express either CD4 or CD8 but not both.

The T cell receptor for antigen:

T-lymphocytes recognize antigens through the use of their antigen receptors (T-cell receptors for antigen, or TCRs). Like antibodies, TCR are specific to antigens and clonally distributed; moreover, they share many structural similarities with antibody molecules. However, TCRs differing from antibodies in a number of aspects. Most importantly, the character of their antigen recognition differs from that of antibodies.

The only form of antigen that the TCR can recognizes is a peptide associated with a self MHC molecule.

Structure of the TCR:

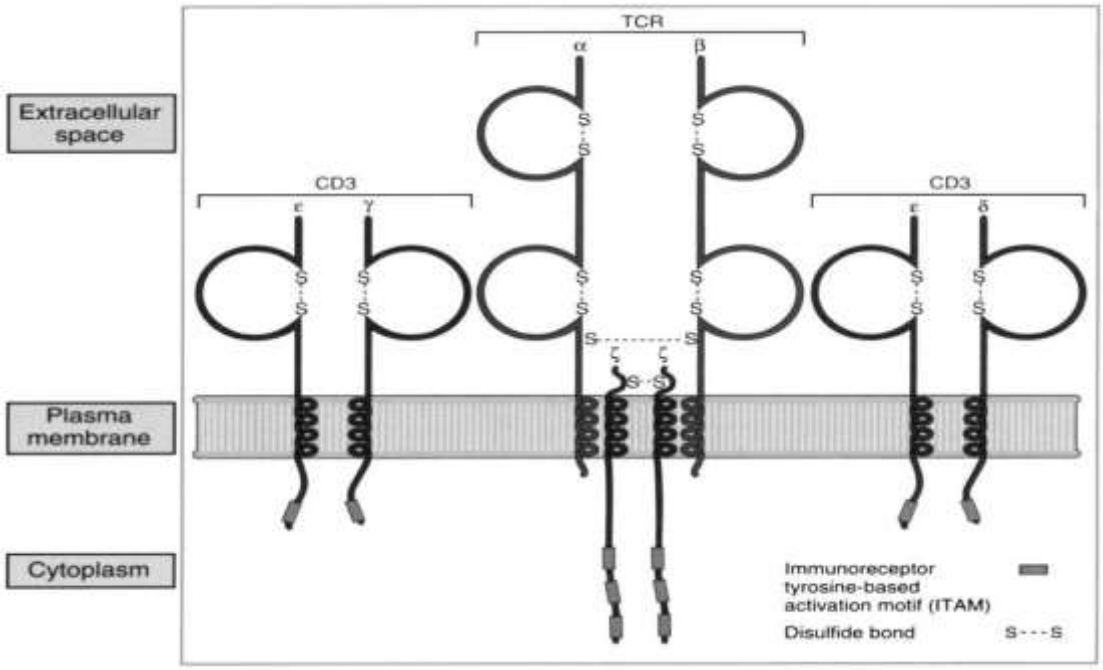
The TCR is a heterodimer, consisting of two polypeptide chains, α and β. There is no dramatic difference in the size of the two chains, so, these cannot be called ‘‘heavy’’ and ‘‘light’’ chains. Each α and each β chain consist of a V- and a C-region. The V-region of both chains is represented by one N-terminal antibody-like V domain, which, in turn, can be subdivided into FR and CDR. The C-region of both chains is represented by one antibody-like C domain, followed by a short transmembrane region and a very short (5 to 12 amino acid residue long) cytoplasmic region.

- There is no such thing as TCR isotypes: neither α nor β chain C-regions contain amino acid sequences that vary from one ‘‘kind’’ of TCR to another.
- TCR chains are always produced in the membrane-associated form and are never secreted.
- No effector function is associated with TCR chains.

- Their only function is to recognize the peptide–MHC complex through their V-regions.

The cytoplasmic portions of both TCR α and TCR β chain are too short to be associated with any enzyme that might mediate transduction signal. The latter process is a function of the polypeptide chains that are expressed by the T lymphocyte in close proximity to the TCR α and β chains. These additional chains have rather long cytoplasmic ‘‘tails’’ and are called the γ, δ, ε, and ζ chains. The first three of these are collectively called CD3

The CD3 and ζ chains are non-covalently associated with the TCR α β heterodimer. It is these chains that transduce the signal inside the cell when the TCR is triggered by its specific peptide–MHC complex. Together, the α β heterodimer, the CD3 and the zeta chain are sometimes called the TCR complex.



Are there any structures that the CD3 and ζ chains recognize?

No. The CD3 and ζ chains have no V-regions and thus they cannot recognize antigens. Moreover, there are no natural ligands or counter-structures that these chains can interact with. Their sole function is to ‘‘sense’’ the triggering of the TCR by its specific antigen, and then to transduce the signal that accompanies such a triggering.

Recognition of antigen by T cells

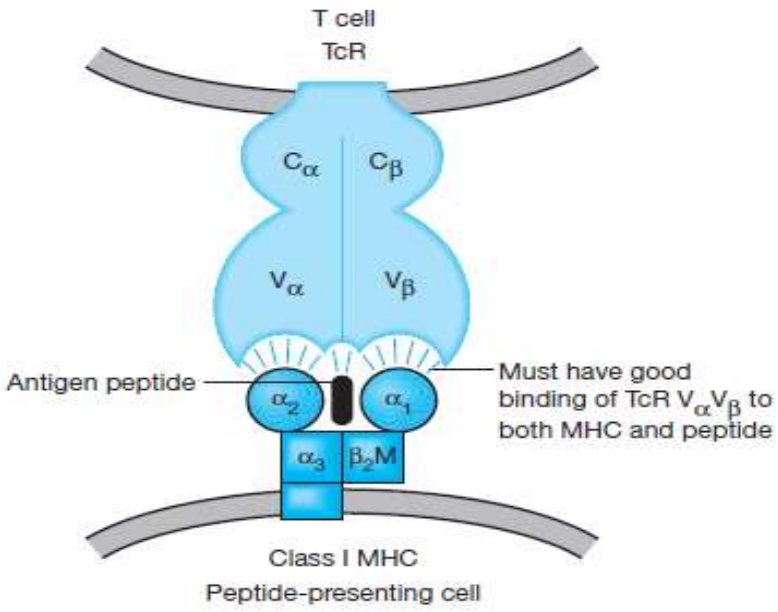


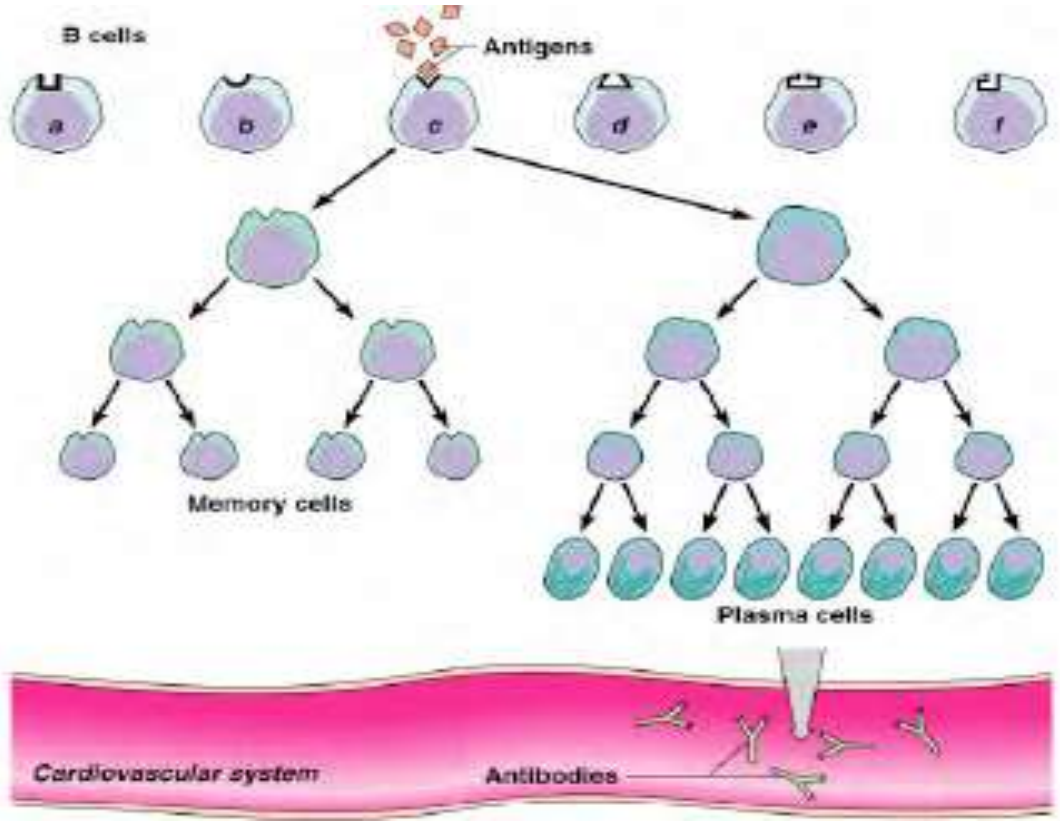
Figure 4.6 Interaction of the TcR with antigen/class I MHC. The antigen-binding site of the TcR is made up of parts of the Vα and Vβ chains. Parts of the binding site interact with the antigenic peptide bound in the groove of the MHC molecule and parts of the binding site interact with the MHC molecule.

Two types of immune response:

- 1. Humoral / Antibody-Mediated Immunity
- involves antibodies produced by B cells to confer immunity
- best against bacteria, toxins, and virus that are free in body fluids
- 2. Cell-Mediated Immunity
- involves T cells that act against foreign organisms or tissues
- works best on bacteria- or virus-infected cells, fungi, protozoa, tissue grafts and cancer

- **<u>B cells and Humoral Immunity</u>**
- B cells produce antibodies = humoral / antibody-mediated immunity
- B cells arise from stem cells in bone marrow
- when mature, migrate to lymphoid tissue
- wait to recognize antigen and be stimulated to produce antibodies
- **<u>Activation of B cells by clonal selection:</u>**

- each B cells produces only one antibody against one antigen/epitope
- recognizes antigen/epitope via IgD on cell surface (receptor)
- when activated it will divide to produce clones.

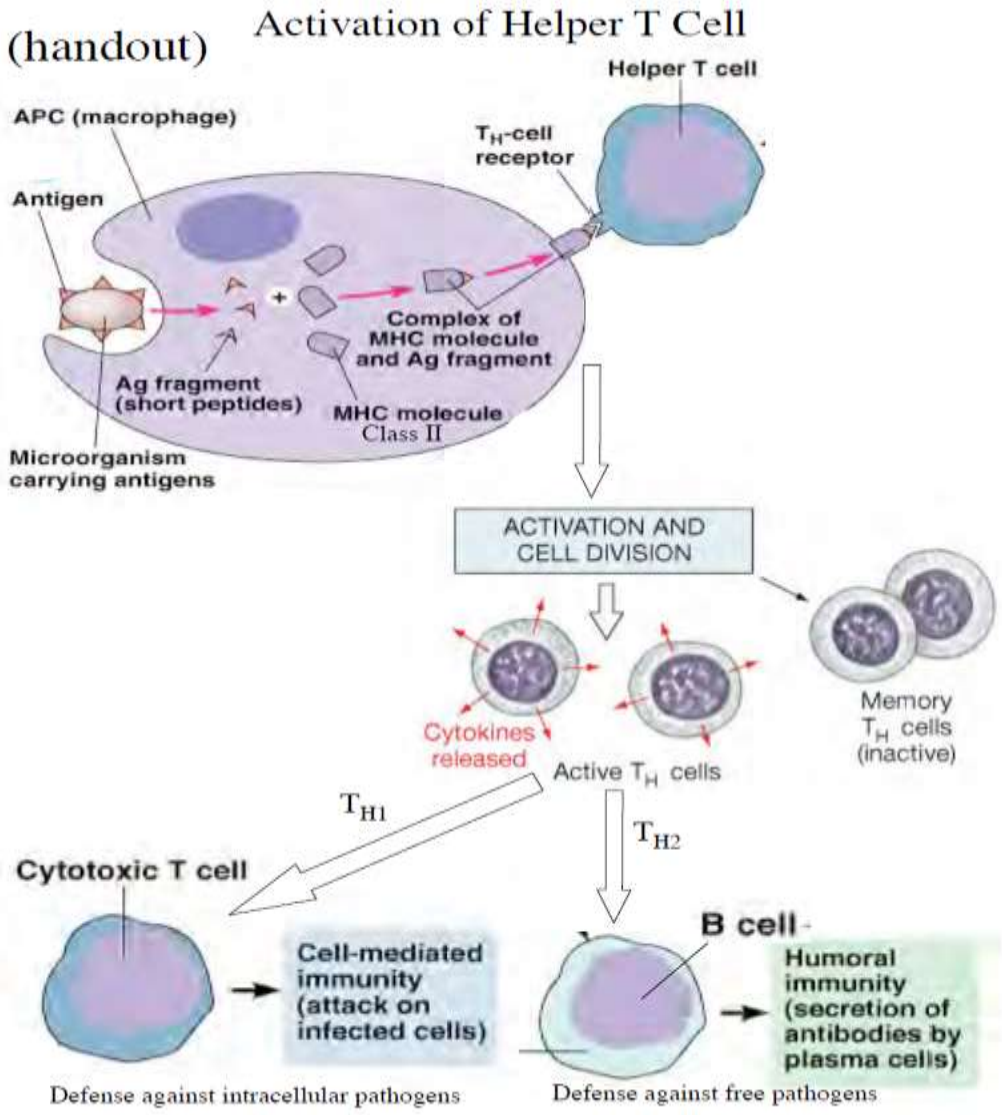


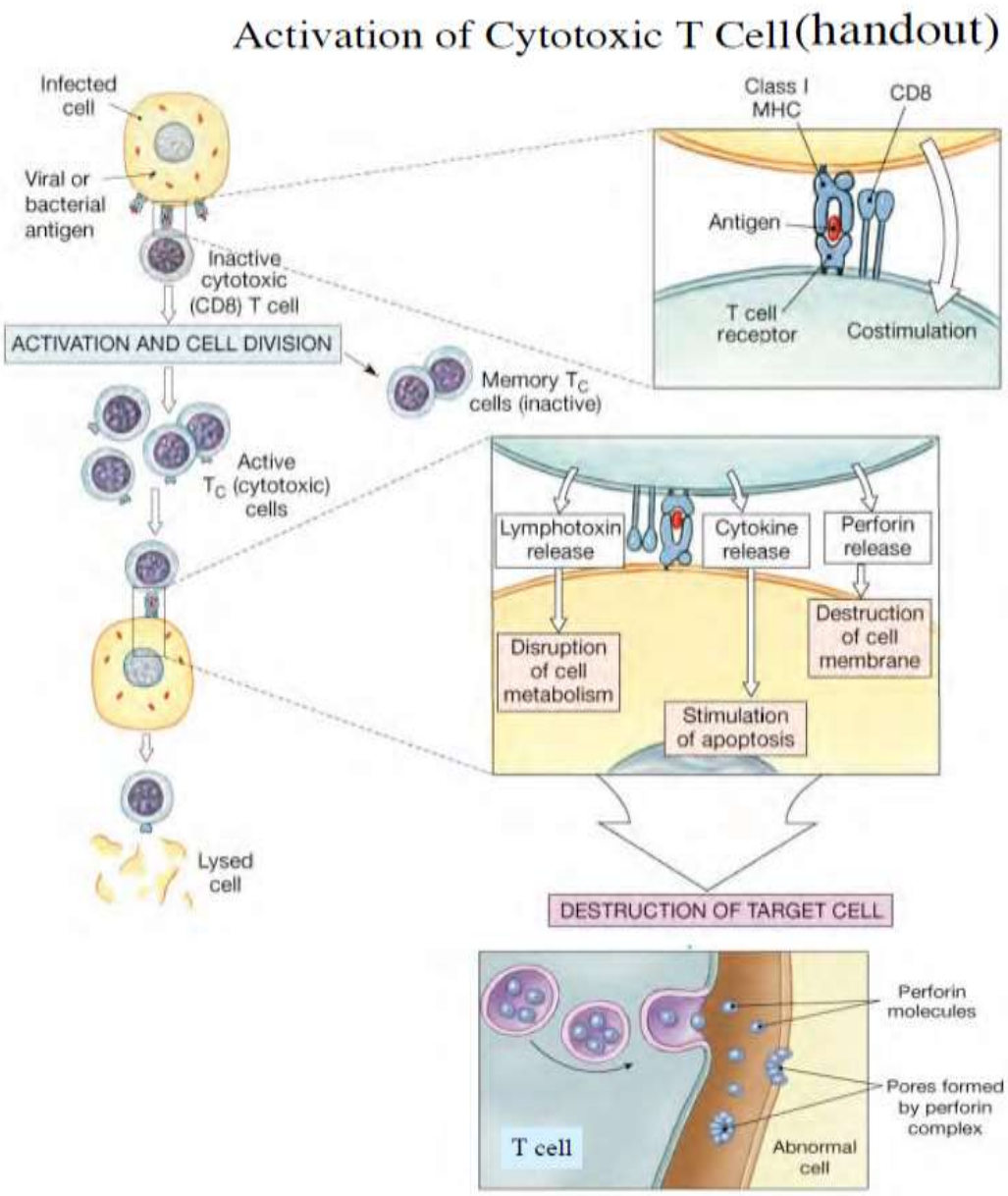
- 1. IgD antibody receptor on B cell binds its specific antigen/epitope
- 2. B cell is activated and undergoes clonal selection: the B cell proliferates and differentiates into two types of cell populations --> Memory B cells and Plasma Cells
- 3. Plasma cells secrete antibodies specific for the original epitope (2000 antibody molecules per second) for 3-5 days [Time from initial antigen binding to antibodies appearing in the blood is 7-10 days]
- 4. Upon second exposure to the same antigen/epitope, memory cells bind antigen and are triggered to differentiate into plasma cells and secrete antibodies. [Time from initial antigen binding to antibodies appearing in the blood is 3-5 days]

T cells and Cell-Mediated Immunity

- **<u>Types of T cells</u>**
- **TH (Helper T cells):** activated by antigen in Class II MHC, respond by secreting cytokines to influence other immune cells

- **TH1**: activate cells related to cell-mediated immunity (TC and Macrophages)
- **TH2**: activate B cells to make antibodies (T-dependent antigens)
- **TC (Cytotoxic T cells):** activated by antigen in Class I MHC, respond by secreting perforin and lysing the target cell. This often requires pre-activation of the TC by a TH1 cell. (Cells expressing foreign antigens in Class I MHC are likely to be infected with virus or are cancerous and thus are quickly destroyed.
- **TS (Suppressor T cells):** regulate the immune response, inhibit T and B cell activity when antigen levels decline

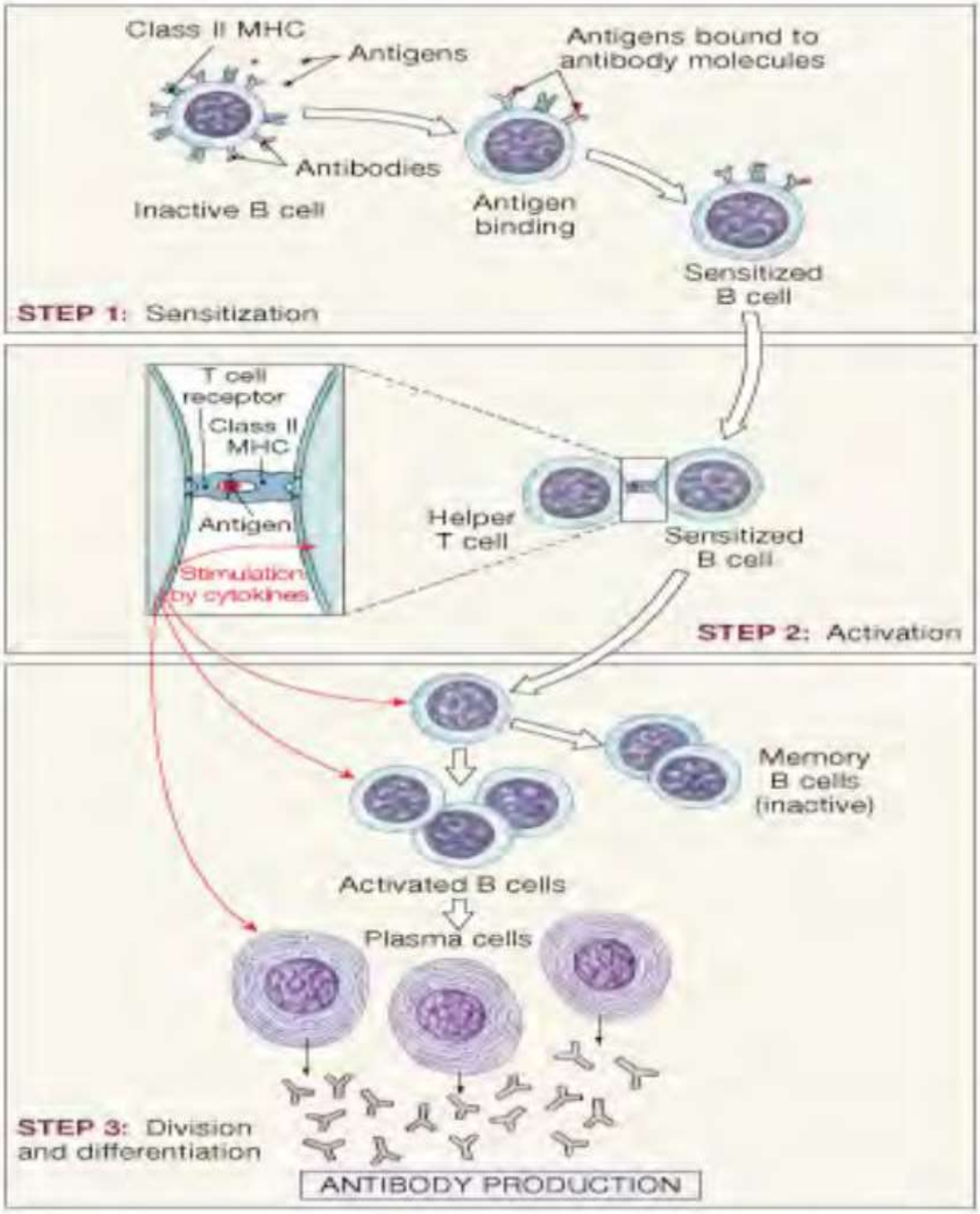




- **<u>Natural Killer Cells (NK cells)</u>**
- not immunologically specific
- attack any abnormal antigen on eukaryotic cells: virus-infected, cancer, large parasites
- lyse target cell by releasing perforins to disrupt membrane
- **<u>Inter-relationship of Cell-Mediated and Antibody-Mediated Immunity</u>**
- T-dependent antigens:
- more common
- protein epitopes

- require TH2 cells to signal B cells to produce antibodies

- **<u>Activation of B cells (T-dependent Antigen). Epitope tends to be protein, produces stronger immune response than T-independent Antigen)</u>**
- B cell binds specific antigen in the IgD receptor and internalizes it.
- B cell transfers antigen to a Class II MHC receptor and return antigen now bound to MHC back to the surface of the cell. B cell is now sensitized.
- A Th2 cell specific for the antigen recognizes and binds to the antigen in the Class II MHC and becomes activated.
- The activated Th2 cell secretes cytokines on the B cell.
- Cytokines activate the B cell.
- The activated B cell undergoes clonal selection producing Memory B and plasma cells.
- Plasma cells secrete antibodies that are specific for the original antigen. Memory cells wait for second exposure.


Class II MHC
Antigens
Antigens bound to antibody molecules
Antibodies
Inactive B cell
Antigen binding
Sensitized B cell
STEP 1: Sensitization
T cell receptor
Class II MHC
Antigen
Stimulation by cytokines
Helper T cell
Sensitized B cell
STEP 2: Activation
Memory B cells (inactive)
Activated B cells
Plasma cells
STEP 3: Division and differentiation
ANTIBODY PRODUCTION

Body Defense Summary

Non-specific defenses and the immune response are integrated: both function together for overall defense