Module 3: Development of immune cells

Lecture 15: Development of Lymphocytes (Part I)

Pluripotent stem cells and fetal liver are considered as hematopoietic stem cells in the body which give rise to lineages of blood cells. Hematopoietic stem cells also differentiate into B cells, T cells, and antigen presenting cells following maturation. The maturation of B cells mostly occurs in the fetal liver before birth and in the bone marrow after birth. The T cells form in the liver before birth and complete maturation in thymus after birth. The most common form of T cells i.e αβ T cells develop in the bone marrow while less common form γδ T cells develop in neonatal liver. The differentiation of B and T lymphocytes from precursor stem cells largely depends on the signals induced by the surface receptors present over the hematopoietic stem cells which induce different transcriptional factors involved in its maturation.

## *15.1 Differentiation of B and T lymphocytes from progenitor cells*

15.1.1 B cells differentiation

Pluripotent hematopoietic stem cells differentiate into B cells under the influence of transcription factors E2A, EBF, and Pax5. These transcription factor works synergistically to induce the transcription of specific genes and their recombination responsible for the development of B lymphocytes. Pluripotent hematopoietic stem cells are differentiated into Pro-B cells which give rise to follicle B cells, marginal B cells, and B-1 B cells.

15.1.2 T cell differentiation

Pluripotent hematopoietic stem cells first give rise to common lymphoid progenitor cells. The common lymphoid progenitor cells can either give rise to natural killer cells or Pro-T cells under the influence of different transcriptional factors. The lymphoid progenitor cells activates the Notch receptor which cleaves and migrates to nucleus to activate transcription factor GATA-3 that in turn give rise to Pro-T cells. These Pro-T cells are further differentiated into αβ and γδ T cells under the influence of interleukin-7. Interleukin-7 is produced by stromal and epithelial cells of bone marrow and thymus, respectively.

Figure 15.1 Differentiation of B and T lymphocytes from stem cells:
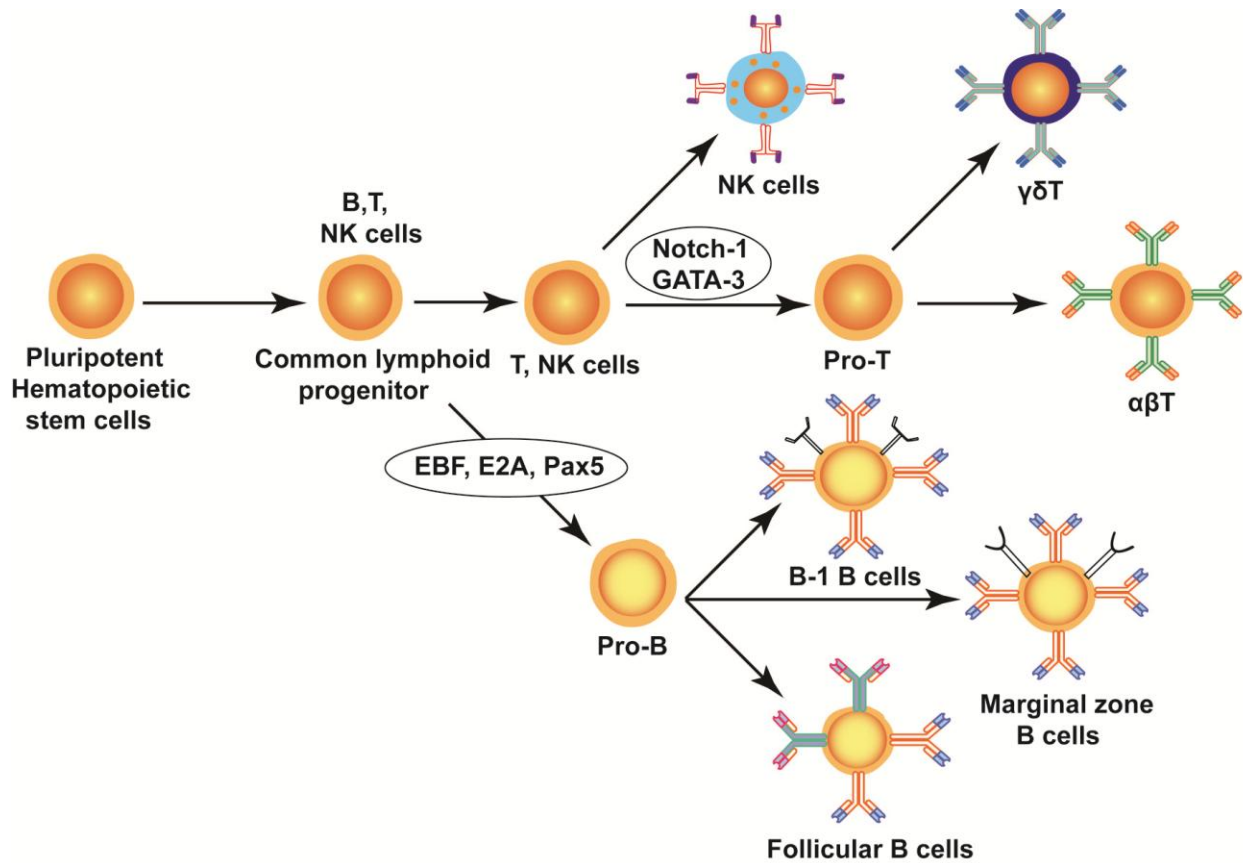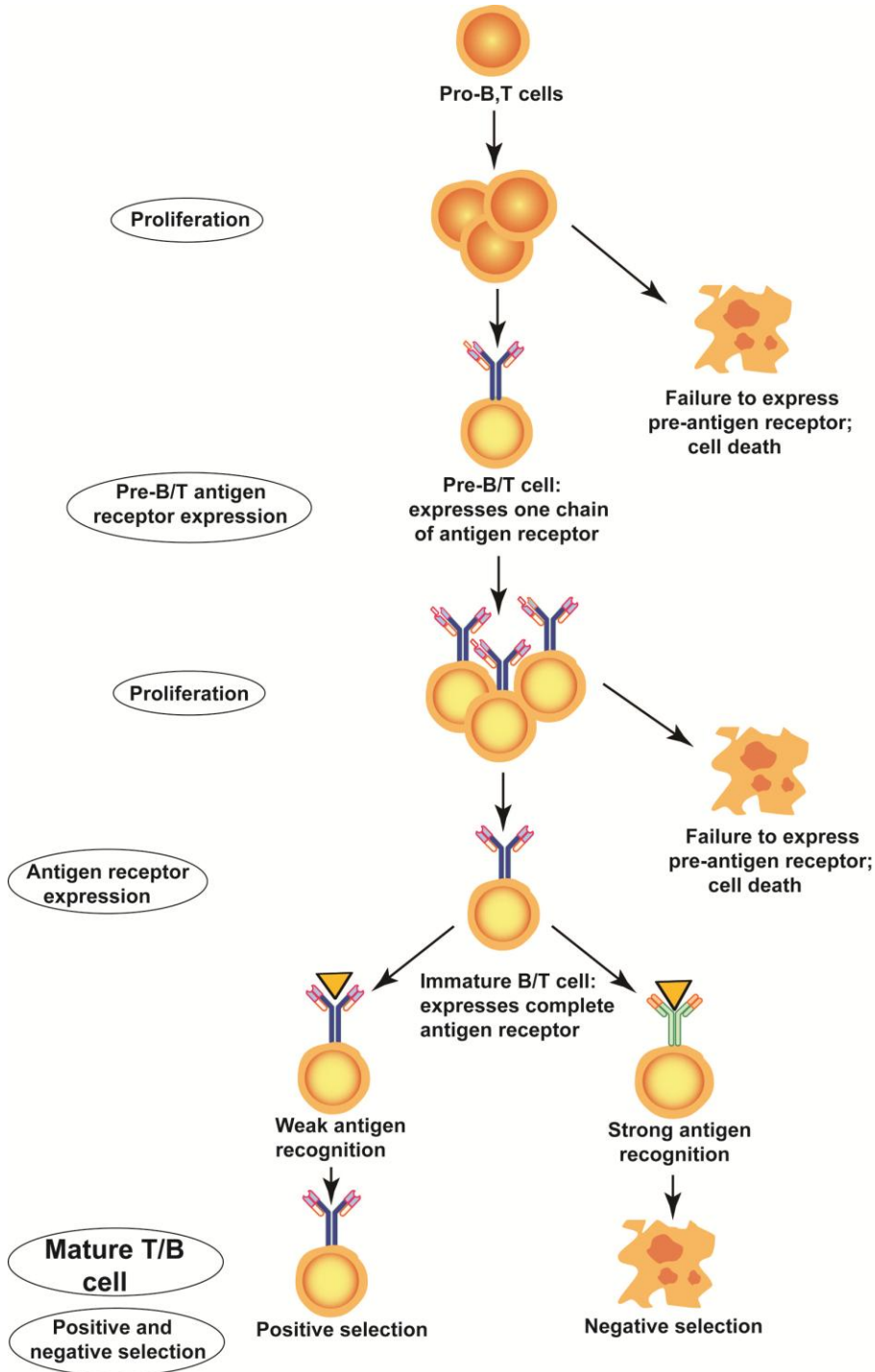

15.2 Expression of antigen receptor

T and B cell express certain specific receptor over their surface that is responsible for their specificity towards different MHC class molecules. All the B and T cells are having unique receptors over their surface that makes it a diverse population of cells present in the human body. The functional antigen receptor genes are rearranged and produced over a B and T lymphocyte during the early embryonic development. It is quite remarkable that an antigen receptor is expressed over an immature lymphocyte before encountering any antigen (clonal selection theory).

15.3 Selection of lymphocyte repertoires

The development of lymphocyte involves many steps that screen the best among all to be continued downstream in the developmental cycle. The first step is to check the integrity of the polypeptide chain of the antigen receptor followed by the complete assembly of the receptor. The cells which pass these steps stood apart from other in terms of successful rearrangement of genes and therefore more likely to undergo the actual maturation step.

The screening also involves the removal of lymphocyte that is reactive to self antigens. The process where the cells are selected for further developmental stages and lineages for the lymphocyte population is called **positive selection**. Alternatively, both B and T lymphocytes are eliminated based on their reactivity to self antigens by the process of **negative selection**. The T lymphocyte reactive towards the self antigens is removed by apoptosis and the phenomenon is called as **clonal deletion**.

Figure 15.2 Different stages of T and B cells maturation:

Pro-B,T cells

Proliferation

Failure to express
pre-antigen receptor;
cell death

Pre-B/T antigen
receptor expression

Pre-B/T cell:
expresses one chain
of antigen receptor

Proliferation

Failure to express
pre-antigen receptor;
cell death

Antigen receptor
expression

Immature B/T cell:
expresses complete
antigen receptor

Weak antigen
recognition

Strong antigen
recognition

Mature T/B
cell

Positive and
negative selection

Positive selection

Negative selection

15.4 Development of lymphocyte subsets

The precursor cells that are positively selected for further developmental steps express both CD4+ and CD8+ on their surface. These cells are differentiated into either CD4+ or CD8+ but not both, any cells expressing both the receptors during the downstream developmental steps are eliminated by apoptosis. The naïve CD4+ cells are differentiated into helper T cells while naïve CD8+ cells into cytotoxic T lymphocyte. Similarly B cell lineages also develop into different subsets, bone marrow derived B cells develop into follicular B cells (mediates T cell dependent immune response) or marginal zone B cells (mediates T cell independent immune response).

Lecture 16: Development of Lymphocytes (Part II)

16.1 Rearrangement of gene in B and T lymphocytes

The genes responsible for the diverse antigen receptors on B and T cells are generated by the arrangement of variable (V), diversity (D), and joining (J) regions in the gene segment. This phenomenon of rearrangement of chromosomal segment is called **V (D) J recombination**. The V(D)J recombination is the reason for the diversity of the immune cells in the body. This was proved by **Susumu Tonegawa** who demonstrated that DNA segments in the loci responsible for light and heavy chain of an immunoglobulin molecule is different in developing B cells than in any other cell types.

16.1.1 Organization of immunoglobulin and T cell receptor gene

The organization of the germline genetic loci of immunoglobulin and T cell receptor gene are similar in terms of their organization.

The immunoglobulin heavy chain is encoded by chromosome 14, κ light chain by chromosome 2, and λ light chain by chromosome 22. The 5' end of the gene contains clusters for the variable region of around 300bp. The joining segments start after the variable region, which is around 30-50 bp long. The diversity region occupies the space between the variable and joining region. The length and size of these three V, D and J regions varies among different species of animals. The immunoglobulin locus also contains different constant region that encodes the C chain of the Ig molecule.

The T cell receptor α and δ chains are encoded by chromosome 14 while β and γ chains by chromosome 7. The loci on the T cells are similar to that of the immunoglobulin. The detailed structure of the genome orientation for both B and T cells are beyond the scope of this course.

16.1.2 V(D)J recombination

The germline genes cannot be transcribed into mRNAs that encode the functional receptor proteins. The functional genes are only generated in developing B and T lymphocytes after rearrangement of V, (D), and J chains. The process involves the selection of one segment of each V, (D), and J chains in any lymphocyte and arrange it into a single exon that encodes the variable region of an antigen receptor. Conserved heptamer (7 bp) and nonamer (9 bp) are located adjacent to the V and J exons. The V (D)

J recombinase recognizes these signals and brings the segments together. The specific factors that mediate the V, (D), and J chain recombination recognizes the **recombination signal sequences (RSS)** that are located at 3' end of V and 5' end of J segment. The V and J chain combine together after deletion of the intervening sequence or inversion of the sequence if they are oriented in the opposite direction.

Figure 16.1 Organization of gene loci of immunoglobulin gene:
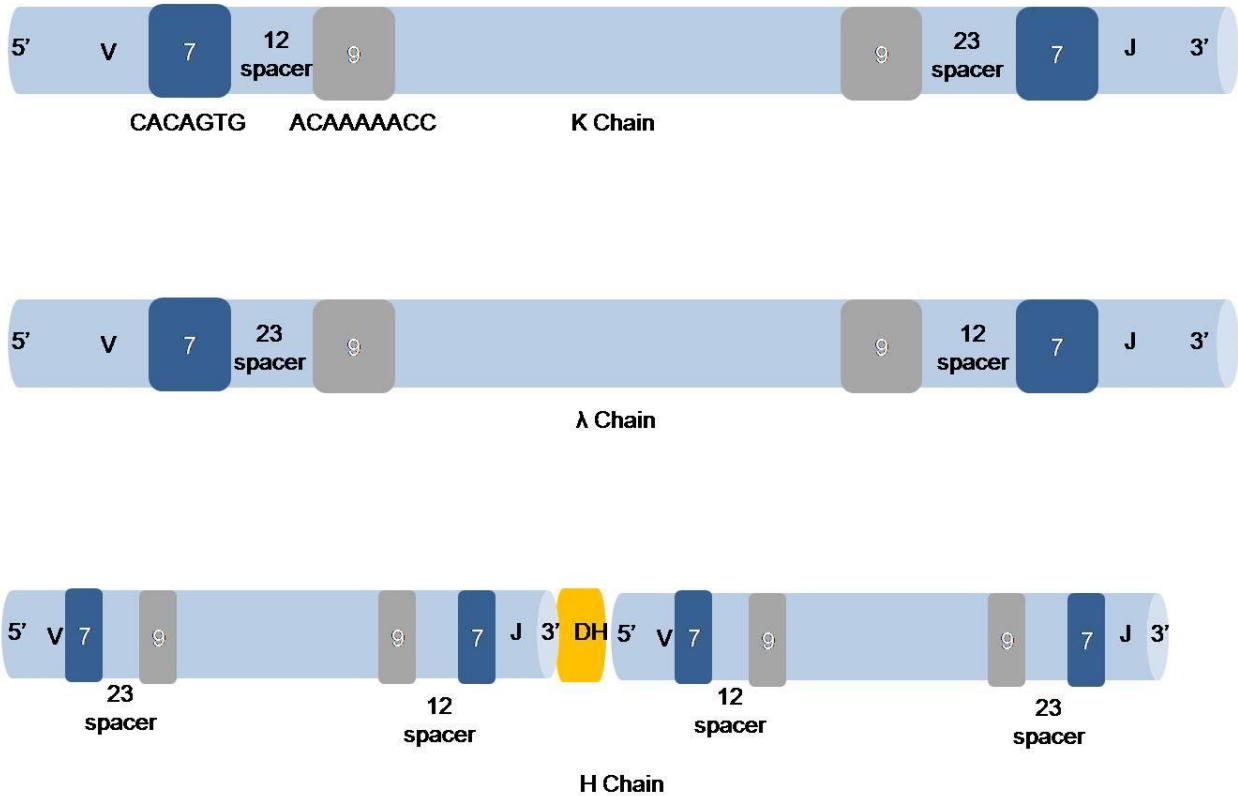
16.2 Mechanism of V (D) J recombination

The recombination of V, (D), and J chains is a type of non homologous recombination which is mediated by many enzymes including **DNA double stranded break repair (DSBR)** enzymes. The whole process is divided into four distinct phases.

Synapsis

Cleavage

Hairpin-opening and processing of ends

Joining

16.2.1 Synapsis

This is the process by which the antigen receptor genes are made accessible for the recombination machinery. The selected regions are brought together by looping of the chromosome for subsequent processes.

16.2.2 Cleavage

DNA in the specific region is broken with the help of recombination activating gene-1 (Rag-1) and Rag-2 to bring the RSS-coding sequence closer. The Rag-1/Rag-2 complex is known as V (D) J recombinase. Rag-1 acts as a restriction endonuclease to recognize and cleave the heptamer sequences. Rag-2 protein helps to bring the Rag-1/Rag-2 tetramer complex together. Rag genes are only expressed in lymphoid origin cells i.e. B and T lymphocytes.

### 16.2.3 Hairpin-opening and processing of ends

The broken ends are modified by addition or deletion of the base pairs to produce maximum diversity among the sequences. **Artemis** an endonuclease opens up the hairpin for any further modification. Another unique enzyme called **terminal deoxynucleotide transferase** (TdT) helps to add the nucleotide sequence in the 3' end of the broken region that again is responsible for the maximum diversity. Nucleotides may be added to asymmetrically cleaved hairpin structure in a template manner those nucleotides are called **P sequences**. Nucleotides may be added to the recombination site in a nontemplated manner by TdT enzyme; those are referred as **N sequences.**

16.2.4 Joining

The broken ends are joined by double stranded repair process. DNA end-binding proteins Ku70 and Ku80 are involved in recruiting protein kinase which helps in the ligation of broken ends and are carried out by DNA ligase.

Figure 16.2 Different events during V(D)J recombination:
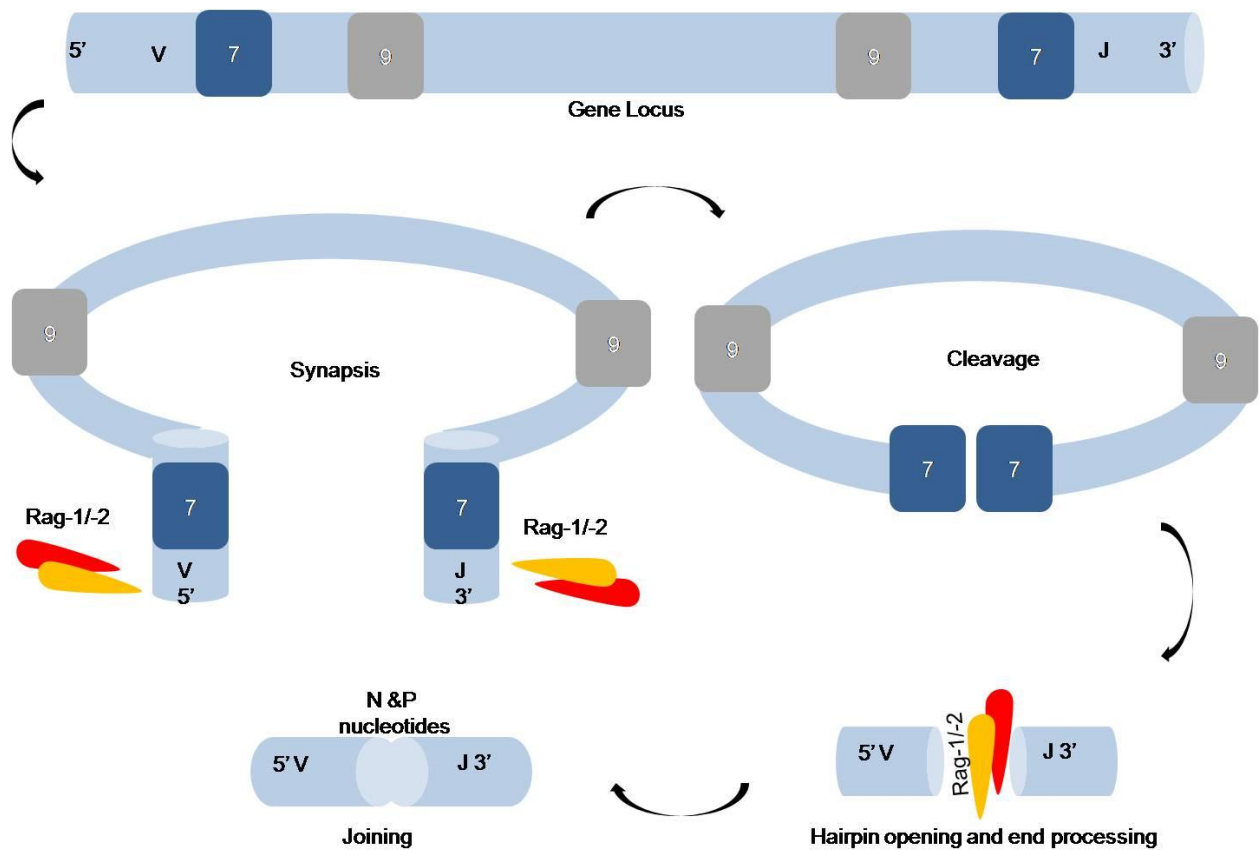
16.3 Development of B lymphocytes

The precursor cells formed from the bone marrow stem cells are called **pro-B cells**. The pro-B cells do not express any antibody. Recombination process of Ig chains starts during pro-B cell stage because of the expression of Rag gene. Once the V (D) J recombination of heavy chain is completed, the pro-B cell is differentiated into **pre-B cells**. Pre-B cell expresses the heavy chain of the Ig over their surface and are identified by the presence of B220 surface markers. Pre-B cells are differentiated into **immature B cells** after the synthesis of light chains of the Ig over their surface. The immature B cells are differentiated into **mature B cells** after the synthesis of mature IgM and IgD molecules over their surface.

16.4 Development of T lymphocytes

The precursor stem cells in the bone marrow are differentiated into **pro-T cells** into thymus. The pro-T cell is differentiated into **pre-T cell** with the recombination of β chain. The pre-T cell express only the β chain of T cell receptor that further differentiates into **double positive** T cells which expresses both α and β chain over the surface. In addition double positive T cell expresses both CD4 and CD8 over their surface. The double positive T cells undergoes positive and negative selection to differentiate into **immature T cells** that express membrane associated α and β chain. The immature T cells are differentiated into **mature T cells** after coming into the peripheral circulation.

Lecture 17: Activation of Lymphocytes (Part I)

17.1 Activation of T lymphocyte

The activation of T lymphocyte is done by antigen loaded over the MHC molecules. Proliferation of T lymphocytes and there differentiation into effector and memory cells requires different co-stimulatory molecules in addition to antigen presenting cells. A T lymphocyte recognizes only the protein antigens that are loaded over the MHC molecule. Sometimes chemicals entering the body through skin also induce the T cell immune responses and are often called contact sensitivity reactions. Differentiated effector T-cells following antigen sensitization produce an effective immune response.

17.2 Co-stimulatory molecules

A naïve T lymphocyte proliferates and differentiates into effector cell with the help of signals provided by antigen presenting cells, and are called as co-stimulatory molecules. In absence of co-stimulation, antigen sensitized T cells either die by apoptosis or do not produce an effective immune response. The best known co-stimulatory molecules are B7-1(CD80) and B7-2(CD86) that are expressed on activated antigen presenting cells. Their ligands are present over the surface of T-cell and are called as CD28. The antigen presenting cells which do not produce any co-stimulatory molecules fail to produce any T-cell immune response. The activated T lymphocyte also expresses CD40 ligands which binds with CD40 present over the antigen presenting cells. The activation of T-cells follows a cascade.

Naïve T-cells activated by peptide MHC complex causes the expression of CD 40 ligand (CD40L) on T-cell. CD40L binds to CD40 present on dendritic cells or antigen presenting cells which lead to expression of B7-1 and B7-2 molecules that binds to CD28 receptor present over the T-lymphocyte. In addition activated dendritic cell also secretes cytokines such as IL-12 which further stimulates the proliferation and differentiation of T-lymphocytes.

The activation of T-lymphocyte by CD28 involves activation of MAP (Mitogen activated protein) kinase pathway (MAP). MAP kinase stimulates the expression of antiapoptotic Bcl-xL, and Bcl-2 which leads to prolonged cell survival. In addition secretion of IL-2 and other cytokines promotes proliferation and differentiation of T-lymphocytes. The

homeostasis of T-cell activation is modulated by inhibitors of CD28.The inhibitors of CD28 are cytotoxic T-lymphocyte antigen4 (CTLA-4) and Programmed death -1 (PD-1). CTLA-4 has a very high affinity for co-stimulatory molecule B7-1 and B7-2. Once activated CTLA-4 completely inhibits the access of CD28 to B7 co-stimulatory molecules.

17.3 Changes in the marker molecules

After activation T lymphocyte undergoes various phases of differentiation that leads to continual changes in the expression of the surface molecule markers. A plasma protein, **CD69** expresses after few hours of T lymphocyte activation, they help to retain the lymphocyte inside lymphoid organs for its differentiation into effector and memory immune cells. The activated T lymphocyte then expresses receptors for cytokines IL-2 called **CD25 (IL-2Rα),** which helps to promote the growth of activated T cells. Following 24 to 48 hours of T cell activation, **ligands for CD40 (CD40L)** expresses over the lymphocyte that helps to produce an effector immune response against peptide loaded over the macrophages and B cells. To balance the activated T cell response **CTLA-4** expresses over the cells to inhibit the exaggerated T cell activation. After these all events of surface expression, T cells express the molecules that help them to migrate to lymphoid organs such as **L-selectin** and **leukocyte function antigen-1 (LFA-1).**

Figure 17.1 Change in the surface marker molecule on the activated T cells:

Change in the expression of surface molecules over activated T cell
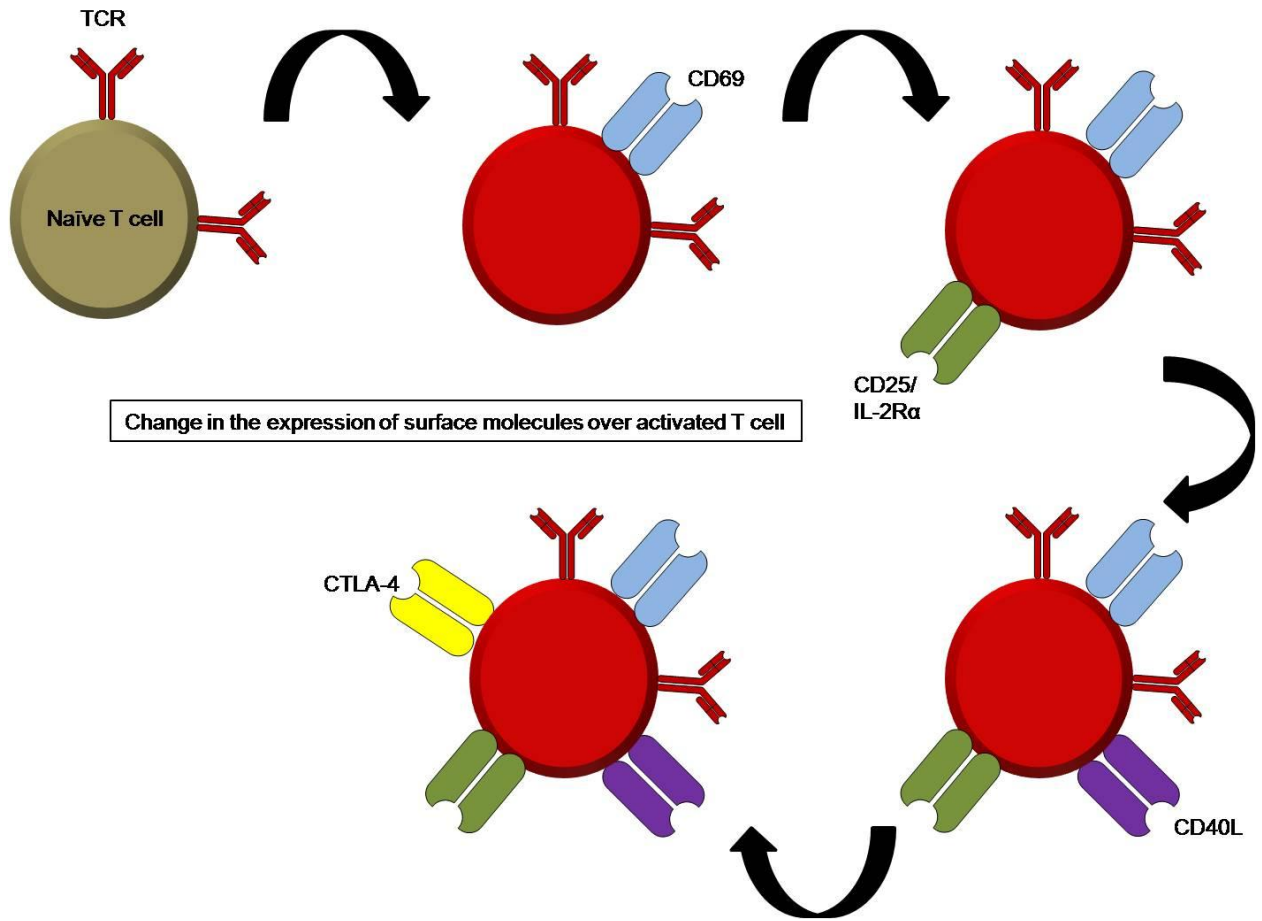
Lecture 18: Activation of Lymphocytes (Part II)

18.1 Differentiation of CD4+ cells into effector cells.

The CD4+ cells are differentiated into three distinct lineages of effectors cells based on the expression of their surface molecules and their ability to secrete different cytokines. The naïve CD4+ cells secrete mainly IL-2 while the effector cell secretes a large variety of cytokines. The CD4+ lymphocyte differentiates into three distinct subsets namely, Th1, Th2, and Th17 under the influence of different cytokine and transcriptional factors. The characteristics of the subsets are summarized in the table below.

Table18.1 Properties of Th1, Th2, and Th17 cells:

Cells	Secreted cytokines	Reactions	Specificity	Role in diseases
Th1	Interferon γ	Activation of macrophages and production of Ig	Intracellular microbes	Autoimmune diseases, tissue repair
Th2	IL-4 IL-5 IL-13	Mast cells and eosinophils activation, IgE production	Helminthic infection	Allergic diseases
Th17	IL-17 IL-22	Neutrophils and Monocyte activation	Extracellular microbes	Autoimmunity

18.2 Differentiation of CD8+ cells into effector cells.

The differentiation of CD8+ cells into effector cytotoxic T lymphocyte requires the help of helper T cells. Antigen loaded over the MHC class I molecules are recognized by CD8+ cells and subsequent expression of costimulatory molecules also helps in the activation of CD8+ differentiation. Complete differentiation of CD8+ cells into effector cells are enhanced by cytokines secreted by T helper cells. In addition T helper cells expressing the CD40L binds to the CD40 present over the antigen presenting cells and stimulates the differentiation of CD8+ cells. In terms of molecular aspect the differentiation of CD8+ requires activation of transcription factors **T-bet** and **eomesodermin**. The differentiated cytotoxic T lymphocytes are capable of producing interferon γ, which helps in phagocytosis and target cell killing.

18.3 Differentiation of memory cells

The effector memory cells are differentiated into long lasting memory cells which are the key components of science behind vaccination. The characteristic features of the memory cells are as follows

i)   Memory cells have the potential to survive in a dormant condition following the antigen stimulation and mount a greater immune response following the second exposure of the same antigen.

ii)   The specific number of memory T cells against a particular antigen is always greater than a naïve T cell against the same antigen at any time in the body.

iii)   The memory T cells express different anti-apoptotic genes (Bcl-2 and Bcl-X_L) that are responsible for their prolonged survival in the body.

iv)   The cell cycle of memory cells is under the control of different cytokines such as IL-7 and is slow in renewing itself that contributes to its longer life span.
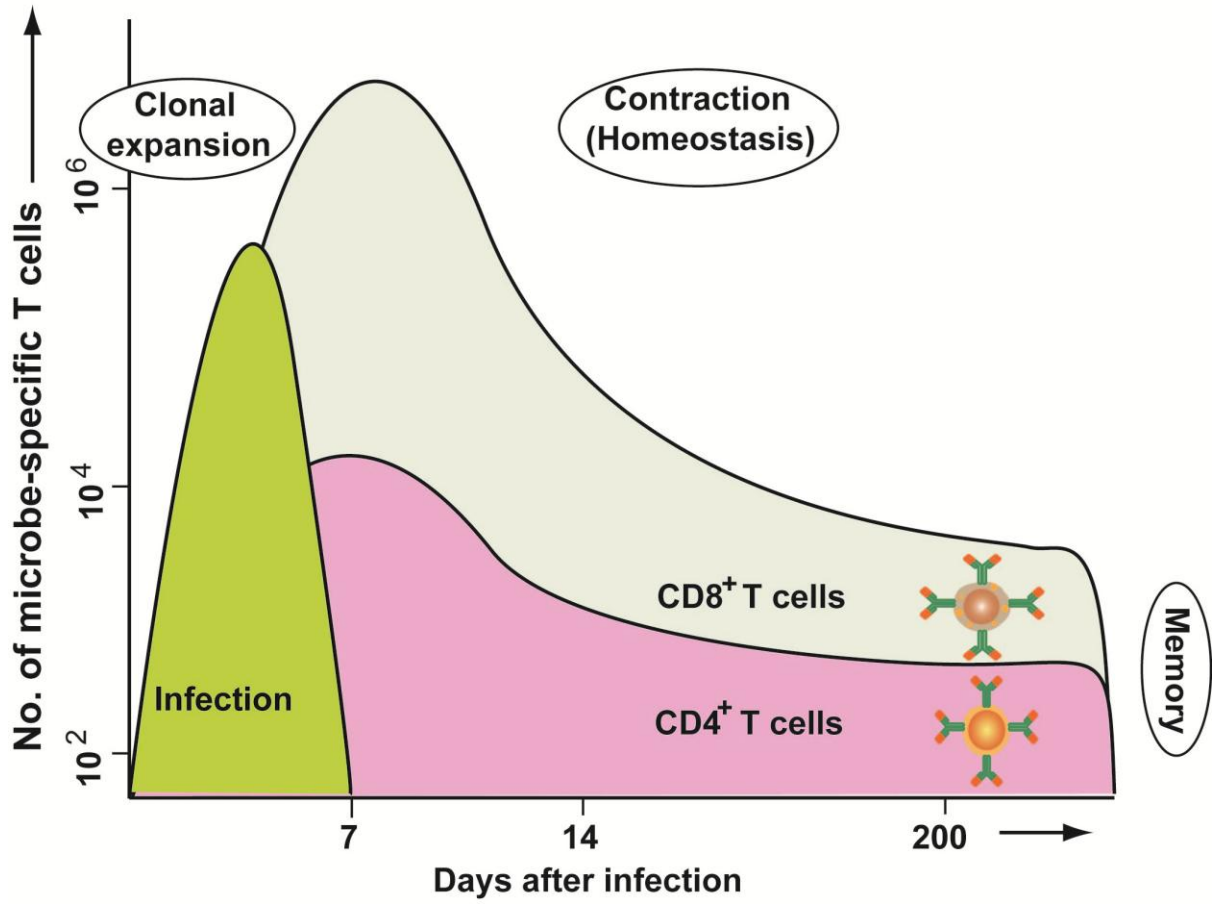
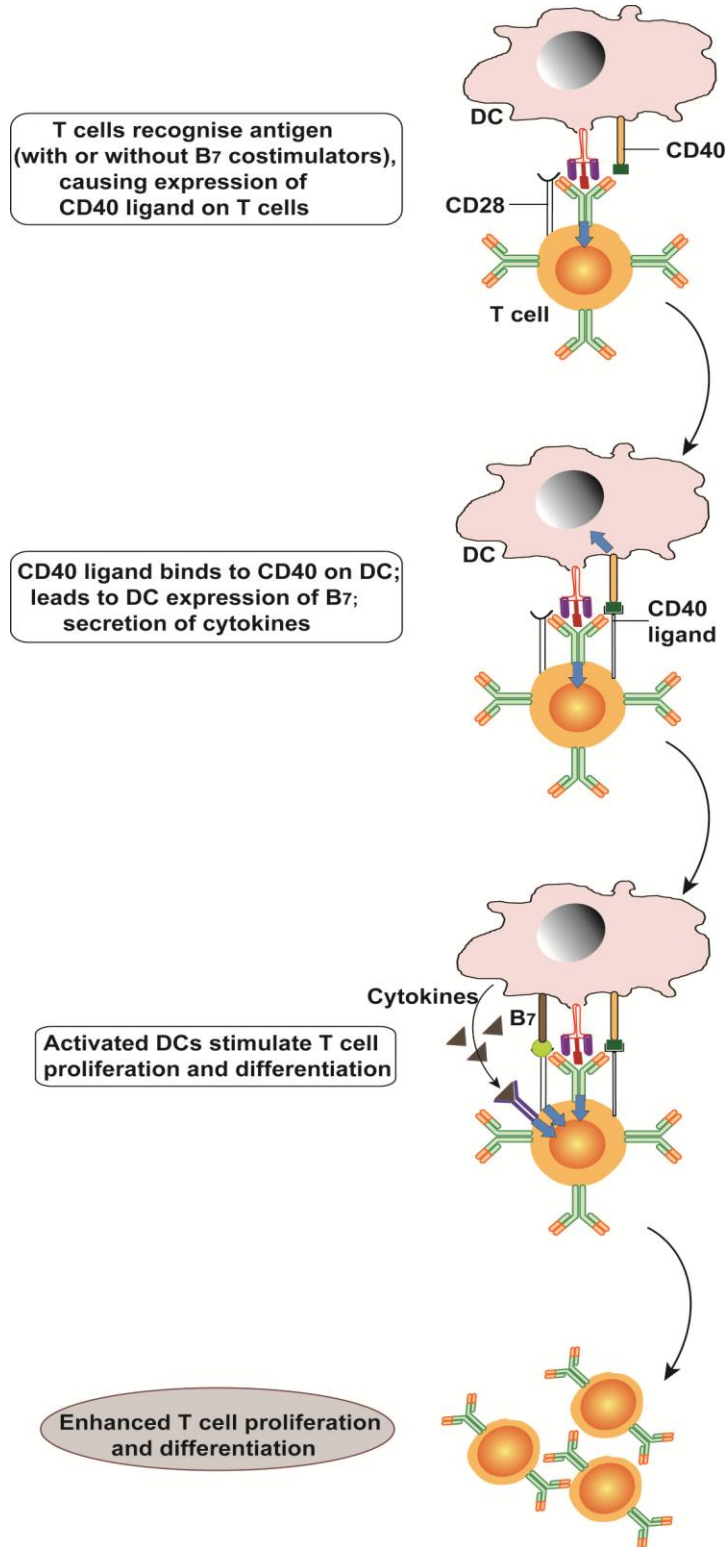**Figure 18.1 Clonal expansion of lymphocyte:**

Figure 18.2 CD40-CD40L interaction in T cell differentiation:

T cells recognise antigen (with or without B7 costimulators), causing expression of CD40 ligand on T cells

DC

CD40

CD28

T cell

CD40 ligand binds to CD40 on DC; leads to DC expression of B7; secretion of cytokines

DC

CD40 ligand

Cytokines

B7

Activated DCs stimulate T cell proliferation and differentiation

Enhanced T cell proliferation and differentiation

Lecture 19: B cell activation and antibody production (Part I)

19.1 General features of humoral immune responses

> ➢ Stimulation of B-cells leads to their spread and clonal expansion followed by differentiation and production of memory B cells and antibody –secreting plasma cells.

> ➢ It is the nature of antigen, involvement of T-cells, prior exposure to same antigen and the site at which activation occurs that decides the amount and type of antibodies produced.

> ➢ Activation of B-cells requires proper antigen antibody recognition and presentation of antigen to CD4+ helper cells.

> ➢ Multivalent antigens that contain several epitope sites over the surface do not require the activation of helper T cells and are called T-independent antigens. These antigens are processed and taken care by B cells.

> ➢ Usually some of the plasma cells are differentiated into long lasting memory cells.

> ➢ Isotype switching is the phenomenon mostly restricted to T cell dependent antigen.

Humoral immune response is governed by the antibodies that are secreted by the activated B cells. B cells can be activated either by direct recognition of antigen by the B cell receptor or by the antigens presented on the T cells. At the beginning B cells are available as a naïve cell expressing IgM and IgD antibodies over their surface. Following the antigen recognition by IgM and IgD they differentiate by clonal expansion into plasma cells and memory cells. Plasma cells are responsible for the secretion of antibodies against the antigen. Moreover isotype switching of Ig side chain in the plasma cells leads to the formation of IgG antibody. Memory cells are high affinity Ig expressing B cells that are used for the immune response against subsequent exposure of the same antigen. Primary immune response is activated by the antigen recognition by the naïve B cells and their differentiation into antibody secreting plasma cells. Secondary immune response is activated by the second exposure of same antigen for which body already made the memory B cells.

Table19.1 Difference between primary and secondary immune response:

Primary immune response	Secondary immune response
Response is generally smaller	Usually larger
Low affinity antibodies are made	High affinity antibodies are made
More IgM response	More IgG response, sometimes IgA and IgE depending on the types of antigen
Activated by all immunogens	Mostly by peptide antigens

19.2 Antigen capturing and recognition by B cells

Naïve B cells are always in circulation in order to capture their desired antigen between one lymphoid organ to the other. Migrations of B cells are modulated by chemokines such as CXCL13 that binds to CXCR5. Antigens are captured by B cells mostly in the lymphoid organ.

Many antigens form complexes after binding with the complement proteins that helps in their effective presentation to a B cell. Presentation of the antigen to B cell receptor is enhanced by complement receptor **CR2** or **CD19** which increases the signaling of B cell and in turn its differentiation.

Blood borne pathogens are captured by dendritic cells and subsequently presented to marginal zone B cells. Similarly polysaccharide antigens are captured by macrophages and then transferred to the marginal zone B cell.

Once cross linked with an antigen the Ig containing B cells gets activated and shows several changes. Activated B cells increase the expression of costimulatory molecules such as B7-1 and B7-2. In addition they increase the expression of cytokines receptors such as IL-4 and chemokines receptors CCR7.

19.3 Humoral response to protein antigens

The activated B lymphocytes migrate to each other and interact under the influence of receptors and cytokines. These interactions result in proliferation and differentiation of B cells. Subsequent interaction of peptide loaded T cells with B cell in extrafollicular site leads to isotype switching and short lived plasma cells are generated These short lived plasma cells migrate to the germinal center to form long lasting plasma cell and memory cells which produce the high affinity antibody.

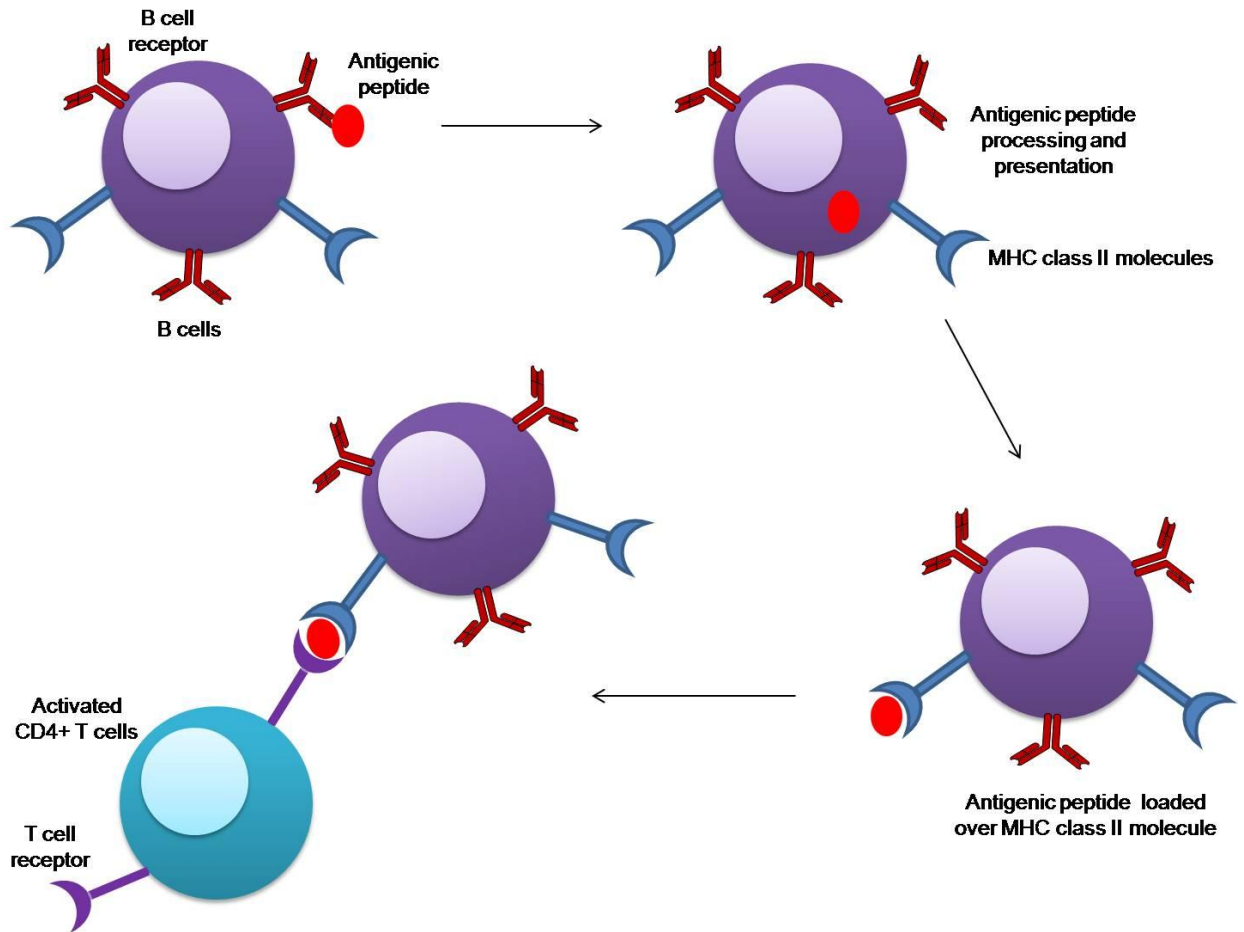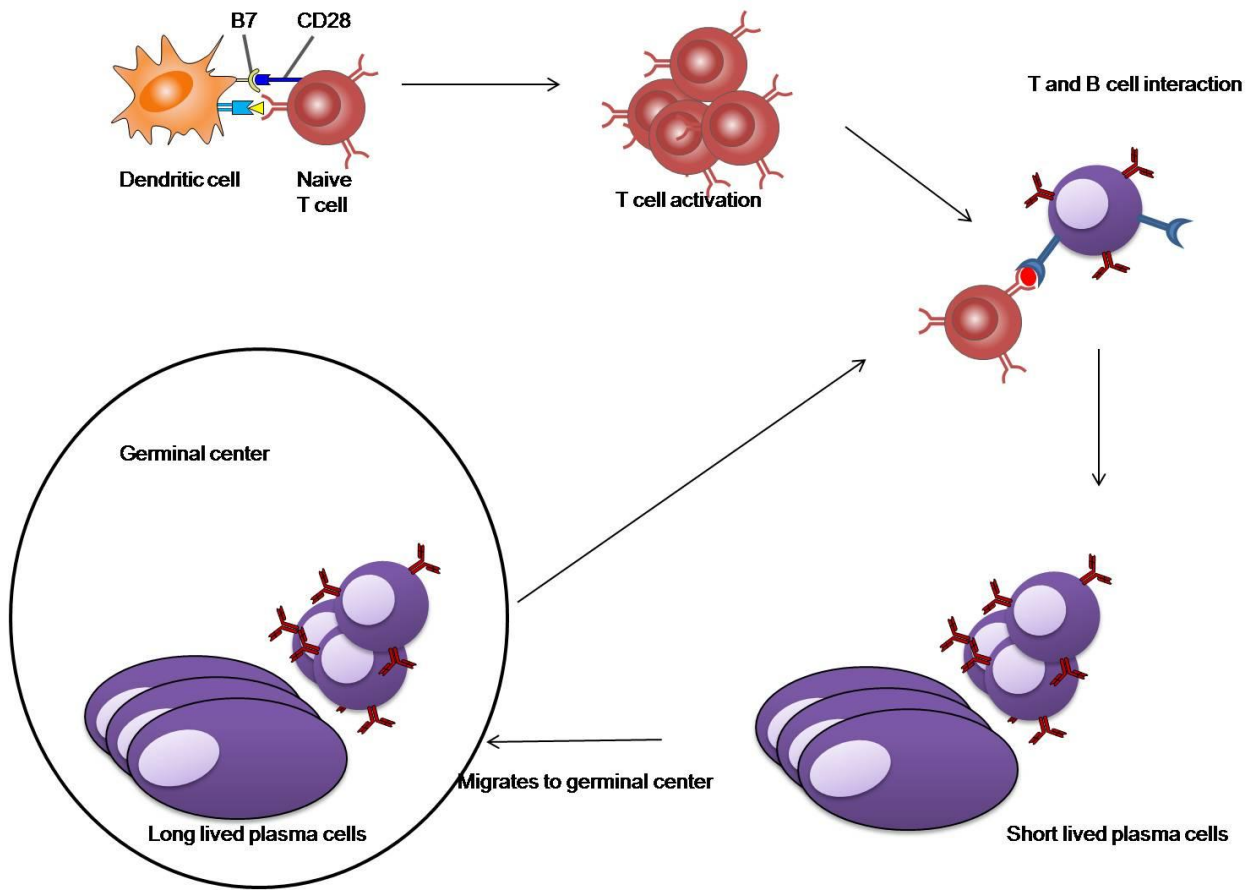**Figure 19.1 Antigen presentation on a B cell to a T cell:**

Figure 19.2 Sequences of events in T cell dependent activation of B cell:

Lecture 20: B cell activation and antibody production (Part II)

20.1 Class switching

Naïve B cells express IgM and IgD over their surfaces which undergo class switching in presence of **CD40 interaction and cytokines** to different heavy chains such as γ, α, and ε. The heavy chain class switching of γ, α, and ε in the Ig molecule cause the formation of IgG, IgA, and IgE antibodies. This remarkable feature of B lymphocytes to secrete different kinds of antibody makes the humoral immune response an ideal feature of the host immunity towards different invading pathogens. The humoral immune response against bacteria and viruses mainly consists of IgG antibody. The IgG antibody helps to neutralize the microorganism and facilitates its phagocytosis by opsonization. The bacterial surface contains polysaccharide, which is a potent inducer of IgM antibody. The viruses and bacteria induce Th1 helper immune response which is a potent inducer of interferon-γ that activates the class switching of Ig mainly to IgG subclasses. The host immune response against helminths is mostly taken care by IgE antibody. The IgE antibody helps in the elimination of helminthic infection with the help of mast cells and eosinophils. In addition, IgE antibody also mediates the allergic reaction. Helminths antigen induces the production of **IL-4** from Th2 cells that helps in the Ig class switching to IgE type. The IgA class switching is stimulated by transforming growth factor- β (TGF-β), which are produced in the mucosal surface by T helper cells.

The interaction of CD40 with CD40L activates the production of enzyme **activation-induced deaminase (AID)** which is an important mediator of Ig class switching and somatic recombination. The enzyme AID deaminates the cytosine residues to uracil in single stranded DNA. The switching region is high in GC contents which makes DNA-RNA hybrid into a loop like structure called **R loop**. R loop is an area where the concentration of U is higher because of the activity of enzyme AID. Another enzyme called **uracil N-glycosylase** removes the U from the R loop making it an abasic region and probable site for many restriction endonucleases. The restriction endonuclease mediated cleavage of DNA strand leads to class switching of immunoglobulins. The

molecular mechanism of class switching in the V (D) J exon is similar to recombination event dealt earlier (lecture 16).

20.2 Differentiation of B cells into plasma cells

Plasma cells are terminally differentiated B cells that are committed for antibody production. They are generated after the activation of B cell by antigen and CD40-CD40L interaction. The differentiation of B cells into plasma cells requires major secretory pathways of endoplasmic reticulum which converts the heavy chain of the immunoglobulin from membrane bound form to the secretory form. The change from the membrane bound to the secretory form requires the major variation in the carboxy terminal of the heavy chain. Another characteristic feature of B cell differentiation is activation of different transcription factors. Two critical steps in the differentiation of B cell to plasma cell, involves down-regulation of transcriptional factor Pax-5 (required for B cell development) and Bcl-6.

20.3 B cell response to T-cell independent antigens

Non-protein antigen such as carbohydrates and lipids stimulates the production of antibody in absence of T helper cells, hence called T independent antigens. Carbohydrate antigens are responded by marginal zone B cell which differentiates into plasma cells to secrete IgM antibody. B-1 cells responds to T independent antigen into the mucosal and peritoneal cavity. The T independent antigens are not processed by MHC molecules and cannot be recognized by helper T cells. The T independent antigens are mostly multivalent and are recognized by the B cell receptor. In addition T independent antigens also activate the complement pathway by binding to complement receptors CR2.

Table 20.1 Difference between T dependent and independent antigens:

T dependent antigen	T independent antigen
Protein in nature	Carbohydrates, lipids or nucleic acid in chemical composition
Isotype switching to IgG, IgA and IgE	No class switching, occasionally some IgG and IgA
Affinity maturation takes place	No affinity maturation
Memory cells are produced	Only in some cases (carbohydrates)

Lecture 21: Immune memory response (Part I)

21.1 Memory B cells

The humoral immune response is vanished from the body because the body simply clears the B cell and plasma cells by apoptosis. In order to continue the cycle some cells need to survive in the body and those survived cells are **memory B cells**. Usually B cells are activated in the lymph node after the encounter of antigen loaded helper T cells. Majority of the B cells migrate to the bone marrow after their differentiation into plasma cells while some remain in the lymph node and differentiate into memory cells in germinal center. They remain in the germinal center under the control of rescue signals. The early screening of the memory cells are done for their binding ability with an antigen. The events activate the CD154 expression in the neighboring T cells which in turn facilitates the expression of bcl-2 in the memory B cells. Bcl-2 is an antiapoptotic protein which allows the prolonged survival of the memory B cells by inhibiting its apoptosis.

Memory cells are the reservoir of antigen sensitized cells that can be called up during the time of surge following invasion of pathogenic microorganisms in the body. There are many different subpopulations of memory T cells in the germinal center of the lymph node. Majority of the memory B cell population consists of long lasting cells having IgG as a B cell receptor; they differ with plasma cells but contain many features of a lymphocyte. They do not require contact of an antigen for their survival, on exposure to antigen they differentiate into plasma cells to secrete antibody without any further mutation in their germ line. The response generated during the second exposure to antigens result in 8-10 fold higher immune response as compared to the primary exposure because of the memory B cells.

Another B cell subpopulation consists of IgM antibody as a B cell receptor. The survival of these memory cells depends largely on the antigen exposure to dendritic cells. One remarkable feature of memory B cells is to produce prolonged antibody over years, which is the basic idea for the generation of any vaccine.

The plasma cells also exist in two subpopulations, one short lived and the other long lived. Short lived plasma cell survives for 1-2 weeks and secretes large amount of antibody on antigen exposure and resides in spleen and lymph node. The long lasting plasma cell survives for years and is confined to bone marrow.

Lecture 22: Immune memory response (Part II)

22.2 Memory T cells

Unlike B cells which produce prolonged antibody, the effector T cells are short lived and their cytotoxicity is seen only in presence of antigens. Prolonged exposure of effector T cells is avoided because of its capability to damage tissues by secreted cytokines. The population of T cells not exposed to antigens (naïve T cell) is in constant circulation between the lymphoid tissue and blood. They differentiate into effector cells only after exposure of an antigen. Their population reaches to the peak following a week of infection when cytotoxic T lymphocyte population starts playing role to clear the infection. Once the infection is cleared, the majority of the T cell population is destroyed by apoptosis. The apoptosis of T cells is modulated by CD95L- CD95 interaction. The survivor of this event becomes long lasting memory T cell population.

Memory T cells can be distinguished from other lymphocytes in terms of their cytokines secretion and by the expression of surface molecules. Memory T cells, express high levels of CD44 over their surface and hence are CD44+. In addition, memory T cells express IL-2Rβ which is a receptor for IL-2 and IL-15. The expression of IL-2Rβ and its binding with IL-15 helps memory T cells for its prolonged survival and slow division. Another cytokine important for the survival of CD4+ T helper cell is IL-7. In absence of IL-15, the memory cells undergo apoptosis. Memory T cells secretes large amount of adhesion molecules that helps in their firm binding with the antigen presenting cells. Memory T cells also secretes large amount of cytokines such as IL-4 and interferon-γ that helps in modulating the T cell immune response. In humans the half life of memory cells are 8-20 years depending upon the health condition and nutritional status of an individual. Interestingly, human memory T cells express TLR-2 after exposure to a lipoprotein antigen (TLR-2 substrate) under the influence of IL-2 and IL-15. This phenomenon suggests that a bacterial pathogen associated molecular pattern may induce the production of memory T cell response. It is amazing to think about all this aspect in terms of evolution and how the memory response gets amplified in higher organism and their ancestor form in lower organism. It is quite obvious that the immune system in its primitive forms is less diverse as compared to higher organism and its complexity increases as we are going up in the hierarchy.

Figure 22.1 Development of memory T cells (Linear model):
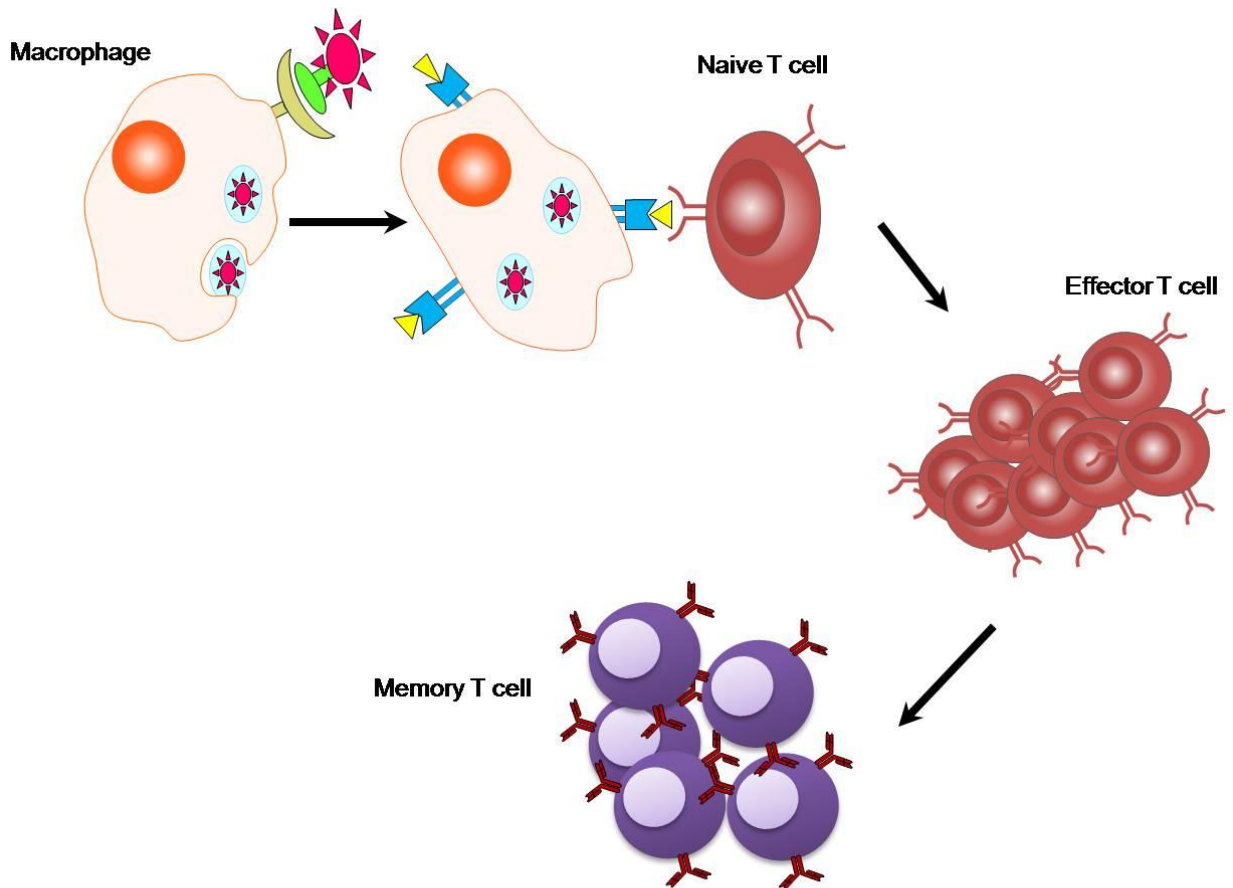
Linear model- Naïve T cells are differentiated into effector and memory cells in response of antigen stimulation and costimulatory molecules. Only effective cells survive and converted into memory cells

Figure 22.2 Development of memory T cells (Branched differentiation model):
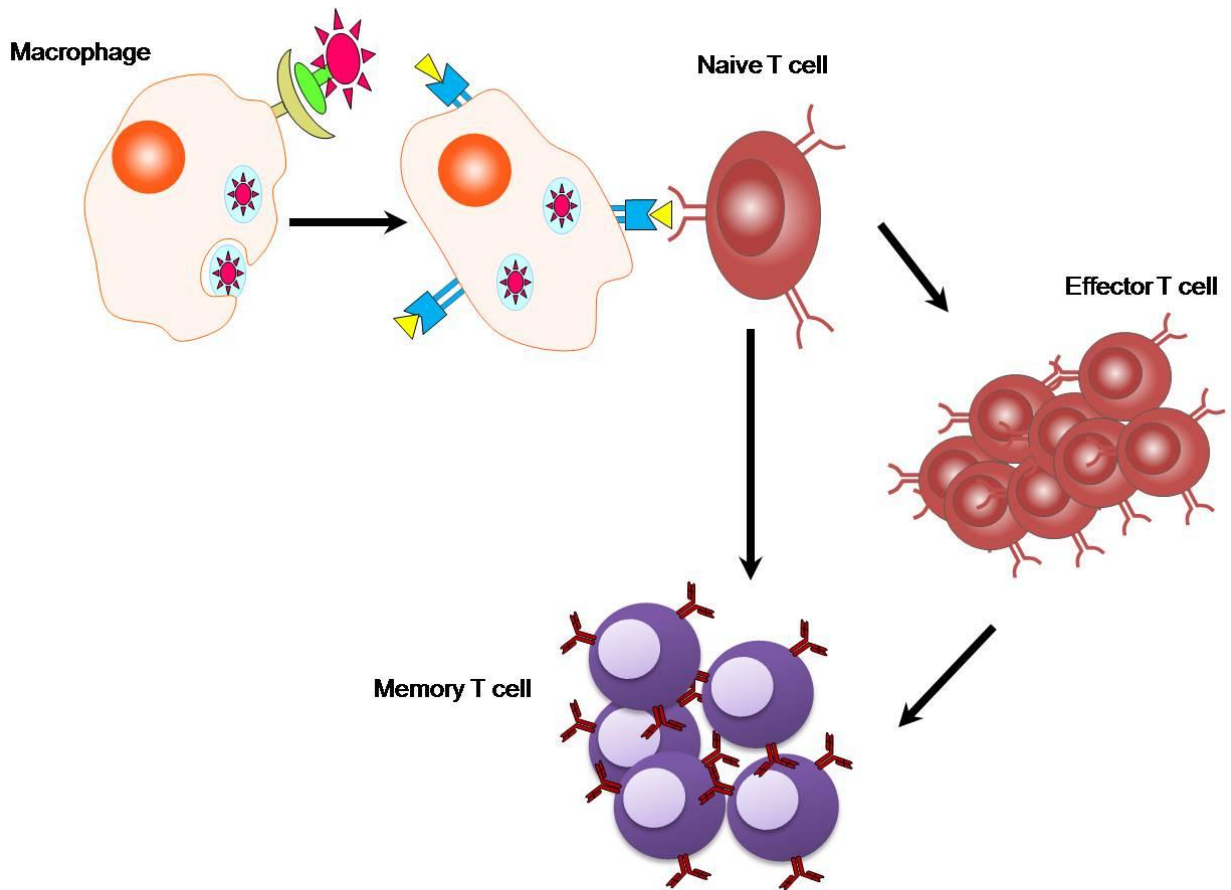
<u>**Branched differentiation model-**</u> Naïve T cells are differentiated into effector and memory cells in response of antigen stimulation and costimulatory molecules differently.