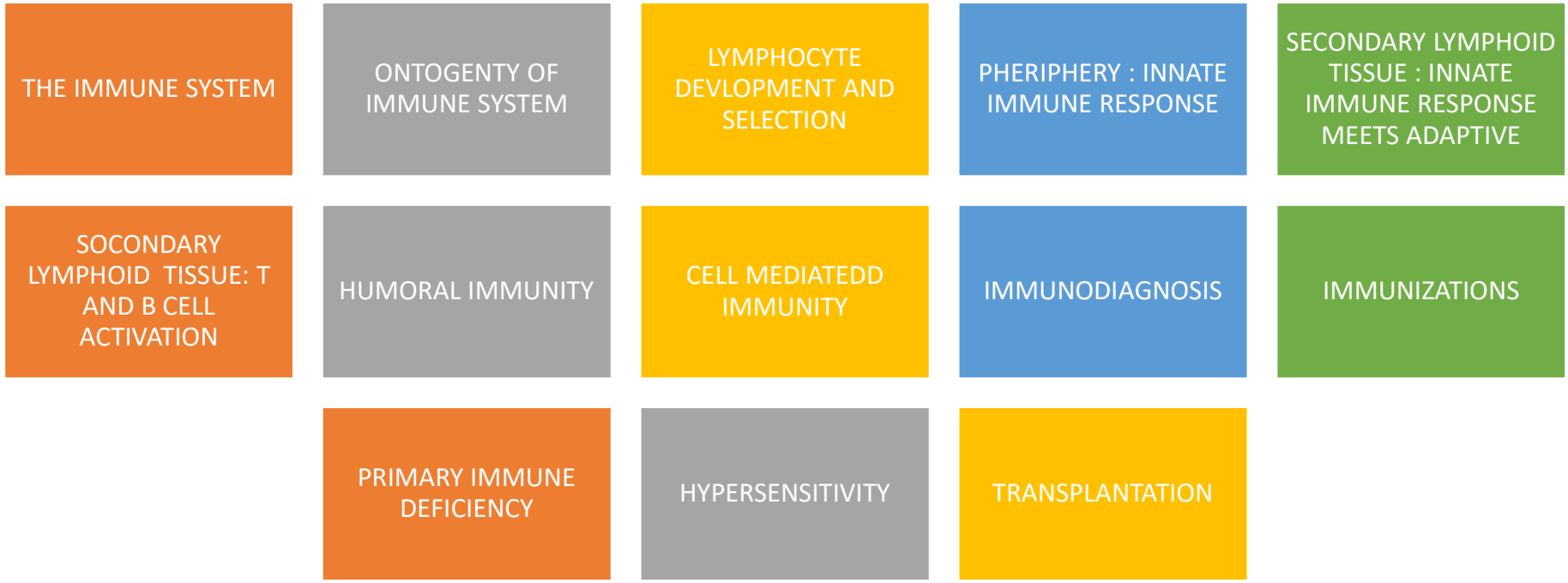
IMMUNOLOGY


THE IMMUNE SYSTEM
ONTOGENTY OF IMMUNE SYSTEM
LYMPHOCYTE DEVLOPMENT AND SELECTION
PHERIPHERY : INNATE IMMUNE RESPONSE
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Immunology

IMMUNOLOGY

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

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SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

ACTIVATION OF T LYMPHOCYTES

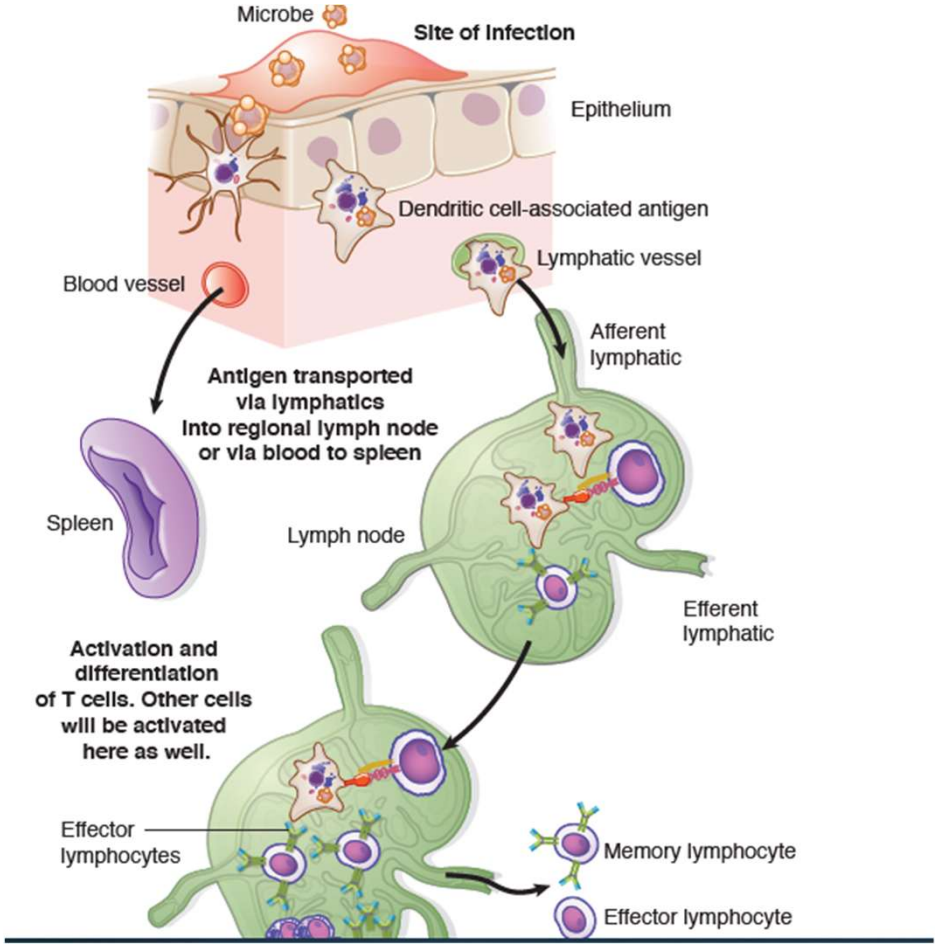
Once antigen is processed and presented to a T cell, the adaptive immune response is initiated. These interactions occur within the secondary lymphoid tissue(LYMPHNODE).

The purpose of these interactions is to generate effector cells, which will ultimately result in the elimination of the infection.

In order to generate specific effector cells, the activation of T cells via the TCR must go through several checkpoints to ensure antigen specific ty and eventual T-cell activation.

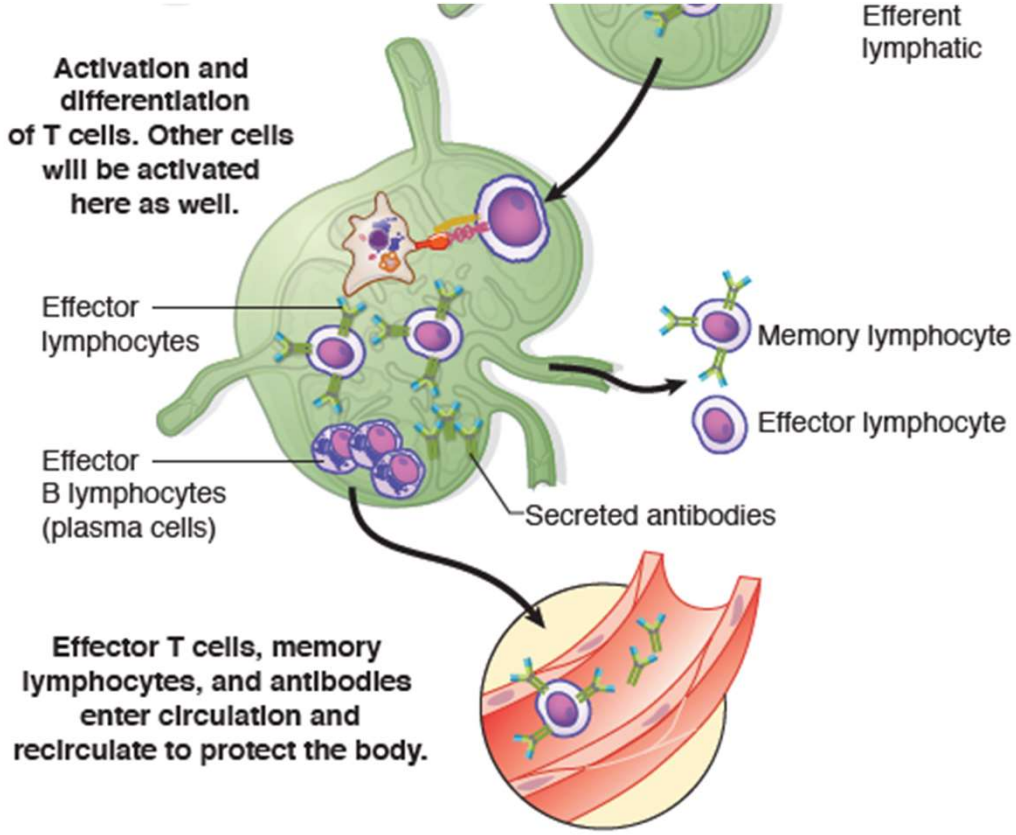
SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Activation of T Cell



SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

ACTRIVATION OF T CELL



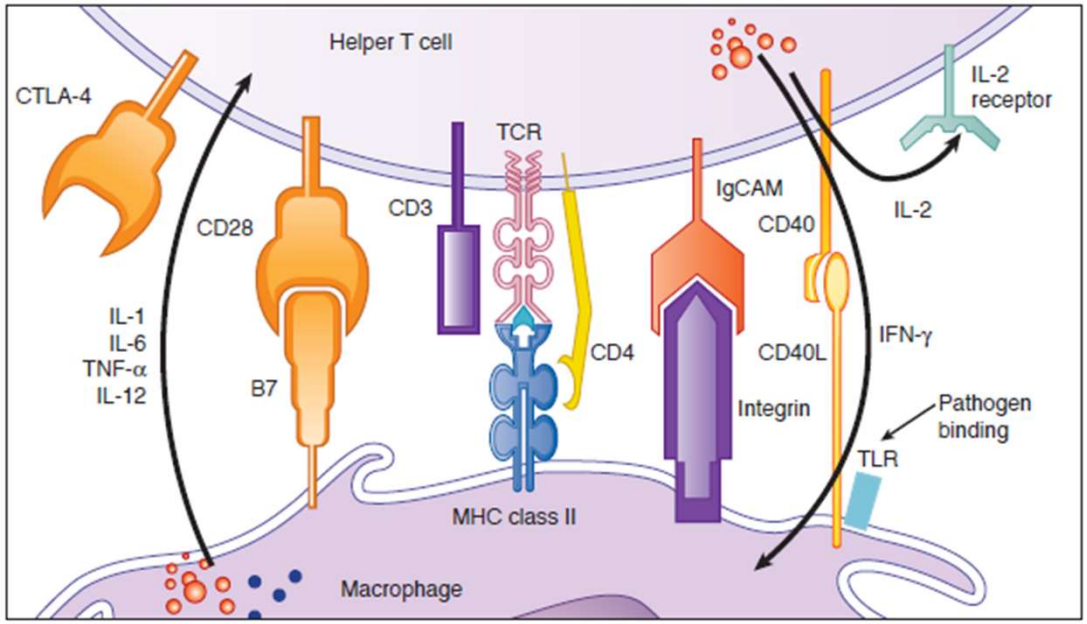
SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

The binding of the TCR of the mature, naive T cell to the MHC peptide complex of the APC provides the first signal to the T cell to begin its activation. This provides the antigenic specific ty of the response. The interaction is stabilized by the coreceptors CD4 and CD8 which bind to MHC class II and MHC class I molecules, respectively.

- Intimately associated with the T cell receptor is the CD3 signal transduction complex. Interaction of cell adhesion molecules on the surface of the APCs and T cells allows for the formation of the immune synapse.
- The costimulatory molecules B7-1 (CD80) and B7-2 (CD86) on APCs bind to CD28 on the mature, naïve T cells, providing the second signal necessary for successful activation. Under normal conditions, B7 is expressed at low levels on APCs. In the presence of infection or inflammation, the expression will increase, enhancing activation of the mature, naïve T cells. Later in the immune response, B7 will preferentially bind to CTLA-4 or PD-1, effectively turning off he T-cell response.
- Cytokines secreted by APCs and the activating T cells themselves induce the proliferation(**clonal expansion**) and differentiation of the T cells into **effector cells** and **memory cells**.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

T CELL ACTIVATION AND MACROPHAGES ADHESION



SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Several surface molecules are involved in the activation of mature, naive T lymphocytes:

First (primary) signal: recognition of the MHC:

Peptide complex by the T cell receptor and coreceptors (CD4 and CD8)

Second (costimulatory) signal: recognition of B7 by CD28

The activated CD4+ (helper) T lymphocytes will begin to produce and secrete cytokines and increase surface expression of cytokine receptors. The first cytokine produced is IL-2, an autocrine signal, which induces T-cell proliferation by binding to a high affinity IL-2 receptor found on the same cells. Unlike helper T lymphocytes, activated CD8+ T lymphocytes secrete low levels of IL-2 and are dependent on the helper T lymphocytes for their proliferation and differentiation.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Clinical Correlate

CTLA-4 is an important immunoregulatory molecule in the immune system. Expressed on both activated Th and TREGs, CTLA-4 is responsible for downregulating the immune response by competitive binding to B7-1 and B7-2 on APCs.

- The manipulation of CTLA-4 has important clinical implications first elucidated by the creation of CTLA-4 knockout mice that resulted In a fatal lymphoproliferative disorder. These deletions may also result in several autoimmune disorders.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Type of Regulation of CTLA-4	Drug Name	Clinical Use
Agonists	Abatacept	Rheumatoid arthritis
	Belatacept	Renal transplants
Antagonists	Ipilimumab	Melanoma and in clinical trials for several other types of cancer

CINICAL CORRELATE

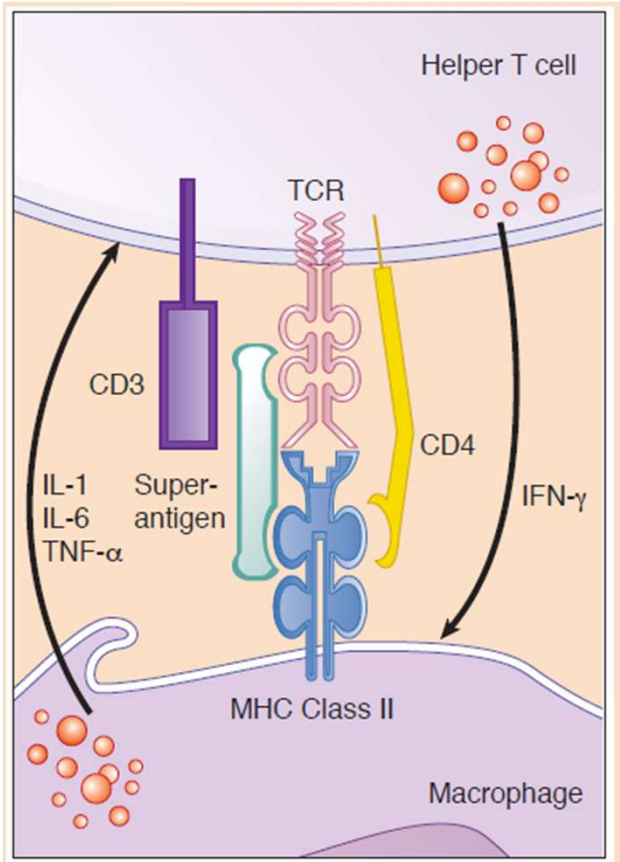
SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Clinical Correlate

Superantigens are viral and bacterial proteins that cross-link the variable b domain of a T-cell receptor to an a chain of a class II MHC molecule outside the normal peptide-binding groove. This cross-linkage provides an activating signal that induces T-cell activation and proliferation, in the absence of antigen-specific recognition of peptides in the MHC class II groove. Because superantigens bind outside of the antigen-binding cleft, they activate any clones of T cells expressing a particular variable b sequence and thus cause polyclonal activation of T cells, resulting in the over-production of IFN-g. This, in turn, activates macrophages, resulting in overexpression of proinflammatory cytokines (IL-1, IL-6 and TNF-a). Excess amounts of these cytokines induce systemic toxicity. Molecules produced during infectious processes and known to act as superantigens include Staphylococcal Enterotoxins, Toxic-Shock Syndrome toxin-1 (TSST-1), and Streptococcal Pyrogenic Exotoxins.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Superantigens



Superantigen Activation

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Development of the Th1, Th2, and Th17 Subsets

Helper T lymphocytes serve as the orchestrators of virtually all the possible **effector mechanisms** that will arise to destroy the pathogen. The effector mechanisms that are controlled by Th cells include antibody synthesis, macrophage activation and CTL killing. The “decision” as to which of these mechanisms should be engaged is based on the characteristics of the invading pathogen and is controlled by the differentiation of specialized classes of helper T cells. All CD4+ T cells require recognition of their specific antigen complexed to MHC class II by their TCR (first signal) and costimulation through the binding of B7 on the professional APC by CD28 (costimulatory signal).

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

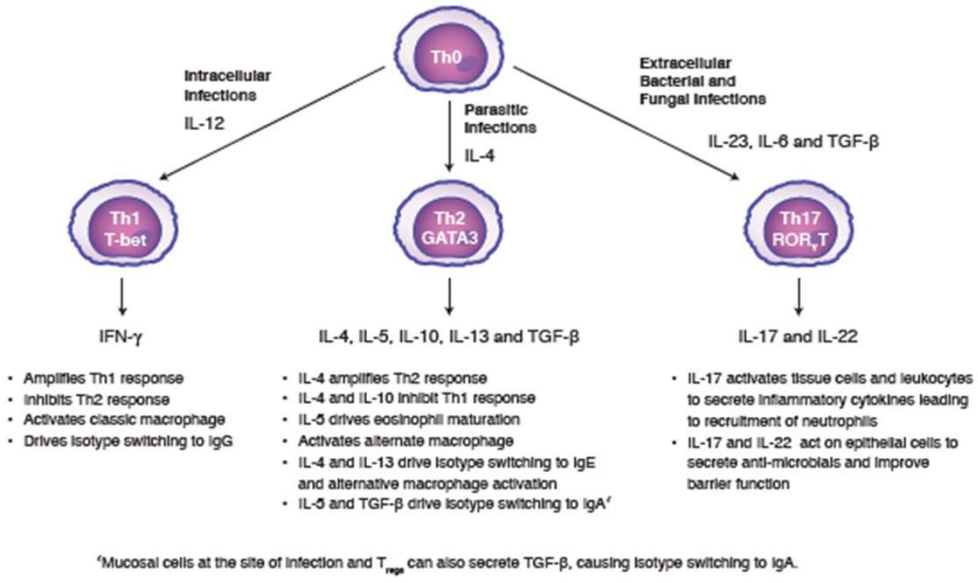
There are 3 major classes of helper T (Th) cell that arise from the same precursor, the naive Th lymphocyte (or Th0 cell):

- Th1
- Th2
- Th17

The pattern of differentiation is determined by the antigen or type of pathogen causing the infection, the cytokines produced in response to the antigen, and the transcription factors stimulated by the cytokines.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Differentiation of Th Cells



SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Th0 to Th1

Differentiation of a Th0 cell into a Th1 cell is stimulated by intracellular pathogens (e.g., viruses and intracellular bacteria). These pathogens induce a strong innate immune response with the resultant production of **IL-12** by macrophages and **IFN-γ** by NK cells increasing the expression of the transcription factor T-bet. In turn, Th1 cells secrete high levels of the inflammatory cytokine IFN-γ which does the following:

- Amplifies the Th1 response
- Inhibits the Th2 response
- Activates classical macrophage
- Enhances isotype switching to IgG

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Th0 to Th2

Differentiation of a Th0 cell into a Th2 cell seems to be encouraged in response to large extracelular parasites such as helminths or allergens. Due to the inability to phagocytose these pathogens, there is not significant macrophage or NK-cell stimulation. In this way, naive Th0 cells seem to produce IL-4 constitutively, and in the absence of IL-12 stimulation, these cells will upregulate their production of IL-4 to encourage differentiation into Th2 cells by induction of the transcription factor GATA-3. Additional IL-4 is produced by the activation of mast cells and eosinophils by the helminths or allergens further driving differentiation into Th2 cells. Several cytokines are produced by Th2 cells, including IL-4, IL-5, IL-10, IL-13 and TGF-β.

- IL-4 causes B lymphocytes to isotype switch predominantly to IgE, which will bind to mast cells, eosinophils and basophils.
- In collaboration with IL-13, IL-4 enhances alternative macrophage activation for tissue repair and increased intestinal mucus secretion and peristalsis.
- The combination of IL-4, IL-10, and IL-13 together promotes a Th2 response while inhibiting the Th1 response.
- IL-5 drives maturation and activation of eosinophils.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Th0 cell into a Th17

Differentiation of a Th0 cell into a Th17 cell occurs in the presence of extracellular bacterial and fungal infections. Local cells react to the infection by secreting IL-1, IL-6, IL-23, and TGF-b, inducing the expression of the transcription factor RORg-T in the Th17 cells. The activated Th17 cells will in turn secrete the cytokines IL-17 and IL-22.

- IL-17 induces local cells to increase chemokine production recruiting neutrophils.
- IL-22 stabilizes interactions between cells in the endothelium decreasing permeability.
- IL-17 and IL-22 induce secretion of anti-microbials by the endothelium.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Th0 to the T regulatory cell (TReg cells)

Another population of T cells that arises from the Th0 is the T regulatory cell (TReg cells). TReg cells regulate (inhibit) Th1 cell function.

- Identified by their constitutive expression of CD25 on the surface and by the expression of the transcription factor FoxP3
- Secrete inflammation inhibiting cytokines such as IL-10 and TGF-b
- Have been shown to be critical for the prevention of autoimmunity

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Development of Cytotoxic T Lymphocytes

Like CD4+ T cells, CD8+ T cells require both a primary and a costimulatory signal to become activated. The main difference between them is that CD8+ T cells recognize their specific antigen presented by MHC class I molecules and rely upon the cytokines produced by T helper cells to proliferate and ultimately differentiate into cytotoxic T lymphocytes (CTLs).

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Clinical Correlate

Tuberculoid vs. Lepromatous Leprosy

The progression of disease with *Mycobacterium leprae* in humans is a well-documented example of the crucial balance between Th1 and Th2 subsets. Leprosy is not a single clinical entity, but rather a spectrum of diseases, with tuberculoid and lepromatous forms at the far poles.

•**Tuberculoid leprosy**, the patient has a strong Th1 response, which eradicates the intracellular pathogens by granuloma formation. There is some damage to skin and peripheral nerves, but the disease progresses slowly, if at all, and the patient survives.

• L**epromatous leprosy**, the Th2 response is turned on, and because of reciprocal inhibition, the cell-mediated response is depressed. Patients develop antibodies to the pathogen that are not protective, and the mycobacteria multiply inside macrophages, sometimes reaching levels of 1010 per gram of tissue. Hypergammaglobulinemia may occur, and these cases frequently progress to disseminated and disfiguring infections.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

ACTIVATION OF B LYMPHOCYTES

As mature naive B lymphocytes leave the bone marrow following successful rearrangement of their membrane immunoglobulin receptor genes, they recirculate throughout the body, attracted to **follicular areas** of the lymph nodes and spleen. If antigen entering these secondary lymphoid organs binds to and cross-links the idiotypes of the immunoglobulin, this provides the first signal for the activationof the B lymphocyte.

Th antigens that B lymphocytes encounter are divided into 2 categories**:**

- **Thymus-independent** (TI) antigens
- **Thymus-dependent** (TD) antigens.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

TI-Antigen Activated B Lymphocytes

Certain mature, naïve B lymphocytes are capable of being activated by macromolecules such as lipids, polysaccharides, and lipopolysaccharides without having to interact with helper T cells. These antigens are called **thymus-independent (TI)** antigens, and they directly stimulate B cells to proliferate and differentiate into plasma cells.

- The response to TI antigens is generally **weaker** than the response to TD antigens, resulting primarily in the **secretion of IgM antibodies** and the **absence of immunologic memory**.
- TI antigens may also act as B-cell **mitogens**, directly causing mitosis regardless of the cell's antigenic specificity.
- B lymphocytes activated by TI antigens are found in the spleen and mucosa.
- The marginal zone B cells are found in the periphery of the splenic white pulp and the B-1 cells in association with the mucosa and peritoneum.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

TD-Antigen Activated B Lymphocytes

Most antigens introduced in the body fall into the category of **thymus-dependent (TD) antigens**. Response to such molecules requires the direct contact of B cells with helper T cells and are influenced by **cytokines** secreted by these cells. After the cross-linking of receptors on the B-cell surface with antigen, the material is endocytosed and processed via the exogenous pathway to generate an MHC class II:peptide complex, which is then inserted into the membrane of the professional APCs. simultaneously, expression of B7 is upregulated on the B lymphocytes, making the cells effective presenters of antigen to CD4+ T cells in the area. Once a CD4+ T cell recognizes its specific peptide displayed on MHC class II molecules, the 2 cells form a **conjugate**.

- The CD4+ T cell is activated and differentiates into a helper T cell.
- The helper T cells rearrange their Golgi apparatus toward the junction with the B cell leading to the directional release of cytokines.
- Expression of CD40L on the surface of the helper T cell is upregulated and interacts with CD40 on the B cell to provide the second signal for B-cell activation.
- The B cells respond by proliferating and differentiating into plasma cells and memory B cells.

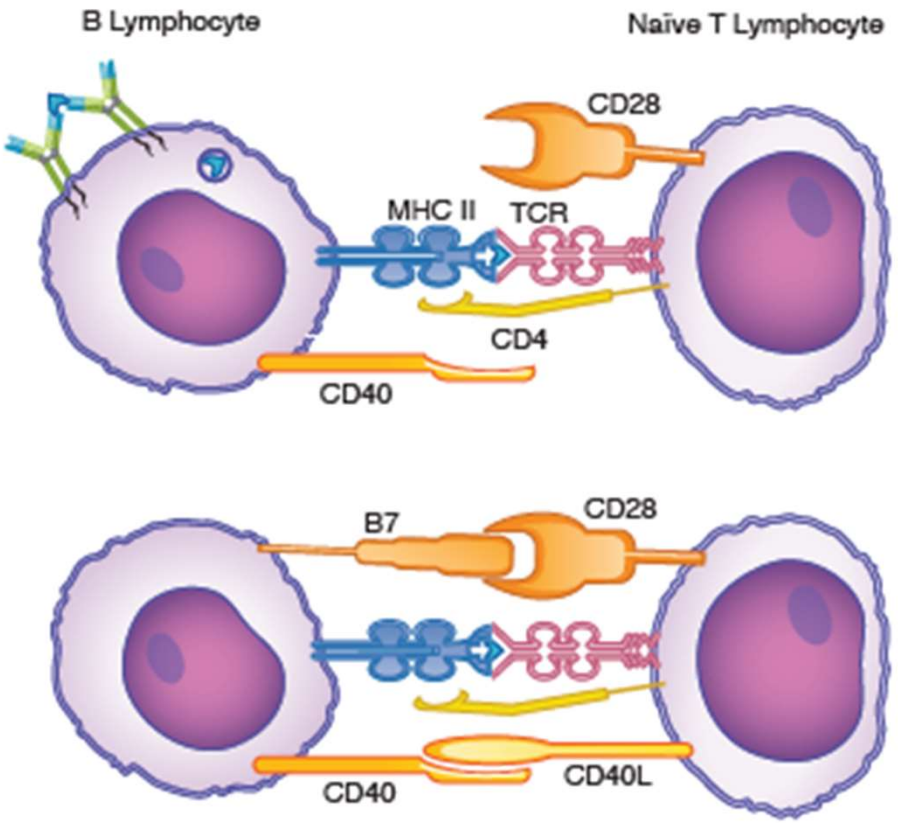
SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

B lymphocytes activated by TD antigens are released in 2 subsequent waves.

- The primary wave of activated B lymphocytes is comprised of strictly IgM-secreting plasma cells which leave the secondary lymphoid tissue shortly after being activated.
- The second wave of activated B lymphocytes remains within the follicles of the secondary lymphoid tissue undergoing clonal expansion producing the germinal centre. During the expansion, the clones will undergo affinity maturation and isotype switching.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Activation of B cells



SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Activation of B Cells

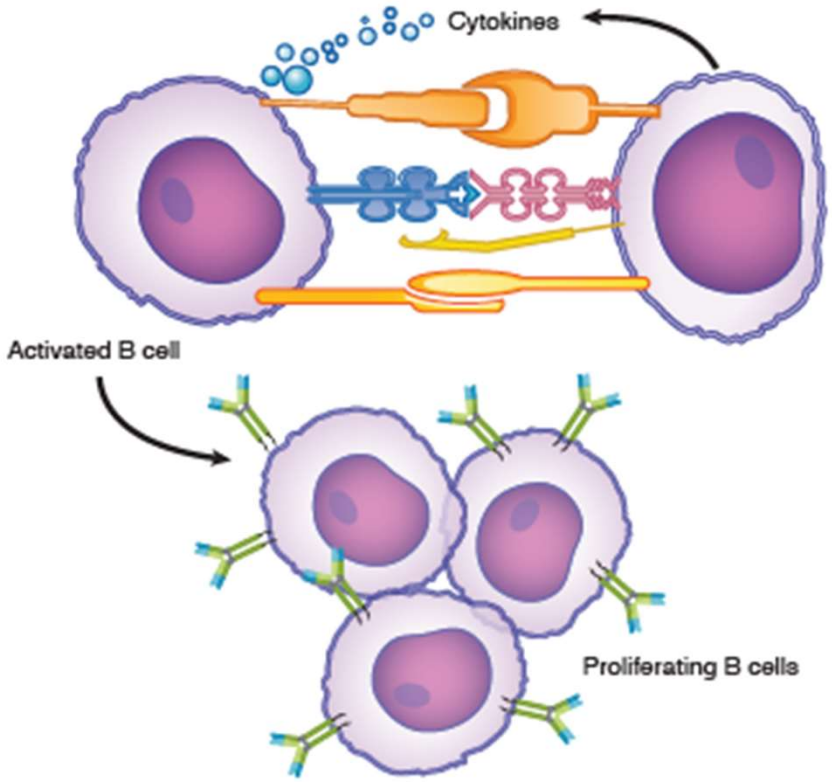


Figure I-6-5. Steps in T-Cell-Dependent B-Cell Activation

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Affinity Maturation

During the activation of B lymphocytes by helper T cells, intense proliferation of the B cells results in the formation of **germinal centers** in the follicles of the secondary lymphoid tissues. These are clones of proliferating, antigen-specific cells. During the intense proliferative response of the B cell, random mutations in the coding of the variable domain region may occur. Th s is called **somatic hypermutation** and creates single point mutations in the antibody idiotype. If these slightly altered idiotypes have increased affi ty for the antigen, then the cell expressing them will be at a selective advantage in competing to bind antigen. Because binding antigen serves as the fi st signal for proliferation, over time clones of cells with higher receptor affinty will begin to predominate in the germinal center. Th s **clonal selection** results in the predominance of clones capable of producing antibodies with increasing affinty for the antigen, a process known as **affinity maturation**. Th s means that although isotype switching will necessarily **decrease the avidity** of the preponderance of antibody molecules as the immune response evolves, this will be substituted by an **increase in antibody affinty** over time.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Isotype Switching

Although all of the antibody molecules secreted by a clone of B lymphocytes will have an identical idiotype (*see* chapter 3), the B cell is induced to make new classes (**isotypes**) of immunoglobulin in response to cytokine-directed instruction from the helper T cells. As the B lymphocyte receives cytokine signals from the helper T cells in the secondary lymphoid organs, it is induced to undergo **isotype switching**, changing the heavy-chain constant domains to classes of antibodies with new and different effector functions. It does this by rearranging the DNA encoding the constant regions of the heavy chain by activating switch regions that cause the intervening DNA to be looped out, excised, and degraded. The idiotype is then joined to a new constant region domain, resulting in an antibody molecule with identical antigenic specific ty but a new effector function. Th s isotype switch is **one-way**; the excised DNA is degraded so a cell that has begun to produce anisotype downstream from IgM coding can never produce IgM again. Th s is why IgM is the principal immunoglobulin of the **primary immune response** when antigen is fi st encountered, and it is replaced in later responses by antibodies of different isotypes. Although IgM antibodies are occasionally produced at low levels during secondary and later immunologic responses, they are always produced by cells encountering that antigen for the fi st time; namely, mature, naive B cells newly emerging from the bone marrow.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Isotype Switching

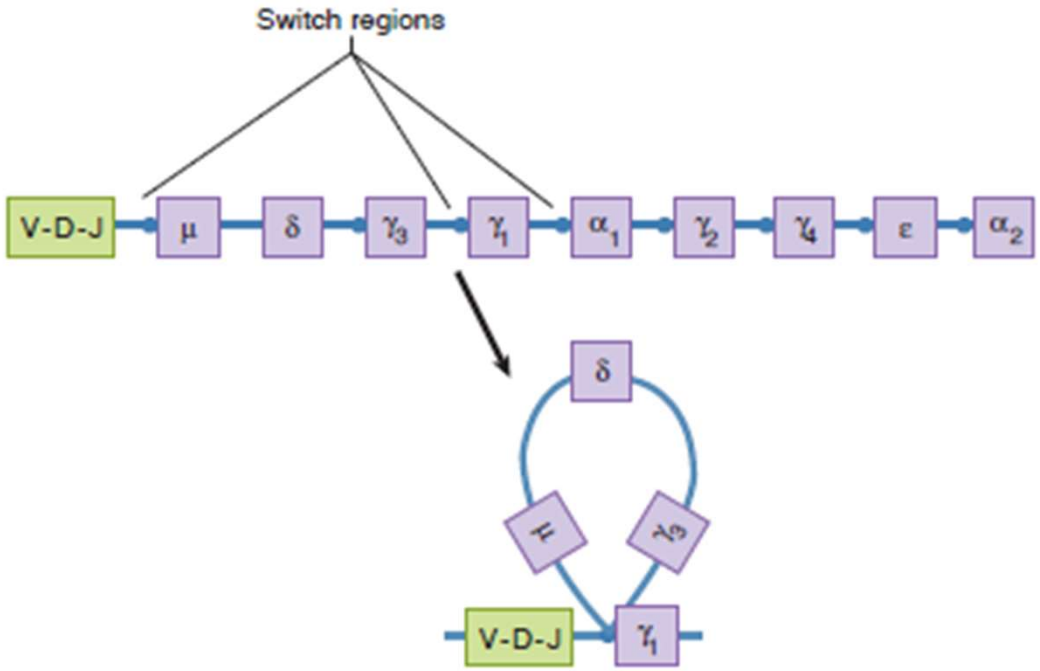


Figure I-6-6. Immunoglobulin Heavy Chain Switching

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Chapter Summary

• Professional APCs migrate to the secondary lymphoid organs, where they present this processed antigen to recirculating naive lymphocytes.

• The binding of the TCR to the peptide/MHC class II complex provides the first signal in T-cell activation.

• Costimulatory interactions between CD28 and B7 provide the second T-cell activation signal.

• Superantigens are viral or bacterial proteins that cross-link the variableâ domain of a T-cell receptor to an á chain of a class II MHC molecule and thereby cause polyclonal activation of T cells, overproduction ofcytokines, and systemic toxicity.

• Activated Th cells act as the orchestrators of the effector mechanisms of the immune response (antibody synthesis, macrophage activation, cytotoxic T cell killing, and NK cell killing).

• Cytokines produced in response to various pathogens drive the differentiation of the T-cell subsets

• Naive Th cells (Th0) differentiate into Th1 cells when IL-12 from macrophages or IFN-γ from NK cells is present in response to intracellular infections. Th1 cells secrete the signature cytokine IFN-γ.

• Naive Th0 cells differentiate into Th2 cells in response to parasite infection or allergens. Th2 cells secrete IL-4, IL-5, IL-6, IL-10, IL-13 and TGF-β.

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Chapter Summary

• Naive Th0 cells differentiate into Th17 cells in response to extracellular infection. Th17 cells secrete IL-17, IL-1, IL-6, and TGF-β driving a strong neutrophil and monocyte response.

• The cytokines produced by Th subsets are cross-regulatory: IFN-γ produced by Th1 cells inhibits Th2 cells, and IL-4 and IL-10 produced by Th2 cells inhibit Th1 cells.

• TReg cells are CD25+ and express the FoxP3 transcription factor. They develop from Th0 cells and are believed to be important in the prevention of autoimmunity.

• Humoral immunity is mediated by antibodies synthesized by B cells and secreted by plasma cells.

• Humoral immunity is the major defense mechanism against extracellular pathogens and toxins.

• Thymus-independent antigens, such as bacterial lipopolysaccharide, cross-link the receptors of B lymphocytes and cause them to proliferate and secrete IgM antibodies. These antigens *do not* create “immunologic memory.”

• Most naturally occurring antigens are thymus-dependent: They require collaboration of helper T cells and B cells.

• Contact between specific B and Th cells involves MHC class II/peptide presentation, costimulatory molecules (B7/CD28), CD40/CD40L binding, and cytokine production

SECONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION

Chapter Summary

- Contact between specific B and Th cells involves MHC class II/peptide presentation, costimulatory molecules (B7/CD28), CD40/CD40L binding, and cytokine production
- Helper T cells direct isotype switching by B cells, which changes the effector function of the antibody produced.
- Helper T-cell activation of B lymphocytes causes intense proliferation in the germinal centres, and somatic hypermutation may cause slight variation in the shape of the idiotype. Clonal selection of the idiotype with the highest affinity for antigen results in “affinity maturation”: a general improvement in the “goodness-of-fit” for the antigen as the immune response progresses.