INTRODUCTION TO T AND B CELLS:

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B cells, also known as B lymphocytes, are a type of white blood cell of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines. In mammals, B cells mature in the bone marrow, which is at the core of most bones. In birds, B cells mature in the bursa of Fabricius, a lymphoid organ. (The "B" from B cells comes from the name of this organ, where it was first discovered by Chang and Glick, and not from bone marrow as commonly believed.) B cells, unlike the other two classes of lymphocytes, T cells and natural killer cells, express B cell receptors (BCRs) on their cell membrane. BCRs allow the B cell to bind to a specific antigen, against which it will initiate an antibody response. Development of B cells develop from hematopoietic stem cells (HSCs) that originate from bone marrow. HSCs first differentiate into multipotent progenitor (MPP) cells, then common lymphoid progenitor (CLP) cells. From here, their development into B cells occurs in several stages (shown in image to the right), each marked by various gene expression patterns and immunoglobulin H chain and L chain gene loci arrangements, the latter due to B cells undergoing V(D) recombination as they develop. Early B cell development: from stem cell to immature B cell B cells undergo two types of selection while developing in the bone marrow to ensure proper development. Positive selection occurs through antigen-independent signaling involving both the pre-BCR and the BCR.[5][6] If these receptors do not bind to their ligand, B cells do not receive the proper signals and cease to develop. Negative selection occurs through the binding of self-antigen with the BCR; If the BCR can bind strongly to self-antigen, then the B cell undergoes one of four fates: clonal deletion, receptor editing, anergy, or ignorance (B cell ignores signal and continues development). This negative selection process leads to a state of central tolerance, in which the mature B cells don't bind with self antigens present in the bone marrow. To complete development, immature B cells migrate from the bone marrow into the spleen as transitional B cells, passing through two transitional stages: T1 and T2. Throughout their migration to the spleen and after spleen entry, they are considered T1 B cells. Within the spleen, T1 B cells transition to T2 B cells. T2 B cells differentiate into either follicular (FO) B cells or marginal zone (MZ) B cells
depending on signals received through the BCR and other receptors. Once differentiated, they are now considered mature B cells, or naive B cells.

Activation
B cell activation occurs in the secondary lymphoid organs (SLOs), such as the spleen and lymph nodes. After B cells mature in the bone marrow, they migrate through the blood to SLOs, which receive a constant supply of antigen through circulating lymph. At the SLO, B cell activation begins when the B cell binds to an antigen via its BCR. Although the events taking place immediately after activation have yet to be completely determined, it is believed that B cells are activated in accordance with the kinetic segregation model, initially determined in T lymphocytes. This model denotes that before antigen stimulation, receptors diffuse through the membrane coming into contact with Lck and CD45 in equal frequency, rendering a net equilibrium of phosphorylation and non-phosphorylation. It is only when the cell comes in contact with an antigen presenting cell that the larger CD45 is displaced due to the close distance between the two membranes. This allows for net phosphorylation of the BCR and the initiation of the signal transduction pathway. Of the three B cell subsets, FO B cells preferentially undergo T cell-dependent activation while MZ B cells and B1 B cells preferentially undergo T cell-independent activation.

B cell activation: from immature B cell to plasma cell or memory B cell
B cell activation is enhanced through the activity of CD21, a surface receptor in complex with surface proteins CD19 and CD81 (all three are collectively known as the B cell coreceptor complex). When a BCR binds an antigen tagged with a fragment of the C3 complement protein, CD21 binds the C3 fragment, co-ligates with the bound BCR, and signals are transduced through CD19 and CD81 to lower the activation threshold of the cell.

T cell-dependent activation
Antigens that activate B cells with the help of T-cell are known as T cell-dependent (TD) antigens and include foreign proteins. They are named as such because they are unable to induce a humoral response in organisms that lack T cells. B cell response to these antigens takes multiple days, though antibodies generated have a higher affinity and are more functionally versatile than those generated from T cell-independent activation. Once a BCR binds a TD antigen, the antigen is taken up into the B cell through receptor-mediated endocytosis, degraded, and presented to T cells as peptide pieces in complex with MHC-II molecules on the cell membrane. T helper (TH) cells, Typically follicular T helper (TFH) cells, that were activated with the same antigen recognize and bind these MHC-II peptide complexes through their T cell receptor (TCR). Following
TCR-MHC-II-peptide binding, T cells express the surface protein CD40L as well as cytokines such as IL-4 and IL-21. CD40L serves as a necessary co-stimulatory factor for B cell activation by binding the B cell surface receptor CD40, which promotes B cell proliferation, immunoglobulin class switching, and somatic hyper mutation as well as sustains T cell growth and differentiation. T cell-derived cytokines bound by B cell cytokine receptors also promote B cell proliferation, immunoglobulin class switching, and somatic hypermutation as well as guide differentiation.[16] After B cells receive these signals, they are considered activated. Now activated, B cells participate in a two-step differentiation process that yields both short-lived plasmablasts for immediate protection and long-lived plasma cells and memory B cells for persistent protection. The first step, known as the extrafollicular response, occurs outside lymphoid follicles but still in the SLO. During this step activated B cells proliferate, may undergo immunoglobulin class switching, and differentiate into plasmablasts that produce early, weak antibodies mostly of class IgM. The second step consists of activated B cells entering a lymphoid follicle and forming a germinal center (GC), which is a specialized microenvironment where B cells undergo extensive proliferation, immunoglobulin class switching, and affinity maturation directed by somatic hypermutation. These processes are facilitated by TFH cells within the GC and generate both high-affinity memory B cells and long-lived plasma cells. Resultant plasma cells secrete large amounts of antibody and either stay within the SLO or, more preferentially, migrate to bone marrow.

**T cell-independent activation**

Antigens that activate B cells without T cell help are known as T cell-independent (TI) antigens and include foreign polysaccharides and unmethylated CpG DNA. They are named as such because they are able to induce a humoral response in organisms that lack T cells.[1] B cell response to these antigens is rapid, though antibodies generated tend to have lower affinity and are less functionally versatile than those generated from T cell-dependent activation. As with TD antigens, B cells activated by TI antigens need additional signals to complete activation, but instead of receiving them from T cells, they are provided either by recognition and binding of a common microbial constituent to toll-like receptors (TLRs) or by extensive crosslinking of BCRs to repeated epitopes on a bacterial cell. B cells activated by TI antigens go on to proliferate outside lymphoid follicles but still in SLOs (GCs do not form), possibly undergo immunoglobulin class switching, and differentiate into short-lived
plasmablasts that produce early, weak antibodies mostly of class IgM, but also some populations of long-lived plasma cells.

**Memory B cell activation**

Memory B cell activation begins with the detection and binding of their target antigen, which is shared by their parent B cell. Some memory B cells can be activated without T cell help, such as certain virus-specific memory B cells, but others need T cell help. Upon antigen binding, the memory B cell takes up the antigen through receptor-mediated endocytosis, degrades it, and presents it to T cells as peptide pieces in complex with MHC-II molecules on the cell membrane. Memory T helper (TH) cells, typically memory follicular T helper (TFH) cells, that were derived from T cells activated with the same antigen recognize and bind these MHC-II-peptide complexes through their TCR. Following TCR-MHC-II-peptide binding and the relay of other signals from the memory TFH cell, the memory B cell is activated and differentiates either into plasmablasts and plasma cells via an extrafollicular response or enter a germinal center reaction where they generate plasma cells and more memory B cells. It is unclear whether the memory B cells undergo further affinity maturation within these secondary GCs.

**B cell types**

- **Plasmablast** - A short-lived, proliferating antibody-secreting cell arising from B cell differentiation. Plasmablasts are generated early in an infection and their antibodies tend to have a weaker affinity towards their target antigen compared to plasma cell. Plasmablasts can result from T cell-independent activation of B cells or the extrafollicular response from T cell-dependent activation of B cells. **Plasma cell** - A long-lived, non-proliferating antibody-secreting cell arising from B cell differentiation. There is evidence that B cells first differentiate into a plasmablast-like cell, then differentiate into a plasma cell. Plasma cells are generated later in an infection and, compared to plasmablasts, have antibodies with a higher affinity towards their target antigen due to affinity maturation in the germinal center (GC) and produce more antibodies. Plasma cells typically result from the germinal center reaction from T cell-dependent activation of B cells, however they can also result from T cell-independent activation of B cells.

- **Lymphoplasmacytoid cell** - A cell with a mixture of B lymphocyte and plasma cell morphological features that is thought to be closely related to or a subtype of plasma cells. This cell type is found in pre-malignant and malignant plasma cell dyscrasias that are associated with the secretion of IgM monoclonal proteins; these dyscrasias include IgM
monoclonal gammopathy of undetermined significance and Waldenström's macroglobulinemia.

- Memory B cell - Dormant B cell arising from B cell differentiation.[1] Their function is to circulate through the body and initiate a stronger, more rapid antibody response (known as the anamnestic secondary antibody response) if they detect the antigen that had activated their parent B cell (memory B cells and their parent B cells share the same BCR, thus they detect the same antigen). Memory B cells can be generated from T cell-dependent activation through both the extrafollicular response and the germinal center reaction as well as from T cell-independent activation of B1 cells.

- Follicular (FO) B Cell (also known as a B-2 cell) - Most common type of B cell and, when not circulating through the blood, is found mainly in the lymphoid follicles of secondary lymphoid organs (SLOs). They are responsible for generating the majority of high-affinity antibodies during an infection.

- Marginal zone (MZ) B cell - Found mainly in the marginal zone of the spleen and serves as a first line of defense against blood-borne pathogens, as the marginal zone receives large amounts of blood from the general circulation. They can undergo both T cell-independent and T cell-dependent activation, but preferentially undergo T cell-independent activation.

- B-1 cell - Arises from a developmental pathway different from FO B cells and MZ B cells. In mice, they predominantly populate the peritoneal cavity and pleural cavity, generate natural antibodies (antibodies produced without infection), defend against mucosal pathogens, and primarily exhibit T cell-independent activation. A true homologue of mouse B-1 cells has not been discovered in humans, though various cell populations similar to B-1 cells have been described.

- B-2 cell - FO B cells and MZ B cells.

- Regulatory B (Breg) cell - An immunosuppressive B cell type that stops the expansion of pathogenic, proinflammatory lymphocytes through the secretion of IL-10, IL-35, and TGF-β. Also, it promotes the generation of regulatory T (Treg) cells by directly interacting with T cells to skew their differentiation towards Tregs. No common Breg cell identity has been described and many Breg cell subsets sharing regulatory functions have been found in both mice and humans.[25] It is currently unknown if Breg cell subsets are developmentally linked and how exactly differentiation into a Breg cell occurs.[25] There is evidence showing that nearly all B cell types can differentiate into a Breg cell through mechanisms involving inflammatory signals and BCR recognition.

B cell-related pathology
Autoimmune disease can result from abnormal B cell recognition of self-antigens followed by the production of autoantibodies. Autoimmune diseases where disease activity is correlated with B cell activity include scleroderma, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and rheumatoid arthritis.

Malignant transformation of B cells and their precursors can cause a host of cancers, including chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, follicular lymphoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and plasma cell malignancies such as multiple myeloma, Waldenström's macroglobulinemia, and certain forms of amyloidosis.

**MHC PROTEINS OR TRANPLANTATION ANTIGENS:**

The **major histocompatibility complex (MHC)** is a set of cell surface proteins essential for the acquired immune system to recognize foreign molecules in vertebrates, which in turn determines histocompatibility. The main function of MHC molecules is to bind to antigens derived from pathogens and display them on the cell surface for recognition by the appropriate T-cells. MHC molecules mediate interactions of leukocytes, also called white blood cells (WBCs), which are immune cells, with other leukocytes or with body cells. The MHC determines compatibility of donors for organ transplant, as well as one's susceptibility to an autoimmune disease via crossreacting immunization. The human MHC is also called the HLA (human leukocyte antigen) complex (often just the HLA). The MHC in mice is called the H-2 complex or H-2. In a cell, protein molecules of the host's own phenotype or of other biologic entities are continually synthesized and degraded. Each MHC molecule on the cell surface displays a molecular fraction of a protein, called an epitope. The presented antigen can be either *self* or *non-self*, thus preventing an organism's immune system targeting its own cells. In its entirety, the MHC population is like a meter indicating the balance of proteins within the cell. The MHC gene family is divided into three subgroups: class I, class II, and class III. Class I MHC molecules have β2 subunits so can only be recognised by CD8 co-receptors. Class II MHC molecules have β1 and β2 subunits and can be recognised by CD4 co-receptors. In this way MHC molecules chaperone which type of lymphocytes may bind to the given antigen with high affinity, since different lymphocytes express different T Cell Receptor (TCR) co-receptors.

Diversity of antigen presentation, mediated by MHC classes I and II, is attained in at least three ways:
An organism's MHC repertoire is polygenic (via multiple, interacting genes);
MHC expression is codominant (from both sets of inherited alleles);
MHC gene variants are highly polymorphic (diversely varying from organism to organism within a species). Major histocompatibility complex and sexual selection has been observed in male mice making mate choices of females with different MHCs and thus demonstrating sexual selection.

Also, at least for MHC I presentation, there has been evidence of antigenic peptide splicing which can combine peptides from different proteins, vastly increasing antigen diversity.

In Immunity of the three MHC classes identified, attention commonly focuses on classes I and II. By interacting with CD4 molecules on surfaces of helper T cells, MHC class II mediates establishment of specific immunity (also called acquired immunity or adaptive immunity). By interacting with CD8 molecules on surfaces of cytotoxic T cells, MHC class I mediates destruction of infected or malignant host cells, the aspect of specific immunity termed cellular immunity. (The other arm of specific immunity is humoral immunity, whose relation to MHC is more indirect.)

**Functions**

MHC is the tissue-antigen that allows the immune system (more specifically T cells) to bind to, recognize, and tolerate itself (autorecognition). MHC is also the chaperone for intracellular peptides that are complexed with MHCs and presented to T cell receptors (TCRs) as potential foreign antigens. MHC interacts with TCR and its co-receptors to optimize binding conditions for the TCR-antigen interaction, in terms of antigen binding affinity and specificity, and signal transduction effectiveness. Essentially, the MHC-peptide complex is a complex of autoantigen/alloantigen. Upon binding, T cells should in principle tolerate the auto-antigen, but activate when exposed to the allo-antigen. Disease states occur when this principle is disrupted. Antigen presentation: MHC molecules bind to both T cell receptor and CD4/CD8 co-receptors on T lymphocytes, and the antigen epitope held in the peptide-binding groove of the MHC molecule interacts with the variable Ig-Like domain of the TCR to trigger T-cell activation Autoimmune reaction: Having some MHC molecules increases the risk of autoimmune diseases more than having others. HLA-B27 is an example. It is unclear how exactly having the HLA-B27 tissue type increases the risk of ankylosing spondylitis and other associated inflammatory diseases, but mechanisms involving aberrant antigen presentation or T cell activation have been hypothesized. Tissue allore cognition: MHC molecules in complex with peptide epitopes are essentially ligands for TCR. T cells
become activated by binding to the peptide-binding grooves of any MHC molecule that T cells were not trained to recognize during thymus positive selection.

**Lymphocytes**

As a lineage of leukocytes, lymphocytes reside in peripheral lymphoid tissues, including lymphoid follicles and lymph nodes, and include B cells, T cells, and natural killer cells (NK cells). B cells, which act specifically, secrete antibody molecules, but do not bind MHC. T cells, which act specifically, as well as NK cells, which act innately, interact with MHC. NK cells express Killer Ig-like receptors (KIRs) that bind to MHC I molecules and signal through ITIM (immunoreceptor tyrosine inhibition motif) recruitment and activation of protein tyrosine phosphatases. This means in contrast to CD8/TCR interaction that activates Tc lymphocytes, NK cells becomes deactivated when bound to MHC I. When MHC class I expression is low, as is typically the case with abnormal cell function during viral infection or tumourigenesis, NK cells lose the inhibitory KIR signal and trigger programmed cell death of the abnormal cell. NK cells thus help prevent progress of cancerous cells by contributing to tumor surveillance.

**MHC class II**

*Main article: MHC class II*

MHC class II can be conditionally expressed by all cell types, but normally occurs only on professional antigen presenting Cells (APCs): macrophages, B cells, and especially dendritic cells (DCs). An APC takes up an antigenic protein, performs antigen processing, and returns a molecular fraction of it—a fraction termed the epitope—and displays it on the APC's surface coupled within an MHC class II molecule (antigen presentation). On the cell's surface, the epitope can be recognized by immunologic structures like T cell receptors(TCRs). The molecular region which binds to the epitope is the paratope. On surfaces of helper T cells are CD4 receptors, as well as TCRs. When a naive helper T cell's CD4 molecule docks to an APC's MHC class II molecule, its TCR can meet and be imprinted by the epitope coupled within the MHC class II. This event primes the naive helper T cell.

According to the local milieu, that is, the balance of cytokines secreted by APCs in the microenvironment, the naive helper T cell (Th0) polarizes into either a memory Th cell or an effector Th cell of phenotype either type 1 (Th1), type 2 (Th2), type 17 (Th17), or regulatory/suppressor (Treg), as so far identified, the Th cell's terminal differentiation. MHC class II thus mediates immunization to—or, if APCs polarize Th0 cells principally to Treg
cells, immune tolerance of—an antigen. The polarization during primary exposure to an antigen is key in determining a number of chronic diseases, such as inflammatory bowel diseases and asthma, by skewing the immune response that memory Th cells coordinate when their memory recall is triggered upon secondary exposure to similar antigens. (B cells express MHC class II to present antigen to Th0, but when their B cell receptors bind matching epitopes, interactions which are not mediated by MHC, these activated B cells secrete soluble immunoglobulins: antibody molecules mediating humoral immunity.)

**MHC class I**

MHC class I occurs on all nucleated cells and also in platelets—in essence all cells but red blood cells. It presents epitopes to killer T cells, also called cytotoxic T lymphocytes (CTLs). A CTL expresses CD8 receptors, in addition to TCRs. When a CTL's CD8 receptor docks to a MHC class I molecule, if the CTL's TCR fits the epitope within the MHC class I molecule, the CTL triggers the cell to undergo programmed cell death by apoptosis. Thus, MHC class I helps mediate cellular immunity, a primary means to address intracellular pathogens, such as viruses and some bacteria, including bacterial L forms, bacterial genus *Mycoplasma*, and bacterial genus *Rickettsia*. In humans, MHC class I comprises HLA-A, HLA-B, and HLA-C molecules.

**Genes**

MHC gene families are found in all vertebrates, though they vary widely. In humans, the MHC region occurs on chromosome 6, between the flanking genetic markers *MOG* and *COL11A2* (from 6p22.1 to 6p21.3 about 29Mb to 33Mb on the hg38 assembly), and contains 224 genes spanning 3.6 megabase pairs (3 600 000 bases). About half have known immune functions. The same markers in the gray short-tailed opossum (*Monodelphis domestica*), a marsupial, span 3.95 Mb, yielding 114 genes, 87 shared with humans.[11] Marsupial MHC genotypic variation lies between eutherian mammals and birds, taken as minimal MHC encoding, but is closer in organization to that of nonmammals, and MHC class I genes of marsupials have amplified within the class II region, yielding a unique class I/II region.[11] Class III functions very differently from class I and class II, but its locus occurs between the other two classes, on chromosome 6 in humans, and are frequently discussed together.