Principles of Adaptive Immunity

Review: Cells of the innate immune system have a series of receptors that recognize different PAMPs that are routinely encountered, but every such receptor is the same on every cell.
In contrast, each antigen/pathogen is recognized by a very small fraction of lymphocytes that have an antigen receptor that binds specifically; these clones are “selected” to fight the invader.

Cells of the adaptive immune system (T cells and B cells) each express one antigen receptor whose antigen specificity is unique to that cell.

B cell antigen receptor (BCR)
-- has a constant region that is similar on all B cells and a variable region that interacts with the antigen (Fig. 3.1).
-- also known as surface immunoglobulin (Ig)
-- Overall the Ig molecule has a Y-shaped structure, with two identical heavy chains and two identical light chains. The antigen-binding variable regions are at the tips of the Y arms and consist of amino acids from both heavy and light chains.
-- Activated B cells can also differentiate into plasma cells make a secreted form of Ig called of antibody (Ab)
-- Naïve cells express only surface Ig; antigen recognition leads to release of secreted Ig of the same specificity.
-- highly specific for the pathogen (Fig. 3.2)
-- constant region of Ab have many functions: binding to complement proteins, binding to receptors on phagocytes. Thus, Ab is a “molecular bridge” between Ag and effector cells or complement

T cell antigen receptor (TCR)
-- two chains, α and β
-- like BCR, has a constant region that is the same on all T cells and a variable region that interacts with the antigen (Fig. 3.1).
-- The antigen-binding variable regions are at the tips of the both chains and consist of amino acids from both.
-- no secreted form of TCR

Schematic overview of an adaptive immune response (Fig. 3.6)
-- it starts with dendritic cells (DC) in tissues. Recognize Ag through innate receptors (e.g. TLR), and migrate to draining lymph node to initiate activation of Ag-specific T cells.
-- DC are an essential connecting link between adaptive and innate immunity
-- antigen-specific lymphocytes undergo clonal expansion (Fig. 3.5)
-- after clonal expansion of T cells, and activation of B cells, effector T cells traffic to the infection site and antibodies also exit the blood at sites of inflammation (Fig. 3.6)

-- part of the antigen seen by Ig or TCR is called the epitope (described more in chapter 4, 5)
-- Ig molecules recognize pathogens or their products directly Fig. 3.12
TCR recognizes pathogens or their products indirectly; recognizes peptide fragments of pathogen proteins in association with host molecules known as major histocompatibility complex (MHC) proteins. (Fig. 3.7)

T cells are specialized to detect the presence of intracellular pathogens like viruses and certain bacteria.

-- a process called antigen processing takes pathogen proteins and digests them into small peptides that bind to MHC molecules and are sent to the cell surface for antigen presentation to T cells.
-- DC are not the only antigen presenting cells (APC), but they are essential for the first step of Ag presentation to naïve T cells (Fig. 3.7). In later stages of the immune response, activated T cells can recognize Ag presented by other types of cells.

Two types of MHC molecule: class I and class II (Fig. 3.8)
CD4 on helper T cells and CD8 on CTL are “co-receptors” that bind to MHC along with the TCR (Fig. 3.9)
- thus, helper T cells are only activated by peptides bound to class II MHC, and CTL are only activated by peptides bound to class I MHC

-- proteins in the cytoplasm (both host and pathogen) are processed in the cytoplasm, the peptides transported to the ER, loaded on MHC class I molecules, and exported to the surface.
-- foreign peptides presented by MHC class I (i.e. viral peptides) cause activation of CTLs and the virally infected cell is killed (Fig. 3.10)

-- proteins in vesicles (i.e. endocytosed bacteria) are processed in those vesicles, loaded on MHC class II molecules, and exported to the surface.
-- foreign peptides presented by MHC class II (Fig. 3.11) cause activation of T helper cells
-- MHC class I expressed on nearly all cells, but MHC class II only on professional antigen presenting cells: DC, MΦ and B cells---different mechanisms for Ag endocytosis in B cells (Fig. 3.13)
  ■ dendritic cells (DC) are usually first to present Ag and activate T cells
  ■ some activated Th cells migrate to tissues and help macrophages (MF) that are presenting the same antigen; increases macrophage ability to kill vesicular bacteria
  ■ other activated Th cells stay in lymph node or spleen and help B cells that are presenting the antigen; increases B cell ability to make antibodies
  ■ most activated CTLs migrate to tissues to seek and kill virally infected cells

How Antibodies Help to Destroy and Clear Pathogens

Antibody-mediated immunity = humoral immunity

Antibodies combat pathogens by three mechanisms (Fig. 3.14)
• neutralization: important for protection from viruses or bacterial toxins
• opsonization: important for allowing phagocytes to recognize extracellular bacteria
• complement activation: enhanced opsonization, recruitment and activation of phagocytes; direct killing by forming pores
Tolerance
Clonal deletion refers to the removal of immature lymphocytes whose receptors are potentially self-reactive. Example for T cell development in Fig. 3.16. The form of cell suicide involved in clonal deletion is called programmed cell death or apoptosis. Self-reactive mature cells can also be inactivated by distinct mechanisms. Together, clonal deletion and inactivation are the basis of immunological tolerance to self. When tolerance is broken, autoimmunity can occur.

Immunodeficiency
Genetic (inherited disease) of varying severity, some can now be managed by antibiotics or cured by bone marrow transplant.
Acquired immunodeficiency diseases—best known is acquired immune deficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV) -- can also occur following chemo or other immunosuppressive treatments

Unhelpful immune responses

Allergy
-- IgE antibodies made against innocuous substances (Fig. 3.18)
-- IgE sticks to receptors on mast cells; binding allergen causes mast cell to release histamine and other substances that lead to allergic symptoms (sneezing, etc.)
-- allergic symptoms are beneficial if allergen is a parasite
-- can be fatal (anaphylaxis)

Autoimmune disease
-- immune response directed against normal, healthy cells
-- can be initiated when pathogens activate a clone of T cells that cross-reacts with a “self antigen” (Fig. 3.17)
-- tissue destruction is often debilitating and can be fatal
-- multiple sclerosis (nerve fibers), type I diabetes (pancreatic β cells), rheumatoid arthritis (joints), Crohn’s disease (intestine)

Transplant rejection
Unusual aspect of MHC molecules is polymorphism = many genetic variants in population. This is main reason for rejection of organ transplants (donor tissue is seen as “foreign”) and is the origin of the name MHC.
-- transplantation of organs, skin, bone marrow and stem cells is limited by immune rejection unless you have an identical twin
-- mediated mainly by T cells recognizing “foreign” MHC from donor; also antibodies and NK cells
-- immunosuppressive drugs can prevent rejection but leave patient susceptible to infection and cancer
Extra:
-- there are several different constant region types called **isotypes**; these confer different effector functions and anatomical location
-- on naïve B cells, before antigen encounter, the two isotypes expressed are IgM and IgD. After activation, B cells can undergo **isotype switching** to either IgG, IgA or IgE
  --different isotypes differ in their heavy chain constant regions
  --each with distinct function and distributed differently in the body

-- isotype switching occurs in the germinal centers of secondary lymphoid tissue; also where B cells undergo **somatic hypermutation** that leads to an increase in Ab affinity for antigen (Fig. 3.15)

The ability of lymphocytes to have a huge array of different antigen specificities is the result of random recombination of gene segments (called V, D and J segments) that encode the antigen-recognition regions of the TCR and BCR. (Fig. 3.3, 3.4). This process of **gene rearrangement** is unique to T and B cells and is called **somatic recombination** because it occurs in somatic cells (not germ cells). Also called V(D)J recombination; see lecture 7.
-- additional diversity created by imprecise joining of gene segments