## 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,  and 

-- 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, M 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 (M) 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  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 (if time allows):

-- 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