Lecture 2: Acquired Immunity

Key Points:

- **Acquired Immunity**
- **Antigen Presentation**
- **Humoral Immunity**
- **B-Cells +B-cell receptor**
- **T-Cells + T-cell receptor**
- **MHC, class I and class II**
- **Spleen**
- **Lymphatic System**
- **Mucosal associated lymphatic tissue**
- **Clonal Selection**

2. Molecules and Cells of the Acquired Immune System.

Humoral Immunity: soluble factors in the serum (e.g. antibodies)
Cellular Immunity: associated with cells

2.1 B-cells:

- Mature in the bone marrow (or bursa in birds)
- **B-cell receptor** binds *foreign* material (proteins, carbohydrates, etc.)
- receptor is a membrane bound antibody (IgM) plus two copies of a hetero-dimeric signaling domain (Ig_α and Ig_β). Cytoplasmic section of Ig_α and Ig_β can be phosphorylated, initiating a kinase signal cascade.
- All B-cell receptors are identical on a single B-cell, but diversity is on the order of 10^8 different B-cells.
- Stimulated B-cells differentiate into plasma cells that secrete copious quantities of antibody.
- Stimulated B-cells also form memory B-cells that do not secrete antibody.
- Stimulation of B-cells is enhanced by T-cells.

2.2 T-cells:

- Produced in bone marrow, but mature in the thymus.
- Recognize foreign *peptides* bound to major **histocompatibility proteins (MHC)** via the **T-cell receptor**.
- T- cell receptor composed of either $\alpha\beta$ chains or $\delta\gamma$ chains.
- Each T-cell has a homogenous population of T-cell receptor, but diversity is estimated to be on the order of 10^{12}.
- Associated with phosphorylation signaling domain (CD3) (Cluster of Differentiation 3), composed of $\zeta\zeta$, $\gamma\varepsilon$, $\varepsilon\delta$ homo/heterodimeric molecules.

T-helper cells (T_H):

- express CD4 (Cluster of Differentiation 4) on surface ($CD4^+$)
- CD4 recognizes class II MHC (*self*) in complex with *foreign* peptides on antigen presenting cells, leading to activation of T_H cell.
- Activation causes release of cytokines that activate B-cells, macrophages, T_c cells.

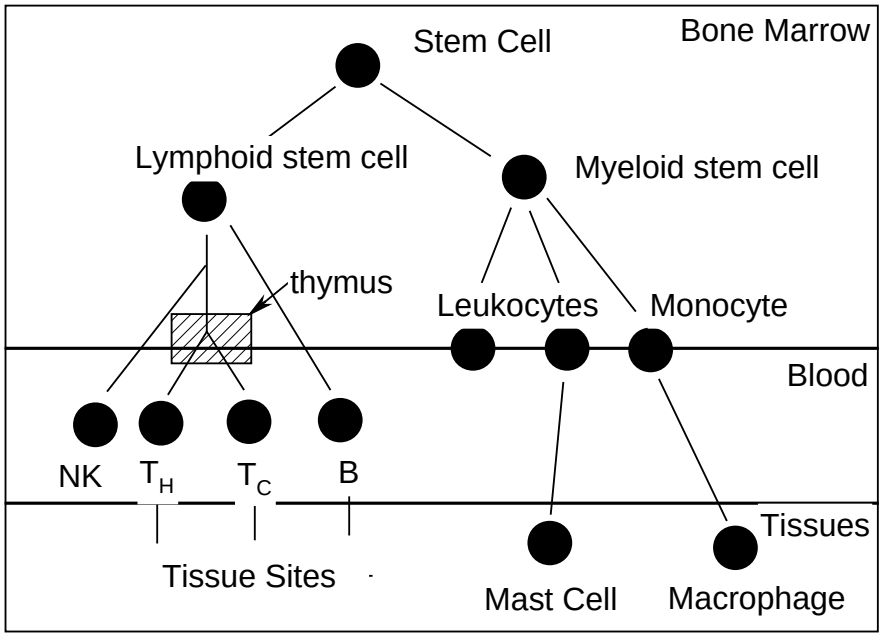
Cytotoxic T cells (T_C)

- express CD8 on cell surface ($CD8^+$).
- CD8 recognizes class I HMC/foreign peptides on almost any cell, leading to formation of a cytotoxic T lymphocyte (CTL)

2.3 MHC Complexes: Heterodimeric and membrane bound**.**

	Class I - MHC	**Class II - MHC**
Composition	α1-α2-α3, β2 microglobulin	α1-α2, β1-β2
Type of cell	All cells	Antigen Presenting Cells (APC): -macrophages -dendritic cells -B lymphocytes
Recognized by:	T_C cells	T_H cells
Associated with:	-viral infection -tumor cells -transplant rejection	-bacterial infection -viral infection -protein allergins -other pathogens

2.4 Development of Immune Cells:



3. Example of Humoral and Cellular Cooperation In Bacterial Infection (A day in the life of a B-cell)

1. Progenitor B-cell develops into mature B cell in bone marrow, developing a unique antibody on its surface.
2. If the antibody does not recognize self, then the mature B-cell is allowed to leave the bone marrow (10^7 new B-cells are produced/day).

3. B-cells that encounter a foreign particle that can bind to the immunoglobulin on the cell surface become stimulated. If the B-cell does *not* have a successful encounter it dies within a few days.
4. In addition to B-cells, macrophages and dendritic cells may also ingest foreign particle.
5. Bound bacteria are internalized by endocytosis (B-cells), or phagocytosis.
6. Bacterial peptides, complexed to class II MHC molecules, are presented on the surface of B-cells, macrophages, and dendritic cells.
7. *Specific* T_H-cells recognize foreign peptide bound to class II MHC, via CD4/T-cell receptor-MHC/peptide interactions, leading to activation of the T_H-cell, cell division of that particular T_H-cell, and subsequent formation of memory T_H-cells.
8. Activated T_H-cells secretes cytokines that activate B-cells.
9. Cytokines induce the differentiation & cell division of B-cells into antibody secreting plasma cells and memory B-cells.
10. Plasma cells can secrete 10^3 molecules of antibody/sec! Fortunately, plasma cells live only a few days, but can produce about 10^{10} antibodies in that time.
11. Antibody produced by plasma cells coats (opsinizes) bacteria, leading to more efficient phagocytosis of the foreign particles as well as cell destruction by complement.
12. Subsequent infection by the same bacteria will lead to a more rapid response because of the presence of memory T- and B-cells. The primary response occurs within 14 days. The secondary response occurs within 3 or 4 days and produces 10-100 fold more antibody.

1. Note that in four days a single E. coli will double about 200 times, giving rise to more bacterial cells than the number of cells in the human host. Clearly, innate responses play an important role.

2. The activation of B- and T-cells by foreign antigen leads to an increase in the number of both types of cells. This antigen-dependent amplification of cells is referred to as **clonal selection**, since a specific sub-population, or clone, of B and T cells is involved.

3. Organs of the Immune System:

3.1 Primary organs:

- Thymus: Responsible for maturation of the T cells. Only T-cells that can recognize *foreign* peptides *in complex with self MHC* are allowed to leave the thymus.
- Bone Marrow: Responsible for maturation of B cells. Only B cells that express an *intact immunoglobulin* that recognizes *foreign* molecules are allowed to leave the bone marrow. B-cells that recognize self are destroyed.

3.2 Secondary organs:

Spleen:
- Traps foreign particles from the blood via dendritic cells. B-cells and T-cells activated by dendritic cells

Lymphatic system:
- Traps local foreign bodies near the source of infections. Drains fluid from cells to lymph nodes and follicles, eventually returning fluid to the blood. Nodes and follicles contain B-cells, T-cells, macrophages, and dendritic cells. Dendritic cells engulf foreign particles, leading to activation of B and T cells.

- Highly organized follicles are present in small intestine (Peyer's patches) and tonsils and are part of the Mucosal-Associated Lymphoid Tissue (MALT)

Mucosal-Associated Lymphoid Tissue:

- Lymphoid follicles adjacent to mucosal membranes (e.g. tonsils, Peyer's patches).
- Specialized M-cell in wall of mucus membrane entraps foreign particle, delivering it to lymphocytes on the other side of the mucosa. This leads to activation of B-cells which migrate to the mucosa and deliver antibodies (IgA class) across the mucosal membrane.

3.3 Circulation Though the Lymphatic System.

- A lymphocyte in the blood will enter the lymphatic system 2-12 hours after it is released from the bone marrow or thymus.
- Approximately $3x10^{11}$ lymphatic cells flow through the system on a given day.
- A similar number are processed through the spleen.
- This high flux of cells insures that a foreign antigen will meet the appropriate B and T cells within a short period of time.