Immune system
Acknowledgement

• Material used in some of the slides was taken from open websites and personnel communications.
• Help from these sites and providers is acknowledged.
THE IMMUNE SYSTEM

• Molecules, cells, tissues and organs which provide non-specific and specific protection against
  • Microorganisms
  • Microbial toxins
  • Tumor cells
  – Crucial to human survival
ORIGIN OF CELLS OF THE IMMUNE SYSTEM

• Derived from common progenitor cell in bone marrow
  – Pluripotent hematopoietic stem cell

• Progenitor Stem Cells
  – Myeloid lineage
    • Monocyte/macrophage, dendritic cells, PMN’s, mast cells
    • Erythroid: Erythrocytes and Megakaryocytes
  – Lymphoid lineage
    • Small and large lymphocytes
Regulation of Hematopoiesis

- Steady state synthesis and normal life span of red and white blood cells is controlled by four factors:
  - Levels and types of cytokines produced by bone marrow cells
  - Production of cytokines by T cells and macrophages
  - Expression of receptors for cytokines on HSC’s
  - Apoptosis

- Importance of Regulation
  - Leukemias
**TABLE 2-1** Some transcription factors essential for hematopoietic lineages

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dependent lineage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GATA-1</td>
<td>Erythroid</td>
</tr>
<tr>
<td>GATA-2</td>
<td>Erythroid, myeloid, lymphoid</td>
</tr>
<tr>
<td>PU.1</td>
<td>Erythroid (maturational stages), myeloid (later stages), lymphoid</td>
</tr>
<tr>
<td>BM11</td>
<td>Myeloid, lymphoid</td>
</tr>
<tr>
<td>Ikaros</td>
<td>Lymphoid</td>
</tr>
<tr>
<td>Oct-2</td>
<td>B lymphoid (differentiation of B cells into plasma cells)</td>
</tr>
</tbody>
</table>

- Genetic regulation of HSC differentiation

**GATA transcription factors** are a family of transcription factors characterized by their ability to bind to the DNA sequence "GATA".

**Oct-2** is a octamer transcription factor which is part of the POU family.

**POU** (pronounced 'pow') is a family of proteins that have well-conserved homeodomains. The acronym POU is derived from the names of three transcription factors: the Pituitary-specific **Pit-1**

the **Octamer transcription factor** proteins **Oct-1** and **Oct-2** (octamer sequence is ATGCAAAAT)

the neural **Unc-86** transcription factor from **Caenorhabditis elegans**.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Role in apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>bcl-2</td>
<td>Prevents apoptosis</td>
<td>Inhibits</td>
</tr>
<tr>
<td>bax</td>
<td>Opposes bcl-2</td>
<td>Promotes</td>
</tr>
<tr>
<td>bcl-X_L (bcl-Long)</td>
<td>Prevents apoptosis</td>
<td>Inhibits</td>
</tr>
<tr>
<td>bcl-X_S (bcl-Short)</td>
<td>Opposes bcl-X_L</td>
<td>Promotes</td>
</tr>
<tr>
<td>caspase (several different ones)</td>
<td>Protease</td>
<td>Promotes</td>
</tr>
<tr>
<td>fas</td>
<td>Induces apoptosis</td>
<td>Initiates</td>
</tr>
</tbody>
</table>
CELLS OF INNATE AND ADAPTIVE IMMUNITY

– Myeloid Lineage
– Referred to as
  • Polymorphonuclear leukocytes (PMN’s)
    – Nuclei are multilobed (2 to 5)
  • Granulocytes
    – Cytoplasmic granules
– Neutrophil: Principal phagocytic cell of innate immunity
– Eosinophil: Principal defender against parasites
– Basophil: Functions similar to eosinophils and mast cells
Neutrophils and macrophages

- Phagocytes - travel throughout body in pursuit of invading pathogens
- Neutrophils are found in bloodstream; most abundant phagocyte, normally representing 50% to 60% of circulating leukocytes
- During acute phase of inflammation, particularly as a result of bacterial infection, neutrophils migrate toward site of inflammation in a process called chemotaxis, and are usually first cells to arrive at scene of infection
- Macrophages are versatile cells that reside within tissues and produce a wide array of chemicals including enzymes, complement proteins, and regulatory factors such as interleukin 1
- Macrophages also act as scavengers, ridding body of worn-out cells and other debris, and as antigen-presenting cells that activate adaptive immune system
Granulocytes

(a) Neutrophil
- Multilobed nucleus
- Glycogen
- Secondary granule
- Primary azurophilic granule
- Phagosome

(b) Eosinophil
- Crystalloid granule

(c) Basophil
- Glycogen
- Granule
Neutrophil

- Granulocyte
  - Cytoplasmic granules
- Polymorphonuclear
- Phagocytosis
- Short life span (hours)
- Very important at “clearing” bacterial infections
- Innate Immunity
Eosinophils

• Kills Ab-coated parasites through degranulation
• Involved in allergic inflammation
• A granulocyte
• Double Lobed nucleus
• Orange granules contain toxic compounds
Basophils

- Might be “blood Mast cells’
- A cell-killing cells
  - Blue granules contain toxic and inflammatory compounds
- Important in allergic reactions
CELLS OF INNATE AND ADAPTIVE IMMUNITY

• Myeloid lineage
  – Monocytes
    • Leukocytes with bean shaped or brain-like convoluted nuclei
    • Circulate in blood with half life of 8 hours
    • Precursors of tissue macrophages
  – Macrophages
    • Mononuclear phagocytic cells in tissue
    • Derive from blood monocytes
    • Participate in innate and adaptive immunity
Monocyte

Circulating precursor cell to macrophage

Macrophage

Phagocytosis and killing of microorganisms. Activation of T cells and initiation of immune responses

Figure 1-9 part 5 of 6 The Immune System, 2/e (© Garland Science 2005)
Monocyte and Macrophage

- Origin
- Migration maturation
- Morphological differences between monocytes and macrophage
- Activation of macrophages
- Macrophage function
  - Phagocytosis
  - Processing Antigen
  - Presenting antigenic peptide with class II MHC to T cells
  - Cytotoxic activity
  - Synthesis and release of cytokines
• Mononuclear Phagocyte System
  – Types of macrophages and their locations
CELLS OF INNATE AND ADAPTIVE IMMUNITY

• Myeloid lineage
  – Dendritic cells
    • Cells with dendriform (star shaped) morphology
    • Interdigitating reticular cells (synonym)
    • Capture and present antigens to T lymphocytes
  – Mast cells
    • Located in mucous membrane and connective tissue throughout body
    • Major effectors cell in allergy
    • Modulation of initial immune response
Dendritic cell

Activation of T cells and initiation of adaptive immune responses

Mast cell

Expulsion of parasites from body through release of granules containing histamine and other active agents
• Mast Cells
  - Origin
  - Location
  - Function
  - Importance in allergic responses
Mast Cells

- Expulsion of parasites through release of granules
- Histamine, leukotrienes, chemokine cytokines
- Also involved in allergic responses
• Dendritic cells
  - Morphology
  - Origin
  - Types
  - Function
  - Follicular dendritic cell
Dendritic cells (DC)

• are phagocytes in tissues that are in contact with the external environment; therefore, they are located mainly in the skin, nose, lungs, stomach, and intestines

• named for their resemblance to neuronal dendrites, as both have many spine-like projections, but dendritic cells are in no way connected to the nervous system

• serve as a link between the bodily tissues and the innate and adaptive immune systems, as they present antigen to T cells, one of the key cell types of the adaptive immune system
CELLS OF INNATE AND ADAPTIVE IMMUNITY

• Lymphoid Lineage
  – Large lymphocytes (large granular lymphocytes)
    • Natural killer (NK) cells (CD16, CD56)
    • Innate immunity to viruses and other intracellular pathogens
    • Participate in antibody-dependent cell-mediated cytotoxicity (ADCC)
  – Small lymphocytes
    • B cells (CD19)
    • T cells (CD3, CD4 or CD8)
    • Adaptive immunity

– Lymphocytes refers to small lymphocytes
Lymphocytes; B cells T cells

• B cells & T cells carry receptor molecules that recognize specific targets
• T cells recognize a “non-self” target, such as a pathogen, only after antigens (small fragments of the pathogen) have been processed and presented in combination with a “self” receptor called a major histocompatibility complex (MHC) molecule
• There are two major subtypes of T cells: the killer T cell and the helper T cell
• Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper T cells only recognize antigens coupled to Class II MHC molecules
• A third, minor subtype are the γδ T cells that recognize intact antigens that are not bound to MHC receptors
• In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface, and recognizes whole pathogens without any need for antigen processing. Each lineage of B cell expresses a different antibody, so the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture
Lymphocytes

- Many types; important in both humoral and cell-mediated immunity
- B-cells produce antibodies
- T-cells
  - Cytotoxic T cells
  - Helper T cells
- Memory cells
Lymphocytes

- **Plasma Cell (in tissue)**
  - Fully differentiated B cells, secretes Ab

- **Natural Killer cells**
  - Kills cells infected with certain viruses
  - Both innate and adaptive
  - Antigen presentation
B Lymphocytes

- Site of maturation
- Membrane receptors
  - Membrane bound immunoglobulin
- Markers of a mature B cell
  - Class II MHC
  - B220
  - CR1 and CR2
  - FcγRII
  - B7-1, B7-2
  - CD40
T Lymphocytes

- Site of maturation
- Membrane receptors
  - T Cell Receptor (TCR)
  - CD4
  - CD8
  - CD28
  - CD45
- Classes of T cells
  - T helper cells ($T^H$)
  - T cytotoxic cells ($T^C$)
  - Function of $T^H$ and $T^C$
- Class restriction
## Comparison of T and B cells

<table>
<thead>
<tr>
<th><strong>T-cells</strong></th>
<th><strong>B-cells</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- responsible for cell mediated immunity</td>
<td>- responsible for Humoral immunity</td>
</tr>
<tr>
<td>- Life span is long</td>
<td>- Life span is short</td>
</tr>
<tr>
<td>- Differentiate inside Thymus Gland</td>
<td>- Differentiate inside Bone Marrow</td>
</tr>
<tr>
<td>- Absence of surface antibodies</td>
<td>- Surface Antibodies present</td>
</tr>
<tr>
<td>- Transformed in small lymphocytes by antigens</td>
<td>- Transformed to plasma cells by antigens</td>
</tr>
<tr>
<td>- secrete Lymphokines</td>
<td>- secrete antibodies</td>
</tr>
<tr>
<td>- sub population are Cytotoxic T, Helper cells and suppressor cells.</td>
<td>- sub population are memory cells and plasma cells</td>
</tr>
<tr>
<td>- stimulate phagocytes and B-cells into activity.</td>
<td>- B-cells or B-lymphocytes produce antibodies</td>
</tr>
</tbody>
</table>
THE CLUSTER OF DIFFERENTIATION (CD)

• CD nomenclature established in 1982
  – 1st International Workshop and Conference on Human Leukocyte Differentiation Antigens (HLDA) held in Paris

• protocol for identification and investigation of cell surface molecules

• intended for classification of many monoclonal antibodies generated by different laboratories around the world against epitopes on the surface molecules of leukocytes

• CD number assigned on basis of 1 cell surface molecule recognized by 2 specific mAb
The \textbf{cluster of designation} (often abbreviated as \textbf{CD}) is a protocol used for the identification and investigation of cell surface molecules present on White blood cells.

- CD molecules can act in numerous ways, often acting as receptors or ligands (the molecule that activates a receptor) important to the cell.
- A signal cascade is usually initiated, altering the behavior of the cell.
- Some CD proteins do not play a role in cell signaling, but have other functions, such as cell adhesion.
- CD for humans is numbered up to 350 most recently (as of 2009).
- If the molecule has not been well-characterized, or has only one \textit{mAb}, it is usually given the provisional indicator "w" (as in "CDw186").
Stammzelle

CD34

CD45
CD15
Granulozyten

CD45
CD14
Monozyten

CD45
CD3
T-Lymphozyten

CD45
CD19
B-Lymphozyten

CD45
CD61
Thrombozyten

CD45
CD4
Helfer-T-Lymphozyten

CD45
CD8
Suppressor-T-Lymphozyten

CD45
CD25
aktivierte T-Lymphozyten
THE CLUSTER OF DIFFERENTIATION (CD)

• CD markers on leukocytes

  Granulocyte          CD45+, CD15+
  Monocyte            CD45+, CD14+
  T lymphocyte        CD45+, CD3+
  T helper lymphocyte CD45+, CD3+, CD4+
  T cytotoxic lymphocyte CD45+, CD3+, CD8+
  B lymphocyte        CD45+, CD19+
  Natural killer cell CD45+, CD16+, CD56+, CD3-
### TABLE 2-5 Common CD markers used to distinguish functional lymphocyte subpopulations

<table>
<thead>
<tr>
<th>CD designation*</th>
<th>Function</th>
<th>B cell</th>
<th>T&lt;sub&gt;H&lt;/sub&gt;</th>
<th>T&lt;sub&gt;C&lt;/sub&gt;</th>
<th>NK cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD2</td>
<td>Adhesion molecule; signal transduction</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD3</td>
<td>Signal-transduction element of T-cell receptor</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>CD4</td>
<td>Adhesion molecule that binds to class II MHC molecules; signal transduction</td>
<td>−</td>
<td>+ (usually)</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD5</td>
<td>Unknown</td>
<td>+</td>
<td>+ (subset)</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>CD8</td>
<td>Adhesion molecule that binds to class I MHC molecules; signal transduction</td>
<td>−</td>
<td>− (usually)</td>
<td>+</td>
<td>+ (variable)</td>
</tr>
<tr>
<td>CD16 (FcyRIII)</td>
<td>Low-affinity receptor for Fc region of IgG</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>CD21 (CR2)</td>
<td>Receptor for complement (C3d) and Epstein-Barr virus</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD28</td>
<td>Receptor for co-stimulatory B7 molecule on antigen-presenting cells</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>CD32 (FcyRII)</td>
<td>Receptor for Fc region of IgG</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD35 (CR1)</td>
<td>Receptor for complement (C3b)</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD40</td>
<td>Signal transduction</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD45</td>
<td>Signal transduction</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD56</td>
<td>Adhesion molecule</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>

*Synonyms are shown in parentheses.
Components of blood

Serum vs. Plasma

• Serum: cell-free liquid, minus the clotting factors
• Plasma: cell-free liquid with clotting factors in solution (must use an anticoagulant)
Components of blood

**Plasma**
- **Water**: 92% by weight
- **Proteins**: 7% by weight
  - Albumins: 58%
  - Globulins: 37%
  - Fibrinogen: 4%
  - Regulatory proteins: 1%
- **Other solutes**: 1% by weight
  - Electrolytes
  - Nutrients
  - Respiratory gases
  - Waste products

**Buffy Coat**
- **Platelets**: 12–300 thousand per cubic mm
- **Leukocytes**
  - Neutrophils: 60–70%
  - Monocytes: 3–8%
  - Eosinophils: 2–4%
  - Basophils: 0.5–1%
  - Lymphocytes: 20–25%

**Erythrocytes**
- **Erythrocytes**: 4.2–6.2 million per cubic mm
### COMPLETE BLOOD COUNT WITH DIFFERENTIAL (CBC WITH DIFF)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Reference</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes (RBC)</td>
<td></td>
<td>4.0 to 5.4 M/μL</td>
</tr>
<tr>
<td>Thrombocytes (Platelets)</td>
<td></td>
<td>145 to 400 K/μL</td>
</tr>
<tr>
<td>Leukocytes (WBC)</td>
<td></td>
<td>4.8 to 10.8 K/μL</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>40 to 74  %</td>
</tr>
<tr>
<td>Band neutrophils</td>
<td></td>
<td>0 to 9</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td>0 to 6</td>
</tr>
<tr>
<td>Basophils</td>
<td></td>
<td>0 to 1</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>15 to 47</td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
<td>0 to 12</td>
</tr>
<tr>
<td>Cell type</td>
<td>Proportion of leukocytes (%)</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>40–75</td>
<td></td>
</tr>
<tr>
<td>Eosinophil</td>
<td>1–6</td>
<td></td>
</tr>
<tr>
<td>Basophil</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Monocyte</td>
<td>2–10</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>20–50</td>
<td></td>
</tr>
</tbody>
</table>
Other Blood Cells

- Megakaryocyte
  - Platelet formation
  - Wound repair
- Erythrocyte
  - Oxygen transport
Organs of the Immune System

- Primary lymphoid organs
  - Bone marrow
  - Thymus gland
- Secondary lymphoid organs
  - Lymph nodes
  - Spleen
  - MALT
- Tertiary lymphoid organs
  - Cutaneous associated lymphoid tissue
LYMPHOCYTES, LYMPHOID TISSUES AND ORGANS

• Lymphocytes originate in bone marrow
• Lymphoid tissues and organs
  – Primary
    • Development and maturation of lymphocytes
    • Bone Marrow (B cells) and thymus gland (T cells)
  – Secondary
    • Mature lymphocytes meet pathogens
    • Spleen, adenoids, tonsils, appendix, lymph nodes, Peyer’s patches, mucosa-associated lymphoid tissue (MALT)
THE LYMPHATIC SYSTEM

• Lymph
  – Fluid and cells in lymphatic vessels

• Lymphatic vessels
  – Collect and return interstitial fluid to blood
  – Transport immune cells throughout body
  – Transport lipid from intestine to blood

• Lymph nodes
  – Kidney shaped organs at intervals along lymphatic vessels

• Other secondary lymphatic tissues and organs
LYMPHOCYTES AND THE LYMPH NODES

• Naïve lymphocytes circulate between blood, lymph and secondary lymph nodes
• Pathogens from infected tissue sites are picked up by lymphatic vessels and arrive at closest lymph node
• T and B cells congregate at specific regions of nodes
• Architecture and size of nodes change in response to activation of lymphocytes
Venous blood returns to the heart

Naive lymphocytes arrive at lymph nodes in arterial blood

arterial blood

left subclavian vein

venous blood

lymphatics

lymph node

Lymphocytes and lymph return to the blood via the lymphatics

Pathogens from site of infection reach lymph nodes via lymphatics

infected peripheral tissue

Figure 1-16 The Immune System, 2/e (© Garland Science 2005)
- **Thymus**
  - Site of T cell development and maturation
  - Anatomical structure
  - Role in immune function
  - Result of disfunction, DiGeorge’s Syndrome
• Age, thymus size and function of the immune system
The lymph node

- Lymphoid follicle (mostly B cells)
- Medullary sinus
- Artery
- Vein
- Efferent lymphatic vessel
- Germinal center
- Marginal sinus

Figure 1-17 The Immune System, 2/e (© Garland Science 2005)
- Lymphatic System and function of lymph nodes
  - Circulation of lymphocytes
  - Interstitial fluid
  - Route of lymph in the lymph node
  - Antigen-stimulated changes in lymph node
    - Follicle
    - Germinal center
LYMPHOCYTES AND THE SPLEEN

• Spleen
  – Lymphoid organ in upper left abdomen
  – Functions
    • Remove damaged or old erythrocytes
    • Activation of lymphocytes from blood borne pathogens

• Architecture of Spleen
  – Red pulp
    • Erythrocytes removed
  – White pulp
    • Lymphocytes stimulated
SECONDARY LYMPHOID TISSUES ASSOCIATED WITH MUCOUS MEMBRANES

• Primary portals of entry for pathogens
  – Respiratory tract
  – Gastrointestinal tract

• Secondary lymphoid tissues
  – Bronchial-associated lymphoid tissue (BALT)
  – Gut-associated lymphoid tissues (GALT)
    • Tonsils, adenoids, appendix, Peyer’s patches

• Pathogens are directly transferred across mucosa by “M” cells
- Mucosal-Associated Lymphoid Tissue (MALT)
  - Tonsils
    - Three locations
    - Structure and function
• Mucosal membrane of GI tract and its MALT defenses

• General defense mechanism

• Anatomical Structure and function
• Anatomical structure and function
  – Outer layer
    • Intraepithelial cells, epithelial cells, M cells
  – Lamina propria
  – Submucosal layer
- M cells in detail
  - Structure
  - Location
  - Function
  - Accessibility and vulnerability
• Cutaneous-Associated Lymphoid Tissue
  
  – Skin
  
  – Anatomical structure and function

  • Epidermal outer layer
  • Function of keratinocytes, sweat and sebaceous secretions and low pH, Langerhan cells
  • Dermal inner layer