CELLS, TISSUES & ORGANS OF IMMUNE SYSTEM

THE LYMPHATIC SYSTEM
Where Are T Cells And B Cell Made?

- Hematopoietic tissue:
  - Bone marrow
  - Lymphoid progenitor cell
  - Hematopoietic stem cell

- Central lymphoid tissue:
  - T lymphocyte
  - Thymus
  - Bursa
  - T cells to diffuse cortex
  - B cells to primary follicle

- Peripheral lymphoid tissue:
  - Spleen, lymph node, tonsil
Maturation of the immune response

- Lymphoid organs are separated into primary and secondary organs
  - Primary --> bone marrow, thymus
  - Secondary or peripheral --> lymphnodes, spleen, mucosal lymphoid tissues (GALT, MALT), provide sites for mature lymphocytes to interact with antigen
Different organs of the immune system

- adenoid
- tonsil
- right subclavian vein
- lymph node
- kidney
- appendix
- lymphatics
- left subclavian vein
- thymus
- heart
- thoracic duct
- spleen
- Peyer's patch in small intestine
- large intestine
- bone marrow
The role of bone marrow in immune maturation

- Microenvironment for differentiation of stem cells
- Site of origin of B and T lymphocytes, all other cells of the immune response

  - “Antigen-independent” maturation of B cells.

- Site for mature re-circulating lymphocyte populations
Bone Marrow

- Cells move out of Bone Marrow into blood
- The bursa in the bird plays the same role for B cell maturation; appendix in rabbit
Thymus

- The thymus is a bi-lobed organ above the heart
- Each lobe is surrounded by a capsule and divided into lobules which are separated from each other via connective tissue called trabeculae
- Each lobe is organized into 2 compartments
- The outer component is the cortex (packed with immature T cells)
- The inner component is the medulla (sparsely populated with more mature thymocytes)
- Criss-crossing the entire organ is a stromal network of epithelial cells, DCs and macrophages
- These cells participate in positive and negative selection of T cells
- Over 95% of the T cells that enter the thymus die by apoptosis within the thymus without reaching maturity
- The thymus involutes with age
Adult THYMUS
One-year old THYMUS
The Thymus
Thymus-structure/function

- Thymic stroma-->
  network of epithelia-
  contains T cell precursors.
- Dendritic cells,
  macrophage and
  medullary epithelial cells
  in thymic medulla
- Sub-capsular epithelium
  underlying capsule-acts
  as barrier
trabecula
capsule

Hassall’s corpuscles (degenerating layers of Epithelial cells)

The Thymus

Cortex

Medulla

Thymocytes

Cortical epithelial cells

Medullary epithelial cells

Dendritic cells (BM origin)

Macrophages
Schematic diagram of T cell maturation within the thymus
Summary of Thymic Development

Anderson and Jenkinson, NRI, 2001
Major Thymocyte Subsets

**CD4-CD8- (Double Negative, DN) cells:** 3-5% of total thymocytes
- Contain least mature cells, considerable cell division
- 2/3rds are triple negative (TN) based on TCR expression
- Can be further divided based on CD44 and CD25 (discussed later)
- TCR $\beta,\gamma$ and $\delta$ rearrangements occur at this stage
- 1/3rd are TCR $\gamma\delta^+$

**CD4+CD8+ (Double Positive, DP) cells:** 80-85% of total thymocytes
- TCR $\alpha$ rearrangement occurs at this stage
- Most have rearranged TCR $\alpha\beta$ genes & express low levels (10% mature level) of TCR
- Small subset has high levels of TCR (most mature, positively selected cells)
- Small subset is actively dividing (earliest DPs)
- Most apoptosis occurs here, very sensitive to apoptosis inducing agents, especially sensitive to glucocorticoids

**CD4+CD8- and CD4-CD8+ (Single positive, SP) cells:** 10-15% of total thymocytes
- Most are mature cells with high levels of CD3 and TCR $\alpha\beta$
- CD4:CD8 approx 2:1 ratio
- Most SP cells are functionally mature and are destined to leave the thymus
- Small subset of SP are immature (ISP) (CD8 in mouse, CD4 in human) and have low CD3 and no TCR $\alpha\beta$ - transitional cells that are on the way from DN -> DP
**T cells**

- **T<sub>C</sub> cell**
  - TCR
  - CD8
  - Recognizes MHC I on all cells
  - Kills: Infected cells, Tumour cells

- **T<sub>H</sub> cell**
  - TCR
  - CD4
  - Recognizes MHC II on APC
  - Helps: B-cells, T cells, Macrophages
Accessory Molecules
Two classes of T-cell receptor

antigen-binding site

α chain β chain

γ chain δ chain

variable region (V)

constant region (C)

transmembrane region

cyttoplasmic tail

α:β T cell

γ:δ T cell

Figure 5.7 The Immune System, 3rd ed. (© Garland Science 2009)
<table>
<thead>
<tr>
<th>Stage of maturation</th>
<th>Stem cell</th>
<th>Pro-T</th>
<th>Pre-T</th>
<th>Double positive</th>
<th>Single positive (immature T cell)</th>
<th>Naive mature T cell</th>
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<tbody>
<tr>
<td>Proliferation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAG expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TdT expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCR DNA, RNA</td>
<td>Unrecombined (germline) DNA</td>
<td>Unrecombined (germline) DNA</td>
<td>Recombined β chain gene [V(D)J-C]; β chain mRNA</td>
<td>Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA</td>
<td>Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA</td>
<td>Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA</td>
</tr>
<tr>
<td>TCR expression</td>
<td>None</td>
<td>None</td>
<td>Pre-T receptor (β chain/pre-T α)</td>
<td>Membrane αβ TCR</td>
<td>Membrane αβ TCR</td>
<td>Membrane αβ TCR</td>
</tr>
<tr>
<td>Surface markers</td>
<td>c-kit⁺ CD44⁺ CD25⁻</td>
<td>c-kit⁺ CD44⁺ CD25⁺</td>
<td>c-kit⁺ CD44⁺ CD25⁺</td>
<td>CD4⁺CD8⁺ TCR/CD3lo</td>
<td>CD4⁺CD8⁻ or CD4⁺CD8⁺ TCR/CD3hi</td>
<td>CD4⁺CD8⁻ or CD4⁺CD8⁺ TCR/CD3hi</td>
</tr>
<tr>
<td>Anatomic site</td>
<td>Bone marrow</td>
<td>Thymus</td>
<td></td>
<td></td>
<td></td>
<td>Periphery</td>
</tr>
<tr>
<td>Response to antigen</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Positive and negative selection</td>
<td>Negative selection</td>
<td>Activation (proliferation and differentiation)</td>
</tr>
</tbody>
</table>
T cells
CD2

• CD2 is a glycoprotein present on more than 90% of mature T-cells and 50-70% of thymocytes.
• This molecule contains two extracellular Ig domains.
• The principle ligand for CD2 is LFA-3 (CD58).
CD2

- CD2 functions both as an adhesion molecule and signal transducer.
- The association of CD2 with the TCR complex helps to aggregate the TCR in the regions of cell–cell contact, allowing the stabilization of low-affinity TCR/MHC interactions.
- Finally, CD2 is involved in the regulation of cytokine production by T cells.
- Stimulation via the CD2 pathway can skew the cytokine profile toward a TH2-like phenotype.
TCRs occur as either of two distinct heterodimers, \( \alpha \beta \) or \( \gamma \delta \), both of which are expressed with the non-polymorphic polypeptides \( \gamma, \delta, \varepsilon, \) and \( \zeta \).

The CD3 polypeptides, especially \( \zeta \) and its variants, are critical for intracellular signaling.
<table>
<thead>
<tr>
<th>Feature</th>
<th>αβ T cells</th>
<th>γδ T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of CD3⁺ cells</td>
<td>90–99%</td>
<td>1–10%</td>
</tr>
<tr>
<td>TCR V gene germ-line repertoire</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>CD4/CD8 phenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4⁺</td>
<td>~60%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CD8⁺</td>
<td>~30%</td>
<td>~30%</td>
</tr>
<tr>
<td>CD4⁺CD8⁺</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CD4⁻CD8⁻</td>
<td>&lt;1%</td>
<td>~60%</td>
</tr>
<tr>
<td>MHC restriction</td>
<td>CD4⁺: MHC class II</td>
<td>No MHC restriction</td>
</tr>
<tr>
<td></td>
<td>CD8⁺: MHC class I</td>
<td></td>
</tr>
<tr>
<td>Ligands</td>
<td>Peptide + MHC</td>
<td>Phospholipid antigen</td>
</tr>
</tbody>
</table>

### TCR Accessory Molecules

#### TABLE 9-4  Selected T-cell accessory molecules

<table>
<thead>
<tr>
<th>Name</th>
<th>Ligand</th>
<th>Adhesion</th>
<th>Signal transduction</th>
<th>Member of Ig superfamily</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>Class II MHC</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD8</td>
<td>Class I MHC</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD2 (LFA-2)</td>
<td>CD58 (LFA-3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LFA-1 (CD11a/CD18)</td>
<td>ICAM-1 (CD54)</td>
<td>+</td>
<td>?</td>
<td>+/(-)</td>
</tr>
<tr>
<td>CD28</td>
<td>B7</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>B7</td>
<td>?</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD45R</td>
<td>CD22</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>CD72</td>
<td>?</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Diseases related to Thymic Defects

• DiGeorge’s syndrome - congenital birth defect in humans; no functional thymus
• Nude mice - fail to develop a thymus
• Experimentally, you can thymectomize mice at a young age as well.
Bone Marrow

1. The site of generation of all immune and blood cells
   \(\Longleftrightarrow\) Hematopoietic Stem Cell

2. Provides Cell-cell interactions and Cytokines for the development of all immune cells.
   \(\Longleftrightarrow\) Stromal reticular cells & other cells
B cell development in the Bone Marrow

Schematic organization of B cell development in the bone marrow

- arteriole
- capillaries
- sinusoid
- central sinus
- endosteum
- adventitial reticular cell
- bony lamella
- reticular cell
- macrophage

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Bone marrow stromal cells drive Pro-B cell proliferation and maturation.

Important molecules and interactions:
SCF-cKit
IL-7-IL-7R
Pre-B cell

$V_H D_H J_H C_\mu$

Surrogate light chain

Vpre-B

$\lambda 5$

Cross-linking by stromal cell ligand

Stops $V_H \rightarrow D_H J_H$

(allellic exclusion) ?

Induces $V_L \rightarrow J_L$ ?

Figure 11-4 part 2
Kuby IMMUNOLOGY, Sixth Edition
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Stages in B-cell maturation in the bone marrow

**H-chain genes**
- Germ line
- $D_H J_H$
- $V_H D_H J_H$

**L-chain genes**
- Germ line
- Surrogate Vpre-B and $\lambda 5$
- Germ-line $\kappa$ and $\lambda$
- Surrogate Vpre-B and $\lambda 5$
- Germ-line $\kappa$ and $\lambda$
- $V_L J_L$

**RAG-1/2**
- $-$
- $+$
- $+$
- $-$
- $-$
- $-$

**TdT**
- $-$
- $+$
- $-$
- $-$
- $-$
- $-$

**Membrane Ig**
- $-$
- $-$
- $-$
- $-$
- $-$
- $-$

**Heavy chain**
- Surrogate light chain
- $\mu$
- Surrogate light chain
- $\kappa$ or $\lambda$

**Light chain**
- Surrogate light chain
- $\mu + \delta$

**Transcription factors**
- Pu.1, Ikaros, others
- BSAP(Pax-5)
- Sox-4
- EBF
- E2A
- Oct-2

**Surface markers**
- c-Kit
- CD45R, CD19, HSA(CD24), Ig-\(\alpha\)/Ig-\(\beta\)
- IL-7R
- CD43
- MLgM
- CD25
- MLgD

*Figure 11-3*
*Kuby IMMUNOLOGY, Sixth Edition*
**Notes**

1. The Ig molecule (either pre-BCR or BCR) can not travel to the surface of the B cell without Igα and Igβ
2. The pre-BCR and BCR consist of an Ig molecule plus Igα and Igβ
3. Igα and Igβ genes turned on at the pro-B-cells stage and remain on until cell becomes and antibody secreting plasma cell
4. Igα and Igβ send signals when receptors are engaged (bound antigen)
Peripheral or Secondary lymphoid tissues

- Trap antigen-bearing dendritic cells
- Initiation of adaptive immune response
- Provide signals that sustain recirculating lymphocytes
Lymph Nodes

- Sites of Immune responses
- Encapsulated bean-shaped structures, reticular network, full of lymphocytes, macrophages, and dendritic cells.
- First organized lymphoid structure to encounter antigens—reticular structures trap antigen
Lymph Nodes

- **Cortex**
  - Contains mostly B cells, macrophages and follicular dendritic cells

- **Paracortex**
  - Primarily T lymphocytes, and dendritic cells

- **Medulla**
  - Sparsely populated with lymphoid lineage cells (mostly plasma cells)
Where are these lymph nodes?
Lymph Nodes

• Range from 1–25 mm diameter
Lymphatic System: Anatomy

(b) Lymph node
artery and vein

Efferent lymph vessel

Clusters of immune cells
intercept pathogens that
invade interstitial fluid.

Capsule

Afferent lymph vessel

Figure 24-2b
Structure/function of the Lymph Node

Germinal center foci
Reach maximum
Size within 4 to 6
days of antigen challenge.
Spleen

- Major role in mounting immune responses to antigens in the bloodstream
  - Filters blood and traps antigens

- Not supplied with lymphatic vesicles
  - Splenic artery carries antigens and lymphocytes
Structure of the Spleen

• Surrounded by a capsule from which a number of trabeculae extend into interior (compartmentalized structure)
Structure of the Spleen

- Spenic red pulp consists of a network of sinusoids
  - Populated by macrophages, RBCs, and a few lymphocytes
  - Site where old and defective RBCs are destroyed and removed
  - Macrophage engulf RBCs
Structure of the Spleen...

- Spenic white pulp surrounds the branches of the splenic artery
  - Forms periarтерiolar lymphoid sheath (PALS), populated primarily by T cells.
  - Primary lymphoid follicles are attached to the PALS, are rich in B cells and some contain germinal centers
  - Marginal zone, peripheral to the PALS, is populated by lymphocytes and macrophages
Spleen

1. The site of immune responses to blood Ags => A filter of blood

2. White pulp => T cell & B cell zones
   Marginal zone (MZ)
   Red pulp (RP)

3. T cells => periarteriolar lymphoid sheaths
   B cells => follicle
   => marginal zone
Organization of a germinal center in the spleen

- PFZ-perifollicular zone
- PALS-periarticular lymphoid sheath
- Co-follicular B-cell corona
- MZ-marginal zone
- RP-red pulp
Loss of spleen (splenectomy)

• Severity depends on age
• In children, splenectomy often leads to increased incidence of bacterial sepsis
• Few adverse effects in adults, can lead to some increase in blood-borne bacterial infections (bacteremia)
MALT or Mucosa-assoc. Lymphoid Tissue

- Mucous membranes lining digestive, respiratory and urogenital system are the major sites of entry for most pathogens.

BALT - Bronchus-associated (respiratory)
GALT - gut-associated (digestive tract)
MALT...

• Have different organizations.
  – Peyer’s patches in intestinal lining well organized
  – Barely organized clusters of lymphoid cells in lamina propria of intestinal villi
  – Tonsils
  – appendix

• Large nos. of plasma cells (more than in the spleen and lymph Nodes)
**M Cells.**

Have a deep invagination or pocket, in the basolateral plasma membrane, which is filled with a cluster of B cells, T cells and Macrophage.

Antigens in intestinal lumen are endocytosed into vesicles and transported from the luminal membrane to underlying pocket membrane.

Vesicles fuse with the pocket membrane, delivering antigens to lymphocytes and macrophage.
Lymphoid Nodules
Jobs of Lymphatic System:

Lymphatic System which consists of vessels and organs plays two vital roles in our lives:

1) The vessels essentially maintain interstitial fluid levels by carrying excess fluids as well as any plasma proteins, back into the CVS.

2) The organs, house critical immune cells such as lymphocytes which carry out our body defense against infection and disease as well as offer acquired immunity.
Lymphatic Characteristics

- **Lymph** – excess tissue fluid carried by lymphatic vessels (general definition)

- **Properties of lymphatic vessels**
  - One way system toward the heart
  - No pump
  - Lymph moves toward the heart
    - Milking action of skeletal muscle
    - Rhythmic contraction of smooth muscle in vessel walls
The diagram illustrates the relationship between the venous system, arterial system, lymphatic system, and the circulation of blood and tissue fluid.

- **Venous system** connects to the arterial system through the heart.
- The lymphatic system includes lymph ducts and lymph trunks, with lymph nodes along the way.
- Lymphatic collecting vessels, with valves, lead to lymph capillaries, which eventually pass through tissue fluid that becomes lymph.
- Blood capillaries are connected to the venous system, and loose connective tissue around capillaries is also depicted.

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Composition of Lymph

• Lymph is usually a clear, colorless fluid, similar to blood plasma but low is protein

• Its composition varies from place to place; after a meal, for example, lymph draining from the small intestine, takes on a milky appearance, due to lipid content.

• Lymph may contain macrophages, viruses, bacteria, cellular debris and even traveling cancer cells.
What Type of Vessels Make up the Lymphatic System?

- The vessels are called lymphatics.
- They are thin-walled and are analogous to veins.
- Small lymphatics are similar to capillaries only more porous; Larger vessels are called collecting vessels: both have valves.
- 2 large Ducts: Right LYMPHATIC DUCT and THORACIC DUCT (BOTH EMPTY INTO THE RT AND LT SUBCLAVIAN VEINS)
- Lymph flows only TO THE HEART (ONE WAY).
- This is a low-pressure, pumpless system. Lymph moves via skeletal muscles and pressure changes in thorax during breathing only.
CIRCULATION IN THE LYMPH VESSELS

Lymph vessels do not have a central pump equivalent to the heart. Their performance depends especially on their compression caused by adjacent muscles. A regular decrease in pressure that occurs inside the thoracic cage during inhalation makes it easy for the lymph to go up from the legs to the trunk of the body. Inside the lymph vessels, there is a valve system that ensures lymph circulation in just one direction and prevents its backflow.
Lymph Carries ...

- Harmful materials that enter lymph vessels
  - Bacteria
  - Viruses
  - Cancer cells
  - Cell debris
Edema is the excess accumulation of fluids in tissue spaces. This can retard normal exchange of nutrients and metabolites. Filtration of the extracellular fluid exceeds drainage. Anything that causes increased capillary pressure, such as decreased plasma protein, increased capillary permeability or lymphatic blockage, can result in swelling and congestion of the extravascular compartment.
Lymphatic Vessels and Valves
Lymphatic System

- Blood circulates under pressure, fluid component (plasma) seeps through capillaries into surrounding tissues
  - Called interstitial fluid
  - An adult-3 liters or more per day
  - Returned to blood through walls of the venules (prevents edema)
  - Remainder of fluid enter lymphatic system
• Porous architecture of lymphatic vessels (allows fluids and cells to enter)

• Thoracic duct = largest lymphatic vessel
  – Empties into L. subclavian vein (lymph from all the body except r. arm and r. side of head)

• Ensures steady-state levels of fluid within the circulatory system
Lymphatic System...

- Heart does not pump lymph
- Lymph flow is achieved by movements of the body’s muscles
- Series of one-way valves produces one-way movement through vessels
- Foreign antigen is picked up by the lymphatic system and carried to lymph nodes
Circulation of lymphocytes in response to infection