Lecture 8: The Development and Survival of Lymphocytes (based on lecture by Dr. Barbara Birshtein)
Questions to Consider

- How does the immune system provide a high degree of sensitivity and specificity to the broad array of pathogens without attacking self?
- How is T cell and B cell maturation different?
- How does a T cell know whether to be a CD4 T cell or a CD8 T cell?
Process of Pathogen Clearance

- **Pathogens:** viruses, bacteria and fungi
- **Phagocytes:** myeloid cells (neutrophils, macrophages, basophils, eosinophils)
- Innate vs Adaptive immunity
Immune System

- Innate immunity-antigen non-specific
  - Pattern recognition receptors (myeloid cells)

- Adaptive, antigen-specific immunity
  - Antigen-recognition by B cells (humoral, antibody-dependent)
  - Antigen-recognition by T cells (MHC)
  - Antigen-presentation, MHC
Role of Bone Marrow-derived Leukocytes In Immunity

Adaptive immune system (lymphoid cells)

Bridge between innate and adaptive immunity

Innate immunity (myeloid cells)

Bone Marrow

Blood
Blood Cells Are Generated and Develop In the Bone Marrow

![Diagram of blood cell generation and development]

STEM CELL | COMMITTED PROGENITORS | DIFFERENTIATED CELLS
---|---|---
pluripotent hemopoietic stem cell | common lymphoid progenitor | NK cell
pluripotent hemopoietic stem cell | common myeloid progenitor | T cell (THYMUS)

---

Figure 22–35. Molecular Biology of the Cell, 4th Edition.
Generation of the T Cell and B Cell Antigen-specific Repertoire Involves the Elimination of Self-reactive Cells

Bone marrow/Thymus

- A single progenitor cell gives rise to a large number of lymphocytes, each with a different specificity
- Removal of potentially self-reactive immature lymphocytes by clonal deletion

Blood/lymphoid tissue

- Pool of mature naive lymphocytes
- Foreign antigen
- Proliferation and differentiation of activated specific lymphocytes to form a clone of effector cells
- Effector cells eliminate antigen
B Cell Development in Bone Marrow Generates IgM+ Cells

**Figure 4-19 Immunobiology, 6/e. © Garland Science 2005**

**Human**

| VDJ | C_μ | C_δ | C_γ3 | C_γ1 | ψC_ε | C_α1 | C_γ2 | C_γ4 | C_ε | C_α2 |

**Membrane-bound IgM (mIgM)**

- Recognition
- Light chain
- Heavy chain
- Ig2 Igμ
- Signaling

**VDJ, VH**
**VJ: VL**
Allelic Exclusion: Each B Cell Only Expresses a Single Ig Gene Allele
B Cells Develop in the Bone Marrow
B Cell Development in Bone Marrow Begins with Heavy Chain Gene Formation

<table>
<thead>
<tr>
<th>Genes</th>
<th>Proteins</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pro-B cell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_H$, $C_\mu$</td>
<td>$DJ_H$, $C_\mu$</td>
<td>No functional protein expressed</td>
</tr>
</tbody>
</table>

The $V_H-DJ_H$ rearrangements occur.

*Figure 7-17 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)*
B Cell Development in Bone Marrow: Pre-B Cells

Pro-B, pre-B
B Cell Development in Bone Marrow Results in IgM+ B Cells

<table>
<thead>
<tr>
<th>Immature B cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDJ&lt;sub&gt;H&lt;/sub&gt;</td>
</tr>
<tr>
<td>VJ&lt;sub&gt;L&lt;/sub&gt;</td>
</tr>
<tr>
<td>V&lt;sub&gt;H&lt;/sub&gt;</td>
</tr>
<tr>
<td>V&lt;sub&gt;L&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

Stop light-chain gene rearrangement

Pro-B, pre-B, B cells
B Cells That Do Not Detect and Bind to Self-antigen Can Leave the Bone Marrow

<table>
<thead>
<tr>
<th>Low-affinity noncross-linking self molecule</th>
<th>No self reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram of B cell with IgM and IgD" /></td>
<td><img src="image2.png" alt="Diagram of B cell with IgM and IgD" /></td>
</tr>
<tr>
<td>Migrates to periphery</td>
<td>Migrates to periphery</td>
</tr>
<tr>
<td><img src="image3.png" alt="Diagram of mature B cell with IgM and IgD" /></td>
<td><img src="image4.png" alt="Diagram of mature B cell with IgM and IgD" /></td>
</tr>
<tr>
<td>Mature B cell (clonally ignorant)</td>
<td>Mature B cell</td>
</tr>
</tbody>
</table>
Autoreactive B cells Die or Can Undergo L Chain Receptor Editing (sequential VJ joining)
Some B Cells Become Anergic
Schematic Of Commitment Of Lymphoid Progenitors To Lymphocyte Formation

1. Cytokine (growth factor)
2. Receptor for cytokine
3. Signaling
4. Tissue-specific transcription factors
B Cell Development Requires Specific Cytokine Receptors and Transcription Factors

<table>
<thead>
<tr>
<th>Multipotent progenitor</th>
<th>Common lymphoid progenitor</th>
<th>Specified B-lineage cell</th>
<th>Pro-B cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3</td>
<td>IL-7R</td>
<td>EBF</td>
<td>CD19</td>
</tr>
<tr>
<td>PU.1</td>
<td>E2A</td>
<td>EBF</td>
<td>Pax-5</td>
</tr>
<tr>
<td>Ikaros</td>
<td></td>
<td>E2A</td>
<td>Igα</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Membrane-bound IgM (mIgM) recognition and signaling:

- Light chain
- Heavy chain
- Igα
- Igβ
B Cell Development Involves Specific Signal Transduction Components

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igα</td>
<td>Signal transduction</td>
</tr>
<tr>
<td>Igβ</td>
<td></td>
</tr>
<tr>
<td>CD45R</td>
<td></td>
</tr>
<tr>
<td>Btk</td>
<td></td>
</tr>
<tr>
<td>Oct-2</td>
<td></td>
</tr>
<tr>
<td>EBF</td>
<td></td>
</tr>
<tr>
<td>Pax-5/BSAP</td>
<td></td>
</tr>
<tr>
<td>GATA-2</td>
<td></td>
</tr>
<tr>
<td>Ikaros</td>
<td></td>
</tr>
</tbody>
</table>

Figure 7-19 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)
After B Cells Leave the Bone Marrow

B1 cells (IgM+, low affinity, low CSR, “innate”, peritoneal cavity)

Marginal zone B cells-spleen, blood-borne antigens

Follicular B cells-spleen, foci, germinal centers, SHM, CSR

Figure 7-40 Immunobiology, 6/e. (© Garland Science 2005)
T Cell Maturation and Selection
Thymus-site Of T Cell Formation

Cortex

Medulla

Figure 7-8 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)
Because T Cells See Antigen (Peptide) In Context Of MHC T Cell Development Requires TCR To Recognize MHC Class I Or II
Thymocytes Undergo Positive and Negative Selection

- **Positive selection**
  - recognition of self-MHC

- **Negative selection**
  - avoid strong binding to self-antigen
T Cell Development in the Thymus Results in Mature Single Positive T Cells

CD4- CD8- (Double-negative DN)
- CD44+ CD25-
- pre-TCR
- proliferation

CD4+ CD8+ (Double-positive DP)
- CD8
- TCR

CD4+ or CD8+ (Single-positive)

Rearrangement
1. D-Jβ
2. V-DJβ
3. V-Jα

TCR beta TCR alpha

Figure 7-13 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)
Thymocyte Selection Occurs in Thymic Architecture

Positive selection involves recognition of self-MHC; cortical epithelial cells
DP to SP (CD4, CD8); mechanism not really known

Negative selection predominantly in medulla (medullary epithelial cells)
Positive and Negative Thymocyte Selection

Figure 24–61. Molecular Biology of the Cell, 4th Edition.
Products of T Cell Development In Thymus

- Alpha-beta T cells
  - CD4 and CD8
- Delta-gamma T cells
- Regulatory T cells
  - CD4+
Genetic Defects in T Cell Development

- VCFS, DiGeorge-no thymus
- X-SCID mutation (common \(\gamma\) chain of multiple receptors- no T cell development
- Lack of MHC class I-no CD8+ T Cells
- Lack of MHC class II-no CD4+ T Cells
- AIRE
- IPEX
Defect in Thymic Protein Synthesis Results in Autoimmunity

- AIRE (autoimmune regulator) is involved in expression of non-thymic tissue-specific, proteins in the thymus.

- Mutations in AIRE result in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) (also known as autoimmune polyglandular syndrome (APS) type I).
Regulatory T cells are Generated in Thymus

- CD4+ CD25+ T cells
- Dependent on Fox P3 transcription factor
- Mutation of FoxP3
  - deficiency of T regs/ IPEX
  - Immunodysregulation
  - Polyendocrinopathy
  - Enteropathy
  - X-linked
  - multi-organ autoimmune disorder
Malignant Transformation in Developing T and B Cells

- Bone marrow, thymus
- TCR, BCR chromosomal translocations
  - aberrant activation of oncogenes
### Developing T Cells Can Become Malignant

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cell</th>
<th>Characteristic cell-surface markers</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common acute lymphoblastic leukemia (C-ALL or B-ALL)</td>
<td>Lymphoid progenitor</td>
<td>CD10, CD19, CD20</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Thymic stromal cell or epithelial cell</td>
<td>Cytokeratins</td>
<td>Thymus</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia (T-ALL)</td>
<td>Thymocyte</td>
<td>CD1</td>
<td>? Notch</td>
</tr>
</tbody>
</table>

*Figure 7-44 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)*
Developing B Cells Can Become Malignant

<table>
<thead>
<tr>
<th>Name of tumor</th>
<th>Normal cell equivalent</th>
<th>Location</th>
<th>Status of Ig V genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>Lymphoid progenitor</td>
<td>Bone marrow and blood</td>
<td>Unmutated</td>
</tr>
<tr>
<td>Pre-B cell leukemia</td>
<td>Pre-B cell</td>
<td></td>
<td>Unmutated</td>
</tr>
</tbody>
</table>

Figure 7-42 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)
Generation of an Effective Primary Immune Repertoire

- B cells in bone marrow and T cells in thymus
- Antigen-binding receptors
  - BCR, TCR/CD4/CD8
- Signals for life and death of cells
  - survival/apoptosis
- Avoid immune deficiency
- Avoid autoimmunity
- Avoid malignancy
T and B Cell Formation in Primary Lymphoid Organs

Questions to Consider

- How does the immune system provide a high degree of sensitivity and specificity to the broad array of pathogens without attacking self?
- How is T cell and B cell maturation different?
- How does a T cell know whether to be a CD4 T cell of CD8 T cell?