Antigen-Independent B-Cell Development

Bone Marrow

1. DNA rearrangements establish the primary repertoire, creating diversity

2. Allelic exclusion ensures that each clone expresses a single antibody on the surface, establishing specificity

3. Deletion of self-reactive clones establishes tolerance

Bone Marrow Stromal Cells Support Early B Lymphopoiesis

Ordered Rearrangement of Ig Genes During B-Cell Development in the Bone Marrow

Heavy chain rearrangement occurs first:
- DJ on both alleles
- V-DJ on one allele

Productive rearrangement (1/9)
- Mu and preBCR (surrogate L.C.)
- V-DJ on second allele

Non-productive rearr. (8/9)
- V-DJ on second allele
- Mu and pBCR
- Non-prod.

1. STOP H.C. rearrangement
2. Proliferation
3. Begin L.C. rearrangement

DEATH

Productive rearrangement produces IgM and the B CELL RECEPTOR on the surface

STOP further L.C. rearrangement

Light Chain Rearrangement: 4 possible alleles, each with 1/3 chance of a productive rearrangement

Kappa usually precedes lambda

Productive rearrangement produces IgM and the B CELL RECEPTOR on the surface

STOP further L.C. rearrangement

CONTINUE DEVELOPMENT

DEATH
Rearrangement of Ig alleles is ordered and regulated to achieve allelic exclusion

Checkpoints which confer allelic exclusion

pBCR

BCR

THE B CELL RECEPTOR

1. Bound antigen is internalized and presented to T cells.
2. Bound antigen gives signals to the B cell to proliferate and differentiate.

Signalling from the BCR

Lack of Btk causes Bruton's XLA (blocked at preB stage)

IgM on B Cell Surface

Recognition of self

No self recognition

1. Proliferation
2. Maturation
3. Exit to periphery

DEATH

Light Chain Receptor Editing to Change the Specificity of Self-reactive Clones

Strong binding of light by self antigen

A new receptor specificity is now expressed

If the new receptor is no longer self reactive, the B cell undergoes apoptosis

If the new receptor is no longer self reactive, the B cell undergoes apoptosis
Ig Gene Status at Different Stages Of Antigen-Independent B-Cell Development

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Antigen-Dependent B Cell Development

In Periphery (spleen and LN)

Antigen and T cells give B cells two signals:
1) proliferate  2) differentiate

T-cell dependent responses are refined two ways:
1) higher affinity antibodies
2) IgG/A/E ("switched") isotypes

Two products of B cell development:
1) plasma cells secrete Ig (final effector)
2) memory cells respond to IIo antigen

Antigen-Dependent B Cell Development

By T-Cell Dependent And T-Cell Independent Antigens
The Germinal Center

T Cell-B Cell Communication
(B cells signal T cells by presenting Ag in association with MHC II)

1. Cell-cell signals from CD40L/CD40 and other surface molecules.
2. Secreted cytokines

T cells provide 2 kinds of help to B cells:

1. Affinity maturation
   a. Somatic hypermutation
   b. Selection for high affinity clones
2. Isotype switch recombination
3. Peripheral tolerance
4. Final maturation to memory or plasma cell.

AFFINITY MATURATION IN THE GC

Proliferation + Somatic Hypermutation → Survivall
(Iterative cycles)

Ag(FDC) + T cell help → Survival

but

T help and no Ag (eliminates low affinity clones)
or

Ag and no T help (eliminates self-reactive clones, giving tolerance)

Pattern of V Gene Mutations Provides Evidence Of Cyclical Mutation and Selection Events

Random mutation combined with selection.
B Cells Making Ig with High Affinity for Antigen Are Selectively Protected from Apoptosis in the Germinal Center.

SELECTIVE SURVIVAL IN GC

1. Selects clones producing high affinity antibody--i.e. affinity maturation
2. Eliminates self-reactive clones--peripheral tolerance.

Hyper IgM Syndrome

1. Mutations in CD40L
2. Mutations in CD40
3. Mutations in AID (or repair enzymes downstream of AID)
4. One or more other genes defined by human disease!

Hypermunoglobulinemia

1. Memory B cells
   - Surface Ig, usually IgG
   - High affinity for antigen
   - Long-lived, even in the absence of antigen
   - Respond rapidly to secondary stimulation

2. Plasma Cells
   - Secrete copious amounts of Ig, no surface Ig
   - Non-dividing
   - Some are short-lived, some become long-lived in the bone marrow

Different Ig Isotypes
Ig Isotypes Have Different Functions and Distributions

<table>
<thead>
<tr>
<th>Functional activity</th>
<th>IgA</th>
<th>IgM</th>
<th>IgG1</th>
<th>IgG2</th>
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<tr>
<td>Neutralization</td>
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Antibodies Activate NK Cell Killing by Engaging Fc Receptors

Antibodies Can Neutralize Pathogens

Antibodies Activate Complement-Mediated Lysis

Opsonization of Pathogens by Antibodies
**SUMMARY**

1. Antigen-independent B-cell development occurs in the bone marrow:
   - DNA rearrangements create a diverse primary repertoire
   - pBCR and BCR provide developmental checkpoints
   - Self-reactive clones are edited or deleted, providing central tolerance

2. Antigen-dependent B-cell development occurs in the spleen and lymph nodes:
   - TI responses involve repeating epitopes and TLR activation
   - TD responses involve cell-cell contact and soluble mediators

3. Peripheral B-cell tolerance occurs by editing, anergy or clonal deletion in the spleen.

4. Affinity maturation and CSR occur in germinal center B cells and require T cells, follicular dendritic cells and antigen. Memory cells and plasma cells emerge from the germinal center reaction.

5. Immune deficiencies result from gene defects in Btk, CD40, CD40L & AID.