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

Heavy chain rearrangement occurs first: DJ on both alleles V-DJ on first allele
- Productive rearrangement (1/9)
- Non-productive rearr. (8/9)
- preBCR (Mu and surrogate L.C.)

Ig Heavy Chain VDJ Recombination--2 DNA Recombinations, DJ and VD

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

pBCR (Mu heavy chain + surrogate light chains) signals
Productive rearrangement produces IgM and the B CELL RECEPTOR on the surface.

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.

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<tr>
<th>Light Chain Alleles</th>
<th>Occurrence</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>K, GL, GL</td>
<td>1/3</td>
<td>PR,GL</td>
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Checkpoints which confer allelic exclusion:
- pBCR
- BCR

Signalling from the pBCR and BCR:
- Lack of Brutons' Tyrosine Kinase causes Bruton's XLA (X-linked agammaglobulinemia).
- B cell development is blocked at the preB stage, due to failure of pBCR. No B cells, no antibodies, causing recurrent bacterial and viral infections.

Central B-Cell Tolerance: Editing and Clonal Deletion (in Bone Marrow):
- IgM on B Cell Surface
- Recognition of self:
  - No self recognition
  - L.C. editing:
    - 1. Proliferation
    - 2. Maturation
    - 3. Exit to periphery
- Recognition of self
- DEATH

The B Cell Receptor:
- Bound antigen gives signals to the B cell to proliferate and differentiate.

Repeated rearrangements are possible at the light-chain loci:
- First VJ recombination
- Second VJ recombination
- Third VJ recombination
- Nonproductive join
- Nonproductive join
- Nonproductive join
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**Antigen-Dependent B Cell Maturation**

**In Periphery (spleen and LN)**

Antigen and T_{H} 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 II^{+} antigen

**T Cell Help Is Required for GC Reactions**

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

T cells provide 2 kinds of help to B cells:
1. Cell-cell signals from CD40L/CD40 and other surface molecules.
2. Secreted cytokines
1. Affinity maturation
   a. Somatic hypermutation—requires AID
   b. Selection for high affinity clones
2. Isotype switch recombination—requires AID
3. Peripheral tolerance
4. Final maturation to memory or plasma cell.

**AFFINITY MATURATION IN THE GC**

Proliferation + Somatic Hypermutation

(Iterative cycles)

Ag(FDC) + T cell help → SURVIVAL/SELECTION

T help and no Ag binding (eliminates low affinity clones) or
Ag binding and no T help (eliminates self-reactive clones, giving tolerance)

**SELECTIVE SURVIVAL IN GC**

Requires: a. High affinity surface Ig
   b. Ag-specific T cell help, esp. via CD40/CD40L

1. Selects clones producing high affinity antibody—i.e. affinity maturation
2. Eliminates self-reactive clones—peripheral tolerance.
CSR Involves DNA Deletion and Loss

T cell secretes cytokines

Specific I region transcription

Isotype switch recombination to specific \( C_{\mu} \) gene segment

Hyper IgM Syndrome

(Increased susceptibility to specific pathogens)

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 remain to be identified

“Germline” (I region) Transcripts Are Necessary For Isotype Switch Recombination

T Cell Cytokines Instruct Choice of Isotype

Hyper IgM Syndrome

Marginal Zone

Germinal Center

Low affinity IgM

Plasma Cell

Memory Cell
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—final B cell effectors**
   - Secrete copious amounts of Ig, no surface Ig
   - Non-dividing
   - Some are short-lived, some become long-lived in the bone marrow

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**ANTIGEN-DEPENDENT B CELL MATURATION**

1. Occurs in periphery (spleen, lymph nodes)
2. Antigen selects specific clones for proliferation and maturation.
3. Bacterial polysaccharides are T-cell independent activators of B cells.
4. Protein antigens require T cells to help B cells mature.
5. T cells and B cells communicate:
   - B cells process antigen and present peptide-MHC to T cells, which stimulates the T cells.
   - T cells provide cell-cell signals via CD40L/CD40
   - T cells provide soluble cytokine signals
6. T-cell dependent B cell maturation occurs in Germinal Centers
7. Affinity maturation in GCs results from somatic hypermutation + selection for high antigen-binding affinity
8. Class switch recombination occurs in GCs
9. Deletion of self-reactive clones provides peripheral tolerance.
10. Memory B cells and plasma cells emerge from the GC reaction.

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**MEMORY B CELLS and a MEMORY RESPONSE**

**MEMORY CELLS**
1. Memory cells are post-GC
   a. High affinity
   b. Switched isotype
2. Memory cells differentiate into plasma cells rapidly
3. Long-lived in absence of antigen.

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**Plasma Cells—Final B-Cell Effectors**

1. One job: secrete antibody
2. Terminally differentiated, post-mitotic
3. Limited half-life