

**Lymphocyte Lineage**      **LOCATION**

Lymphocyte Lineage	LOCATION		
<b>Lymphoid Precursors</b>	<b>BONE MARROW</b>	<b>B Cells</b>	<b>T Cells</b>
<b>pro-B Cell</b>	<b>BONE MARROW</b>	<p>express CD19 and CD 10</p> <p>1st expression of RAGs</p> <p>D-J recombination occurs in Ig H chain <i>at both alleles</i></p> <p>V-DJ recombination <i>at one allele, and if needed the other allele</i> occurs: only in committed B cell precursors</p> <p>TdT is highly expressed</p>	<p>IL-7 Receptor expression</p> <p><b>pro-T Cell</b>      <b>THYMUS</b></p> <p>do not express TCR, CD3 or <math>\zeta</math> chains</p> <p><b>double negative thymocytes</b></p> <p>majority of double negative thymocytes will give rise to <math>\alpha\beta</math> TCR expressing T cells</p> <p>1st expression of RAGs</p> <p>D<math>\beta</math>-J<math>\beta</math> rearrangement occurs <i>at both alleles</i></p> <p>TdT is highly expressed</p>
<b>pre-B Cell</b>	<b>BONE MARROW</b>	<p>earliest synthesis of cytoplasmic <math>\mu</math> chain</p> <p>Ig H gene transcribed to make primary transcript w/ VDJ and <math>\mu</math> and <math>\delta</math> C genes</p> <p>poly A tails added to primary nuclear transcripts</p> <p>RNA splicing to form functional mRNA of <math>\mu</math> H chains, which is subsequently translated</p> <p><math>\mu</math> H chain associates w/ surrogate L chains forming pre-B cell receptors (preBCR)</p> <p>preBCR associates w/ Ig <math>\alpha</math> and Ig <math>\beta</math> and signals via btk (tryosine kinase)</p> <p>preBCR signals: allelic exclusion and L chain rearrangement</p>	<p><b>pre-T Cell</b>      <b>THYMUS</b></p> <p><b>double negative thymocytes</b></p> <p>V<math>\beta</math>-DJ<math>\beta</math> rearrangement occurs</p> <p>poly A tails added to primary nuclear transcripts</p> <p>RNA splicing of sequences between VDJ and C regions to form mature mRNA, which is subsequently translated</p> <p><math>\beta</math> chain protein expressed on cell surface in association w/ pre T<math>\alpha</math> and w/ CD3 and <math>\zeta</math> proteins forming pre-TCR</p> <p>preTCR signals: inhibit further <math>\beta</math> locus rearrangements, proliferation of pre-T cells, recombination at <i>both</i> <math>\alpha</math> chain loci, and transition to double positive stage</p> <p>preTCR down-regulates RAG proteins via tyr kinase signaling resulting in <math>\beta</math> chain allelic exclusion</p> <p>rearrangement of TCR<math>\alpha</math> (only V-J; no D segments) chain genes via 2nd wave of RAG expression</p> <p>expression of TCR <math>\alpha\beta</math> heterodimers in assoc. w/ CD3 and <math>\zeta</math>, which turns off RAG genes</p> <p>cells located in thymic cortex, where they are subjected to <i>positive and negative selection</i></p> <p><b>double positive thymocytes</b></p>

**immature B cells**     **BONE MARROW**

recombination in  $\kappa$  or  $\lambda$  L chain (V-J)  
recombination via 2nd wave of RAG expression

splicing of RNA transcript links VJ to C region

TdT expression lower than during H chain recombination

$\kappa$  locus rearranges before  $\lambda$  locus  
successful rearrangement leads to: allelic exclusion

L chain assembles w/  $\mu$  H chain in assoc. w/ Ig  $\alpha$  and Ig  $\beta$

no proliferation or differentiation in response to Ag's

leave BM and complete maturation in lymphoid organs

**mature naïve B cells**     **exit BONE MARROW and circulate**

coexpression of  $\mu$  and  $\delta$  H chains in assoc. w/  $\kappa$  or  $\lambda$  L chains

alternative RNA splicing leads to formation of either: membrane bound IgM or IgD

migrate to peripheral lymphoid organs via CXCR5 mediated chemotaxis

**T<sub>H</sub> induced activation**

Ag binds B cell Ig, is processed and presented, and also induces B7 expression

T<sub>H</sub> binds MHC II/Ag and B7 (via TCR and CD28) causing CD40L expression on T<sub>H</sub>

CD40L binds CD40 inducing germinal center formation leading to affinity maturation

**"dark zone"**     AID causes hypermutation in previously rearranged V region of H and L chains

**"light zone"**     hypermutated B cells interact with and internalize Ag presented by FDCs, with high affinity mutants receiving *1st survival signal*

**single positive (immature T cell)**     **THYMUS**

CD4+/CD8- and CD8+/CD4- cells generated during negative and positive selection

CD4+ cells acquire ability to produce cytokines and CD40L

CD8+ cells produce molecules to kill other cells

**mature naïve T cell**

**activation**

TCR, CD4 (or CD8), CD28,  $\zeta$ , and LAT located in lipid rafts

after TCR binds MHC/Ag, CD4 (or CD8) binds invariant region of MHC II (or MHC I) leading to increase binding affinity and signaling through Src and Lck tyr kinases

Lck activates ITAM on  $\zeta$  → ZAP-70 activation → LAT activation → PLC activation → IP<sub>3</sub> (from PIP<sub>2</sub> cleavage) →  $\uparrow$ Ca<sup>2+</sup> (with calmodulin) → activates calcineurin → dephosphorylates NFAT → IL-2 and IL-2R transcription

CD28 binds B7 → PI 3-kinase activation in T cell → phosphorylates PIP<sub>2</sub> → PIP<sub>3</sub> → binds PH domain → PLC activation (see above)

**"light zone"**  
**"light zone"**

internalized Ag then presented to T<sub>H</sub> cells  
activated T<sub>H</sub> cells express CD40L which binds CD40 on B cells giving *2nd survival signal*  
affinity maturation continues for several iterations  
CD40L binds CD40 and T<sub>H</sub> releases cytokines to induce Ig class switching  
cytokines specifies transcription of "I-region promoter" which determines switch region to be looped and cut. This requires AID  
Ig mRNA transcript modulated by differential polyadenylation and splicing determining whether Ig will be membrane-bound or secreted

**Ag induced activation**

Ag cross-links membrane Ig inducing tyrosine phosphorylation of ITAMs attached to Igα and Igβ  
3 pathways activated (Syk tyr kinase, Ras-MAP kinase, PLC) leading to gene activation via NFAT, NFκB, and AP-1  
C3d (complement fragment that binds to microbe) binds CR2 co-receptor complex at same time Ig binds Ag

**activated B cells** **PERIPHERAL LYMPHOID ORGANS**

**plasma cells**

terminally differentiated

**memory cells** **BLOOD, LNs, & MARGINAL ZONE (spleen)**

circulate and reside in blood, LNs and marginal zone of spleen

**activated T cells**

**memory cells**