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Events in antigen driven B cell differentiation

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- Mature B cells get sent to secondary lymphoid tissue
  - Antigens bind to B cells that have appropriate IgM
  - Binding causes those B cells to activate and divide
  - Clonal selection
- B cell surface
  - IgM and IgD on surface associated with Igα and Igβ
  - Igα/β exactly the same on all B cells (not clonally distributed)
  - Activation involves phosphorylation of tyrosines on Igα/β
  - Cross-linking required for signal transduction
    - Must bind to multiple IgM and signal must come from multiple Igα/β
    - This is why small fragments cannot initiate the immune response
- T cell help
  - Occurs in germinal centers
    - Areas of massive b cell proliferation in secondary lymphoid tissue
    - Arise from follicles
  - Differentiation to plasma and memory cells
    - Cell division
    - Morphological changes
    - Secretion of antibodies
    - Affinity maturation
    - Switch to IgG, IgA, IgE
    - Generation of memory B cells
      - Upon second encounter w/ antigen, get activated
      - Proliferate, differentiate to plasma cells much faster
  - Stages in T cell help
    - Naïve B cell takes up antigen via Ig receptors
    - Antigen broken down and returned to cell surface where fragments are bound to MHCs
    - T cell recognizes the antigen:self complex and is activated
    - CD40 ligand on T cell surface binds to CD40 on B cell surface leading to full B cell antigen-driven differentiation
    - B cell surface protein B7 upregulated and engages CD28 on Th cell for full activation of both cells
  - Antibody response to small group of antigens is possible w/o T cells b/c of extensive cross-linking
    - Proliferation is modest
    - Little switching to non-IgM isotypes
  - Results of differentiation
    - Secretion of antibodies
    - Heavy chain swtich via DNA deletion
      - Not reversible
      - Different than VDJ recombination
      - Uses different signals - switch regions - 2-8 kb regions about 2 kb 5' of each C regeion gene except Cδ
      - Different location (on exons)
      - During antigen-driven differentiation
    - Secretion of various interleukins
      - Directs antibody response to specific isotypes
      - I.e. IL-4 production critical to swtich recombination to ε and expression of IgE
      - Induced isotypes should be suited for pathogen which induced them

- Somatic hypermuation
  - Rearranged V(D)J genes only
  - During antigen-driven differentiation
  - 0.01-0.1% per nucleotide per division
  - Single nucleotide changes not at junctions
  - Can result in conservative mutation, stop codon or better fit
  - Since random, increases diversity and affinity but at a significant cost