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Events in antigen driven B cell differentiation

Wednesday, February 13, 2008

10:00 AM

- 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 Ig α and Ig β
 - Ig α / β exactly the same on all B cells (not clonally distributed)
 - Activation involves phosphorylation of tyrosines on Ig α / β
 - Cross-linking required for signal transduction
 - Must bind to multiple IgM and signal must come from multiple Ig α / 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 switch 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 region gene except C δ
 - 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 switch recombination to ϵ and expression of IgE
 - Induced isotypes should be suited for pathogen which induced them

- Somatic hypermutation
 - 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