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B cell development and activation

Tuesday, February 12, 2008

11:00 AM

- Toll-like receptors
 - Recognize bacteria and viruses in innate immunity
 - Bind to pattern molecules not expressed by humans but shared by groups of pathogens
 - Expressed by many cells, including leukocytes
 - Consequences of TLR signaling
 - Production of cytokines and chemokines and subsequent inflammation
 - Production of type I interferons
 - Killing or inhibition of viruses and intracellular bacteria
 - Up-regulation of co-stimulatory molecules that help activate T and B lymphocytes
 - NOD receptors
 - Expressed in cytoplasm --> viral defense
 - Contain nucleotide-binding oligomerization domain
- Cells associated w/ innate immunity
 - Macrophages and neutrophils
 - "B1" B cells - make most of the antibodies in serum; bind to common epitopes
 - Dendritic cells
 - γ - δ T cells
 - NK T cells
 - Lymphocytes slightly larger and more granular than T and B lymphocytes
 - Kill cells that do not express MHC class I molecules
 - Some have Fc receptor to bind antibody and kill cell (antibody-dependent cell-mediated cytotoxicity)
- B Cell Differentiation
 - Occurs in bone marrow from pluripotent stem cells
 - Stem Cell has nothing on it
 - Pro B cell gains CD19, CD20, other CD antigens
 - Cluster of differentiation
 - Found on groups of cells at same stage of differentiation
 - CD45 on all cells, but can be as specific as CD8+ T cells (killer T)
 - Can be used to define state of development of a cell
 - Detected by monoclonal antibodies
 - Flow Cytometry (FACS) - expression of a cell surface molecule
 - Binds an antibody tagged w/ fluorescent molecule to a cell surface molecule
 - Analyze amount of antibody bound
 - Laser beam aimed at stream of fluid w/ three detectors
 - ◆ Forward scatter - how big
 - ◆ Side scatter - granulation
 - ◆ Emission spectrum - amount of antibody on cell
 - Each cell is represented as one dot
 - CD19 vs. IgM graphs on pg80
 - Early pro-B cell undergoes D-J rearrangement on H chain
 - Late pro-B cell undergoes V-DJ rearrangement on H chain
 - Pre B cell has μ chain in cytoplasm
 - Pre B cell receptor
 - Positive signaling w/ μ heavy chain only
 - H chain is VDJ rearranged, begin light chain gene management
 - Small pre B cell undergoes V-J rearrangement of L chain
 - Immature B cell has IgM on surface

- VJ rearranged on L chains, VDJ rearranged on H chain
- Expression of IgM receptors
- Bruton's agammaglobulinemia
 - x-linked disease
 - Failure to produce antibodies
 - Repeated infections
 - Almost no production of B cells in bone marrow
 - ◆ Mutation in Bruton's tyr kinase activated upon engagement of the pre B cell receptor
 - ◆ Signal from μ on surface of pre B cells doesn't reach nucleus - positive signaling fails
- Mature B cell has IgD and IgM on cell surface
 - B cell development depends on adherent cell part of bone marrow and cytokines (IL-7) --> B cell development requires a signal
 - Final product is naïve
 - Antigen independent B cell differentiation in bone marrow results in 10 mm diff clones of B cells each w/ different epitope (receptor repertoire)
 - Each antibody is made by one clone of B cells hence immunoglobulins are clonally distributed
- Immature B cells w/ an Ig that binds to a self antigen sends negative signal
 - Results in deletion of immature B cells in bone marrow
 - Clonal deletion - part of self-tolerance for B cells
- Allelic exclusion
 - In a b cell clone only one of two antibody loci is expressed
 - A B cell could express two heavy chains and four light chains (κ and α), it only expresses one of each
- Where does the B cell diversity come from?
 - Constant region - one gene; if there were two genes, single amino acid changes would occur and there would soon be two isotypes
 - Variable region - many genes for the three kinds of variable regions
 - V κ encodes aa 1-95
 - 1500 kb of DNA; 79 genes
 - Half are pseudogenes
 - V genes are 5 to 20 kb apart
 - Most 3' V κ is 23 kb 5' of C κ
 - J κ encodes aa 96-107
 - 5 regions
 - Lies 1.2 kb 5' of C κ
 - C κ encodes aa 108-214
 - Recombination Signal Sequences
 - Each V is followed by: V codon 95CACAGTG--spacer--GGTTTTTGT
 - Each J preceded by: ACAAAAACC--spacer--CACTGTG-J codon 96
 - True for variable regions and J segments associated w/ heavy chain, κ and λ light chain genes
 - V(D)J recombination mediated by lymphoid recombination activating genes: RAG1/2
 - Mutation in genes lead to severe combined immunodeficiency (no B or T cells) or Omenn's syndrome (milder)