

Author(s): Aken Desai, Michael Mathis, 2008

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Joining variable and constant regions

Wednesday, February 13, 2008
9:00 AM

- λ light chain
 - L1-V λ 1 up to LV λ -29 --- J1-C1---J2-C2---...
 - Multiple C- λ genes, each w/ one J region
 - J defines which constant region is used
- κ light chain
 - L1-V κ 1 up to Lv κ -40---J κ 1-5--C κ
 - Only one C κ gene
- Heavy chain
 - LVheavy51---Dheavy1-27---Jheavy1-6---C μ
 - D segments encode 2-8 amino acids are preceded and followed by recombination signal sequences
 - Heavy chain variable encodes amino acids 1-99, J encodes additional 14-20 amino acids
- Light Chain Transcription
 - Germline DNA
 - VJ joined
 - Primary transcript mRNA
 - Splicing to make continuous mRNA w/ LVJC
 - Translated to polypeptide to make light chain and L spliced off
- Heavy chain transcription
 - Germline DNA recombined
 - DJ regions joined
 - V and DJ regions joined
 - Transcription to mRNA
 - Splicing to make continuous LVDJC
 - Translation
- Methods to generate diversity
 - Germline
 - Use of variable region genes
 - Several D's
 - Four to ten J's
 - Combinatorial
 - Joining of any variable region to any D to any J
 - Combination of any heavy chain variable region with any light chain variable region
 - $50 V \times 30 D \times 6 JH = 9000$ heavy variable chains
 - $40 V \times 5 J\kappa = 200$ variable κ chains
 - $30 V \times 10 J\lambda = 300$ variable λ chains
 - $9000 \times (200+300) = 4.5$ million possible binding sites
 - Junctional diversity
 - Generated during V(D)J joining by variation in exact point of recombination
 - V-D, D-J in heavy chains
 - V-J in light chains
 - RAGs cut off recombination sequences and ligates them to release them
 - Exonuclease cuts off nucleotides and releases coding sequences to be ligated together
 - The exonuclease works anywhere
 - Same number of codons but a different sequence
 - Particularly prevalent in light chain variable region
 - N region addition
 - Addition of nucleotides by terminal deoxynucleotide transferase to V, D, or J ends

- Not encoded by a template
 - Rare in light chains
- When in B cell differentiation do Ig gene rearrangements take place?
 - In pro B cells, D is rearranged to a heavy chain J segment on both chromosomes at random
 - Heavy chain V region is rearranged to DJ on one chromosome
 - If out of frame/pseudogene, tries on other chromosome
 - If it fails again, B cell stops development
 - If μ heavy chain is expressed, becomes a pre B cell and also attempts light chain V-J rearrangement
 - Further VH-DJ joining shut off
 - κ is favored 20:1 over λ
 - Since there are four loci that could undergo VJ rearrangement, this step is usually successful
 - There are also several VJ rearrangements possible w/in a single locus
 - If light chain is produced and IgM goes to cell surface, immature B cell
 - If light chain is expressed, VL-JL joining shut off
 - Feed-back regulation is basis of allelic exclusion
 - Prevents expression of two heavy chains or two light chains
- How does B cell switch from membrane bound IgM to secreted form?
 - Alternative RNA splicing
 - Secreted μ has 20 aa sequence after C region
 - Membrane bound has 41 aa after C region
 - This sequence has n-terminal negative AA, then 26 uncharged aa (α helix) then positive charges at the C-term
 - This makes it stick in the membrane
 - 2 Poly(A) sites
 - Secreted transcription ends at first
 - Transmembrane ends at second
 - MC region in btwn the two
 - After those two poly(A) sites, C δ genes then another poly(A) region
 - If transcription continues to this point, mainly IgD expressed
 - C μ genes get cut out