Introduction to Immunology

Antigen Receptors and Generation of Antibody and T-Cell Receptor Diversity

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Adaptive Immunity

The Adaptive or Acquired Immune Respone:

- Is the response of antigen-specific lymphocytes to antigen, including the development of immunological memory
- Are mediated by the clonal selection of antigen-specific lymphocytes
- Immunoglobulins and T-cell receptors are the highly variable recognition molecules of adaptive immunity

Effector Molecules of Adaptive Immunity

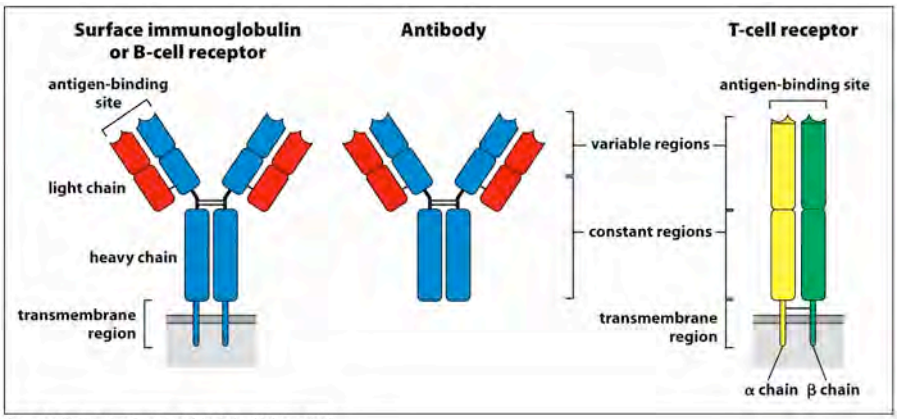


Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)

The Antibodies Made Against a Pathogen Are Highly Specific for That Pathogen

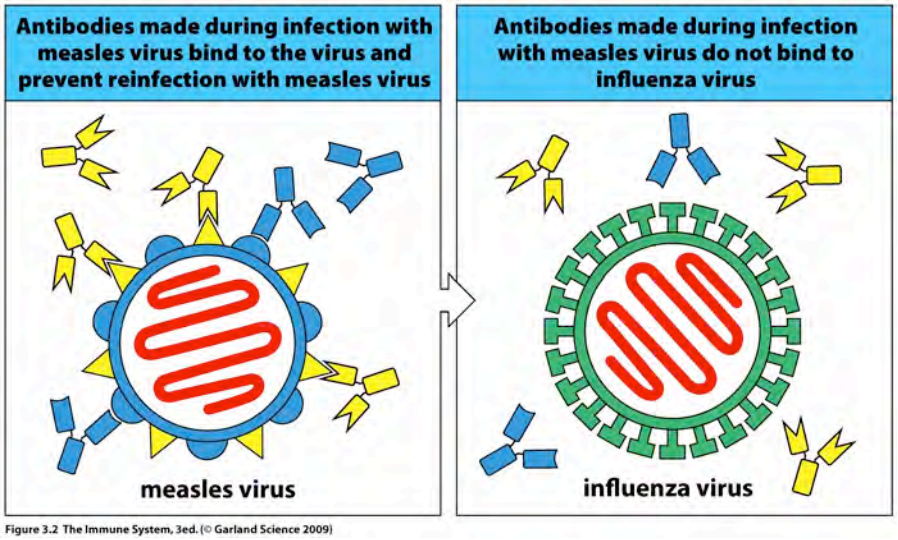


Figure 3.2 The Immune System, 3ed. (© Garland Science 2009)

The Diversity of Antibodies and T-Cell Receptors Is Generated by Gene Rearrangement Through Somatic DNA Recombination

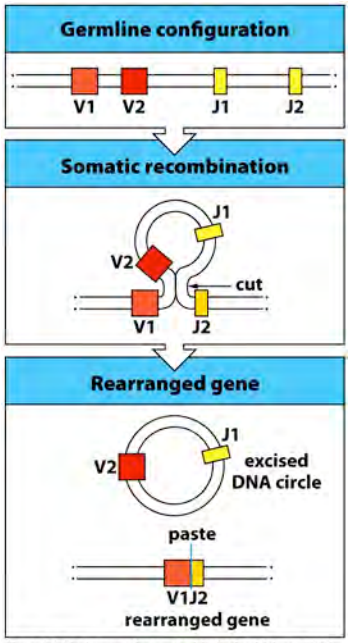


Figure 3.3 The Immune System, 3ed. (© Garland Science 2009)

Gene Rearrangement Produces a Diversity of Antigen Receptors in Lymphocytes

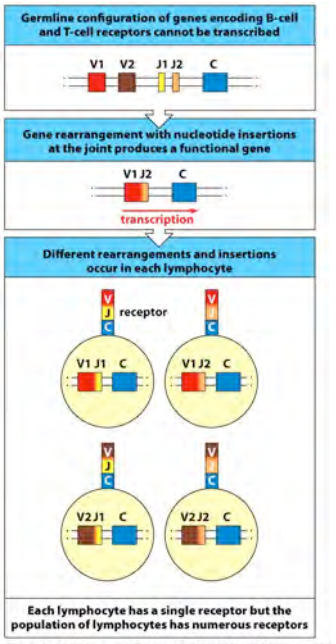


Figure 3.4 The Immune System, 3ed. (© Garland Science 2009)

Clonal Selection of B and T Lymphocytes

1. During development, progenitor cells give rise to large numbers of circulating lymphocytes, each having a different form of cell-surface receptor

2. The receptors of only a few circulating lymphocytes interact with any given pathogen

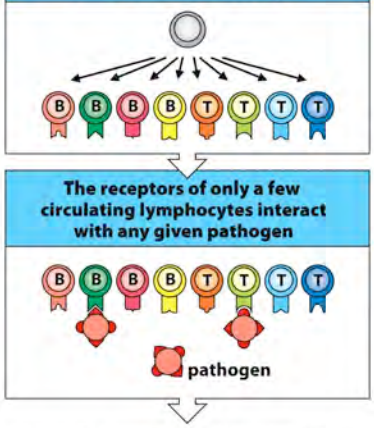


Figure 3.5 part 1 of 2 The Immune System, 3ed. (© Garland Science 2009)

3. Pathogen-reactive lymphocytes are triggered to divide and proliferate

4. Pathogen-activated lymphocytes differentiate into effector cells that eliminate the pathogen

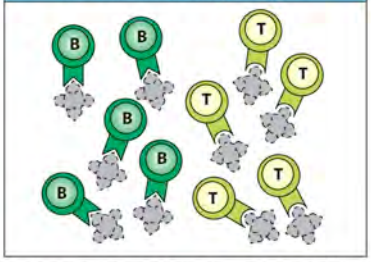
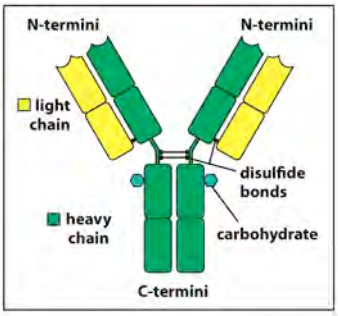


Figure 3.5 part 2 of 2 The Immune System, 3ed. (© Garland Science 2009)

The Immunoglobulin Molecule:

- Made up of 2 identical heavy chains and 2 identical light chains

- The antibody molecule has 2 functional domains



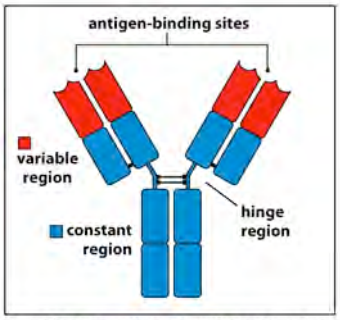
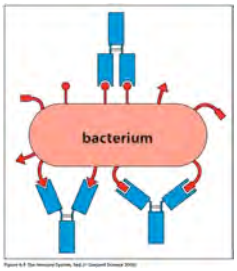


Figure 4.2 The Immune System, 3ed. (© Garland Science 2009)

Features of the Immunoglobulin Molecule

- The flexible hinge allows it to bind with both arms to antigens on the surfaces of pathogens
- The heavy and light chains are made from a series of similar protein domains



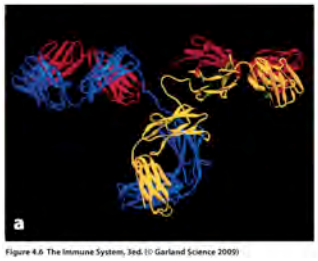
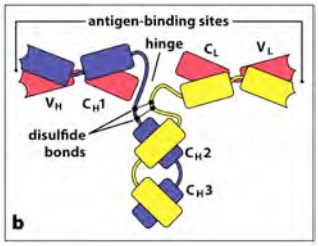
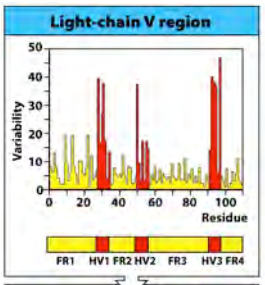


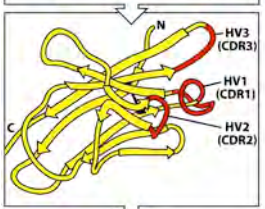
Figure 4.6 The Immune System, 3ed. (© Garland Science 2009)



The Hypervariable Regions of Antibody V Domains Lie in Discrete Loops at One End of the Domain Structure

- The hypervariable loops contribute much of the antigen specificity of the antigen-binding site





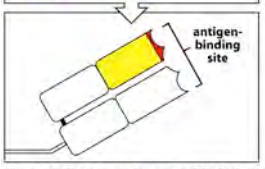


Figure 4.8 The Immune System, 3ed. (© Garland Science 2009)

Hypervariable Regions in Heavy and Light-Chains

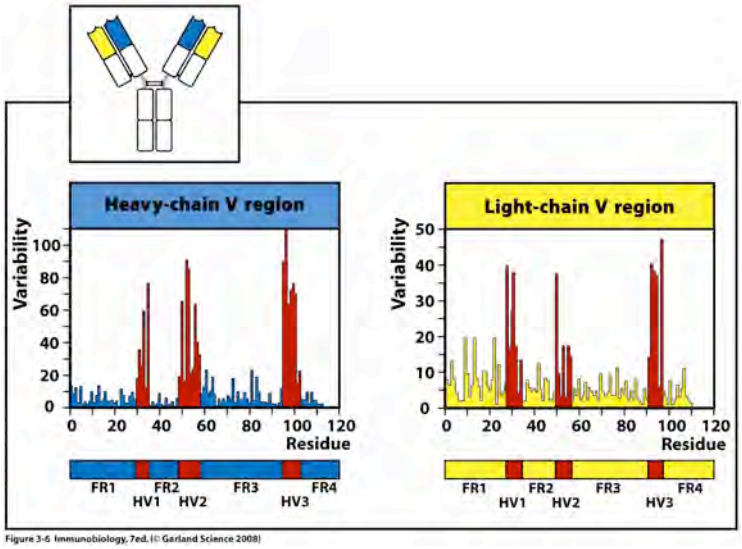


Figure 3-6 Immunobiology, 7ed. (© Garland Science 2008)

Antigen-Binding Sites Can Have Diverse Structures

- Epitopes of antigens can bind to pockets, grooves, extended surfaces, or knobs in antigen-binding sites

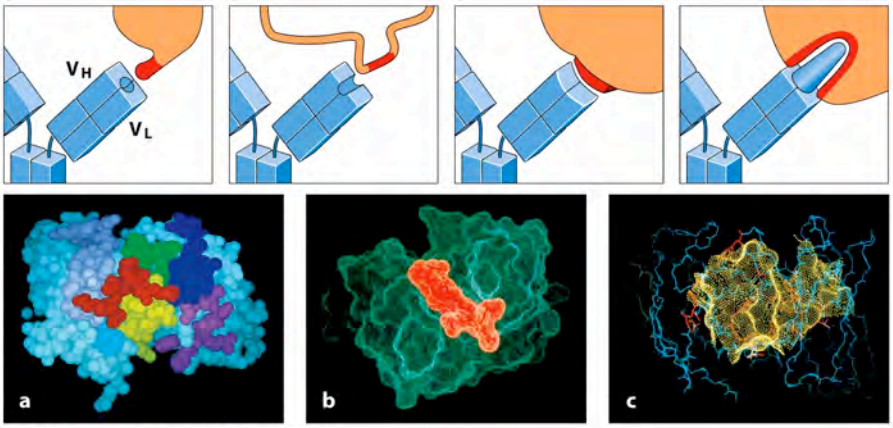


Figure 4.11 The Immune System, 3ed. (© Garland Science 2009)

The Structure of the Human Immunoglobulin Classes

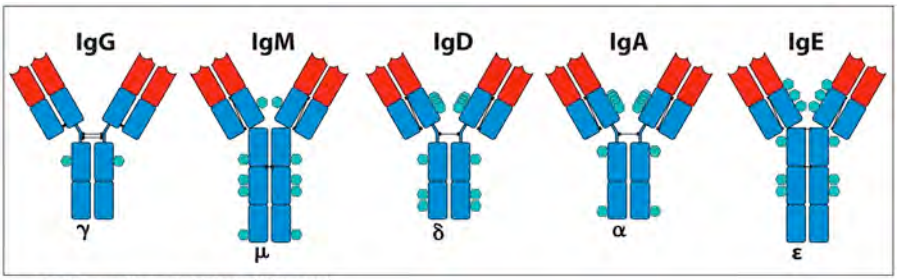


Figure 4.5 The Immune System, 3ed. (© Garland Science 2009)

- Newly generated, antigen experienced or 'naïve' B cells express IgM and IgD on their cell surface

Coexpression of IgD and IgM is Regulated by RNA Processing

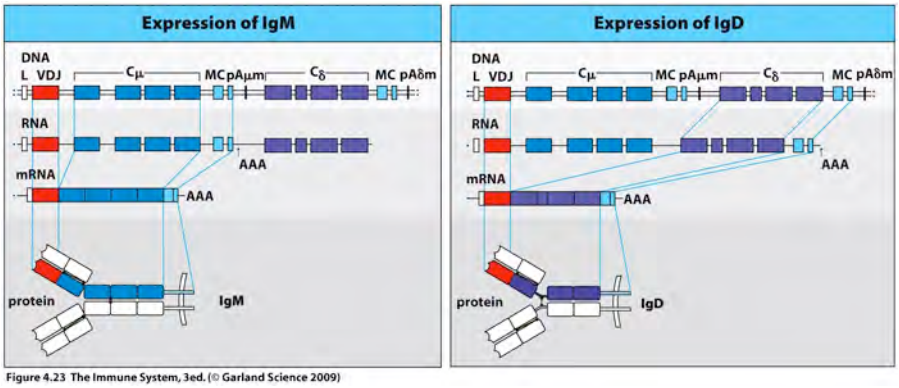


Figure 4.23 The Immune System, 3ed. (© Garland Science 2009)

Ig Isotypes Have Different Functions and Distributions

Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	+	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activates complement system	+++	–	++	+	+++	–	+	–

Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (mono-mer)	+
Mean serum level (mg ml^{-1})	1.5	0.04	9	3	1	0.5	2.1	3×10^{-5}

Figure 9-19 Immunobiology, 7ed. (© Garland Science 2008)

Production of a Mouse Monoclonal Antibody

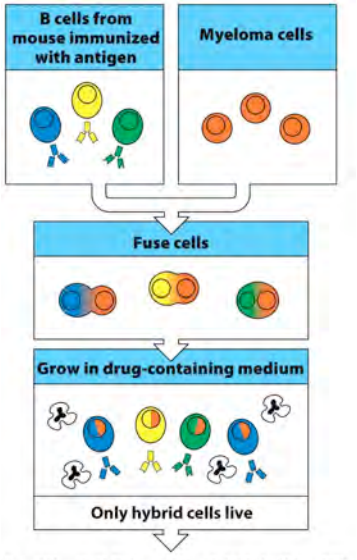


Figure 4.13 part 1 of 2 The Immune System, 3ed. (© Garland Science 2009)

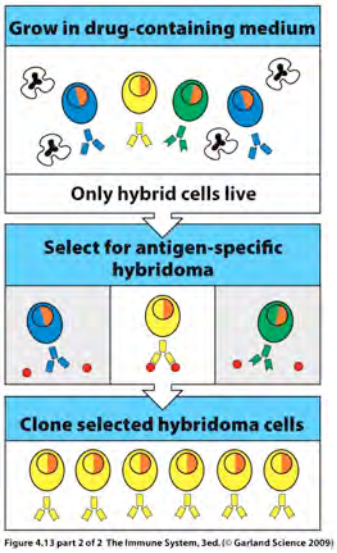


Figure 4.13 part 2 of 2 The Immune System, 3ed. (© Garland Science 2009)

Use of Monoclonal Antibodies in Flow Cytometry

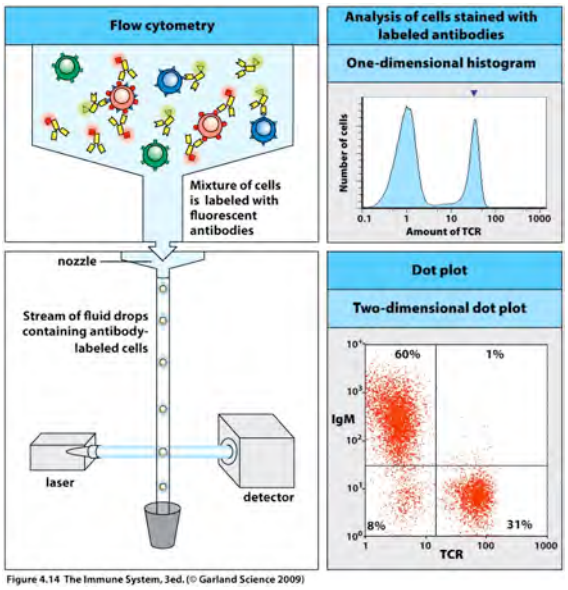


Figure 4.14 The Immune System, 3ed. (© Garland Science 2009)

Monoclonal Antibodies as Treatment for Disease

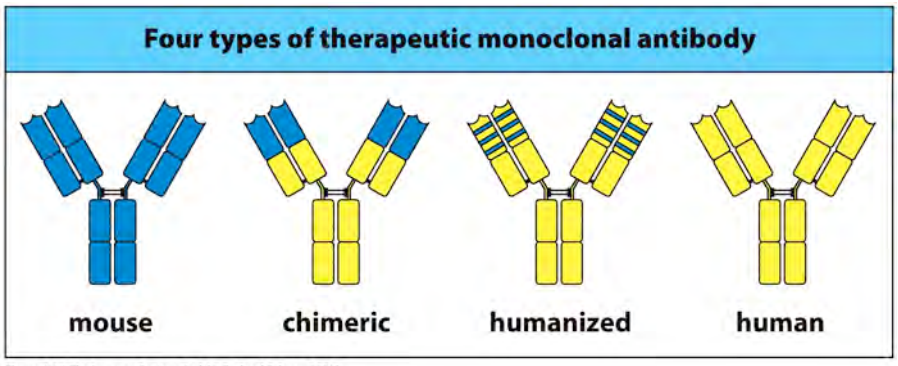


Figure 4.15 The Immune System, 3ed. (© Garland Science 2009)

Similarity between Antibody and T-Cell Receptor

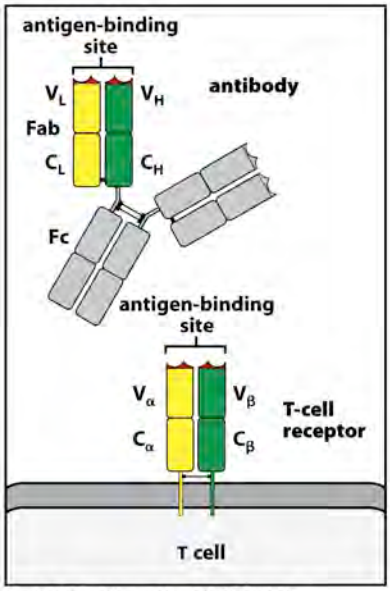


Figure 3-11 Immunobiology, 7ed. (© Garland Science 2008)

Germline Organization of the Human Heavy Chain And Light Chain Loci

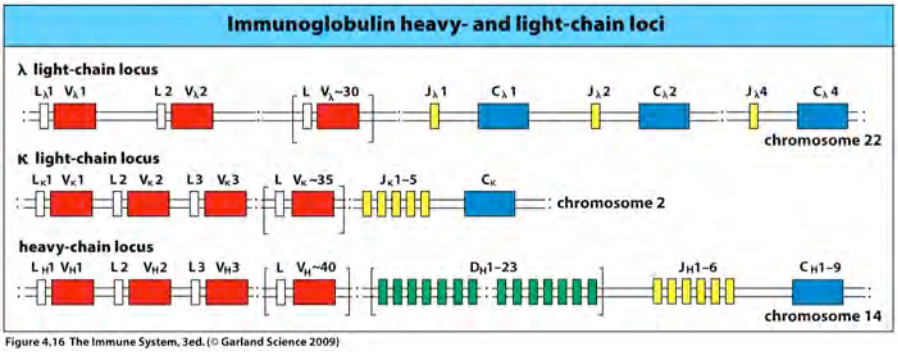


Figure 4.16 The Immune System, 3ed. (© Garland Science 2009)

V-Region Sequences are Constructed from Gene Segments

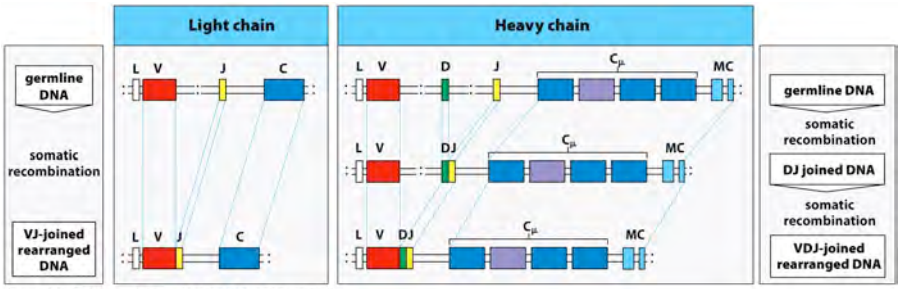


Figure 4.17 The Immune System, 3ed. (© Garland Science 2009)

- Combinatorial diversity (V_H, D_H, J_H & V_L, J_L)

Number of gene segments in human immunoglobulin loci

Segment	Light chains		Heavy chain
	κ	λ	H
Variable (V)	31–36	29–33	38–46
Diversity (D)	0	0	23
Joining (J)	5	4–5	6
Constant (C)	1	4–5	9

Figure 4.18 The Immune System, 3ed. (© Garland Science 2009)

Each V, D, or J Gene Segment is Flanked By Recombination Signal Sequences (RSS)

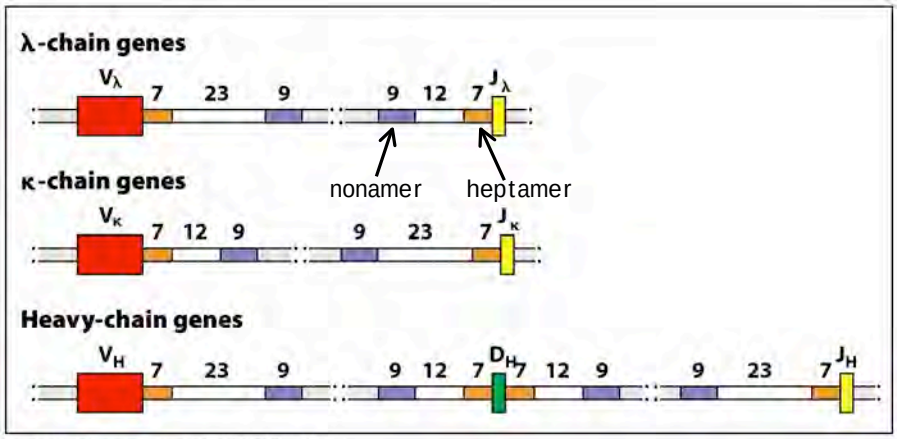


Figure 4.19 The Immune System, 3ed. (© Garland Science 2009)

Gene Segments Encoding the Variable Region Are Joined by Recombination at RSSs

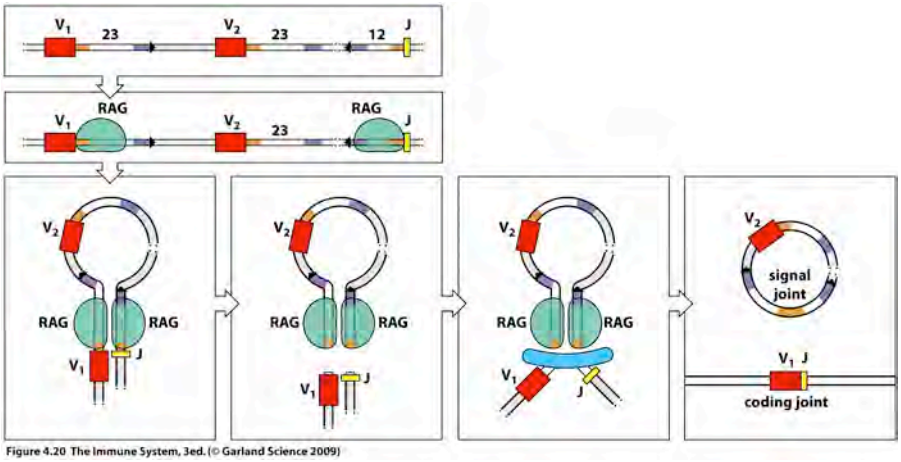


Figure 4.20 The Immune System, 3ed. (© Garland Science 2009)

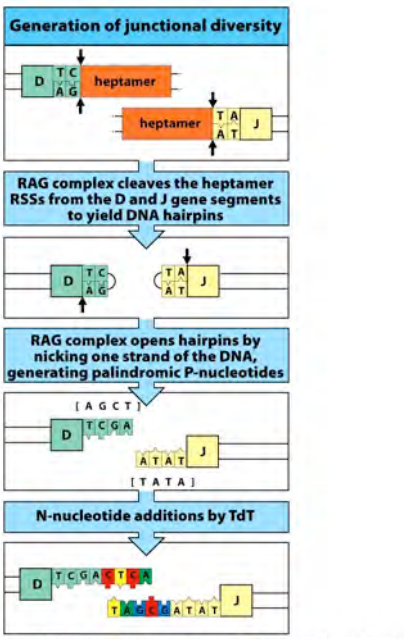


Figure 4.21 part 1 of 2 The Immune System, 3ed. (© Garland Science 2009)

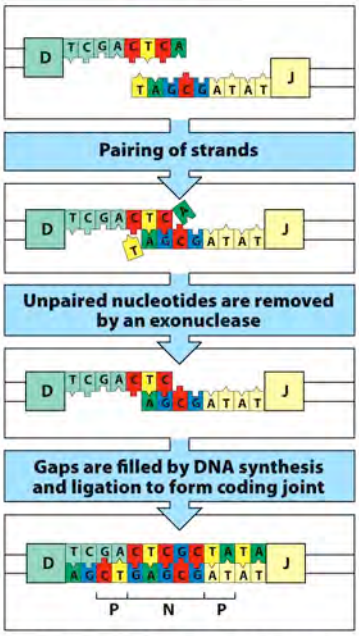


Figure 4.21 part 2 of 2 The Immune System, 3ed. (© Garland Science 2009)

Junctional Diversity

- Mediated by the V(D)J recombinase (including RAG)
- Recombination occurs at RSS sequences
- Addition of non-germline encoded nucleotides:
  - P nucleotides, as a result of opening of the 'hairpin'
  - N nucleotides (for Nontemplated) by the enzyme TdT
- The region encodes the 3rd hypervariable region in the antigen-binding site of the antibody molecule

Rearrangement of V, D, and J segments Produces a Functional Heavy-Chain Gene

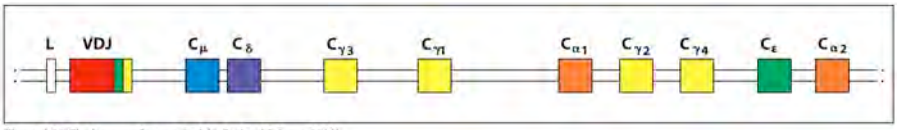
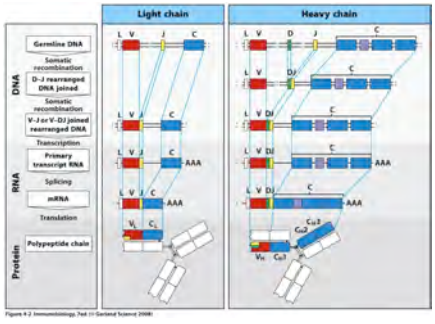


Figure 4.22 The Immune System, 3ed. (© Garland Science 2009)

3 Processes Establish Diversity of Pre-Immune Repertoire:

- Combinatorial diversity (V_H, D_H, J_H & V_L, J_L)
- Junctional diversity
- Combinatorial diversity through HC and LC combinations



- It is estimated that these processes could give rise to 10^{11} different antibody specificities that comprise the antigen receptor repertoire of naïve B-cells

Not All Rearrangements Lead to Suitable Antigen-Receptor:

- Some V_H and V_L gene segments are pseudogenes
- Junctional diversity can lead to reading frame shifts
- Junctional diversity can introduce translational stop codons

Additional Complexities:

- Each cells has 2 HC and 4 LC alleles
- Generation of autoreactive antibody receptors

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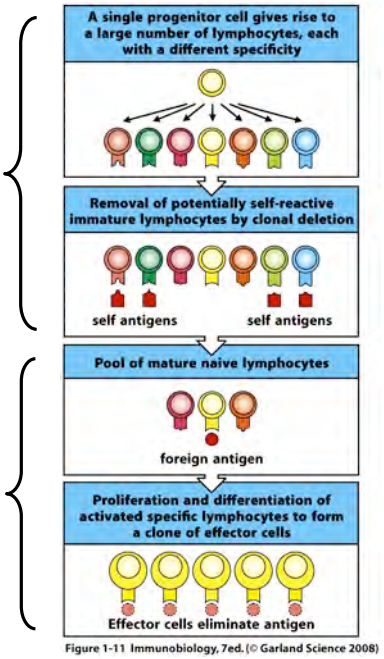
It results a considerable cell wastage!

How is the generation of the pre-immune repertoire regulated?

B-Cell Biology

Antigen-Independent B-Cell Development

Antigen-Dependent B-Cell Development



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B-Cell Biology

Antigen-Independent B-Cell Development

- Generation of B Cells in the Bone Marrow

Antigen-Dependent B-Cell Development

- Ig Class Switch, Somatic Hypermutation
- Germinal Center Reaction