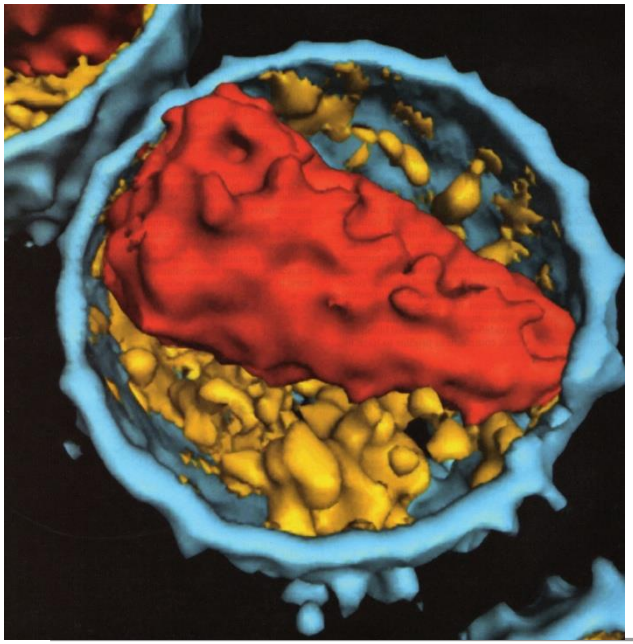


The internal structure of the human immunodeficiency virus which can slowly destroy the adaptive immune system.

Chapter 3

Principles of Adaptive Immunity

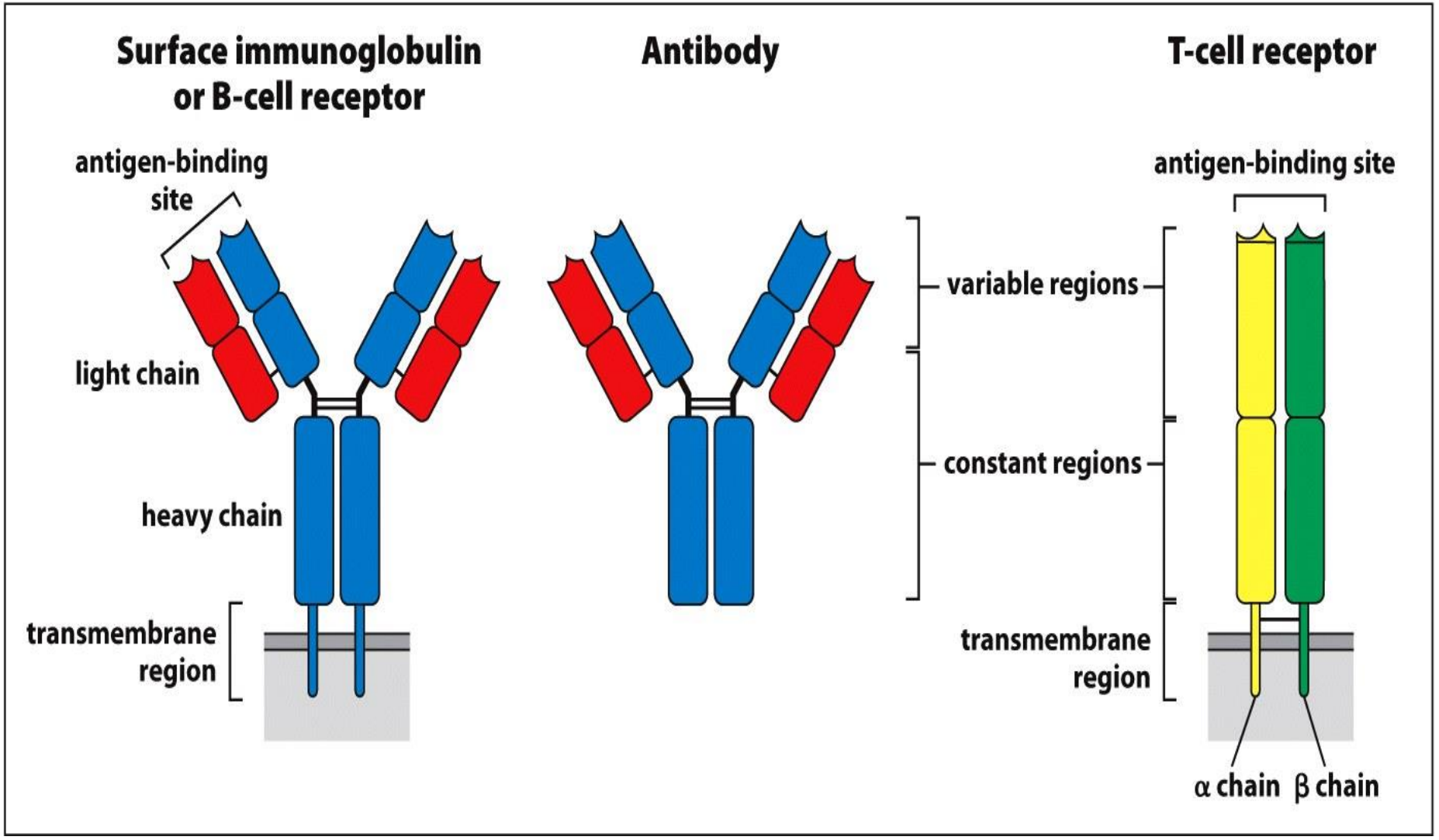


Figure 3.1 Comparison of the structures of surface immunoglobulin, antibody, and the T-cell receptor. The heavy chains of surface immunoglobulin, also known as the B-cell receptor, and antibody are shown in blue, the light chains in red. The α chain of the T-cell receptor is shown in yellow, the β chain is shown in green.

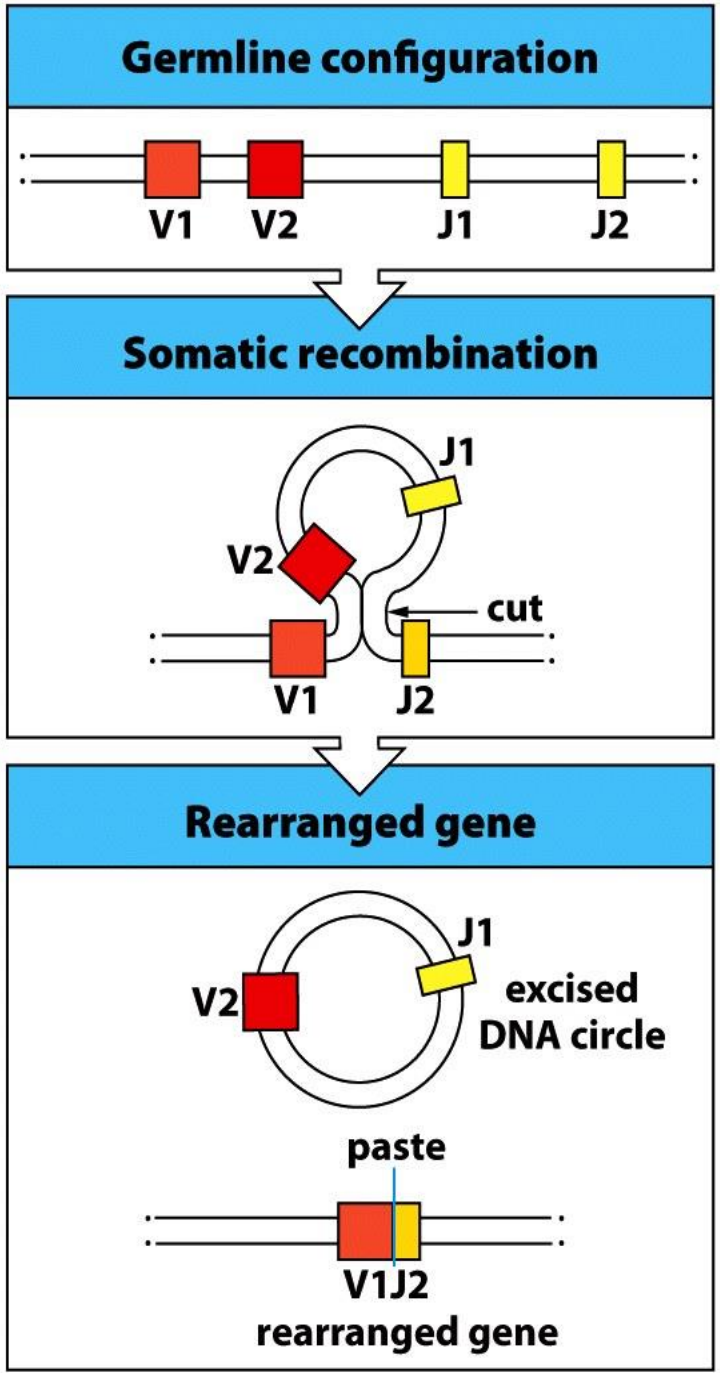


Figure 3.3 The type of gene rearrangement that occurs in immunoglobulin and T-cell receptor genes. In this simplified example the unrearranged DNA contains two alternative V segments and two alternative J segments. A functional exon encoding the variable region consists of one V segment joined to one J segment. This rearrangement is achieved by a process of 'cut and paste' in which the intervening DNA is removed as a circle.

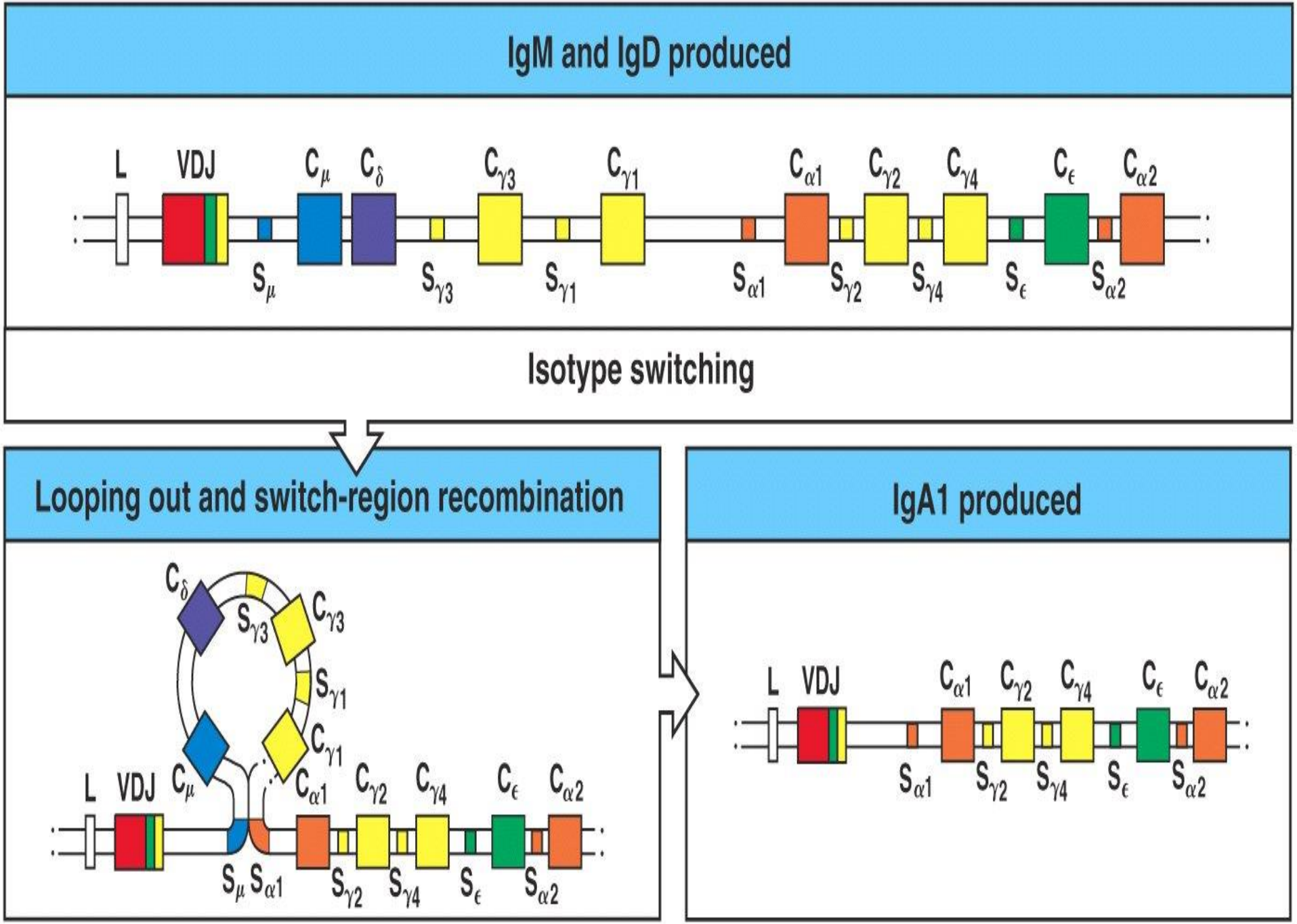


Figure 2-27 The Immune System, 2/e (© Garland Science 2005)

	Immunoglobulin class or subclass								
	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA1	IgA2	IgE
Heavy chain	μ	δ	γ_1	γ_2	γ_3	γ_4	α_1	α_2	ϵ
Molecular weight (kDa)	970	184	146	146	165	146	160	160	188
Serum level (mean adult mg ml^{-1})	1.5	0.03	9	3	1	0.5	2.0	0.5	$5x10^{-5}$
Half-life in serum (days)	10	3	21	20	7	21	6	6	2

Figure 2-28 The Immune System, 2/e (© Garland Science 2005)

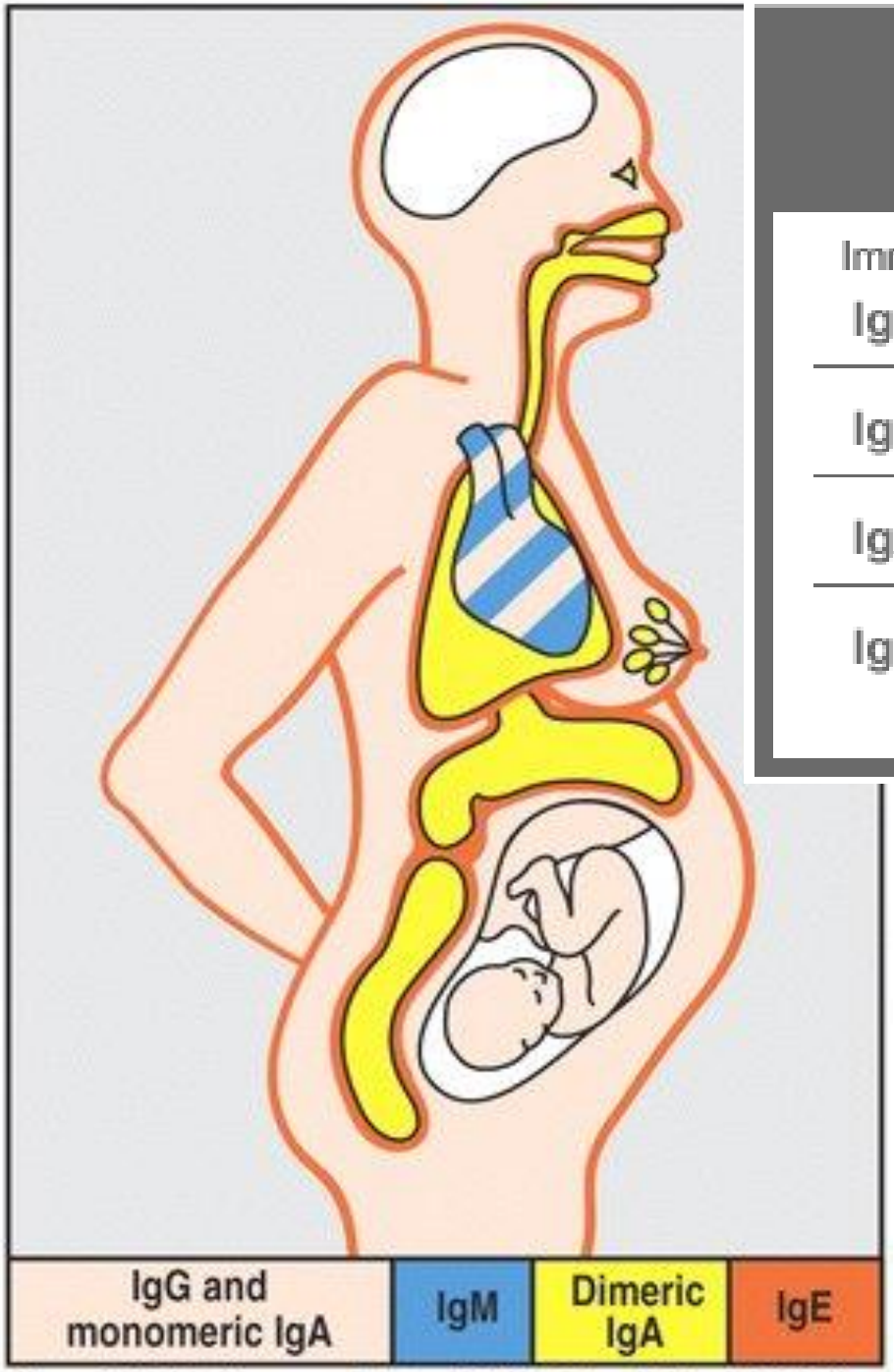
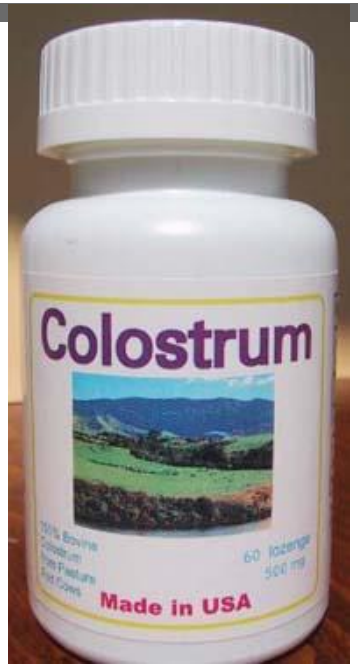


Figure 7-19 The Immune System, 2/e (© Garland Science 2005)

Immunoglobulin Found in Bovine Colostrum and Milk

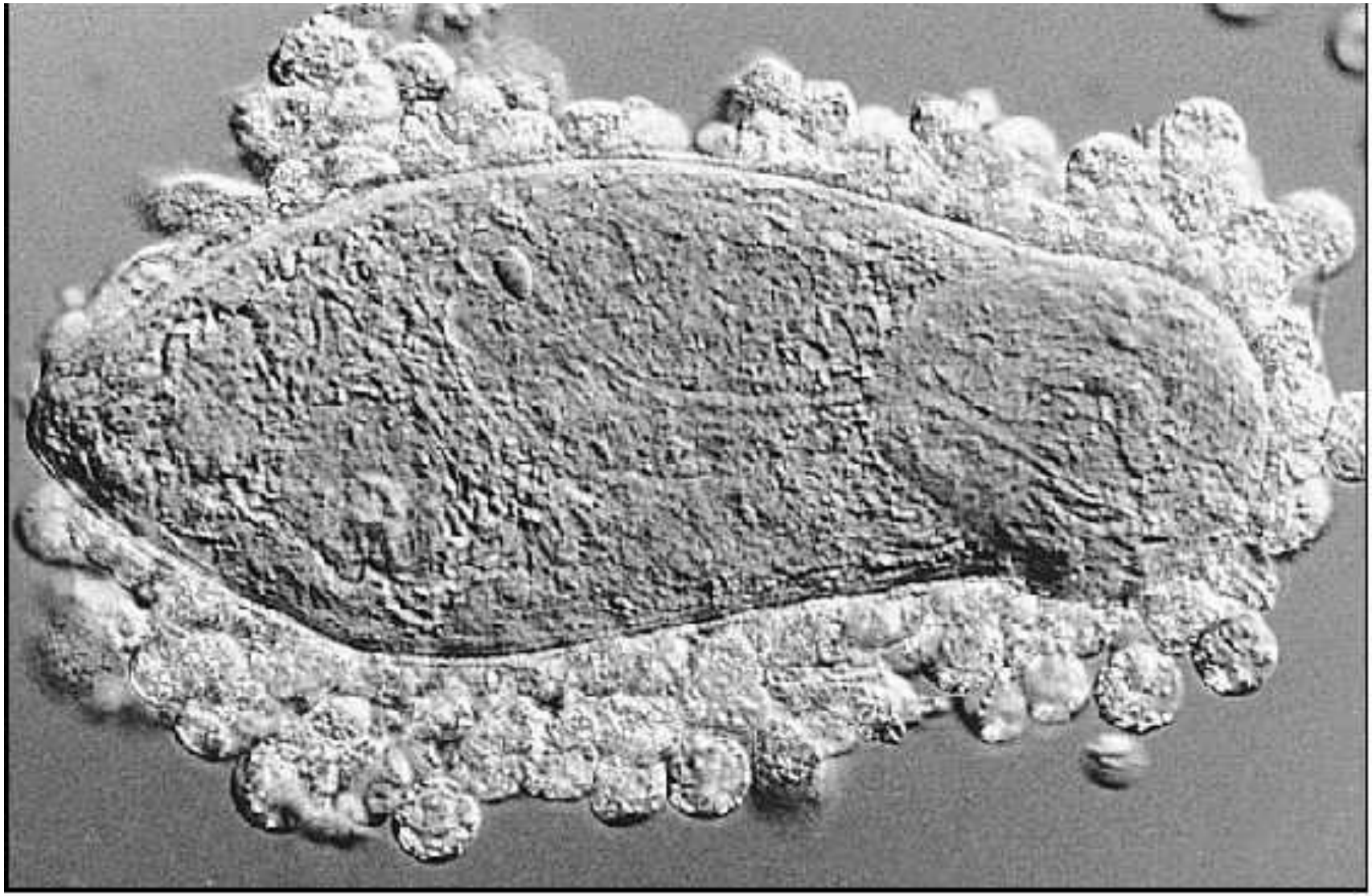
Immunoglobulin	Colostrum g/L	Milk g/L
IgG1	50 - 90	0.3 - 0.4
IgG2	1.5 - 2.0	0.03 - 8.08
IgA	3.0 - 6.5	0.04 - 0.06
IgM	3.8 - 6.0	0.03 - 0.05

A dapted from Pakkanen and Aalto (1997)



IgE coated parasites activate eosinophils

to pour out its toxic granules



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

Property	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml^{-1})	1.5	0.03	9	3	1	0.5	2.1	$5x10^{-5}$

Figure 2-29 The Immune System, 2/e (© Garland Science 2005)

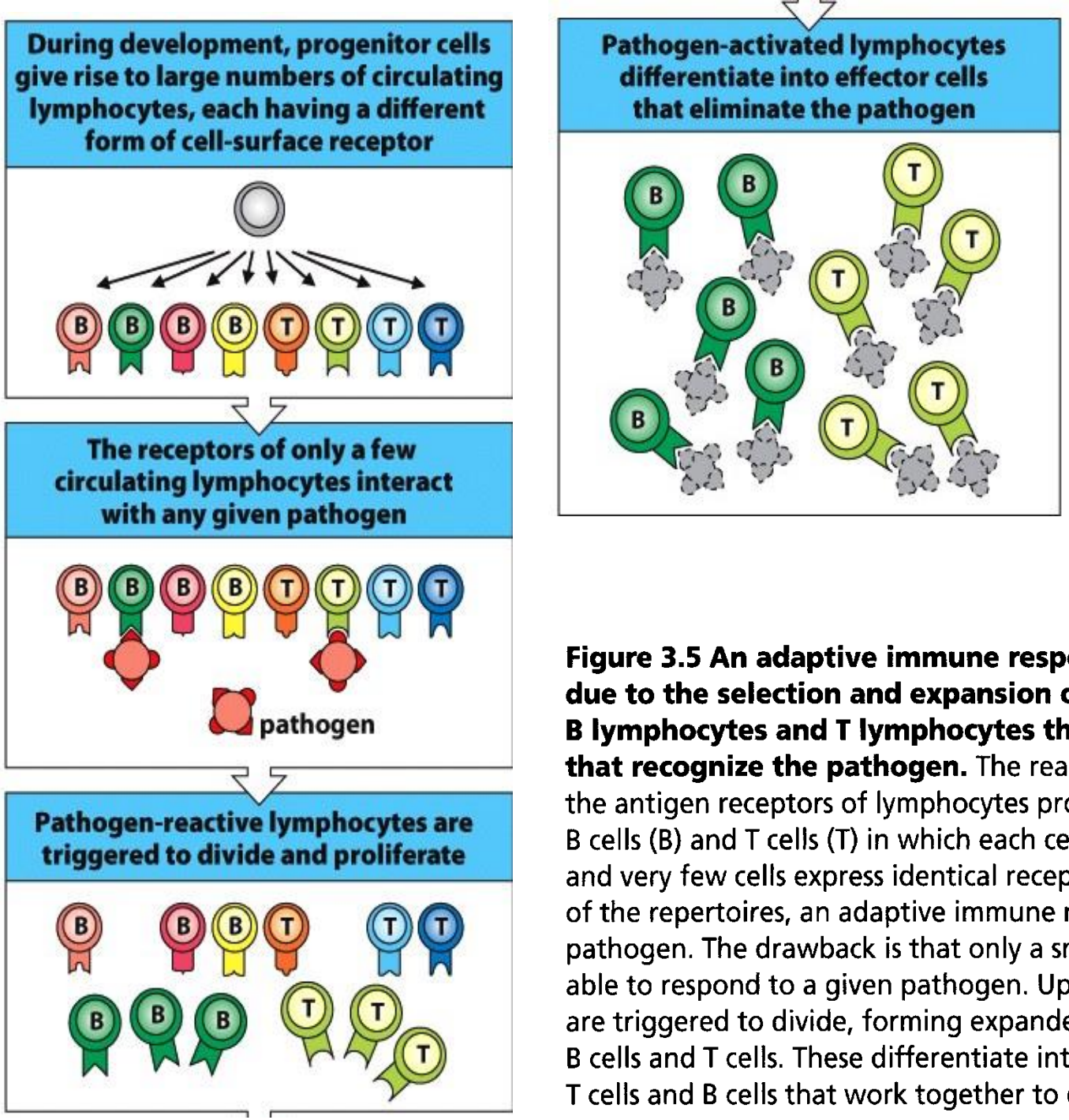


Figure 3.5 An adaptive immune response to a pathogen is due to the selection and expansion of the small fraction of B lymphocytes and T lymphocytes that carry surface receptors that recognize the pathogen. The rearranging genes that encode the antigen receptors of lymphocytes produce vast repertoires of B cells (B) and T cells (T) in which each cell expresses a single receptor and very few cells express identical receptors. Because of the breadth of the repertoires, an adaptive immune response can be made to any pathogen. The drawback is that only a small number of cells will be able to respond to a given pathogen. Upon infection these few cells are triggered to divide, forming expanded clones of pathogen-specific B cells and T cells. These differentiate into large numbers of effector T cells and B cells that work together to eliminate the infection.

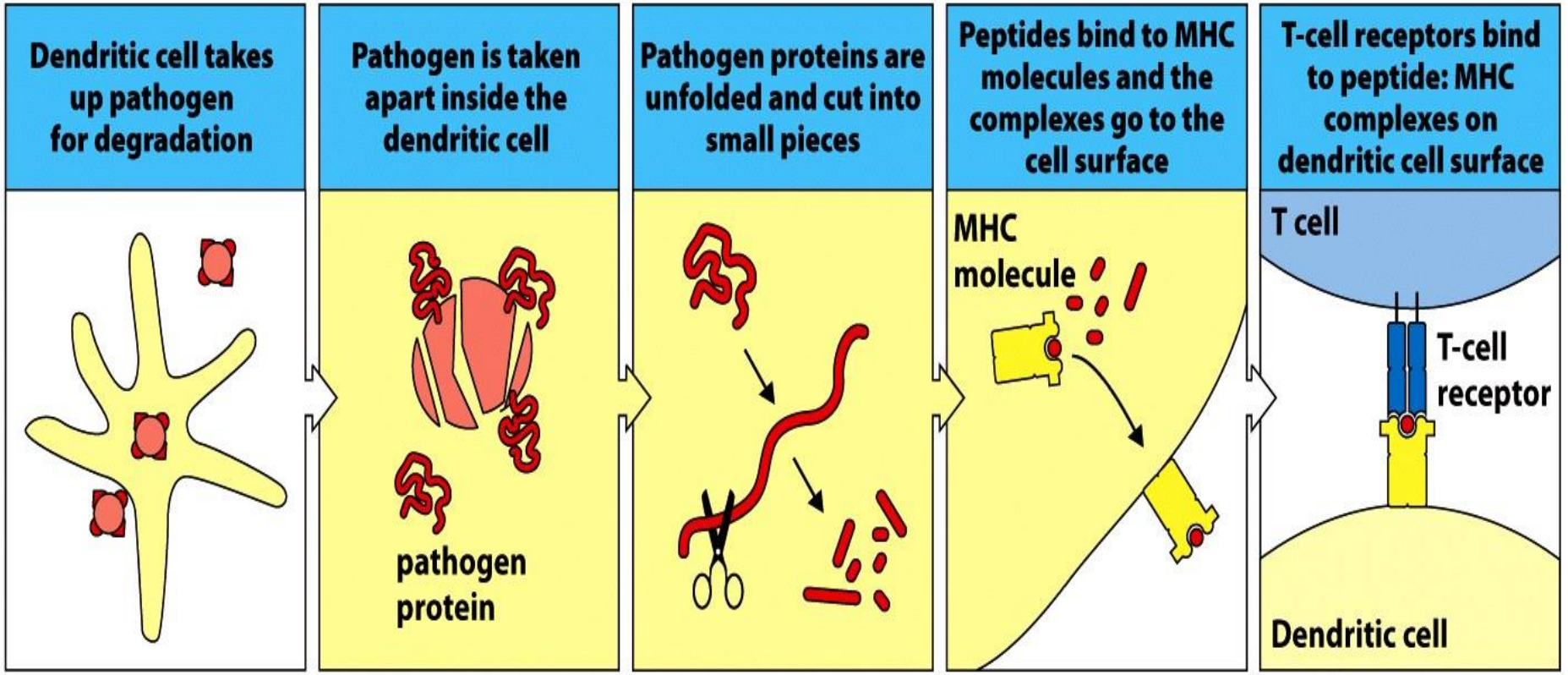


Figure 3.7 T-cell receptors recognize peptide antigens produced by the degradation of pathogen proteins. Dendritic cells internalize pathogens and degrade their proteins into small peptides and amino acids. Some of the peptides are bound inside the cell by proteins called MHC molecules, which carry the peptides to the dendritic cell surface. Once at the surface, the complex of MHC molecule and peptide antigen is accessible to the receptors of circulating T cells. If there is a match between the antigen and the T-cell receptor, the T cell will stay in contact with the dendritic cell and be stimulated to divide and differentiate. Although other types of cell have MHC molecules and present peptide antigens, the dendritic cell is the most adept at this and is responsible for the initiation of a primary immune response—that is, the immune response to a pathogen when it infects a person and causes disease for the very first time.

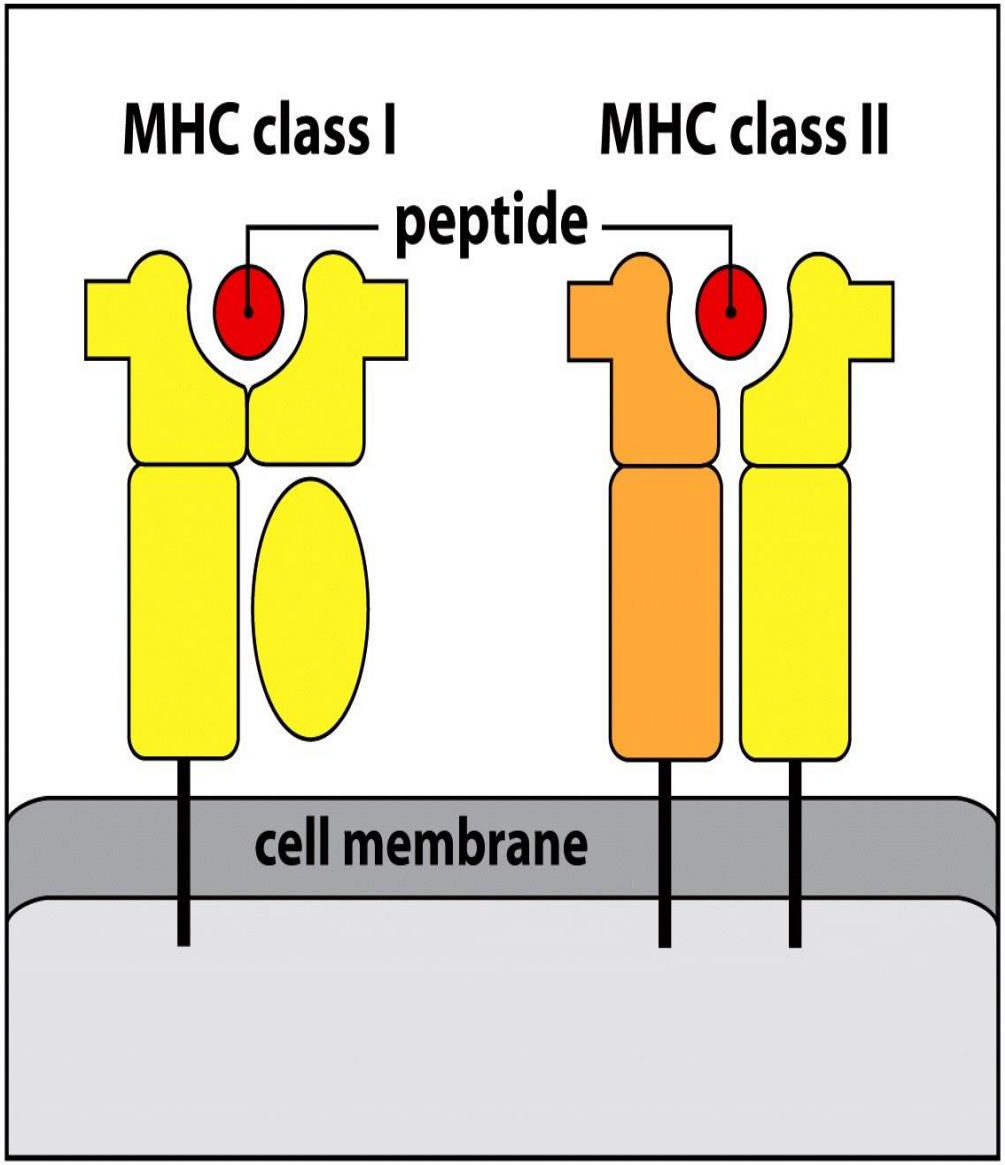


Figure 3.8 There are two types of MHC molecule, MHC class I and MHC class II. The two classes of MHC molecule have similar overall three-dimensional structures. Where they differ is in their constituent polypeptide chains. An MHC class II molecule is made of two similarly sized polypeptides that contain two extracellular domains and are anchored in the plasma membrane. In the MHC class I molecule, a larger polypeptide contains three extracellular domains and is anchored in the plasma membrane; a smaller polypeptide comprises the fourth extracellular domain and is not attached to the membrane.

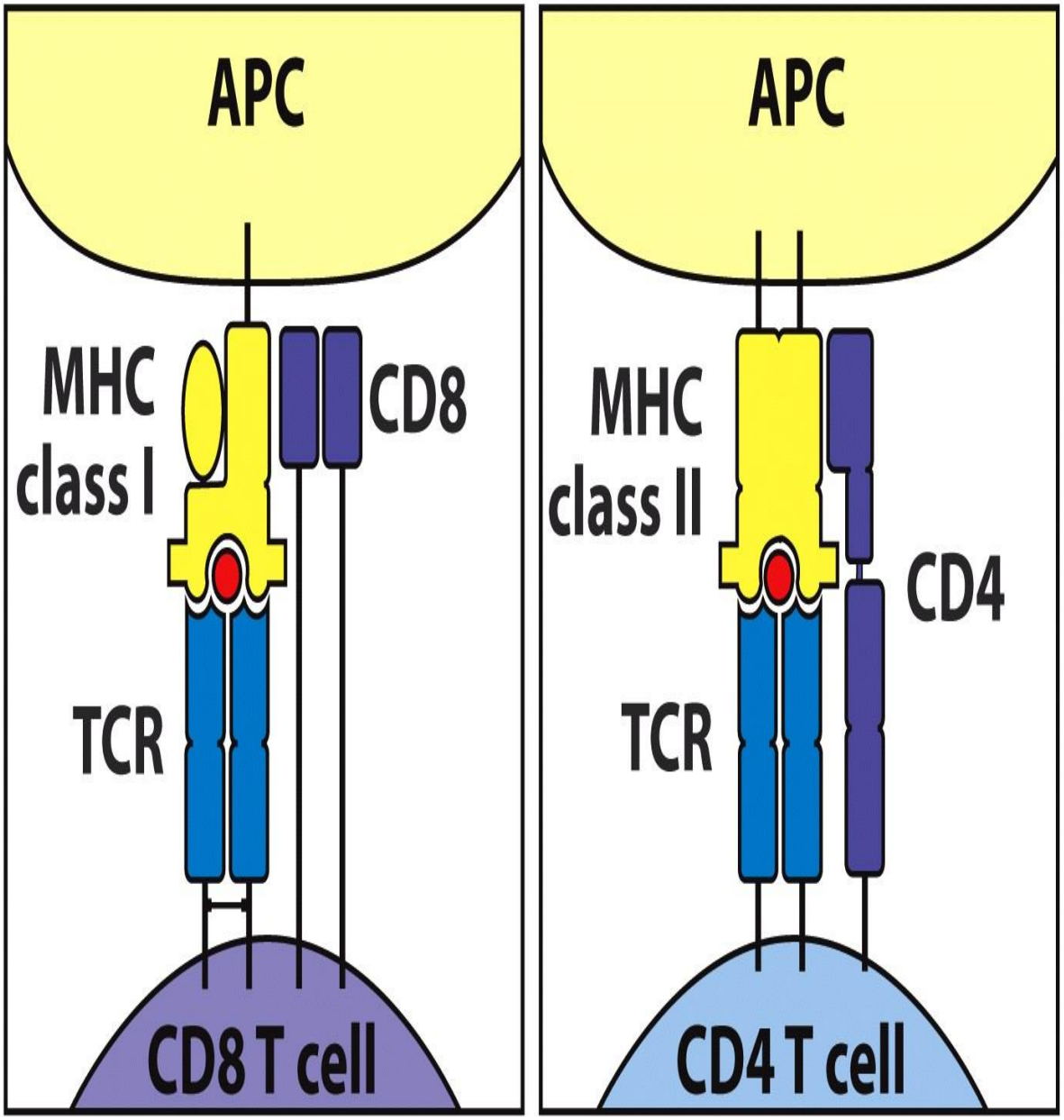


Figure 3.9 MHC class I and MHC class II molecules bind to different T-cell co-receptors. Left panel: the CD8 co-receptor of a CD8 T cells binds to an MHC class I molecule on an antigen-presenting cell (APC). Right panel: the CD4 co-receptor of a CD4 T cell binds to an MHC class II molecule on an APC. TCR, T-cell receptor. Although CD4 and CD8 perform an analogous function they have different polypeptide chains and three-dimensional structures.

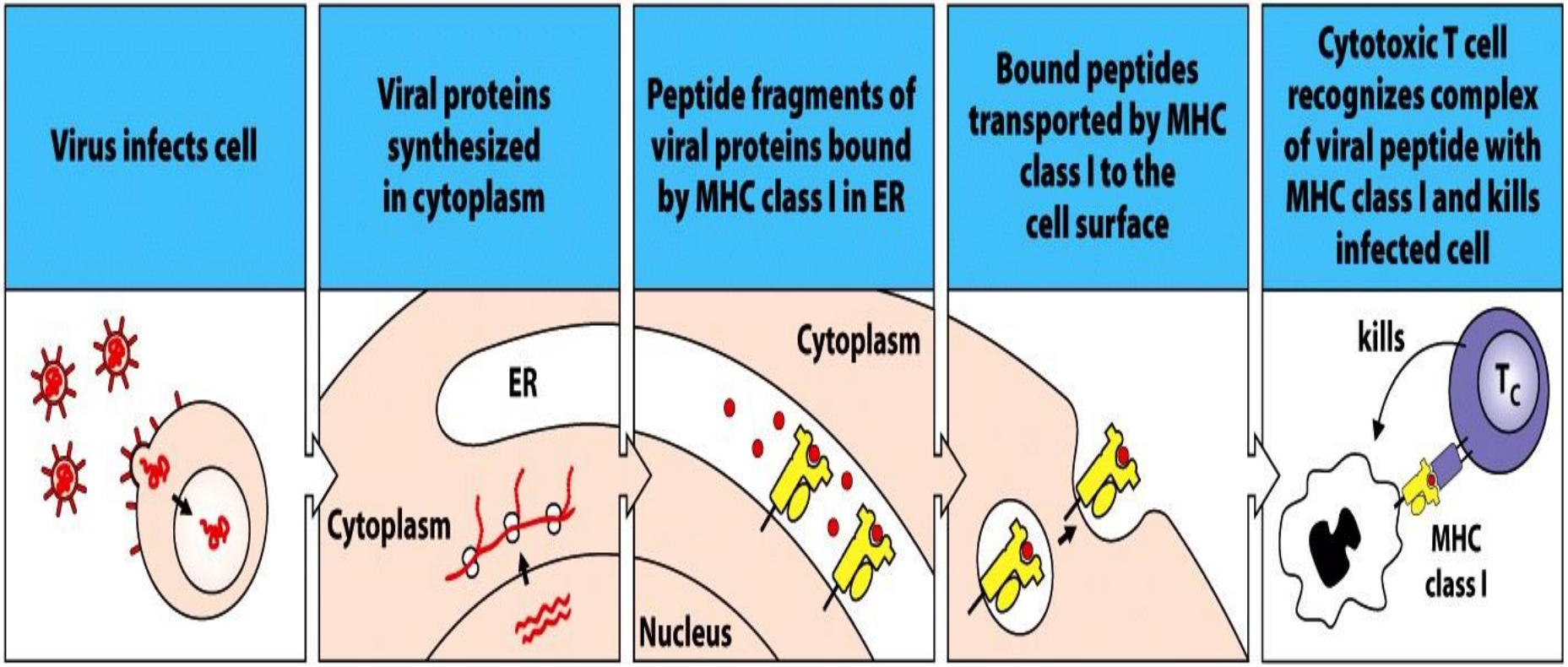


Figure 3.10 The MHC class I pathway presents antigens derived from intracellular infections to cytotoxic CD8 T cells. In virus-infected cells, new viral proteins are made on ribosomes in the cytoplasm. Some of these proteins are degraded in the cytoplasm and the resultant peptides are transported into the endoplasmic reticulum (ER). MHC class I molecules bind peptides in the ER and then transport them to the surface of the infected cell, where they can be recognized by a virus-specific effector cytotoxic T cells (T_C). The cytotoxic T cell kills the virus-infected cell.

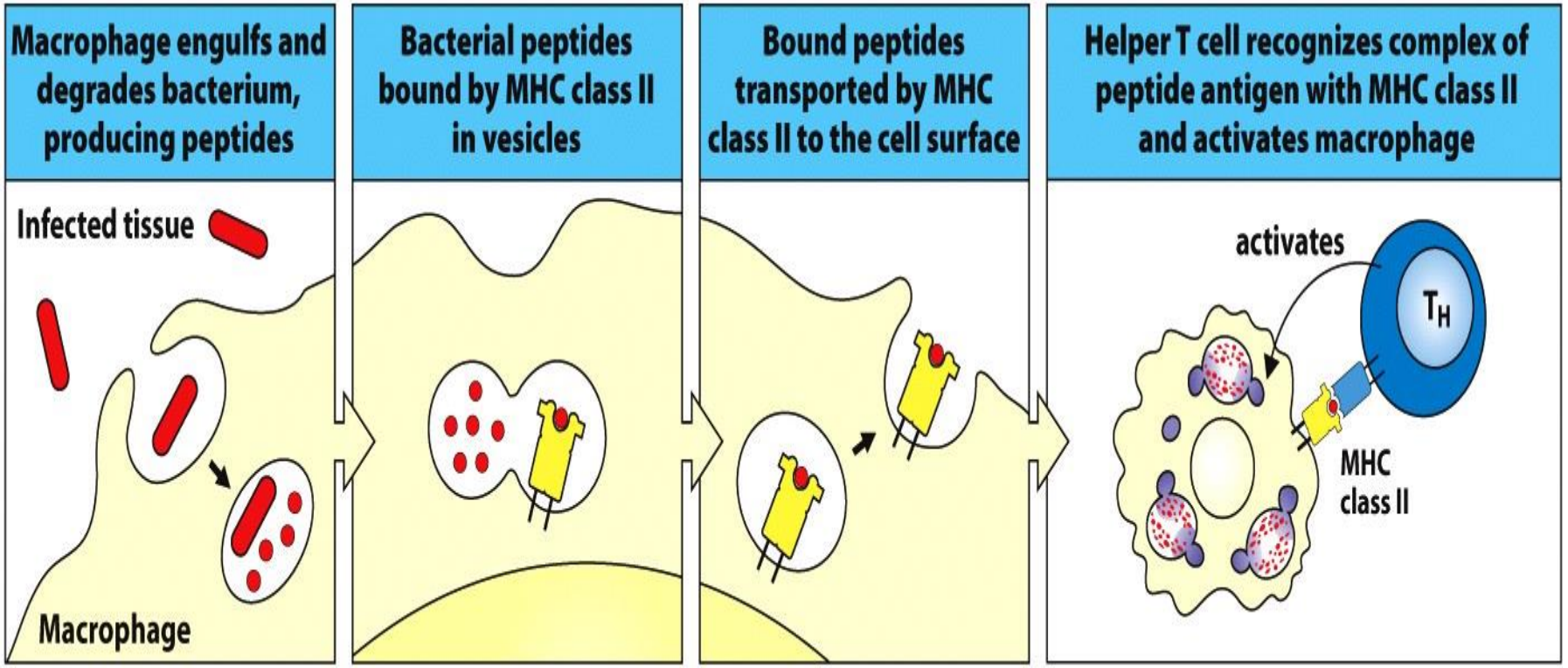


Figure 3.11 The MHC class II pathway presents antigens derived from extracellular infections to helper CD4 T cells. In a tissue infected with bacteria, a resident macrophage is shown phagocytosing extracellular bacteria and degrading their proteins in endocytic vesicles. MHC class II molecules bind peptides in endocytic vesicles and transport the peptides to the cell surface, where they are recognized by a helper CD4 T cell (T_H). Through cell contact and release of cytokines the helper T cell activates the macrophage, making it more effective in killing bacteria.

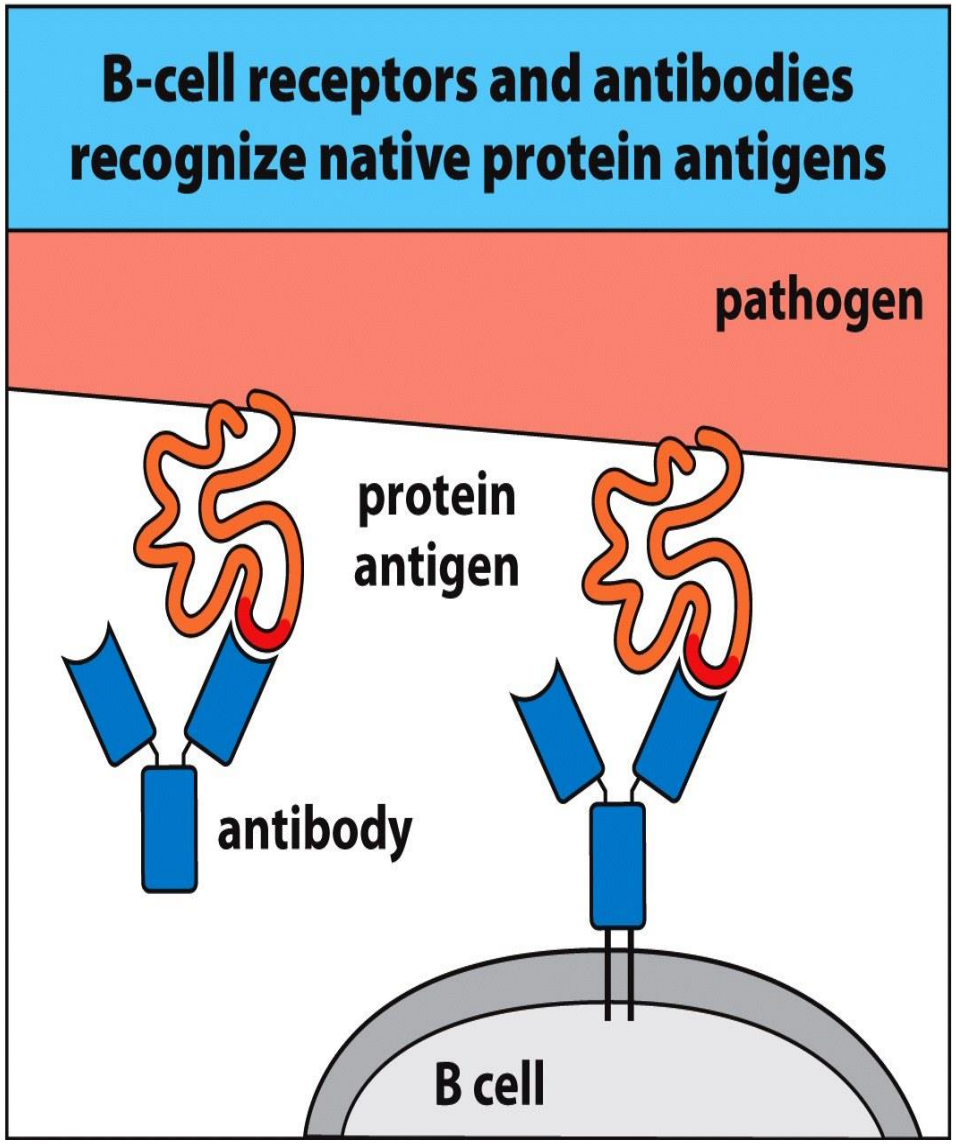


Figure 3.12 B cells recognize native macromolecules on the outside surfaces of pathogens. Whereas T-cell receptors recognize only short degraded fragments of a pathogen's proteins bound by MHC molecules, the immunoglobulin receptors and soluble antibodies of B cells directly recognize the native conformations of proteins, as well as the many other types of macromolecule present on pathogen surfaces, including carbohydrates, proteoglycans, glycoproteins, and glycolipids.

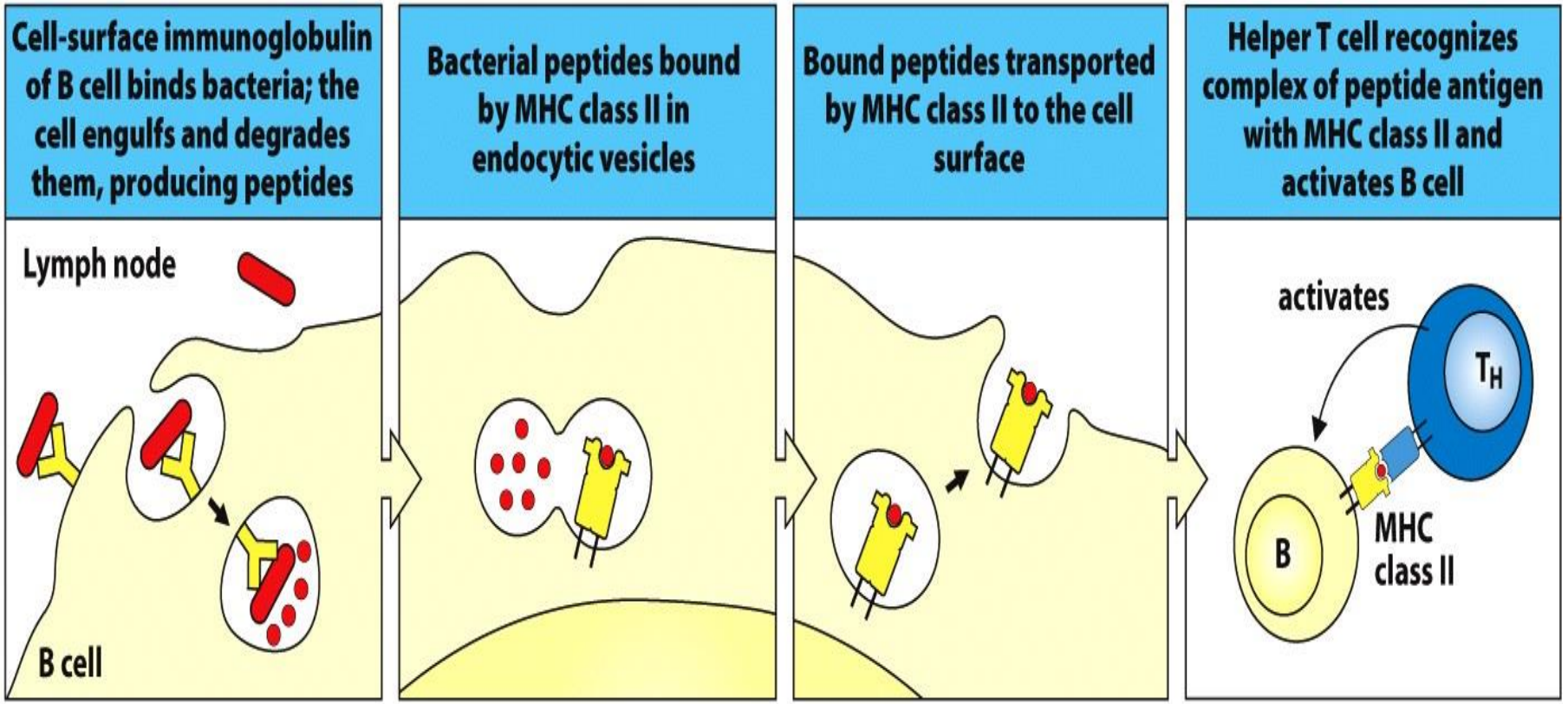


Figure 3.13 Helper CD4 T cells help activate B cells to make antibody. Pathogens are brought by the lymph from a site of infection to the draining lymph node. In the lymph node a pathogen-specific B cell binds the pathogen (illustrated here as a bacterium) via its cell-surface immunoglobulin. The bound bacterium is endocytosed and its proteins are degraded into peptides. Some of these are bound by MHC class II molecules in endocytic vesicles and transported to the cell surface, where they can be recognized by the antigen receptor of a helper CD4 T cell (T_H). Through cell contact and secretion of cytokines the helper T cell helps to activate the B cell fully. That then divides and differentiates into plasma cells secreting antibody against the bacterium (not shown).

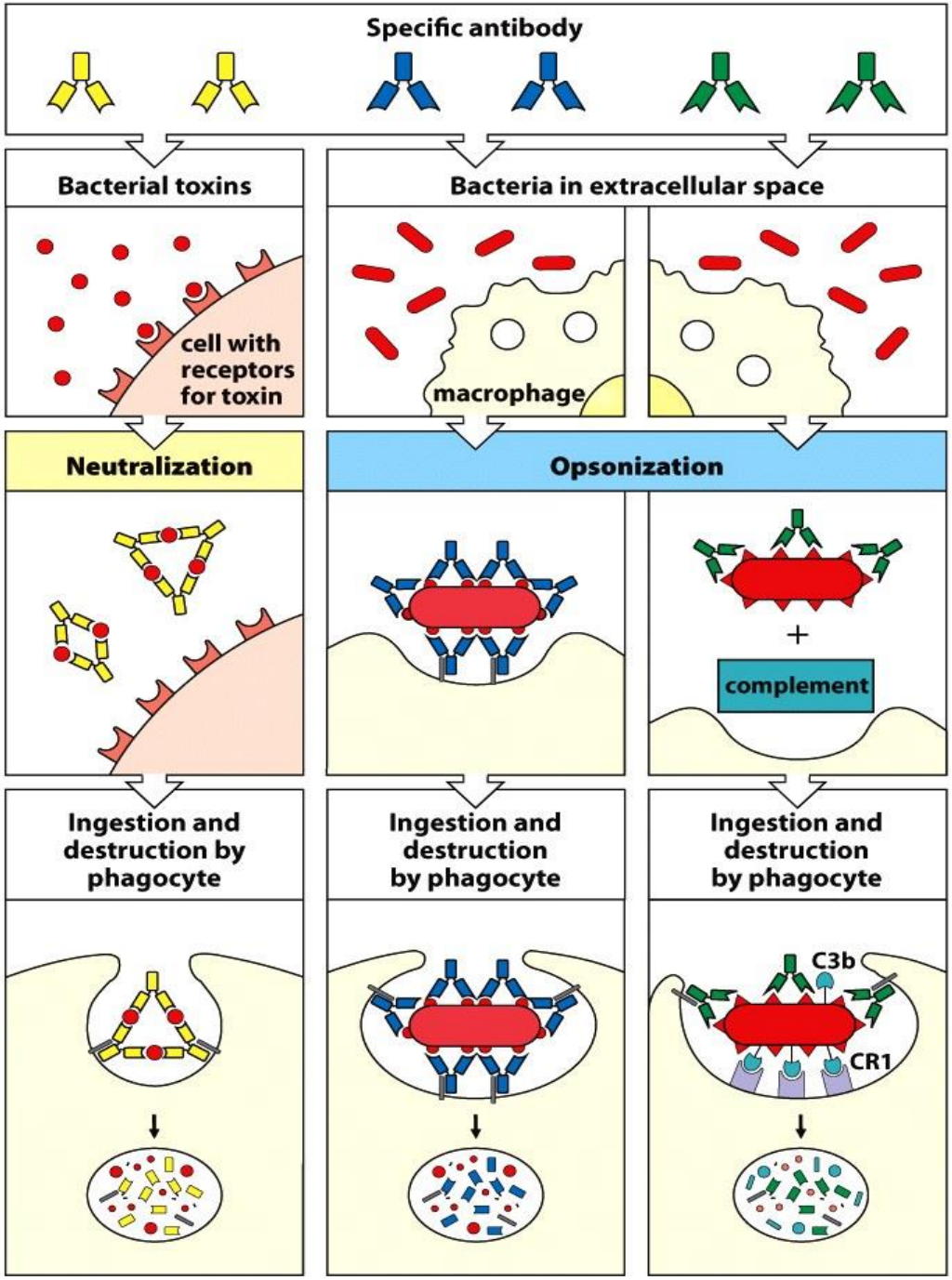


Figure 3.14 Mechanisms by which antibodies combat infection. Left panels: antibodies bind to a bacterial toxin and neutralize its toxic activity by preventing the toxin from interacting with its receptor on human cells. The complex of toxin and antibodies binds to macrophage receptors through the antibody's constant region. Finally the macrophage ingests and degrades the complex. Center panels: the opsonization of a bacterium by coating it with antibody. When the bacterium is coated with IgG antibodies, their constant regions point outward and can bind to the receptors on a phagocyte, which then ingests and degrades the bacterium. Right panels: opsonization of a bacterium by a combination of antibody and complement. The bacterium is first coated with IgG molecules, which trigger the classical pathway of complement activation. C3b fragments fixed to the bacterial surface provide ligands for the complement receptor CR1 on macrophages. The combined interaction of phagocyte receptors for complement and for the constant region of IgG makes for efficient phagocytosis.

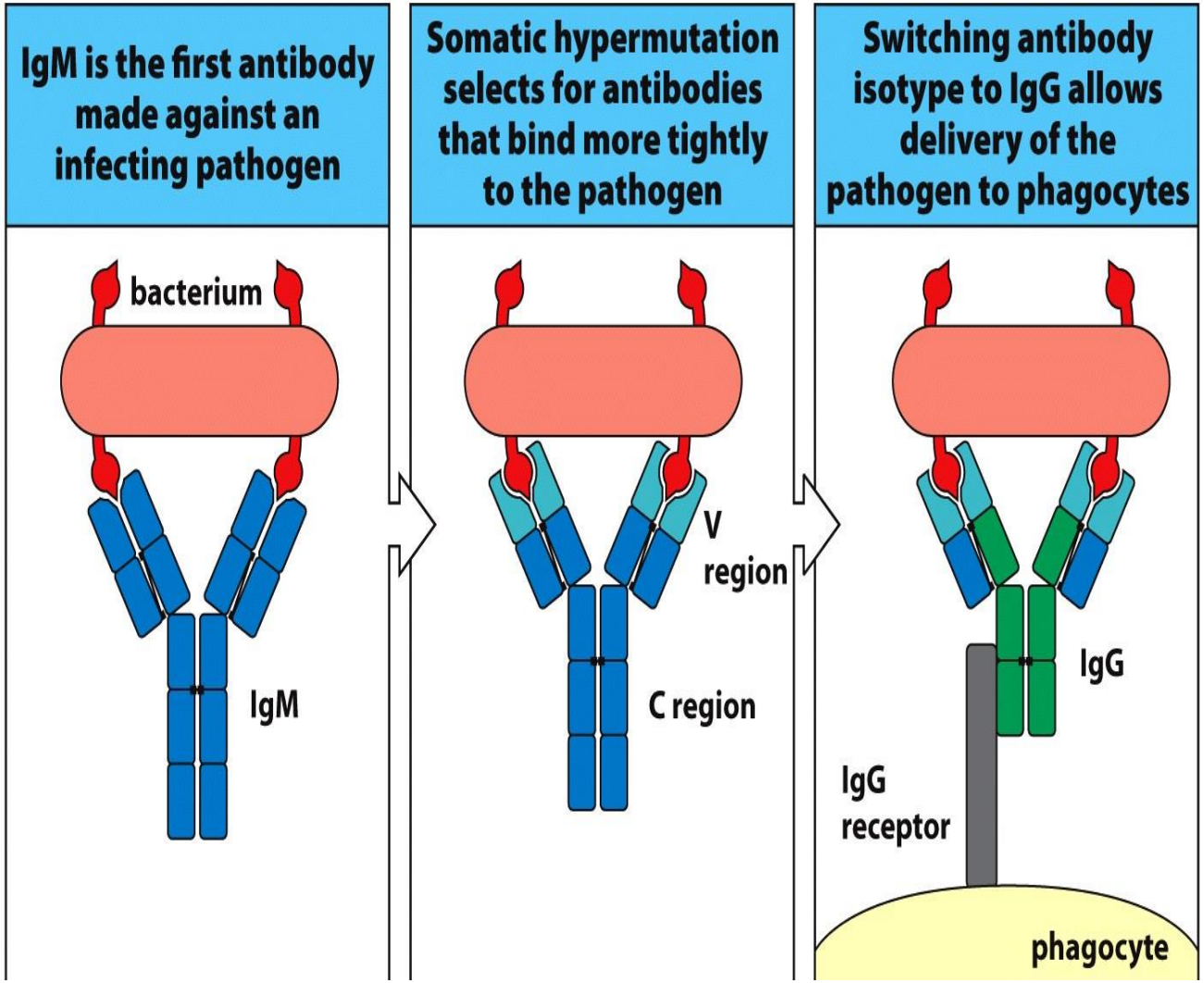


Figure 3.15 Somatic hypermutation and isotype switching during an adaptive immune response improve the quality of the antibody that is made. At the beginning of an adaptive immune response to infection, IgM is the only antibody made (left panel). In the population of B cells that are making pathogen-specific IgM, somatic hypermutation of the variable regions of the heavy- and light-chain genes produces some new variant antibodies that bind more tightly to the pathogen (center panel). Isotype switching to IgG changes the constant region of the heavy chain (right panel). In this case it provides the antibody with a binding site for a receptor on phagocytes that is specific for IgG and does not bind IgM. Binding of the IgG-coated pathogen to this IgG receptor ensures its phagocytosis and destruction. Whereas somatic hypermutation strengthens the antigen-binding properties of the antibodies, isotype switching improves their recruitment of effector functions. Together these two processes improve the ability of antibodies to remove pathogens.

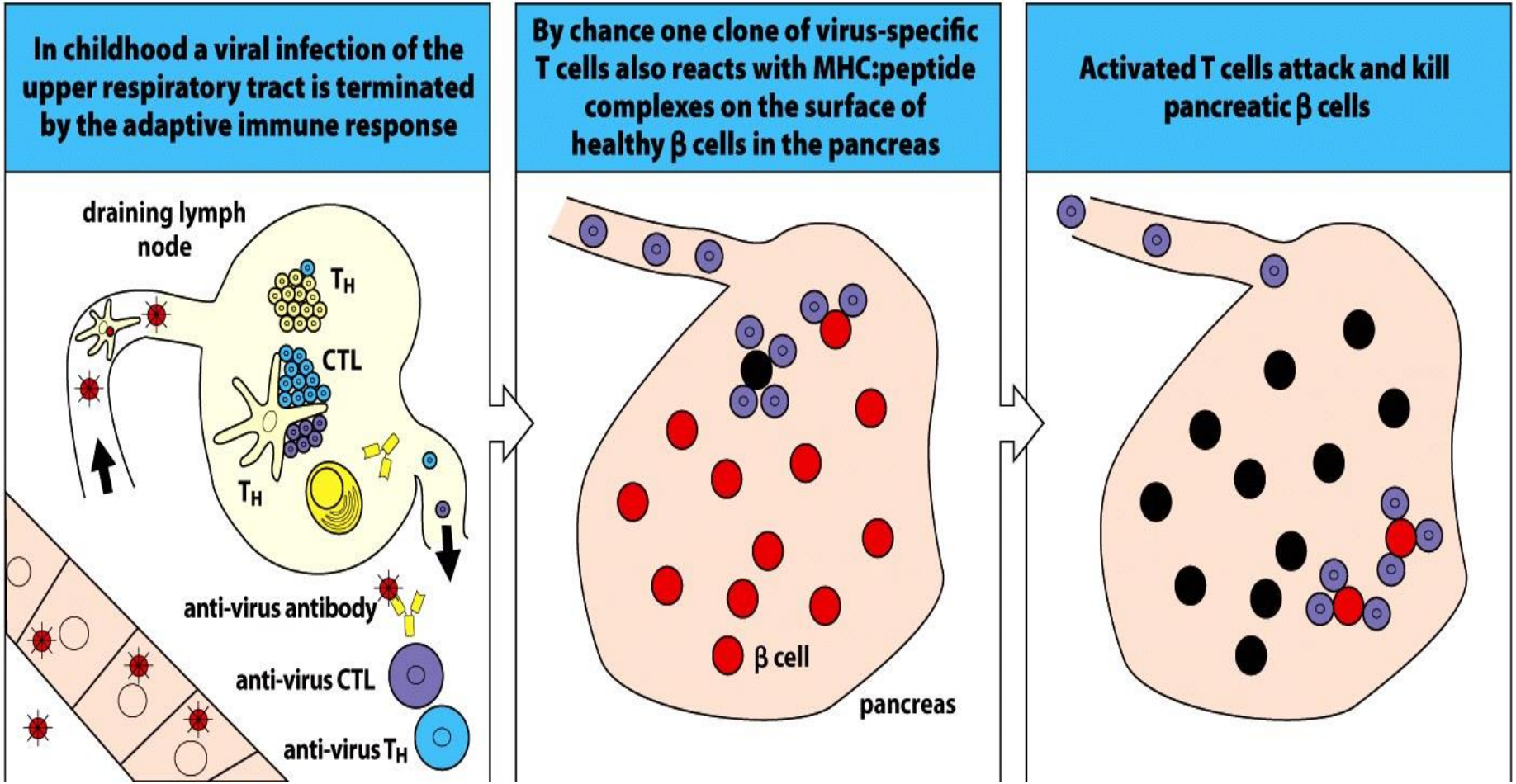


Figure 3.17 The adaptive immune response to a pathogen can sometimes trigger autoimmune reactions that eventually cause disease. Insulin-dependent diabetes mellitus (type 1 diabetes mellitus) is an autoimmune disease in which the insulin-producing β cells of the pancreas are gradually destroyed. A history of viral infection, for example with the Coxsackie viruses, has been correlated with type 1 diabetes and in such cases the autoimmunity might be a secondary consequence of the adaptive immune response to the virus. This could happen if a clone of T cells activated by the virus has, by chance, a T-cell receptor that reacts with an peptide:MHC complex present on the surface of pancreatic β cells. This peptide:MHC complex will then continually re-stimulate the T cells, which in turn persistently attack the β cells.

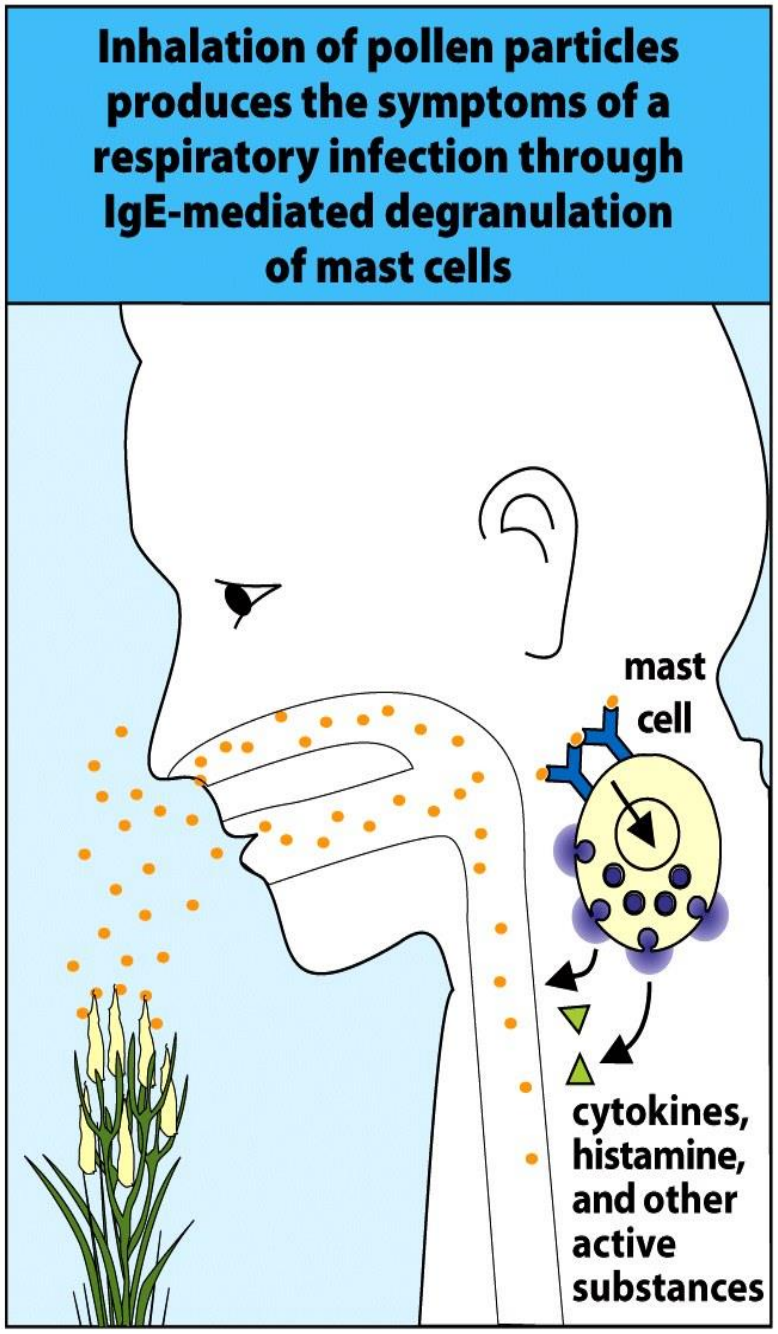
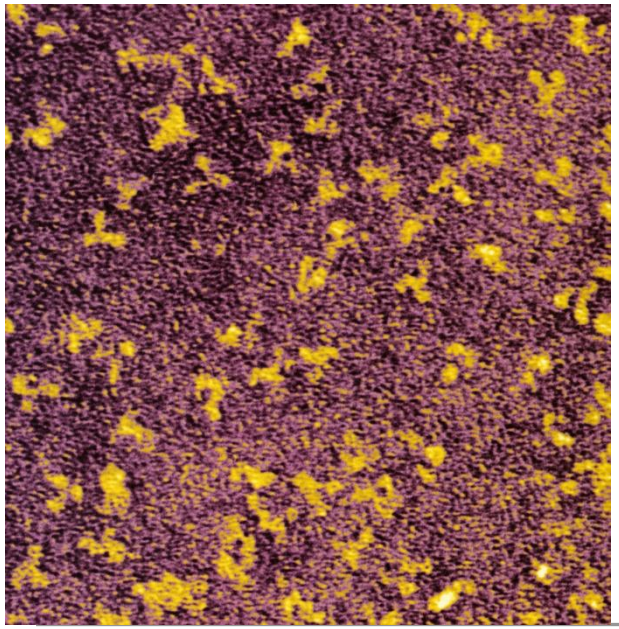


Figure 3.18 Many allergies are caused when antibodies of the IgE isotype are made against innocuous substances. The example shown here is of an allergy to airborne pollen, such as ragweed pollen, that is breathed in and stimulates an allergic response in the mucosa of the respiratory system. For genetic and environmental reasons some people make an IgE antibody response to an antigen in the pollen. Once made, the IgE antibody becomes bound to mast cells in the mucosal tissues, where it acts as a receptor. On subsequent exposure to pollen, the pollen allergen binds to and cross-links the cell-bound IgE, sending a signal for the mast cell to release the granules it contains. These granules contain cytokines and other substances, such as histamine, that induce inflammation, sneezing, and other symptoms that are usually associated with infectious diseases.



Individual molecules of human immunoglobulin G, the predominant antibody in blood and connective tissue.

Chapter 4

Antibody Structure and the Generation of B-Cell Diversity

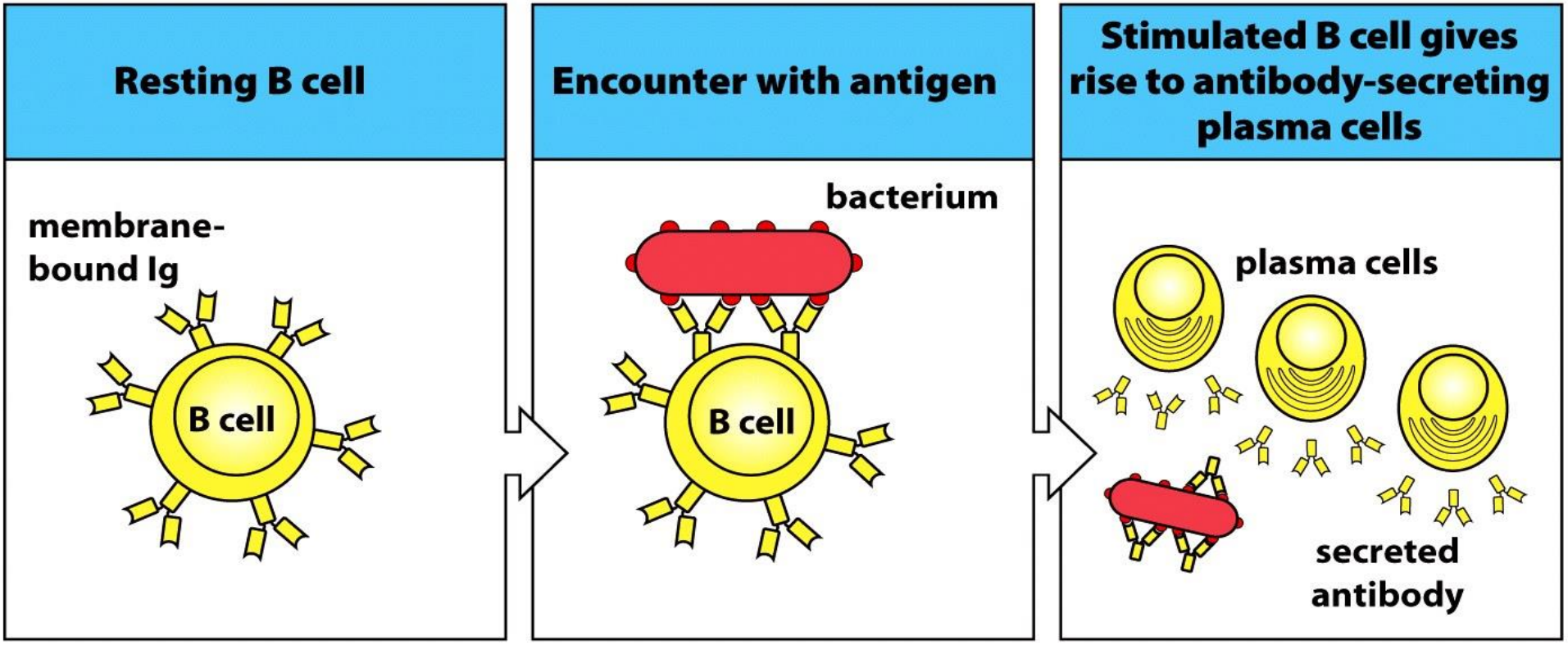
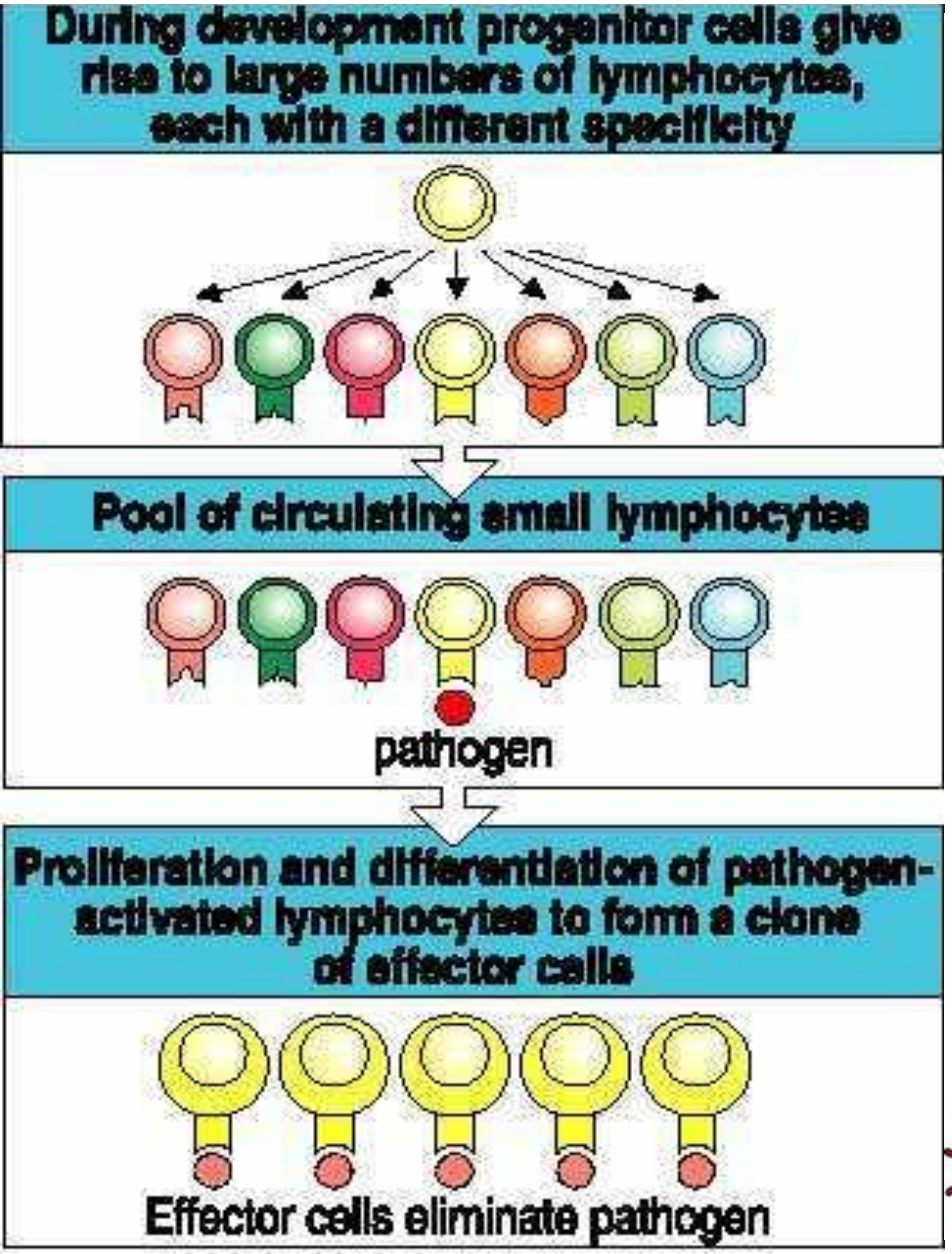
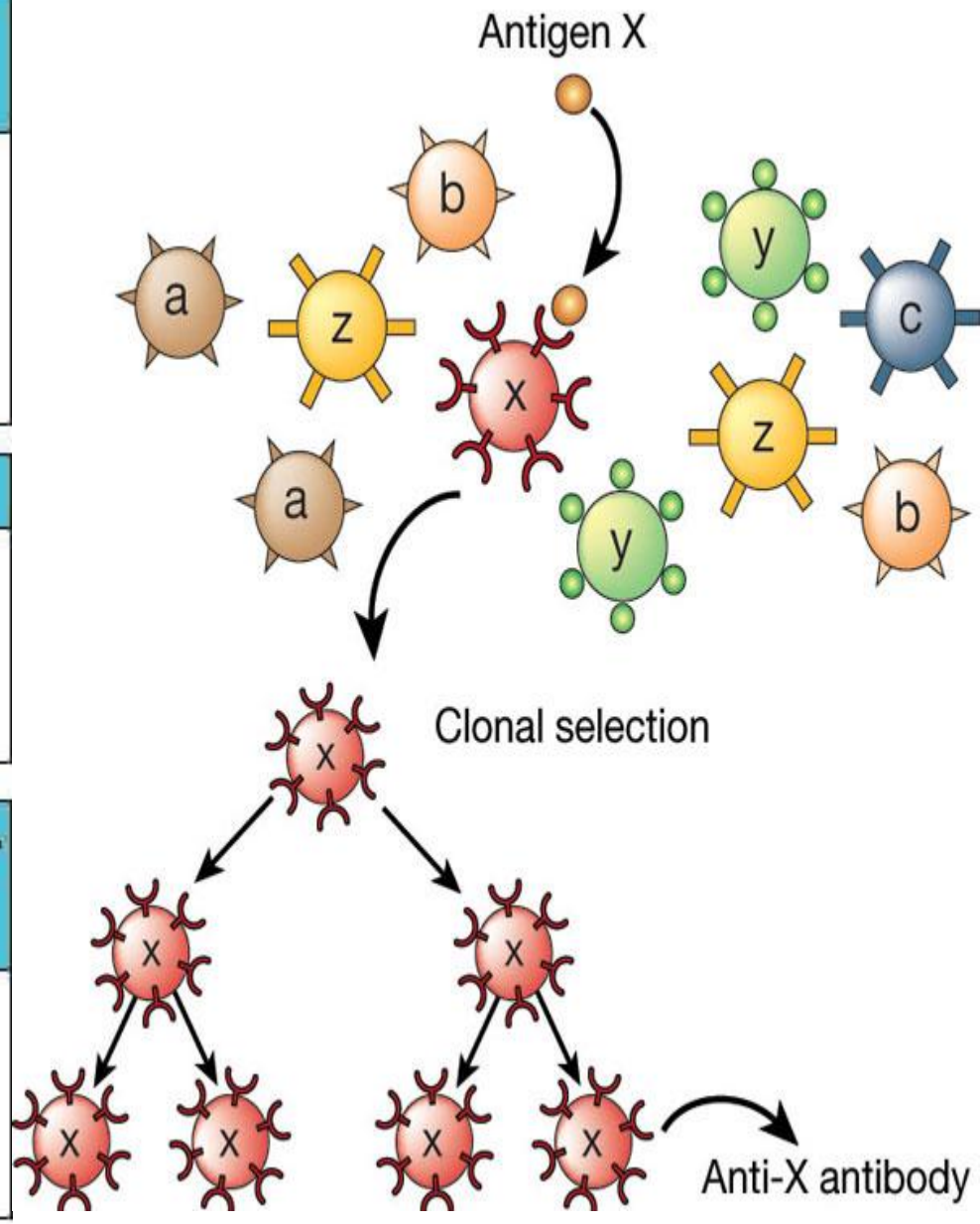


Figure 4.1 Plasma cells secrete antibody of the same antigen specificity as the membrane-bound immunoglobulin expressed by their B-cell precursor. A mature B cell expresses membrane-bound immunoglobulin (Ig) of a single antigen specificity. When a foreign antigen first binds to this immunoglobulin, the B cell is stimulated to proliferate. Its progeny differentiate into plasma cells that secrete antibody of the same specificity as the membrane-bound immunoglobulin.

Clonal Selection Theory





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or Medicine

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The Nobel Prize in 1960

"for discovery of acquired immunological tolerance"

Frank Macfarlane Burnet

Australian

Clonal Selection Theory

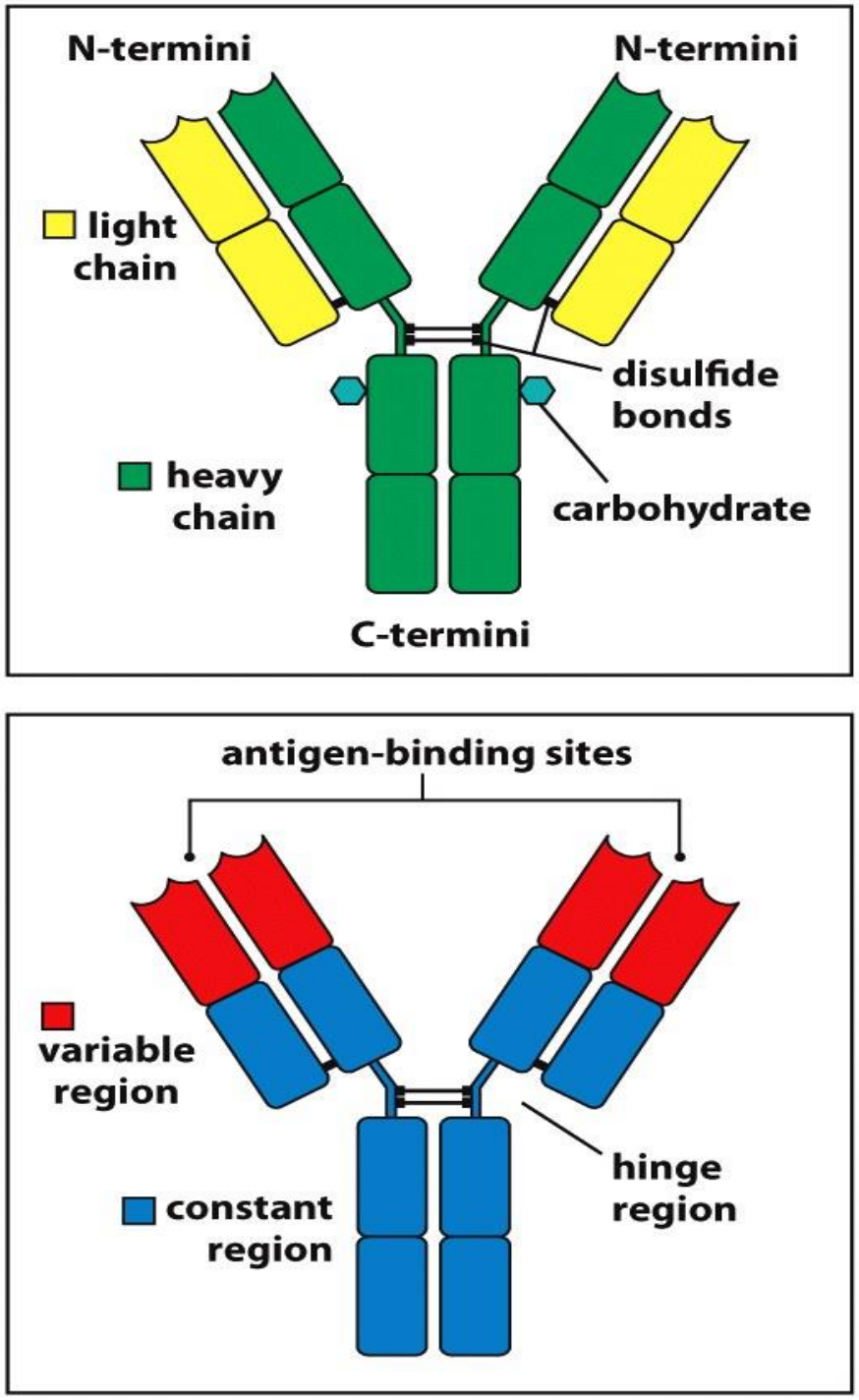

Figure 4.2 The immunoglobulin G (IgG) molecule. As shown in the top panel, each IgG molecule is made up of two identical heavy chains (green) and two identical light chains (yellow). Carbohydrate (turquoise) is attached to the heavy chains. The lower panel shows the location of the variable (V) and constant (C) regions in the IgG molecule. The amino-terminal regions (red) of the heavy and light chains are variable in sequence from one IgG molecule to another; the remaining regions are constant in sequence (blue). The carbohydrate is omitted from this panel and from most subsequent figures for simplicity. In IgG a flexible hinge region is located between the two arms and the stem of the Y.

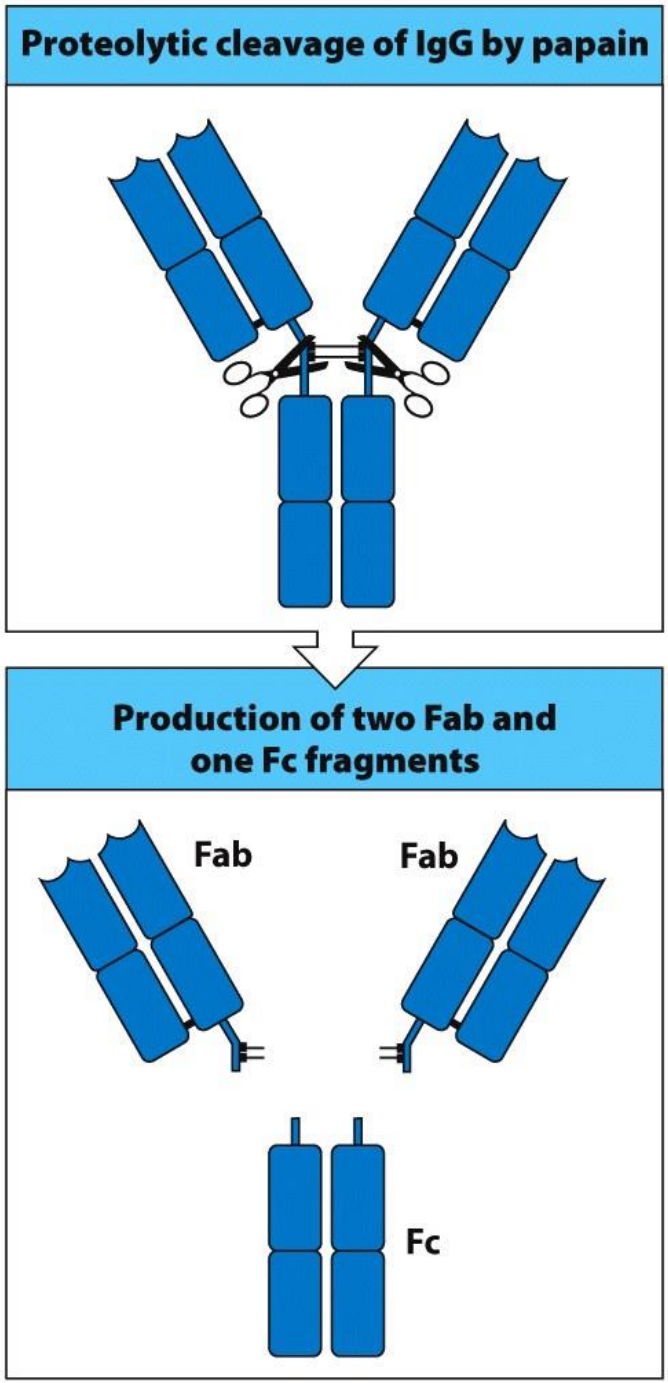

Figure 4.3 The Y-shaped immunoglobulin molecule can be dissected with a protease. Treatment of IgG with the enzyme papain results in proteolytic cleavage of the hinge of each heavy chain, as shown by the scissors, and reduction of the disulfide bonds that connect the two hinges. The IgG molecule is thus dissected into three pieces: two Fab fragments and one Fc fragment. Reduction of the disulfide bonds is not due to papain activity but is caused by free cysteine in the reaction mixture, which is needed to stabilize the enzyme.

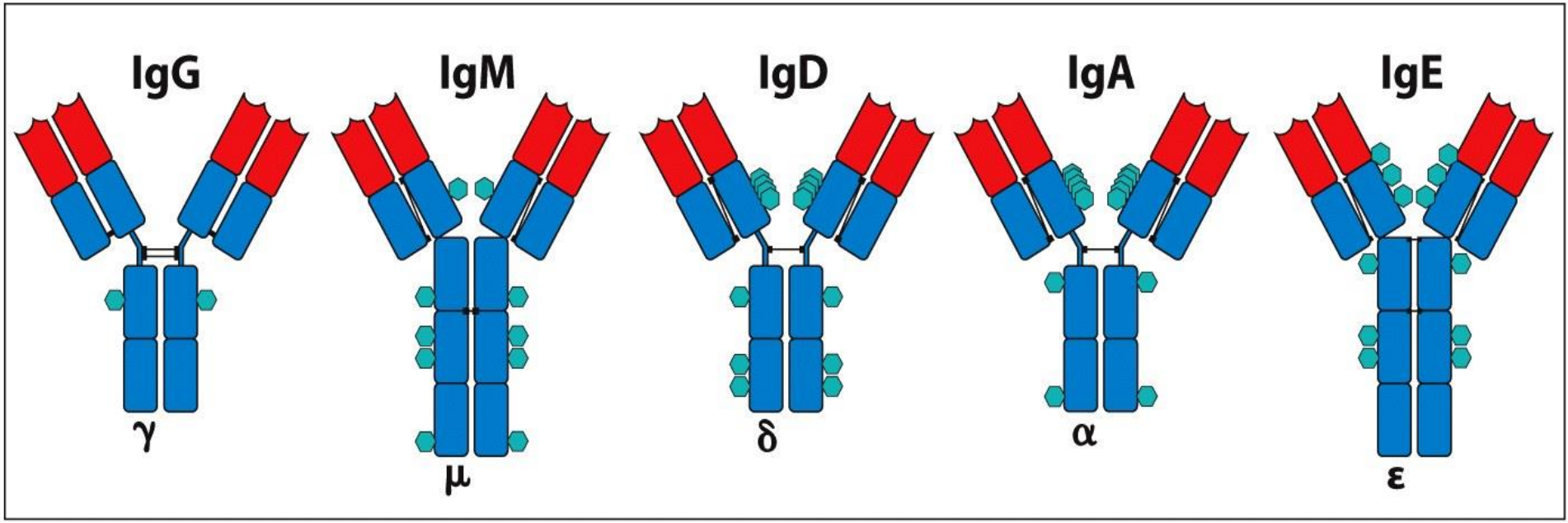

Figure 4.5 The structures of the human immunoglobulin classes. In particular, note the differences in length of the heavy-chain C regions, the locations of the disulfide bonds linking the chains, and the presence of a hinge region in IgG, IgA, and IgD but not in IgM and IgE. The heavy-chain isotype in each antibody is indicated by the Greek letter. The isotypes also differ in the distribution of *N*-linked carbohydrate groups (turquoise). All these immunoglobulins occur as monomers in their membrane-bound form. In their soluble, secreted form, IgD, IgE, and IgG are always monomers, IgA forms monomers and dimers, and IgM forms only pentamers.

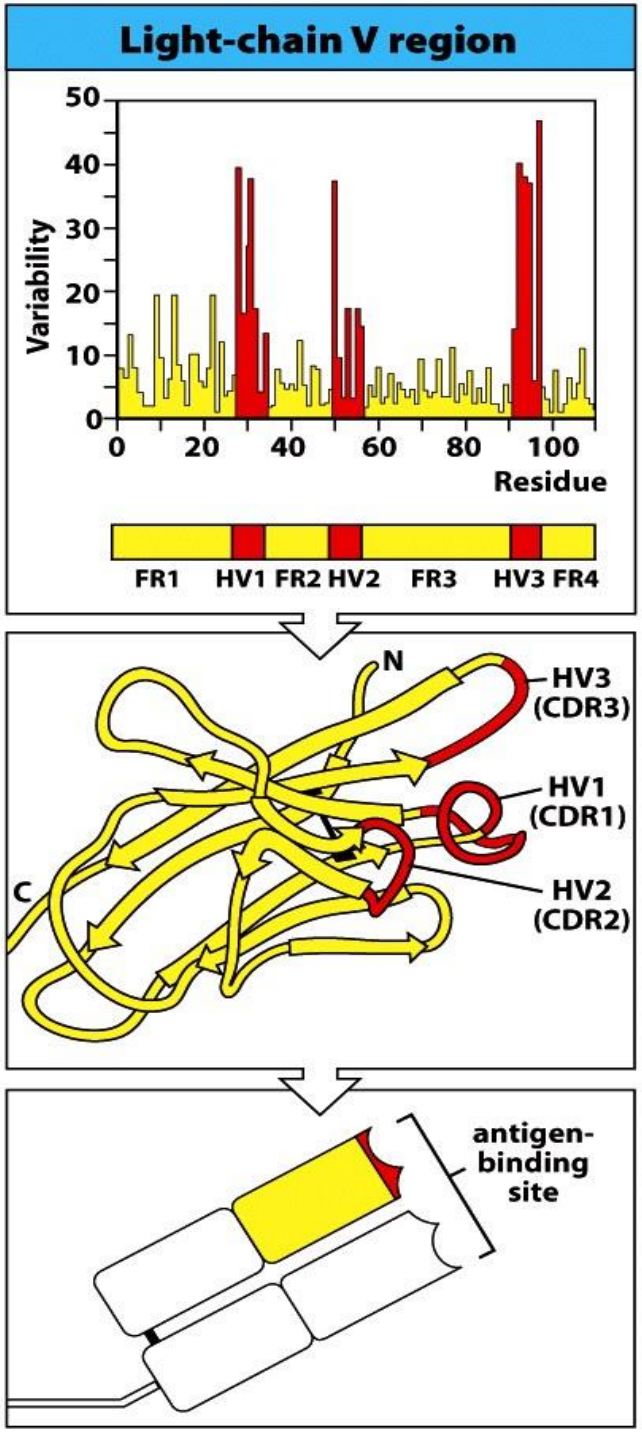

Figure 4.8 The hypervariable regions of antibody V domains lie in discrete loops at one end of the domain structure. The top panel shows the variability plot for the 110 positions within the amino acid sequence of a light-chain V domain. It is obtained from comparison of many light-chain sequences. Variability is the ratio of the number of different amino acids found at a position to the frequency of the most common amino acid at that position. The maximum value possible for the variability is 400, the square of 20, the number of different amino acids found in antibodies. The minimum value is 1. Three hypervariable regions (HV1, HV2, and HV3) can be discerned (red) flanked by four framework regions (FR1, FR2, FR3, and FR4) (yellow). The center panel shows the correspondence of the hypervariable regions to three loops at the end of the V domain farthest from the C region. The location of hypervariable regions in the heavy-chain V domain is similar (not shown). The hypervariable loops contribute much of the antigen specificity of the antigen-binding site located at the tip of each arm of the antibody molecule. Hypervariable regions are also known as complementarity-determining regions: CDR1, CDR2, and CDR3. The bottom panel shows the location of the light-chain V region in the Fab part of the IgG molecule.

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The Nobel Prize in 1972

Antibody Structure and Molecular Immunology

Gerald M. Edelman, Rodney R. Porter

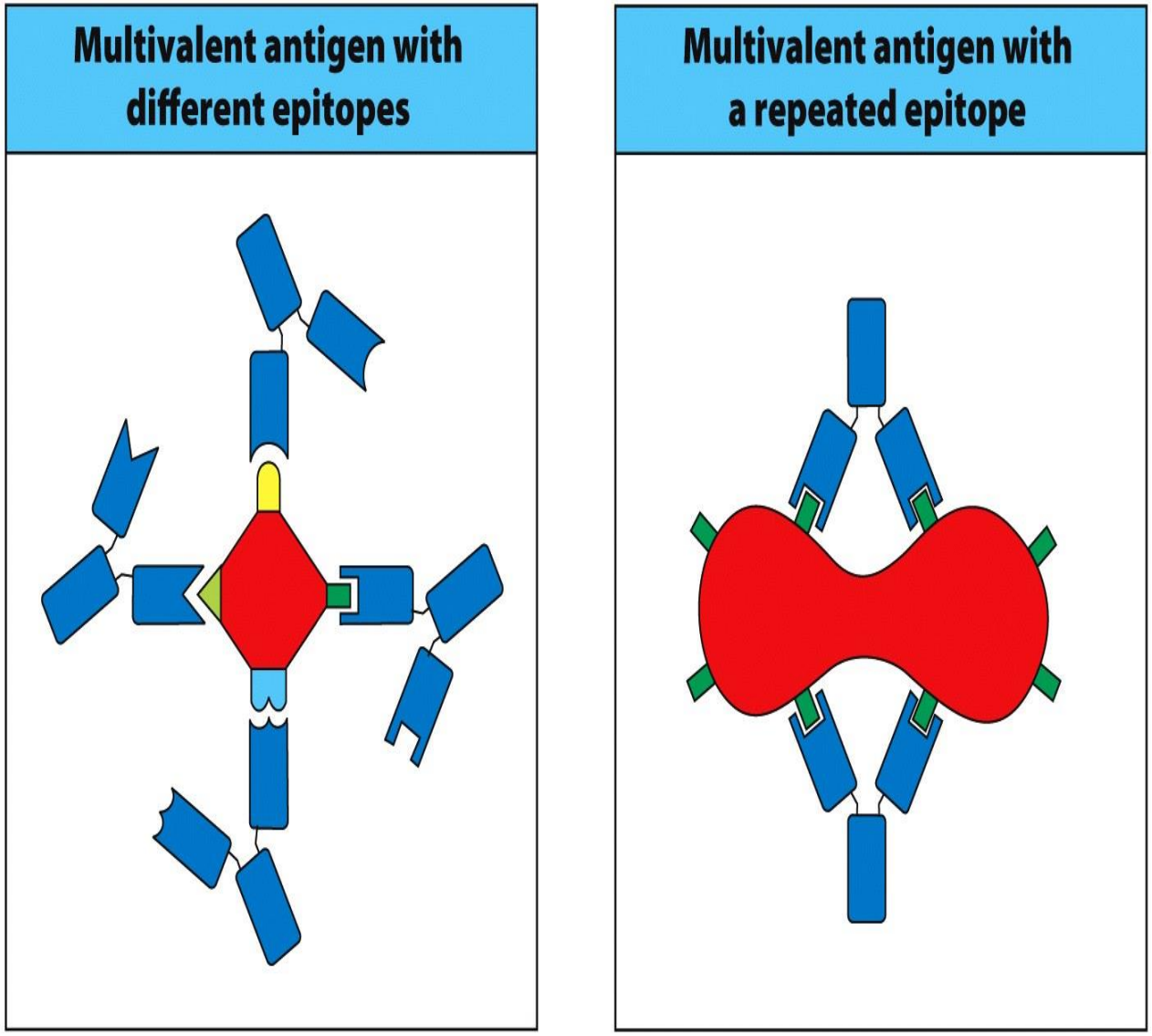
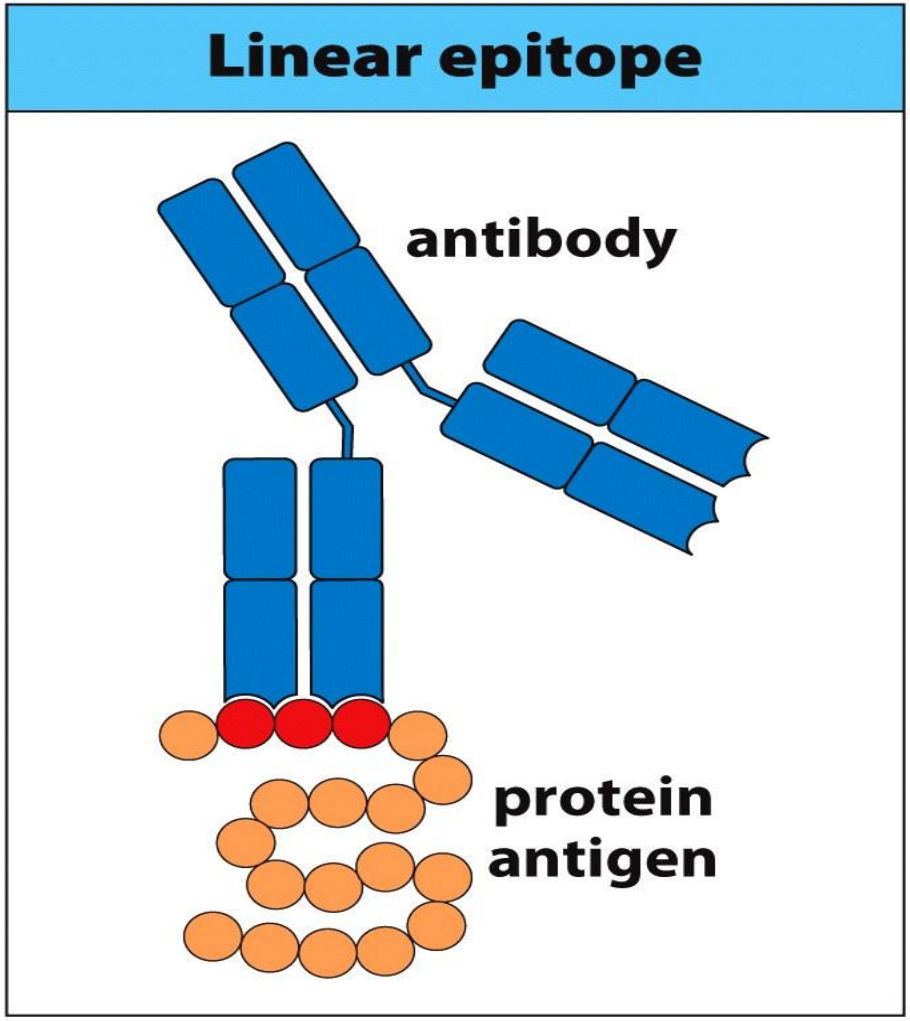


Figure 4.10 Two kinds of multivalent antigen. Many soluble protein antigens have several different epitopes, but each is represented only once on the surface of the protein. This situation is depicted in the left panel, where four IgG molecules with different specificities all bind to the protein antigen using a single Fab arm. On pathogen surfaces there are numerous copies of the same epitope, as illustrated for poliovirus in Figure 4.9. This situation, depicted in the right panel, allows many IgG molecules with identical antigenic specificity to bind to the multivalent antigen with both Fab arms.



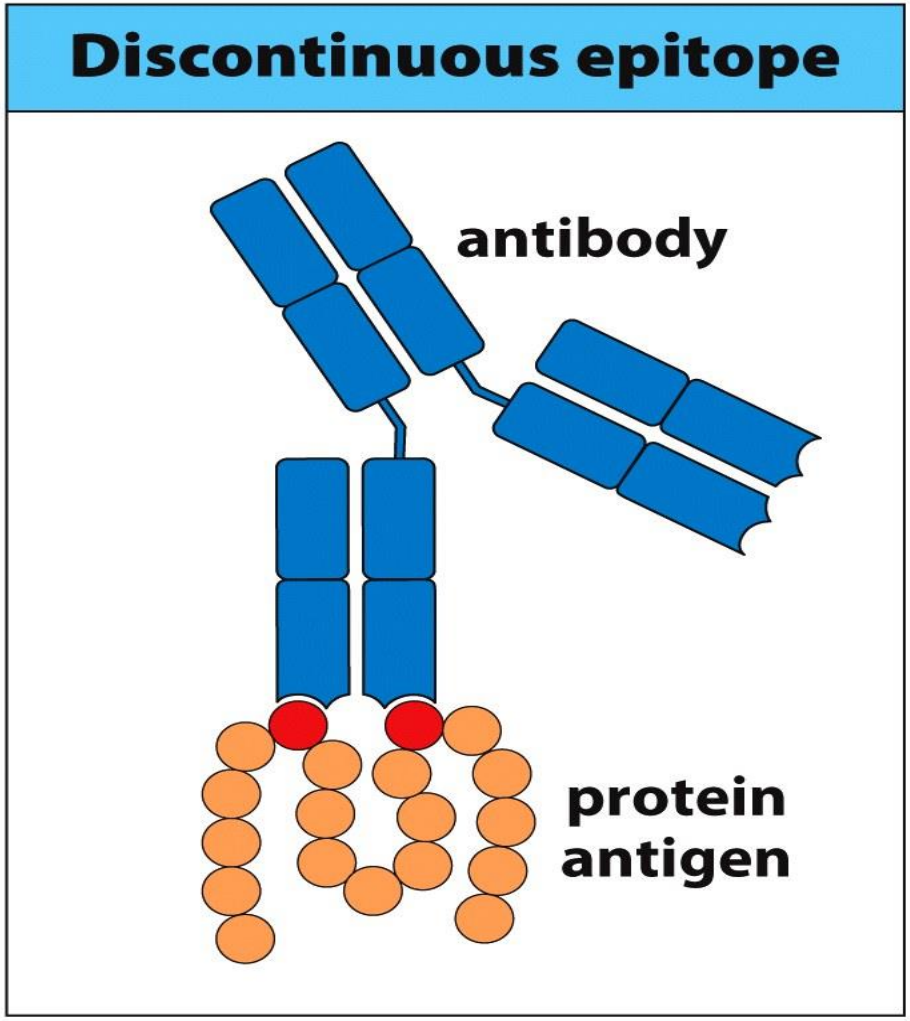


Figure 4.12 Linear and discontinuous epitopes. A linear epitope of a protein antigen is formed from contiguous amino acids. A discontinuous epitope is formed from amino acids from different parts of the polypeptide that are brought together when the chain folds.

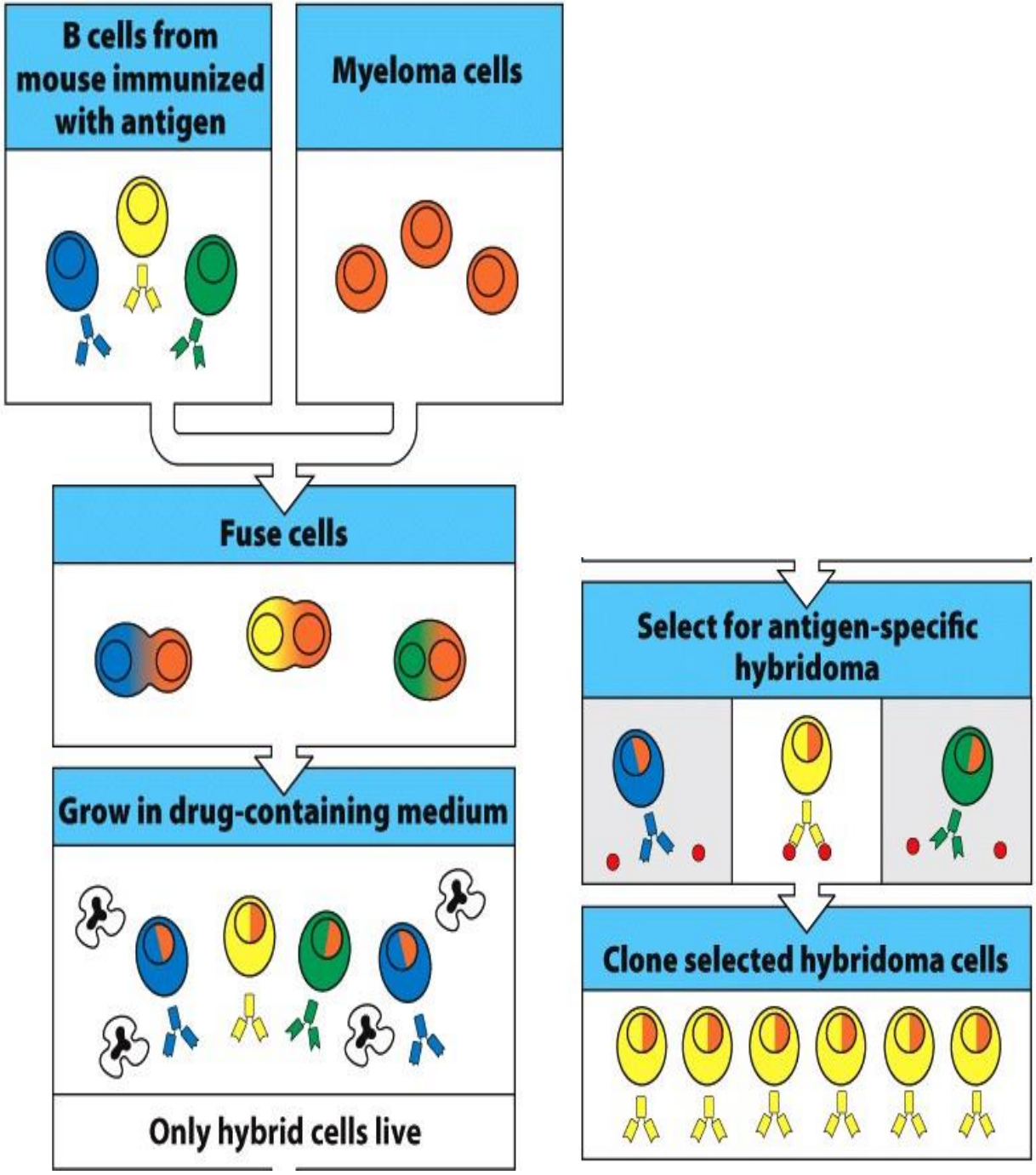


Figure 4.13 Production of a mouse monoclonal antibody. Lymphocytes from a mouse immunized with the antigen are fused with myeloma cells by using polyethyleneglycol. The cells are then grown in the presence of drugs that kill myeloma cells but permit the growth of hybridoma cells. Unfused lymphocytes also die. Individual cultures of hybridomas are tested to determine whether they make the desired antibody. The cells are then cloned to produce a homogeneous culture of cells making a monoclonal antibody. Myelomas are tumors of plasma cells; those used to make hybridomas were selected not to express heavy and light chains. Thus, hybridomas only express the antibody made by the B-cell partner.

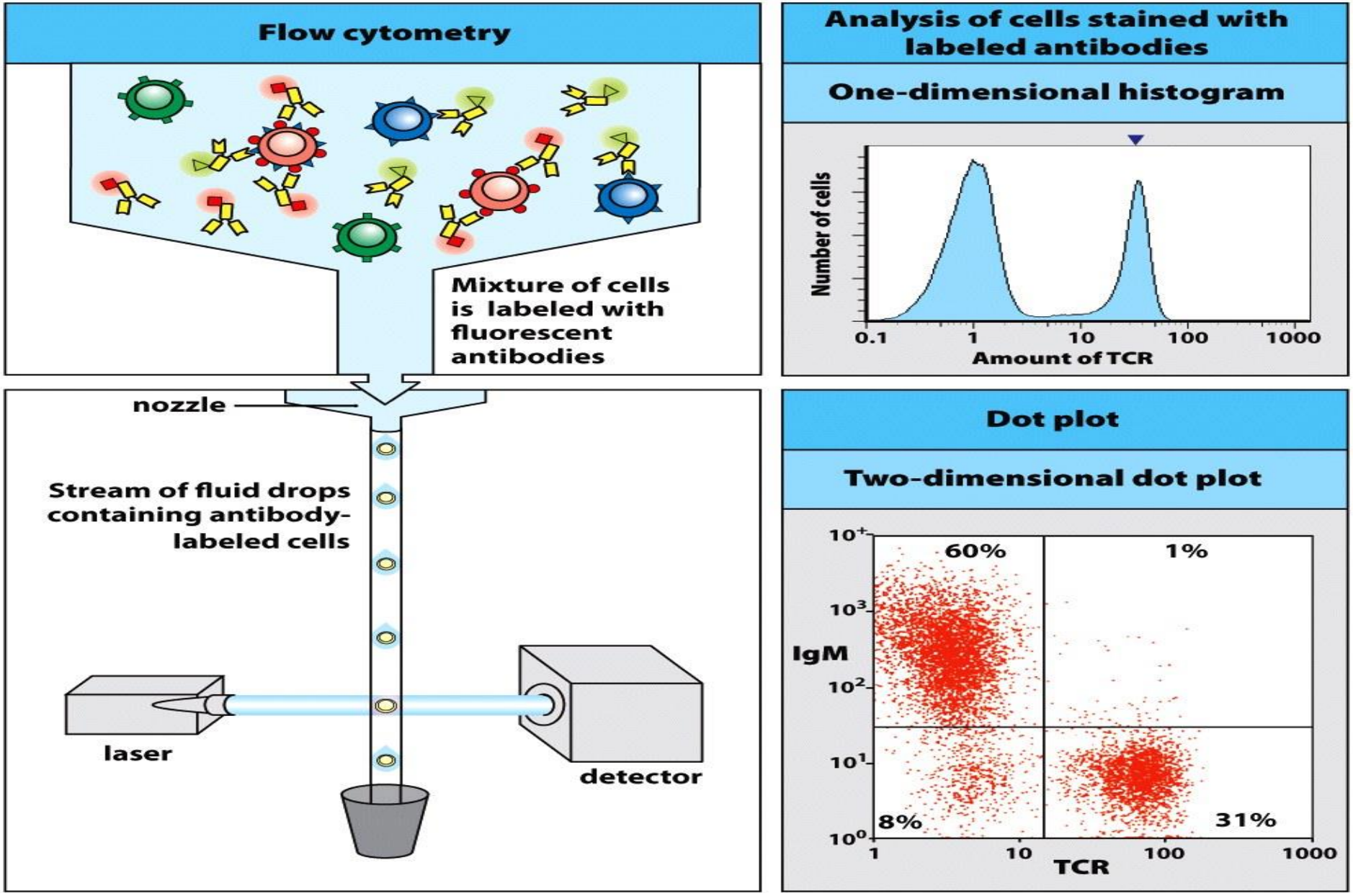


Figure 4.14 The flow cytometer allows individual cells to be identified by their cell-surface molecules. The left-hand

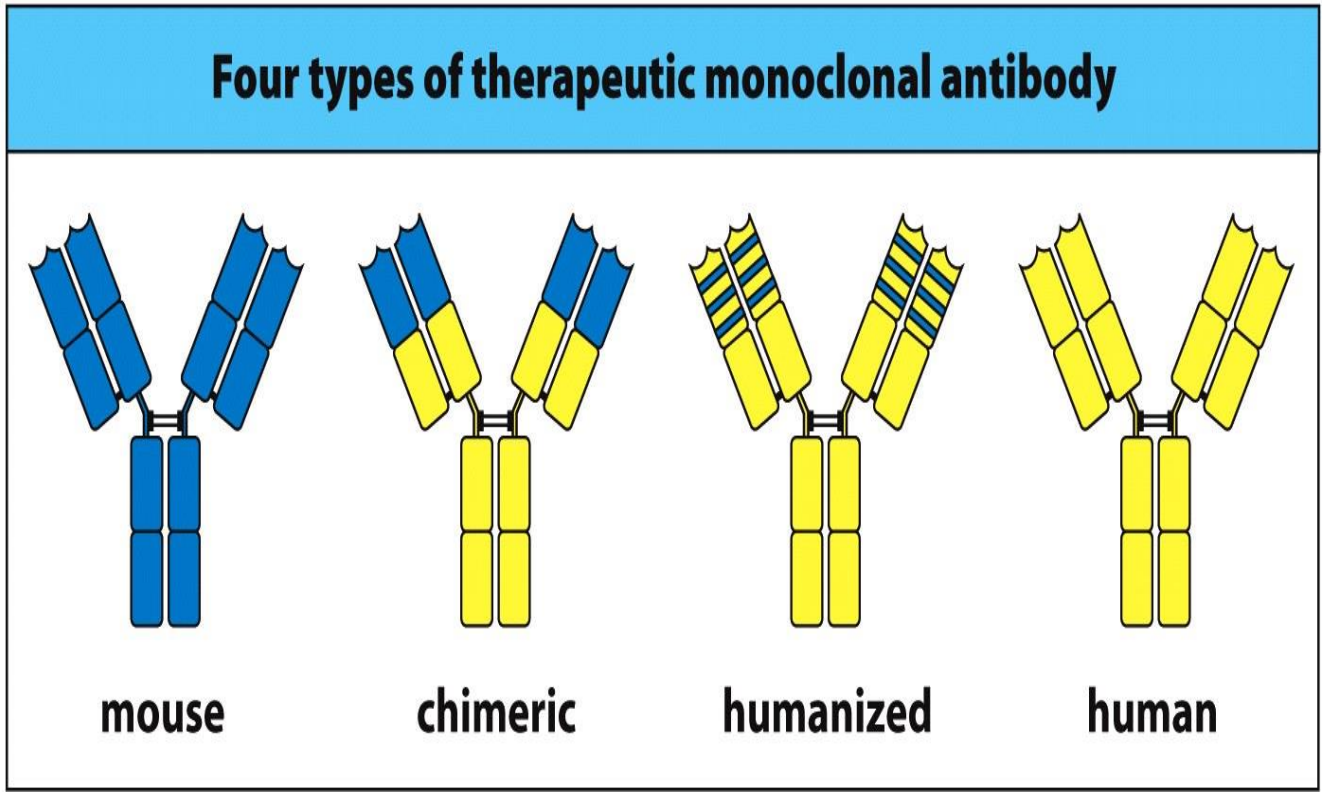


Figure 4.15 Monoclonal antibodies as treatments for disease. Mouse monoclonal antibodies were the first antibodies used therapeutically, but the human immune system perceives the mouse protein as foreign and makes antibodies that bind to the mouse antibodies and get rid of them. To reduce this problem, chimeric antibodies have been made in which the constant regions of mouse monoclonal antibodies (blue) are replaced with human constant regions (yellow). Taking this approach further are humanized antibodies, in which only the CDR loops are of mouse origin. Fully human antibodies can now be made from human hybridomas or by mice in which the mouse immunoglobulin genes are replaced by human immunoglobulin genes. All four types of antibody have been used therapeutically.

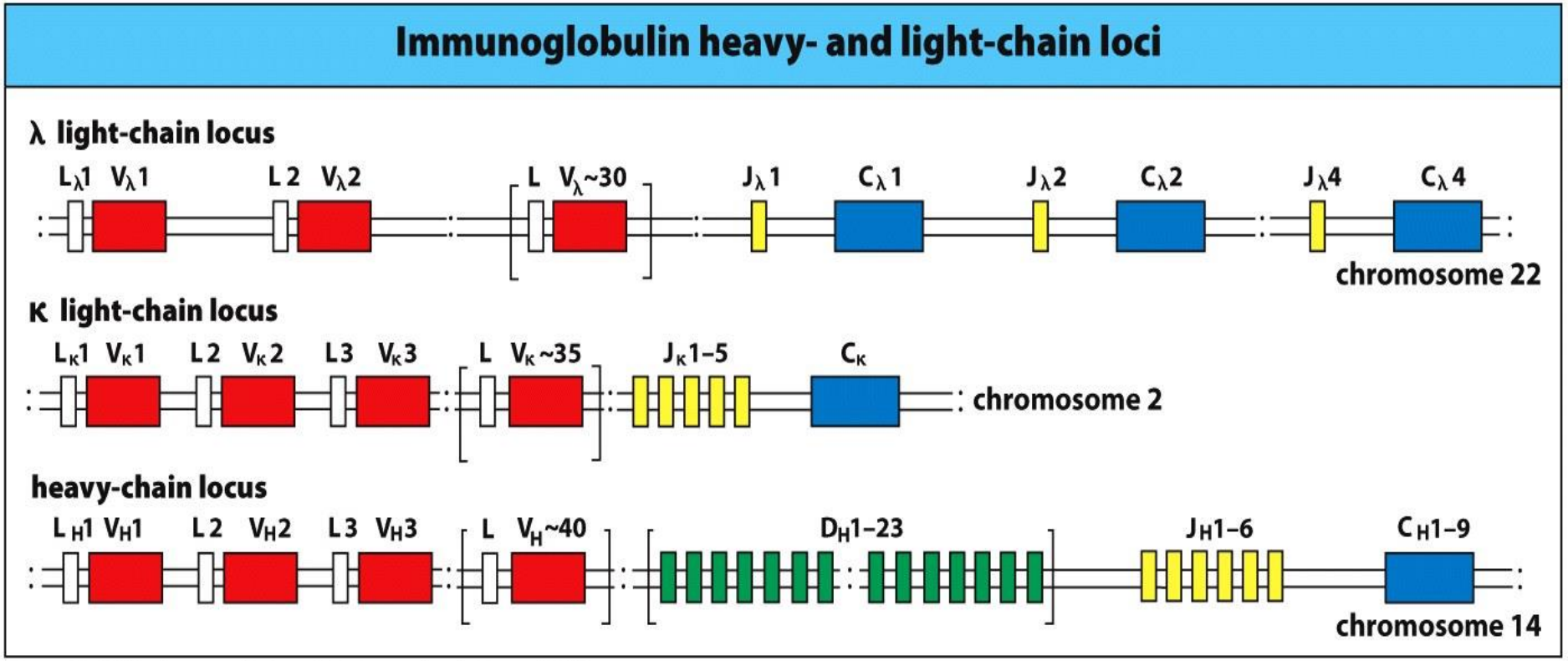


Figure 4.16 The germline organization of the human immunoglobulin heavy-chain and light-chain loci. The upper row shows the λ light-chain locus, which has about 30 functional V_λ gene segments and four pairs of functional J_λ gene segments and C_λ gene segments. The κ locus (center row) is organized in a similar way, with about 35 functional V_κ gene segments accompanied by a cluster of five J_κ gene segments but with a single C_κ gene segment. In approximately half of the human population, the entire cluster of V_κ gene segments is duplicated (not shown, for simplicity). The heavy-chain locus (bottom row) has about 40 functional V_H gene segments, a cluster of about 23 D segments and 6 J_H gene segments. For simplicity, a single C_H gene (C_H1–9) is shown in this diagram to represent the nine C genes. The diagram is not to scale: the total length of the heavy-chain locus is more than 2 megabases (2 million bases), whereas some of the D segments are only six bases long. L, leader sequence.

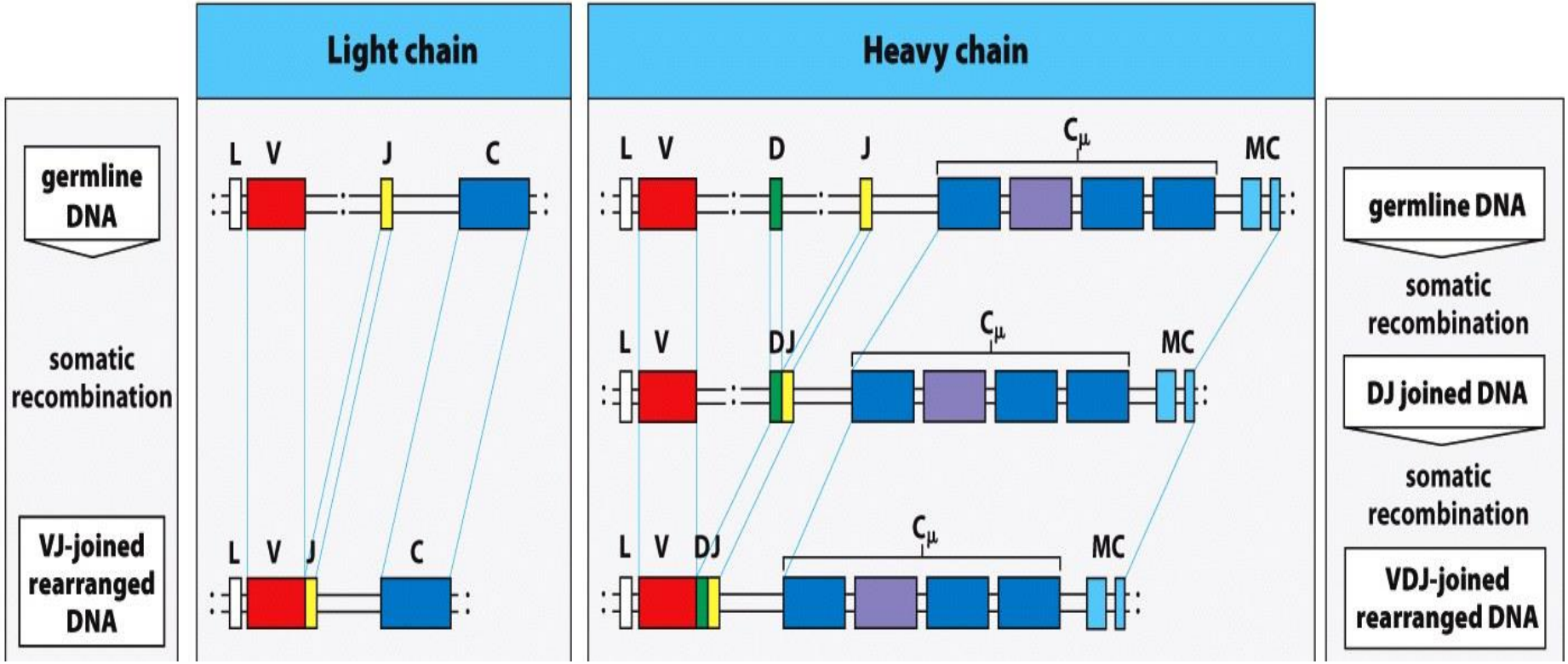


Figure 4.17 V-region sequences are constructed from gene segments. Light-chain V-region genes are constructed from two segments (left panel). A variable (V) and a joining (J) gene segment in the genomic DNA are joined to form a complete light-chain V-region (V_L) exon. After rearrangement, the light-chain gene consists of three exons, encoding the leader (L) peptide, the V region, and the C region, which are separated by introns. Heavy-chain V regions are constructed from three gene segments (right panels). First the diversity (D) and J gene segments join, then the V gene segment joins to the combined DJ sequence, forming a complete heavy-chain V-region (V_H) exon. For simplicity, only the first of the heavy-chain genes, C_μ, is shown here. Each immunoglobulin domain is encoded by a separate exon, and two additional membrane-coding exons (MC, colored light blue) specify the hydrophobic sequence that will anchor the heavy chain to the B-cell membrane.

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 numbers of functional gene segments available to construct the variable and constant regions of human immunoglobulin heavy chains and light chains.

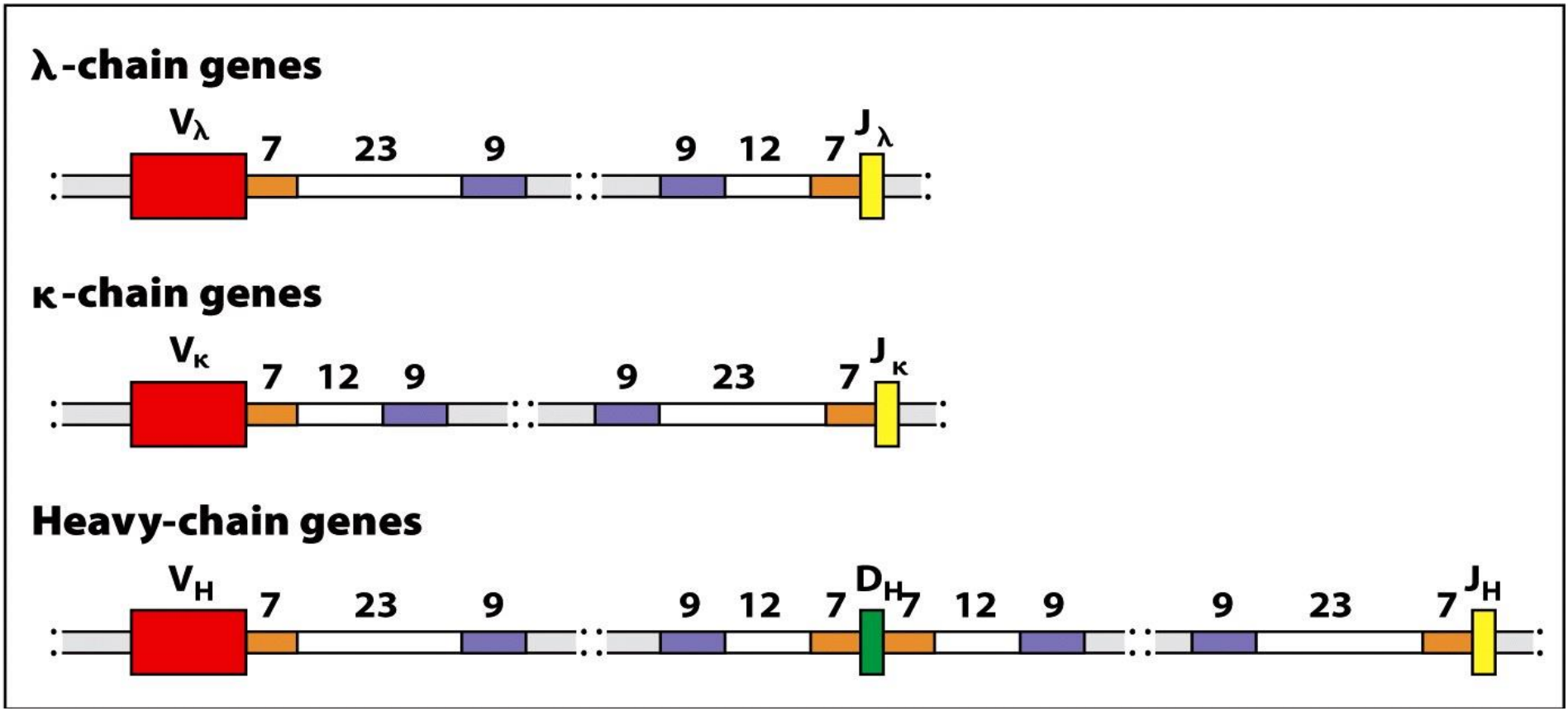


Figure 4.19 Each V, D, or J gene segment is flanked by recombination signal sequences (RSSs). There are two types of RSS. One consists of a nonamer (9 bp, shown in purple) and a heptamer (7 bp, shown in orange) separated by a spacer of 12 bp (white). The other consists of the same 9- and 7-nucleotide sequences separated by a 23-bp spacer (white).

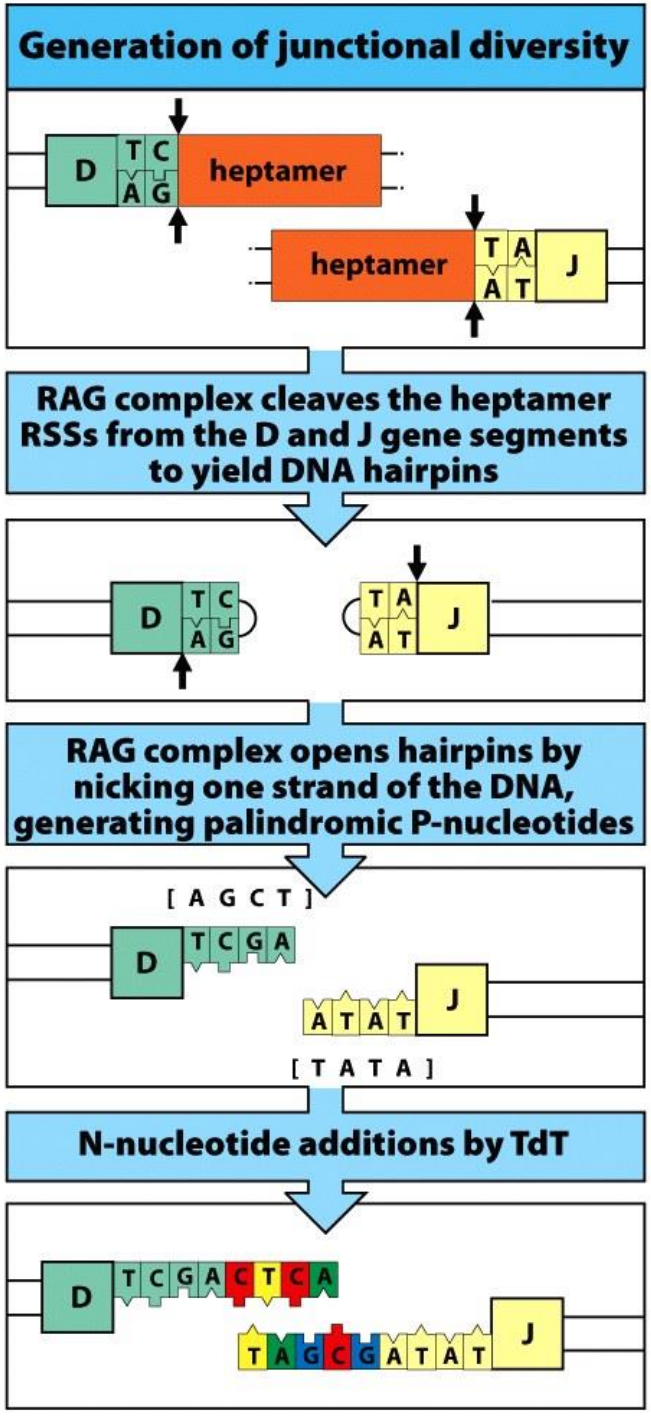
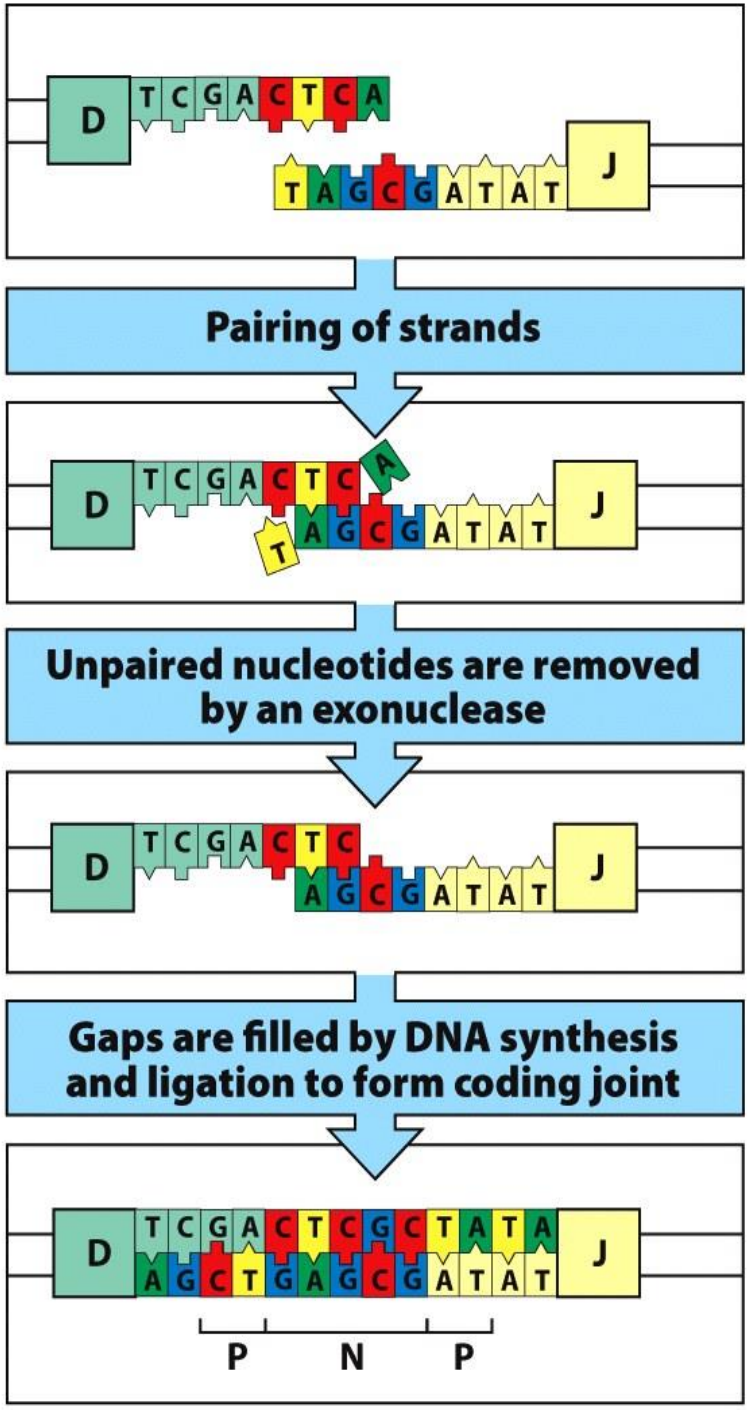


Figure 4.21 The generation of junctional diversity during gene rearrangement. The process is illustrated for a D to J rearrangement. The RSSs are brought together and the RAG complex cleaves (arrows) between the heptamer sequences and the gene segments (top panel). This leads to excision of the DNA that separates the D and J segments. The ends of the two DNA strands of the D and J segments are joined to form hairpins. Further cleavage (arrows) on one DNA strand of the D and J segments releases the hairpins and generates short single-stranded sequences at the ends of the D and J segments. The extra nucleotides are known as P nucleotides because they make a palindromic sequence in the final double-stranded DNA (as indicated on the diagram). Terminal deoxynucleotidyl transferase (TdT) adds nucleotides randomly to the ends of the single strands. These nucleotides, which are not encoded in the germline, are known as N nucleotides. The single strands pair, and through the action of exonuclease, DNA polymerase, and DNA ligase the double-stranded DNA molecule is repaired to give the coding joint.



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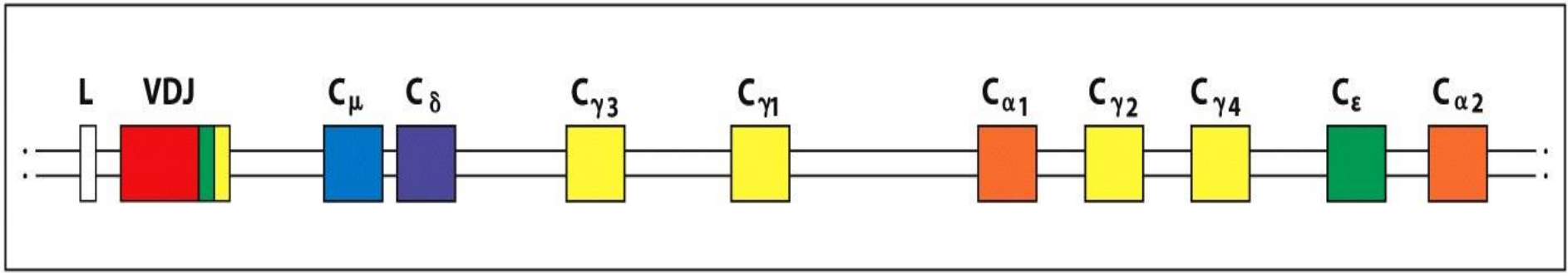


Figure 4.22 Rearrangement of V, D, and J segments produces a functional heavy-chain gene. The assembled VDJ sequence lies some distance from the cluster of C genes. Only functional C genes are shown here. The four different γ genes specify four different subtypes of the γ heavy chain, whereas the two α genes specify two subtypes of the α heavy chain. For simplicity, individual exons in the C genes are not shown. The diagram is not to scale.

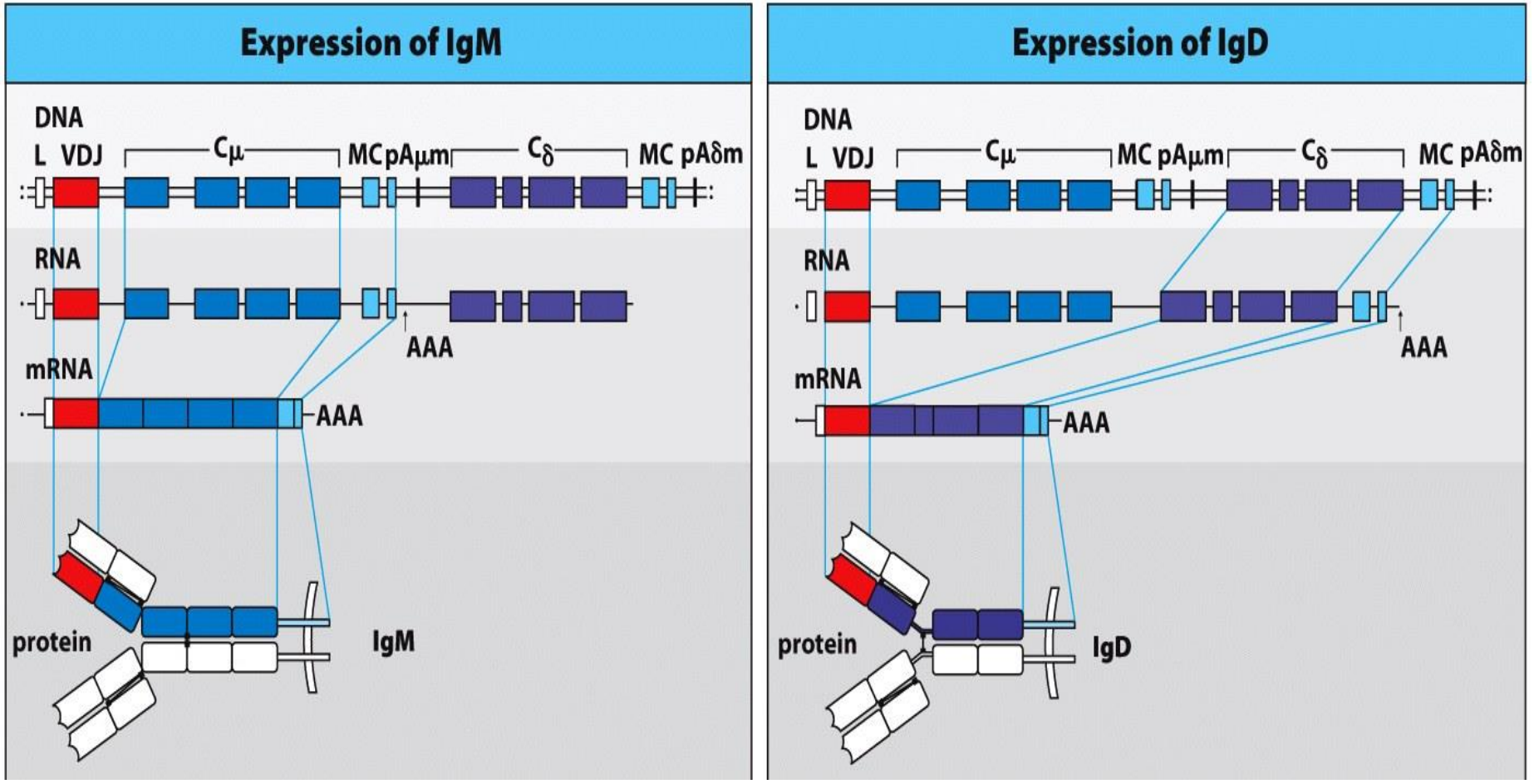


Figure 4.23 Coexpression of IgD and IgM is regulated by RNA processing. In mature B cells, transcription initiated at the V_H promoter extends through both the C_μ and C_δ genes. For simplicity we have not shown all the individual C-gene exons but only those of relevance to the production of IgM and IgD. The long primary transcript is then processed by cleavage, polyadenylation, and splicing. Cleavage and polyadenylation at the μ site (pAμm; the 'm' denotes that this site produces membrane-bound IgM) and splicing between C_μ exons yields an mRNA encoding the μ heavy chain (left panel). Cleavage and polyadenylation at the δ site (pAδm) and a different pattern of splicing that removes the C_μ exons yields mRNA encoding the δ heavy chain (right panel). AAA designates the poly A tail. MC, exons that encode the transmembrane region of the heavy chain.

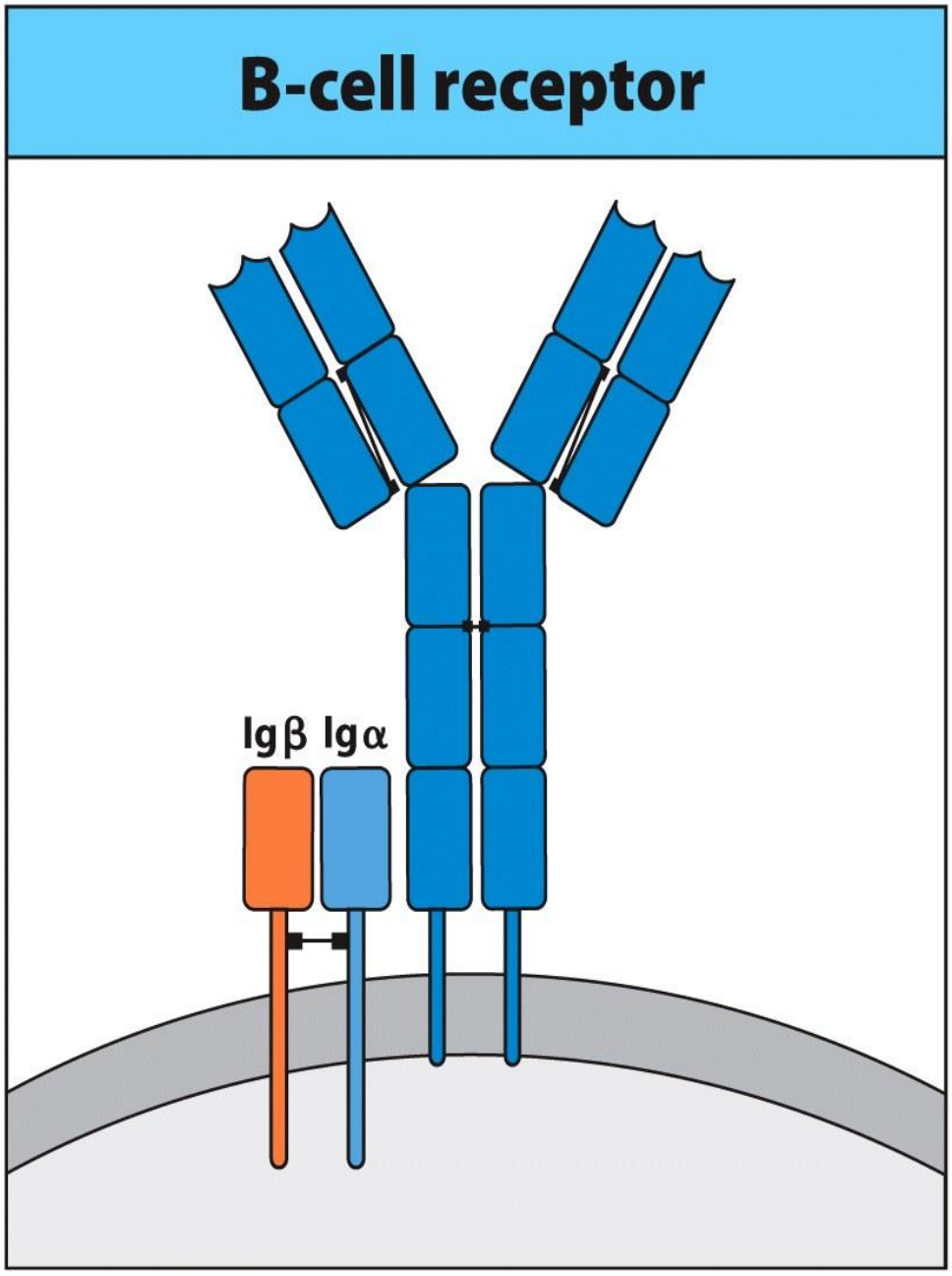


Figure 4.25 Membrane-bound immunoglobulins are associated with two other proteins, Igα and Igβ. Igα and Igβ are disulfide-linked. They have long cytoplasmic tails that can interact with intracellular signaling proteins, and the complex of immunoglobulin with Igα and Igβ serves as the functional B-cell receptor. The immunoglobulin shown here is IgM, but all isotypes can serve as B-cell receptors.

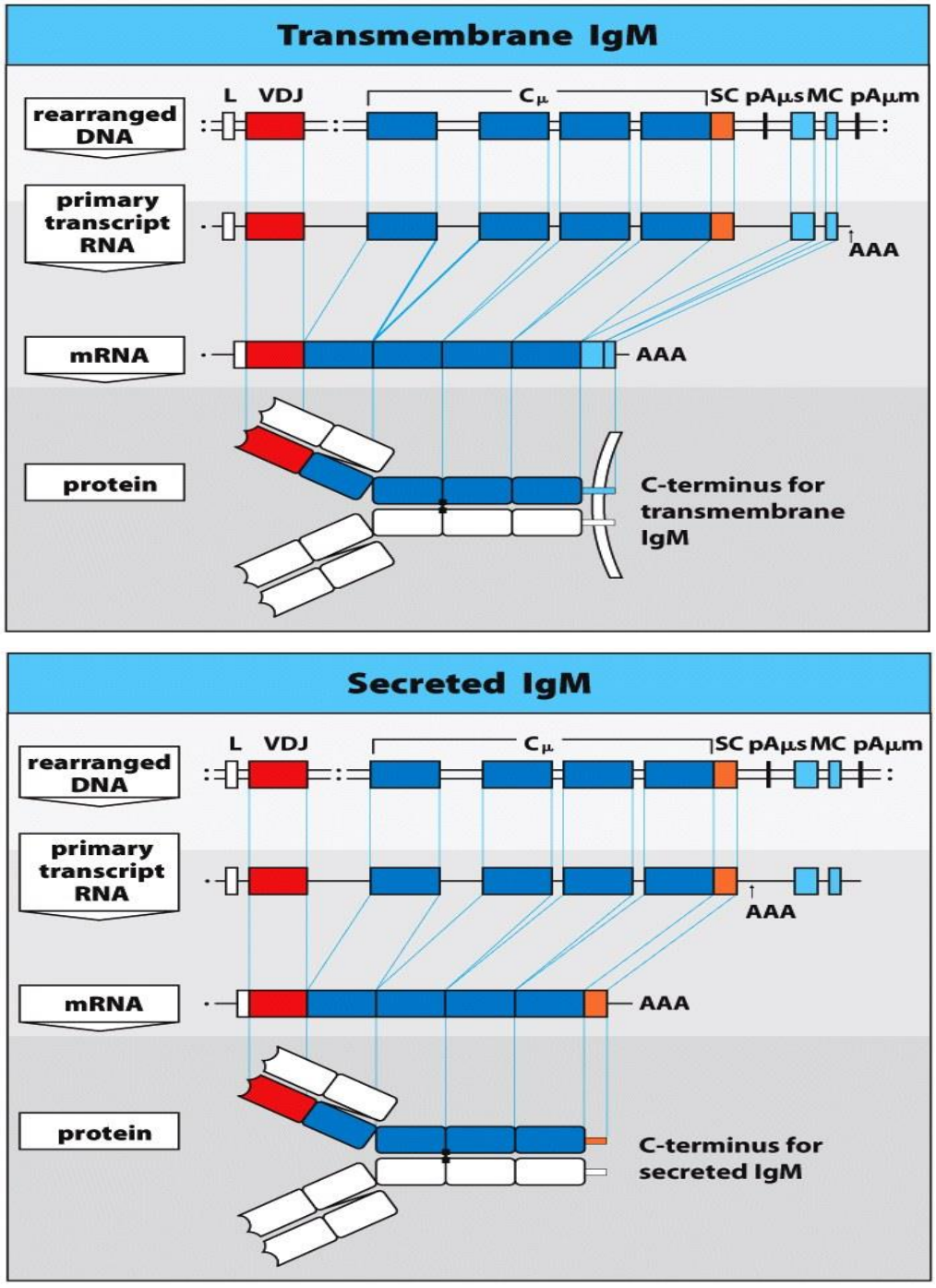


Figure 4.26 The surface and secreted forms of an immunoglobulin are derived from the same heavy-chain gene by alternative RNA processing. Each heavy-chain C gene has two exons (membrane-coding (MC), light blue) encoding the transmembrane region and cytoplasmic tail of the surface form of that isotype, and a secretion-coding (SC) sequence (orange) encoding the carboxy terminus of the secreted form. The events that dictate whether a heavy-chain RNA will result in a secreted or transmembrane immunoglobulin occur during processing of the initial transcript and are shown here for IgM. Each heavy-chain C gene has two potential polyadenylation sites (shown as pAμs and pAμm). In the left panel, the transcript is cleaved and polyadenylated at the second site (pAμm). Splicing between a site located between the fourth C_μ exon and the SC sequence, and a second site at the 5′ end of the MC exons, removes the SC sequence and joins the MC exons to the fourth C_μ exon. This generates the transmembrane form of the heavy chain. In the right panel, the primary transcript is cleaved and polyadenylated at the first site (pAμs), eliminating the MC exons and giving rise to the secreted form of the heavy chain. AAA designates the poly A tail.

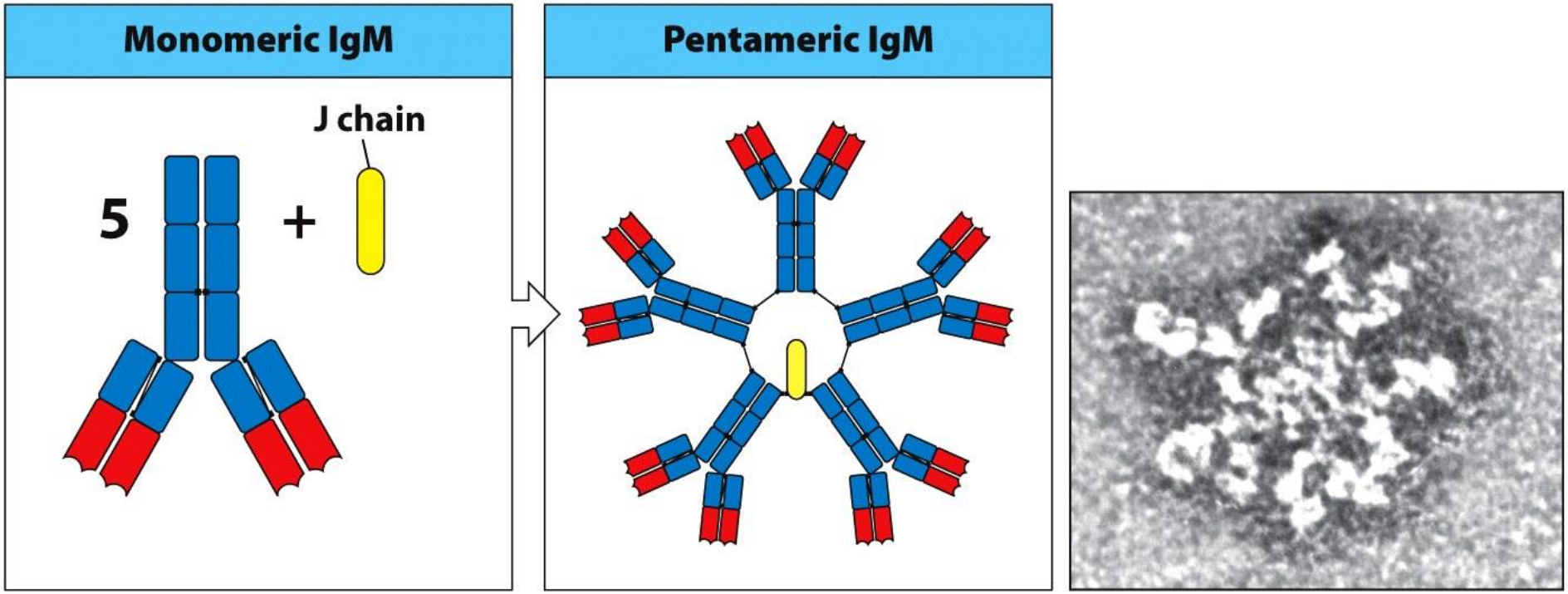
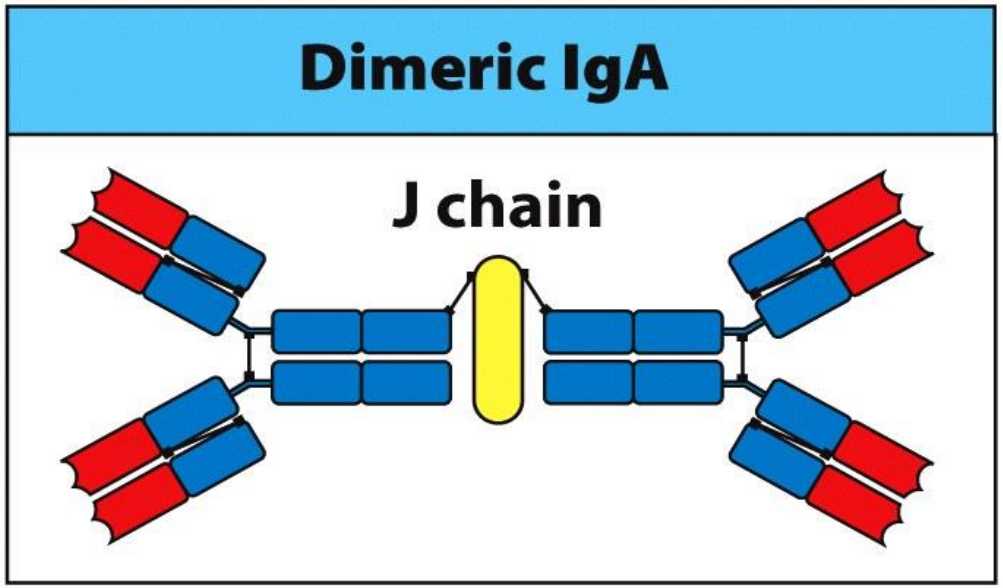


Figure 4.29 IgM is secreted as a pentamer of immunoglobulin monomers. The left two panels show schematic diagrams of the IgM monomer and pentamer. The IgM pentamer is held together by a polypeptide called the J chain, for joining chain (not to be confused with a J segment). The monomers are cross-linked by disulfide bonds to each other and to the J chain. The right panel shows an electron micrograph of an IgM pentamer, showing the arrangement of the monomers in a flat disc. The lack of a hinge region in the IgM monomer makes the molecule less flexible than, say, IgG, but this is compensated for by the pentamer having five times as many antigen binding sites as IgG. Faced with a pathogen having multiple identical epitopes on its surface, IgM can usually attach to it with several binding sites simultaneously. Photograph (× 900,000) courtesy of K.H. Roux and J.M. Schiff.



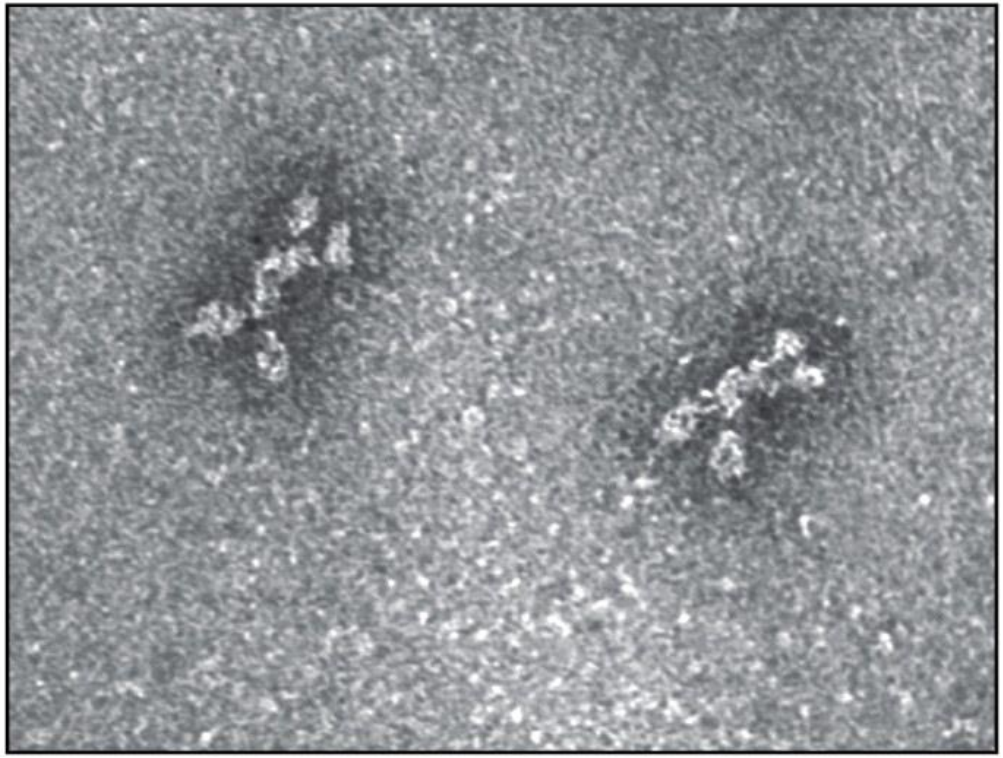


Figure 4.33 IgA molecules can form dimers. In mucosal lymphoid tissue, IgA is synthesized as a dimer in association with the same J chain as that found in pentameric IgM. In dimeric IgA, the monomers have disulfide bonds to the J chain but not to each other. The bottom panel shows an electron micrograph of dimeric IgA. Photograph (× 900,000) courtesy of K.H. Roux and J.M. Schiff.

Figure 4.35 The changes in the immunoglobulin genes that occur over a B cell's lifetime.

Changes in immunoglobulin genes during a B cell's life			
	Event	**Mechanism**	**Permanence of change to the B cell's genome**
1	V-region assembly from gene fragments	Somatic recombination of genomic DNA	Irreversible
2	Generation of junctional diversity	Imprecision in joining rearranged DNA segments adds nongermline nucleotides (P and N) and deletes germline nucleotides	Irreversible
3	Assembly of transcriptional controlling elements	Promoter and enhancer are brought closer together by V-region assembly	Irreversible
4	Transcription activated with coexpression of surface IgM and IgD	Two patterns of splicing and processing RNA are used	Reversible and regulated
5	Synthesis changes from membrane Ig to secreted antibody	Two patterns of splicing and processing RNA are used	Reversible and regulated
6	Somatic hypermutation	Point mutation of genomic DNA	Irreversible
7	Isotype switch	Somatic recombination of genomic DNA	Irreversible