plasma membrane, into the second messengers inositol-1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). While the latter activates protein kinase C, IP_3 stimulates the release of calcium ions from the ER. Ca^{2+} then acts as another second messenger and modulates the activity of a number of proteins to induce a cellular response.

1.5 The Immune System

Animals (as well as virtually all other living organisms) are continually subject to attack by disease-causing pathogens. As a countermeasure, animals have evolved an immune system to protect themselves. The immune system must detect and destroy a wide variety of infectious agents, including viruses, microorganisms, and parasitic worms (Chapters 5 and 6), distinguishing them from the organism's own cells. More recently, it has become evident that the immune system not only fights invading pathogens but also provides an important defense against the development of cancer. It does this by recognizing and destroying transformed cells.

The cells of the immune system are distributed throughout the body and in the bloodstream. Blood cells fall into three different categories: (i) red blood cells (erythrocytes) primarily carry oxygen and carbon dioxide; (ii) platelets (thrombocytes) are involved in the formation of blood clots; and (iii) white blood cells (leukocytes) are the cells of the immune system. The formation of different blood cells, a process called hematopoiesis, is illustrated in Figure 1.26.

Immune cells can be further categorized as being part of the *innate* or *adaptive immune system* (Figure 1.27). The innate immune system is the first line of defense. It recognizes the general characteristics of pathogens and provides a rapid, nonspecific response. In addition, it activates a second layer of response, the adaptive

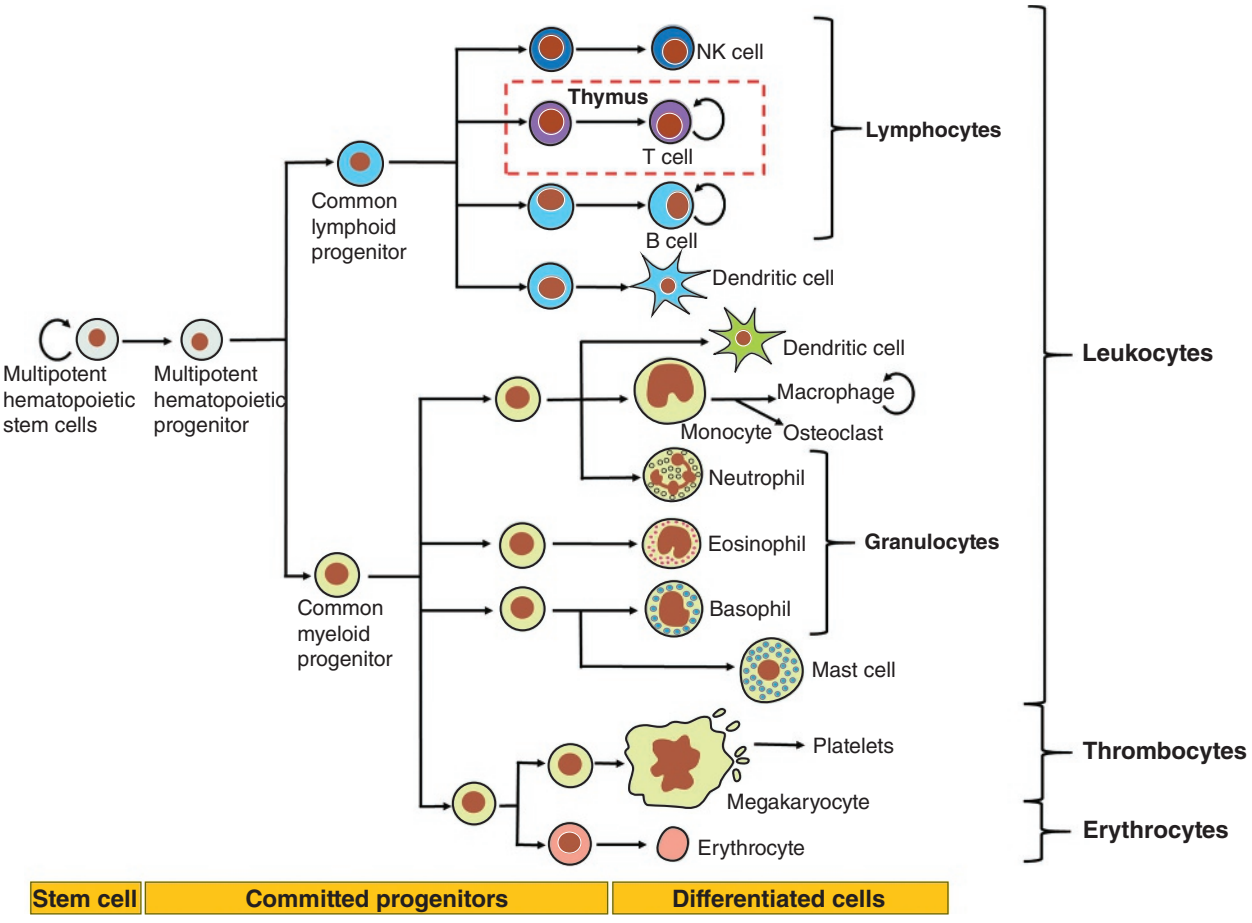

Figure 1.26 Hematopoiesis. Multipotent hematopoietic stem cells differentiate into committed progenitors and then develop into the terminally differentiated cells. In adult mammals, the cells shown develop primarily in the bone marrow. Exceptions are T lymphocytes, which differentiate in the thymus, and macrophages and osteoclasts that develop from blood monocytes. Dendritic cells may also derive from monocytes. NK cell: natural killer cell. *Source:* [2] / Taylor & Francis Group.

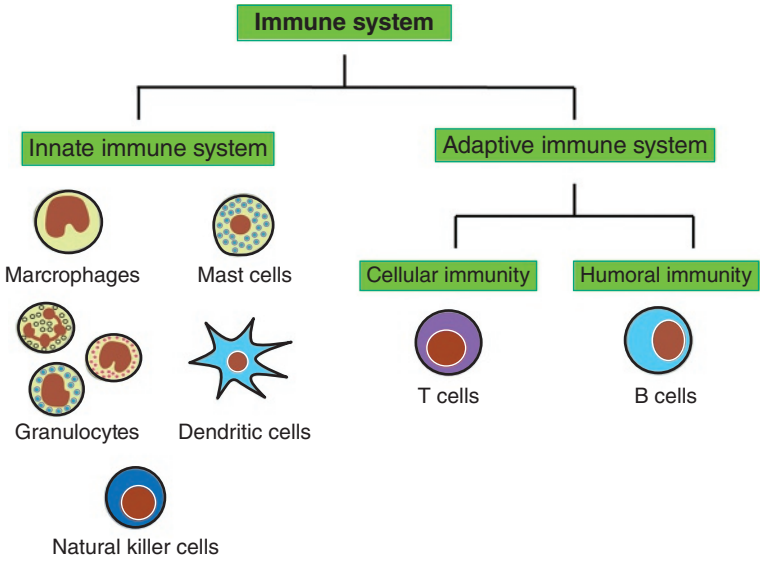

Figure 1.27 Cells of the immune system. The cells of the innate immune system include macrophages that digest pathogens, mast cells that release histamine and other substances that induce inflammation, granulocytes (neutrophils, eosinophils, and basophils) that release toxic substances and promote inflammation, dendritic cells that present antigens and induce the adaptive immune system, and natural killer cells that destroy infected cells (as well as cancer cells). The key components of the adaptive immune system are T lymphocytes (or T cells) that mediate cellular immunity and B lymphocytes (or B cells) that constitute humoral immunity.

immune system, which provides a specific defense against a given target. Two types of adaptive immunity can be distinguished: cellular and the humoral immunity. This is outlined in Section 1.5.2.

1.5.1 The Innate Immune System

The innate immune system detects macromolecules that represent a danger to the organism and generates the means to destroy them. It provides an immediate defense against infection, but does not confer specific, long-lasting, protective host immunity. The innate immune system does not identify a specific microbe. Rather, it recognizes general patterns that are known as pathogen-associated molecular patterns (PAMPs). The characteristics of invading pathogens that can distinguish them from host cells include components of the outer bacterial membrane (lipopolysaccharides) and viral double-stranded RNA molecules. PAMPs act as agonists for pattern recognition receptors (PRRs) on innate immune cells.

One of the first responses of the innate immune system is the stimulation of inflammation. Acute inflammation is initiated by cells present in the tissue; these cells include macrophages, dendritic cells, and mastocytes. Upon activation, these cells release inflammatory mediators (e.g. histamine, bradykinin, and/or cytokines) that establish a physical barrier against the spread of infection and trigger additional immune system effectors.

Different types of specialized phagocytes destroy harmful particles, such as bacteria, small parasites, fungi, and viruses, by internalization (phagocytosis, Figure 1.28). Macrophages and neutrophils are the most important phagocytes in the defense against infection. The process of phagocytosis starts with the recognition of the microorganism by PRRs. The invading microorganism is then internalized into the so-called phagosome, a membrane-bound vacuole, which fuses with lysosomes. Lysosomes

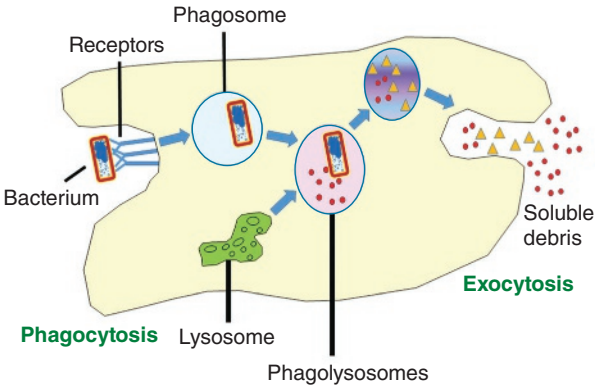

Figure 1.28 Phagocytosis. Bacteria are recognized by special pattern recognition receptors (PRRs) on the surface of phagocytes. The bacterium is taken up by a process called phagocytosis and is then trapped in a compartment known as phagosome, which fuses with a lysosome. Several enzymes then destroy the pathogen; the soluble debris is released by exocytosis.

contain digestive enzymes in an acidic environment that kill and degrade the microorganism.

Antigen presentation is an important process of the adaptive immune system. Some phagocytes (macrophages and dendritic cells) move molecules from engulfed pathogens that have been degraded by the proteasomes (described in Section 1.3.6) back to the surface of their cells. These molecules are then presented to other cells of the immune system. Such cells are known as antigen-presenting cells (APCs). APCs break down foreign proteins into peptides in the proteasome. The peptides formed are then bound to the so-called major histocompatibility complex (MHC), which carries them to the surface and presents them to lymphocytes. In humans, MHC is also called human leukocyte antigen (HLA). HLA is an important determinant of the compatibility of donors for organ transplants. Cells express different types of MHC molecules: MHC class I is expressed on almost all nucleated cells. The expression of MHC class II is restricted to special cells, including thymic epithelial cells, dendritic cells, B cells, and some macrophages. By activating lymphocytes, APCs connect the innate and the adaptive immune systems.

1.5.1.1 The Complement System

The complement system is another part of the immune system that helps to clear pathogens from an infected organism. Since it does not adapt to a specific pathogen and does not change over the lifetime of an individual, the complement system is considered part of the innate immune system. However, it can be activated by the adaptive immune system. The complement system consists of more than 25 proteins, most of which circulate in the blood as inactive precursors. The major components of the complement cascade are named with the letter "C" followed by a number. Cleavage products are assigned as "a" and "b," with "b" being the *b*igger fragment.

The complement cascade can be activated by three pathways: the classical, lectin, and alternative pathways (Figure 1.29a). The classical pathway is triggered by activation of the C1 complex, which consists of the C1q protein and the proteases C1r and C1s. C1q binds to antibody–antigen complexes on the surface of pathogens but can also be activated by direct binding to the surface of bacteria. The C1 complex then splits C2 and C4, and the cleavage products C4b and C2a form the C3 convertase that promotes the cleavage of C3 into C3a and C3b.

The lectin pathway functions in an analogous manner, except that the initial step consists of activation of mannose-binding lectin (MBL) by mannose residues on the pathogen surface. This activates MBL-associated serine proteases (MASPs) followed by cleavage of C2 and C4 and formation of the C3 convertase, as in the classical pathway.

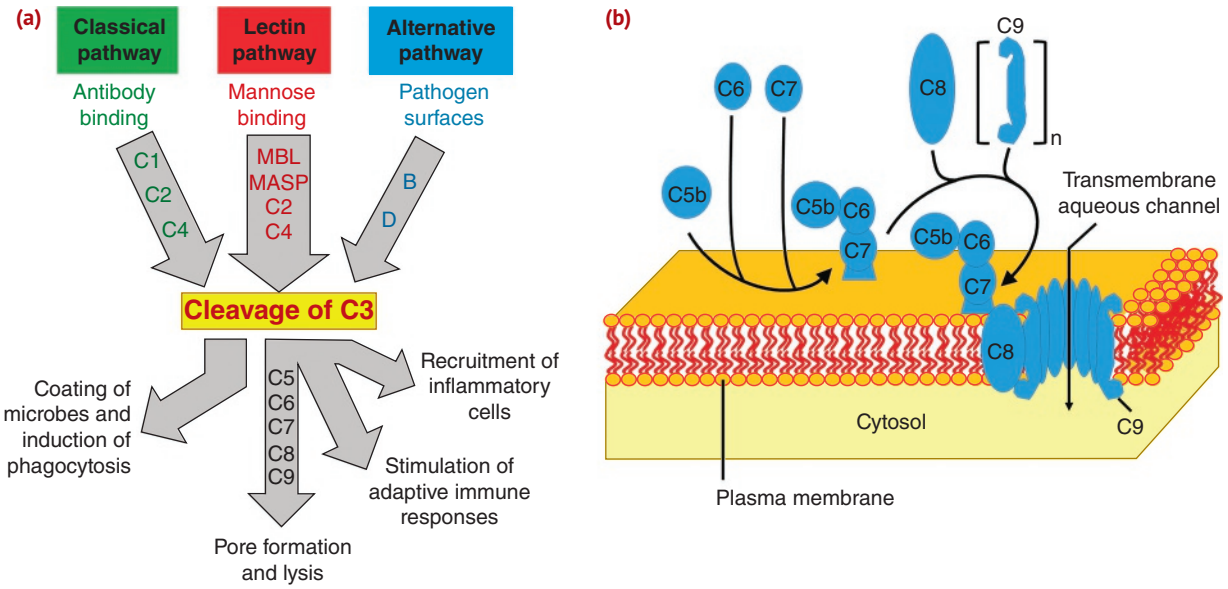

Figure 1.29 Complement system. (a) The complement system can be activated by the classical, lectin, and alternative pathways. A central step is the activation of C3. Activation of the complement system results in the killing of a foreign cell, stimulation of phagocytosis, triggering of inflammation, and adaptive immune responses. (b) The late components C5b–C9 form a membrane attack complex that leads to osmotic lysis of the microbe or infected host cell. MBL: mannose-binding lectin; MASP: MBL-associated serine protease. *Source:* [2] / Taylor & Francis Group.

The alternative pathway is continuously activated at a low level due to spontaneous hydrolysis of C3. The cleavage product C3b is rapidly inactivated by the two factors H and I. However, binding of C3b to the surface of a pathogen protects the C3b from inactivation and leads to the activation of factors B and D, resulting in the formation of an alternative C3 convertase.

Production of the cleavage product C3b by any of the three pathways mediates the main functions of the complement system. These include the coating of microbes and induction of phagocytosis, recruitment of inflammatory cells, and stimulation of the adaptive immune response. In addition, the late components C5–C9 form a pore in the target cell's plasma membrane, the so-called membrane attack complex (MAC; Figure 1.29b). This channel allows free ingress of water and egress of electrolytes, which causes osmotic lysis of the target cell.

1.5.2 The Adaptive Immune System

The adaptive immune response is primarily based on two types of lymphocytes: B cells confer humoral immunity (*humor* is an archaic term for fluid) by producing antibodies (known as immunoglobulins), whereas T cells mediate cellular immunity. The adaptive immune response is triggered by antigens (*anti*body *gen*erators) and macromolecules (in most cases proteins or carbohydrates) that are recognized as foreign.

1.5.2.1 Cellular Immunity

The main function of the cellular immune system is to prevent the spread of viral infection by killing virus-infected cells. In addition, the cellular immune system is effective against intracellular bacteria and parasites, where they are protected from attack by antibodies. The cellular immune system is also effective against certain types of cancer. The cells of the cellular immune system mature in the thymus and are referred to as T cells. The major populations of T cells are helper T cells (T_H), cytotoxic T cells (T_C), regulatory T cells (T_{reg}), memory T cells, and natural killer T cells (not to be confused with the natural killer cells of the innate immune system). A common characteristic of T cells is the presence of a T cell receptor (TCR) on the cell surface. This receptor is composed of two chains that form the antigen recognition site. The best-understood populations are the αβ T cells, in which the TCR is composed of an α and a β chain. TCRs possess unique antigen specificity, which is determined by the structure of the antigen-binding site formed by the two chains. The diversity of TCRs is based mainly on somatic recombination, as described for immunoglobulins in the following section. The T cell population is further categorized by the additional proteins found on their surface. The *cluster of differentiation* (CD) system is used for immunophenotyping cells according to cell surface markers. Conventional αβ T cells develop into two classes expressing either the CD4 or the CD8 glycoprotein.

TCRs, together with the respective CD proteins, bind to the MHC proteins displaying antigenic fragments on the surface of APCs, as described in the previous section. T cells expressing CD4 (abbreviated as $CD4^+$ T cells) interact with MHC class II molecules, while $CD8^+$ cells interact with MHC class I molecules (Figure 1.30). Binding of a T cell to an APC displaying an antigen–MHC complex causes it to reproduce, a process called clonal selection. As a consequence, the

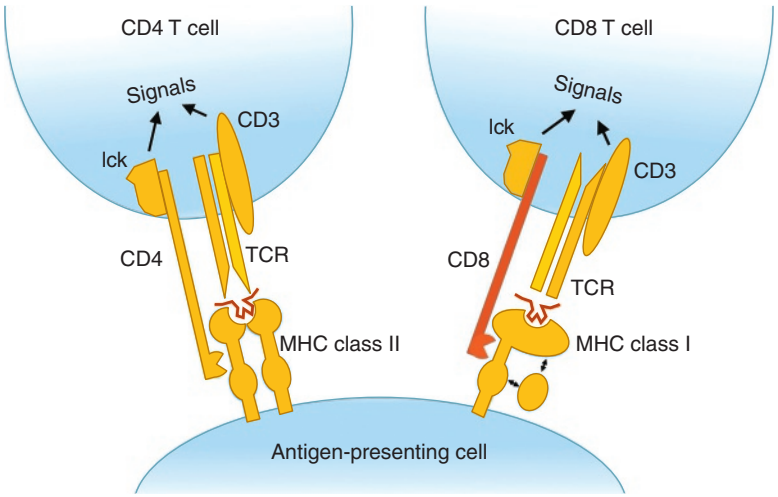

Figure 1.30 Interaction between T cells and APCs. T cell receptors (TCRs) and CD4 or CD8 molecules on the surface of T cells interact with proteins of the major histocompatibility complex (MHC) that present a peptide processed from an invading pathogen. CD4 interacts with MHC class II; CD8 binds to MHC class I. CD4 and CD8 are associated with additional factors that mediate signaling to activate the T cell. *Source:* [6] / John Wiley & Sons.

T cells are produced in large quantities after recognizing an invading pathogen.

CD4 is expressed on T helper cells (T_h cells), which assist other lymphocytes by releasing cytokines. These cytokines induce the maturation of B cells into plasma cells, which release antibodies and activate memory B cells, cytotoxic T cells, and macrophages (Figure 1.31). Upon activation, T_h cells proliferate and differentiate into several subtypes, the two most important of which are known as T_h1 and T_h2 cells. These two types of helper cells are activated by different partners and release different kinds of cytokines that have specific effects. T_h1 cells are important for the immune reaction against intracellular bacteria and protozoa, while T_h2 cells mediate the immune reaction against helminths (parasitic worms).

T_h17 cells are another subset of T helper cells developmentally distinct from T_h1 and T_h2 lineages. They are defined by their production of interleukin-17 (IL-17). T_h17 cells are mainly relevant for protecting against extracellular pathogens, including fungi. They play an important role in maintaining mucosal barriers and contributing to pathogen clearance at mucosal surfaces. They also induce defense against extracellular bacteria in peripheral organs by neutrophil granulocytes. However, T_h17 cells are also associated with autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and psoriasis.

As will be outlined in Section 5.1.1, the human immunodeficiency virus (HIV) uses CD4 as a cellular entry receptor. At a later stage of the infection, massive destruction of $CD4^+$ cells leads to the development of the acquired immunodeficiency syndrome (AIDS).

Another important class of T cells is the regulatory T cells (T_{regs}). The intensity of the immune response must be constantly controlled to destroy cancer cells and pathogens while suppressing autoimmunity against normal tissue. T_{regs} produce several inhibitory cytokines, including transforming growth factor-β (TGF-β) and Interleukin-10. One of their main functions is to suppress or downregulate the induction and proliferation of effector T cells.

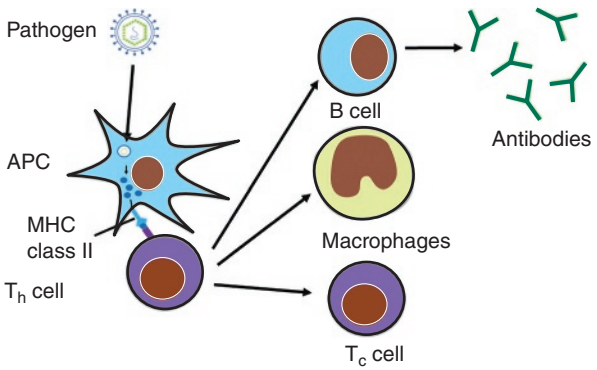

Figure 1.31 The function of T helper cells (T_h cells). T_h cells are activated by binding to antigen–MHC class II complexes on the surface of APCs. By releasing stimulatory signals (cytokines), they induce the maturation of B cells and the activation of macrophages and cytotoxic T cells.

Cytotoxic T cells (T_C cells) express the CD8 glycoprotein. They destroy cells infected with a virus (or other pathogens) and tumor cells. After recognizing a specific antigen–MHC class I complex, the activated T cell releases cytotoxins, such as perforin, which form pores in the target cell's plasma membrane. This allows water and another toxin called granulysin (a protease) to enter the target cell and kill it.

Some T cells, known as memory T cells, persist for a long term after an infection has resolved. They constitute an immune system "memory" of past infections and quickly expand into large numbers of effector T cells upon re-exposure to their cognate antigen. They induce a faster and stronger immune response than the first time the immune system encountered the pathogen.

1.5.2.2 Humoral Immunity

The humoral immune response is largely mediated by B cells, which mature in the bone marrow. The principal function of the humoral immune system is the production of antibodies against soluble antigens. B cell precursors display immunoglobulins on their surface (Figure 1.32). They can be activated in a T cell-dependent or T cell-independent manner. The latter process is triggered when a B cell encounters its matching antigen. The antigen–antibody complex is taken up by the B cell and digested into peptides, which are bound by an MHC class II molecule and then displayed on the cell surface. In doing so, B cells perform the role of APCs. The antigen–MHC complex is recognized by a T cell, which releases cytokines that activate the B cell. B cell activation includes a combination of clonal proliferation and differentiation into effector B cells known as plasma cells. Plasma cells produce and secrete millions of copies of the antibody that recognizes the antigen. Although most B cell progeny are plasma cells, others develop into memory B cells that have a similar function as memory T cells.

Antibodies are large, Y-shaped glycoproteins. In mammals, there are five different classes of antibodies: IgA, IgD, IgE, IgG, and IgM (Ig stands for immunoglobulin). While the monomeric structures of all the isotypes are similar, two classes can form multimers: IgMs are pentamers and IgAs are dimers consisting of linked monomeric units. The five isotypes differ in their biological properties, functional locations, and ability to deal with different antigens. The antibody isotype of a B cell

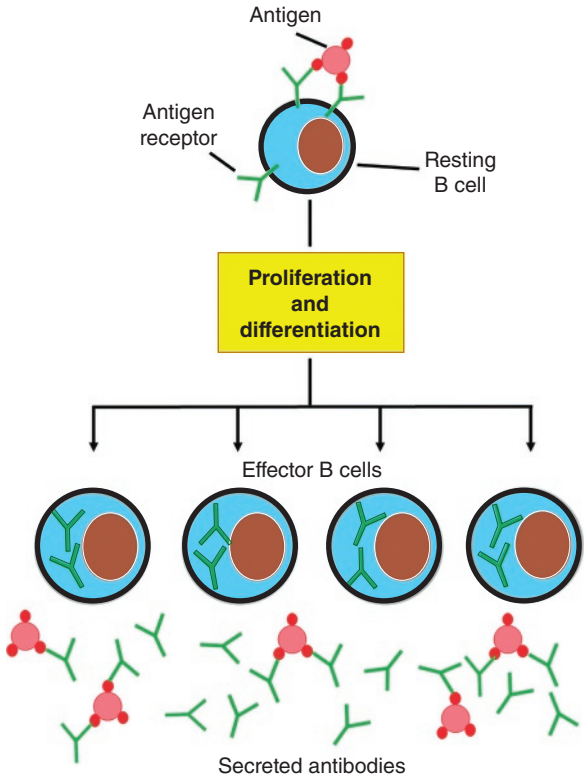

Figure 1.32 B cell activation. Activation of a B cell includes recognition of the antigen by the antigen receptor on the surface of the B cell. The activation may be T cell-dependent or T cell-independent. The activated B cell proliferates and differentiates to a plasma cell that secretes antibodies. *Source:* [2] / Taylor & Francis Group.

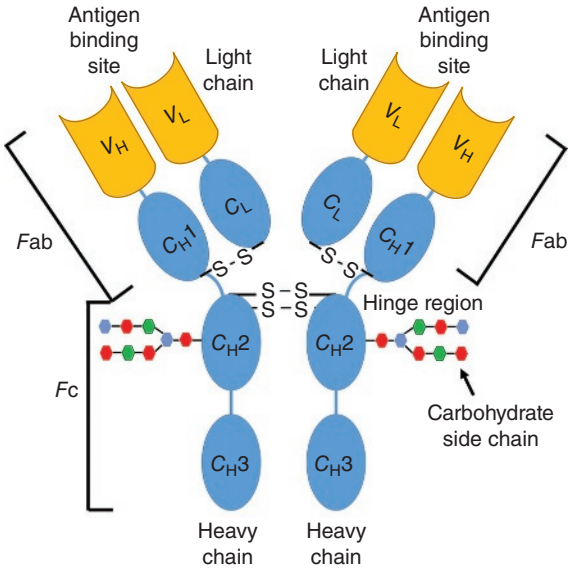

Figure 1.33 Structure of immunoglobulin G (IgG). An antibody is made up of two identical heavy and two identical light chains connected by disulfide bonds. Each chain is composed of several immunoglobulin domains. The heavy chain has one variable (V_H) and three constant regions (C_H1-C_H3). The light chain is only composed of one variable (V_L) and one constant chain (C_L). The arms of the Y are known as the *Fab* for antigen-binding fragment and are composed of one constant and one variable domain from each heavy and light chain of the antibody. The two variable domains form the site for antigen binding. The base of the Y is called the *Fc* for crystallizable fragment. It plays an important role in modulating immune cell activity.

changes during the differentiation process (*immunoglobulin class switching* or *isotype switching*). This switch occurs by exchanging the constant region of the heavy chain while retaining the variable region that determines antigen specificity. Immature B cells express IgM in a cell surface-bound form. At a later stage, these cells express surface IgD in addition to IgM. When activated to plasma cells, B cells produce antibodies in a secreted rather than membrane-bound form. Secreted IgMs are important for the rapid elimination of pathogens in an early stage of the B cell response, before there is sufficient IgG. In the final step of isotype switching, cells change from producing IgD or IgM to the production of the IgE, IgA, or IgG classes of immunoglobulin.

IgG is the most abundant class of antibody in the blood, providing most of the antibody-based immunity against invading pathogens. Its general structure is depicted in Figure 1.33. IgGs protect the body from infection by several mechanisms. The antibody may bind to the pathogen and cause its immobilization and binding together via agglutination, preventing its entry into host cells. This is also the way IgG neutralizes toxins. An additional defense mechanism mediated by IgG is *opsonization*; here, the IgG coats the surface of the pathogen, permitting its recognition and ingestion by phagocytic immune cells. IgGs also activate the classical pathway of the complement system (Section 1.5.1.1) and induce antibody-dependent cellular cytotoxicity (ADCC). In this process, the binding of antibodies to surface antigens marks the target cell for lysis by an effector cell of the immune system (e.g. an NK cell).

The human immune system can produce antibodies against virtually any antigen it encounters. Estimates suggest that humans produce more than 10^7 different antibodies (some estimates reach an order of 10^{12}). As the human genome encodes only around 20 000 genes (Chapter 7), each antibody cannot be encoded by a specific gene. Instead, antibody diversity is achieved by two mechanisms: *somatic recombination* and *hypermutation*. Immunoglobulin genes exist as discrete groups of gene segments. Somatic rearrangements are also known as V(D)J recombination. The variable region of each heavy or light chain is encoded by several gene segments. Heavy chains are composed of variable (V),

diversity (D), and joining (J) segments; light chains consist of only V and J segments. Multiple copies of each segment in a tandem arrangement exist in the genome. During B cell differentiation, intrachromosomal recombination occurs, and an immunoglobulin variable region is assembled by randomly combining one V, one D, and one J segment for the heavy chain, or one V and one J segment for the light chain. As the multiple copies of each type of gene segment can be combined in different ways, this process allows the generation of a large number of different antibodies.

An additional layer of diversity is achieved by two types of somatic mutations: (i) During the recombinant joining of the different segments, a terminal deoxynucleotidyl transferase randomly adds up to 30 bp that increase variability. (ii) The variable regions mutate at rates that are at least a million-fold higher than the rates of spontaneous mutation in other genes. This somatic hypermutability is presumably mediated by error-prone DNA polymerases.

The enormous diversity of antibodies has attracted the interest of researchers, who have used them for technical and medical purposes. As will be outlined in detail in Section 10.2.1, monoclonal antibodies are among the most successful classes of modern biomolecular drugs.

This brief introduction does not adequately reflect the enormous complexity of the immune system, which would be beyond the scope of any introduction to molecular medicine. The interested reader is referred to a more in-depth introduction given in the textbooks cited in the references listed below.

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Acknowledgments

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Exercises

1 Give a definition of *molecular medicine*.

A Molecular medicine is a discipline dedicated to understanding normal and pathological cellular processes at the molecular level.

2 How long does the development of a new drug usually take and how high is the average cost?

A 12–15 years.

B Costs range from US$318 million to US$2.8 billion.

3 Name the major organelles of a eukaryotic cell and explain their main functions.

A The nucleus contains the genetic material. The nucleolus is the largest structure in the nucleus, which primarily serves as the site of ribosome synthesis and assembly.

B Mitochondria function as “cellular power plants”. They are the site of oxidative metabolism that leads to the production of ATP.

C The endoplasmic reticulum (ER) and the Golgi apparatus play an important role in the post-translational modification and sorting of proteins.

D Peroxisomes and lysosomes have important metabolic function, primarily in degradative processes.

4 What is *apoptosis*? How is apoptosis induced? What are the major proteins that control this process?

A Apoptosis is the process of programmed cell death.

B Apoptosis may be induced by the extrinsic or the intrinsic pathway.

C The process is mainly controlled by *caspases*.

5 What does the central dogma of molecular biology describe? Which exceptions do you know?

A The genetic information is stored in DNA, which is copied by replication. The genetic information stored in DNA is transcribed into RNA, followed by translation into an encoded protein.

B Retroviruses contain RNA that is reverse-transcribed into DNA, and other viruses contain RNA that is directly replicated into new RNA molecules.

6 What is a frameshift mutation?

A Frameshift mutations occur by the introduction or deletion of one or multiple nucleotide(s) and may change all the codons so that a nonsense protein is synthesized.

7 What are the three main processes of posttranscriptional processing of a pre-mRNA?

A *Capping* is the addition of a 5′-5′ bridged 7-methylguanosine to the 5′ end of the mRNA.

B A *poly(A) tail* is added to the 3′ end of the mRNA.

C Noncoding sequences (*introns*) are removed by *splicing*.

8 What is the complex called that mediates the splicing reaction and what is it composed of?

A *Spliceosome.*

B It consists of five RNA molecules (U1, U2, U4, U5, and U6) and more than 100 proteins that form small nuclear ribonucleoprotein complexes (snRNPs).

9 Around what proteins is the DNA wound in eukaryotes and what are their main types of regulatory modification?

A Histone proteins.

B Acetylation, methylation, phosphorylation, and ubiquitinylation.

10 What is the difference between euchromatin and heterochromatin?

A Euchromatin is relatively lightly packed chromatin that is transcriptionally active.

B Heterochromatin is non-expressed eukaryotic chromatin that is highly condensed.

11 What is *epigenetics*?

A The term *epigenetics* describes heritable changes in the level of gene expression that are not caused by changes in the DNA sequence and also refers to stable, long-term alterations in transcriptional levels that are not necessarily heritable.

12 What is *genomic imprinting*?

A *Genomic imprinting* is an epigenetic phenomenon in which the expression of certain genes depends on the parent of origin. Imprinted genes are silenced so that the respective genes are expressed only from the non-imprinted allele inherited from the mother or from the father.

13 What is a *proprotein* (or *zymogen*)?

A A proprotein or zymogen is an inactive precursor of a protein that is activated by limited proteolysis.

14 What are the two main systems for protein degradation:

A *Lysosomal* protein degradation is normally nonselective.

B Specific protein degradation starts with the attachment of *ubiquitin* to a protein targeted for degradation, followed by degradation by the *proteasome*.

15 Classify hormones according to the distance over which they act and according to their chemical composition.

A *Endocrine* (long distance), *paracrine* (neighboring cells), and *autocrine* hormones (act on the cell from which they were released).

B Peptide hormones (e.g. insulin), steroid hormones (e.g. testosterone), amino acid derivatives (e.g. epinephrine).

16 Which are the three main signaling pathways?
- **A** Pathways involving *G protein-coupled receptors*, *receptor tyrosine kinases*, and *phosphoinositide*.

17 What is a *second messenger*? Name two examples.
- **A** Second messengers are signaling molecules that transfer extracellular events such as the binding of a hormone to a receptor on the cell surface to a target molecule inside the cell.
- **B** Cyclic AMP (cAMP), Calcium ions (Ca^{2+}).

18 What is the main function of thrombocytes?
- **A** Thrombocytes, also known as platelets, react to bleeding from blood vessel injury by clumping, thereby initiating a blood clot.

19 What is the function of the *innate immune system*?
- **A** The innate immune system is the first line of defense against infection. It detects macromolecules that represent a danger to the organism and generates means to destroy them.

20 Through which pathways can the *complement system* be activated? How do the late components of the complement system destroy a microbe or infected host cell?
- **A** Classical, lectin, alternative pathway.
- **B** They form a membrane attack complex that leads to osmotic lysis of the targeted cell.

21 Which type of lymphocytes is the adaptive immune response based on and what type of immunity do they confer?
- **A** B cells that mature in the bone marrow confer humoral immunity.
- **B** T cells that mature in the thymus confer cellular immunity.

22 Describe the structure of immunoglobulin G (IgG).
- **A** IgGs consist of two light and two heavy chains. They are Y-shaped glycoproteins. The chains are connected by disulfide bridges.
- **B** Trypsin cleavage of the IgG results in the F_{ab} (antigen binding) fragment and the F_c (crystallizable) fragment.
- **C** The two variable domains of a heavy and a light chain form the site for antigen binding.

Study Questions

1 Can you explain the phases of research and preclinical testing of a new compound and its evaluation in clinical trials?
2 Describe the phases of the cell cycle.
3 Explain the processes of *replication, transcription*, and *translation.*
4 What is alternative splicing?
5 Draw the structure of a chemical synapse.
6 What are the steps of signaling in the pathway starting with a G protein-coupled receptor?
7 Describe the process of hematopoiesis, i.e. the differentiation of a hematopoietic stem cell into differentiated blood cells.
8 Can you explain how the enormous diversity of antibodies in an organism is generated?