1 Overview of the Immune System and Its Pharmacological Targets

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Learning Objectives

1. Describe the process of hematopoiesis and the various types of hematopoietic cells.
2. Describe the processes involved in the education and shaping of immune cells.
3. Describe the role of cell surface receptors and cytokines during immune responses and explain their importance in cell-to-cell communication.
4. Compare and contrast innate and adaptive immune responses in terms of cell types, humoral factors, magnitude, and kinetics.
5. Explain the contribution of immune cells and their mediators to the development of primary and secondary immune responses.
6. Discuss the role of primary and secondary lymphoid organs in the development and activation of immune cells.
7. Describe the various classes and types of immunotherapeutic drugs and discuss their mechanism of action.
8. Describe adverse reactions that can occur with the use of immunotherapeutic drugs.
9. Explain the development of hypersensitivity reactions to immunological drugs.

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Introduction

Since ancient times, humans across many cultures have recognized the vital role that **inflammation** plays in health and disease. The Jews considered blood to be the most sacred of all organs, possessing the life of an animal. Similarly, ancient Egyptians distinguished between good and bad wounds on the basis of the presence or absence of signs of inflammation, while the Hindus in India developed an early system of medicine to treat various inflammatory illnesses. In 460 B.C., the Greek physician Hippocrates first introduced terms such as *edema* and categorized illnesses as acute or chronic. He is also credited with further developing the concept of inflammation and correlating its presence with the resolution and healing of diseases. Based on the Hippocratic canon, the Roman writer Aulus Cornelius Celsus in the first century A.D. accurately described inflammation as consisting of four main characteristics: redness (*rubor*), warmth (*calor*), pain (*dolor*), and swelling (*tumor*). This description of inflammation has stuck with us through the centuries and modern medicine considers the development of inflammation to be critical in the battle against infection and disease.

The nineteenth and twentieth centuries significantly advanced our understanding of how inflammation affects health and disease. The advent of the compound microscope finally

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allowed scientists to study the various components of blood, leading to the discovery and characterization of many hematopoietic cell types. Other scientists also discovered tiny organisms called 'microbes' that were ubiquitous throughout nature and hypothesized to cause the development of disease. This was followed by an elegant series of experimental studies by the scientists Robert Koch and Louis Pasteur, who formally established the role of microbes in causing infectious diseases, thus paving the way for understanding the functions of blood cells such as macrophages and mast cells in fighting disease. By the mid-twentieth century, several new advances in immunology had been made including the discovery of **antibodies**, **B cells**, and **T cells**, and their critical role in fighting infectious organisms. Then in 1957, Frank Burnet proposed the **clonal selection theory**, providing an explanation for how immune cells respond to specific infectious antigens, and serving as the basis for our understanding of adaptive immunity. Collectively, these and many other findings had firmly entrenched in the minds of immunologists that inflammation is the body's response to infection. Indeed, as the well-respected immunologist Charles Janeway famously described it several years later, "the immune system evolved to discriminate infectious nonself from noninfectious self" Immunol Today. 1992 Jan;13(1):11–6.

In recent years, work done by immunologists, has led to the discovery and identification of a number of other cell types, receptors, and soluble mediators called **cytokines** (a list of cytokines, their receptors and functions is provided in Table 1.1) that have shaped our current understanding of immunity and how inflammation works. These discoveries have painted a rather complex picture of inflammation that cannot be described solely in terms of the host response to infection or the cardinal characteristics of inflammation first described by Celsus. Indeed, recent studies suggest a far more complicated interplay between various players in regulating the development of inflammation. These include the hematopoietic cells of the immune system, genetic polymorphisms, epigenetic factors, microbes, and several other environmental factors that have the ability to promote or inhibit the development of inflammation. Furthermore, it has now become apparent that inflammation is not simply the body's response to infection, but can also develop towards a host of other antigenic substances including innocuous allergens, food particles, toxic gases, environmental pollutants, and any substance with the potential to cause injury or damage to the host. Lastly, it is now well-established that while the immune system plays a vital role in conferring protection from foreign agents, it is also responsible for the induction of unmitigated inflammatory responses against normal cellular components, leading to chronic inflammatory diseases and autoimmunity. In fact, the persistence of chronic inflammation underlying many different diseases has led to the suggestion that 'inflammation' may be the key to unraveling the unified theory of disease. In support, chronic inflammation is now known to be causative or a co-culprit in a number of conditions not typically associated with inflammation including cardiovascular insults (atherosclerosis, coronary artery disease), neurological diseases (Alzheimer's disease, multiple sclerosis), type 2 diabetes, and cancer.

In this book, we examine the effects of inflammation in the pathogenesis of various diseases and explore the functions of currently approved immunotherapeutic drugs used in their treatment. Specific emphasis will be placed on the roles of immune cells, membrane-bound receptors, and soluble mediators in propagating or preventing a disease and their consideration as established or putative targets for immunotherapy. In the next few sections, a brief synopsis of the immune system including its development and function is provided. This is followed by an overview of the various classes and types of drugs used in immunotherapy. The principles underlying innate and adaptive immune responses as well as therapeutic modulation of the immune system is described in detail in subsequent chapters.

Table 1.1 List of cytokines involved in immune responses

Cytokine/chemokine	Receptor	Produced by	Functions
IL-1α and IL-1β	IL-1R type 1 and type 2	Macrophages, lymohocytes, neutrophils, keratinocytes, fibroblasts, other cells	Proinflammatory cytokine; can act as pyrogen; involved in T_H17 differentiation
IL-1Ra	IL-1R type 1 and type 2	Macrophages, endothelial cells, epithelial cells, neutrophils, keratinocytes, fibroblasts, other cells	Competitive inhibitor of IL-1
IL-2	IL-2R	Activated T cells, DCs, NK cells, NKT cells, mast cells, innate lymphoid cells (ILCs)	Proliferation of T, B, NK cells and ILCs
IL-3	IL-3R	T cells, mast cells, eosinophils, macrophages, NK cells, stromal cells, other cells	Hematopoiesis; growth factor for mast cells, basophils, eosinophils, DCs
IL-4	IL-4R type I and type II	T_H2 cells, basophils, mast cells, eosinophils, NKT cells, γδ T cells	T_H2 differentiation; B cell activation; IgE class switching; upregulation of MHC II; upregulation of CD23 (low affinity receptor for IgE) and IL-4R
IL-5	IL-5R	T_H2 cells, activated eosinophils, mast cells, NK cells, NKT cells, ILC2 cells	Eosinophil differentiation, migration, activation, function, and survival; wound healing
IL-6	IL-6R (soluble IL-6R and gp130)	Endothelial cells, fibroblasts, monocytes, macrophages, T cells, B cells, granulocytes, mast cells, keratinocytes, other cells	Acute phase response; T-cell differentiation, activation, and survival; B-cell differentiation and production of antibodies; leukocyte trafficking and activation; osteoclastogenesis; synovial fibroblast proliferation and cartilage degradation; other functions
IL-7	IL-7R and soluble IL-7R	Monocytes, macrophages, DCs, epithelial cells, B cells, stromal cells	B and T cell development; T cell survival; development and maintenance of ILCs; other functions
IL-8 (CXCL8)	CXCR1 and CXCR2	Monocytes, macrophages, neutrophils, lymphocytes, epithelial cells, keratinocytes, smooth muscle cells, other cells	Chemotactic factor for neutrophils, NK cells, T cells, basophils, eosinophils; angiogenesis
IL-9	IL-9R	T_H2 cells, T_H9 cells, T_H17 cells, mast cells, ILC2s, T_{reg} cells	Proliferation of T cells and mast cells; IgE production; mucus production
IL-10	IL-10R1/ IL-10R2 complex	T_H2 cells, T_{reg} cells, T_H1 cells, macrophages, DCs, B cells, mast cells, other cells	Suppression of DC and T cell function; stimulation of mast cells, NK cells, and B cells
IL-11	IL-11Rα and gp130	Bone marrow stromal cells, fibroblasts, epithelial cells, osteoblasts, other cells	Hematopoietic growth factor for erythroid and myeloid lineages; bone remodeling and stimulation of osteoclasts; epithelial cell repair
IL-12	IL-12Rβ1 and IL-12Rβ2	Macrophages, neutrophils, DCs, B cells, other cells	Development and maintenance of T_H1 cells; NK cell activation; DC maturation; cytotoxic responses

(continued)

Table 1.1 (continued)

Cytokine/chemokine	Receptor	Produced by	Functions
IL-13	IL-13R type I (IL-13Rα1 and IL-4Rα) and type II (IL-13Rα2)	T_H2 cells, mast cells, basophils, eosinophils, NKT cells, ILC2 cells	IgE class-switching; mucus secretion; epithelial cell turnover; MHC II upregulation; smooth muscle hyperreactivity; defense against parasites
IL-14 (alpha-taxilin)	IL-14R	T cells, T cell lymphomas	Proliferation of activated and cancerous B cells
IL-15	IL-15R	Monocytes, macrophages, DCs, CD4 T cells, stromal cells, keratinocytes, other cells	NK cell proliferation and activation; differentiation of γδ T cells; development and maintenance of NK, NKT, and memory CD8 T cells; suppression of CD4 T cells; prevention of eosinophil apoptosis
IL-16 (pro-IL-16)	CD4	Epithelial cells, fibroblasts, T cells, eosinophils, mast cells, DCs	Chemotactic factor for CD4 and CD8 T cells, mast cells, eosinophils, monocytes
IL-17A and IL-17F	IL-17RA	T_H17 cells, CD8 T cells, γδ T cells, NK cells, NKT cells, neutrophils, ILCs	Neutrophil recruitment and activation; promotion of inflammation
IL-17B, IL-17C, IL-17D	IL-17RB; IL-17RA-E; IL-17RD or SEF[a] or IL-17RLM	IL-17B: neuronal cells; IL-17C: epithelial cells; IL-17D: resting B and T cells, skeletal cells, heart, lung, brain, pancreatic cells	Induction of antimicrobial peptides, cytokines, chemokines, metalloproteinases; IL-17B: chondrogenesis and osteogenesis; IL-17C: intestinal barrier modulation; IL-17D: suppression of myeloid progenitor cells
IL-18	IL-18R	Macrophages, DCs, epithelial cells, keratinocytes, osteoblasts, other cells	Promotion of NK cell cytotoxicity; production of IFN-γ in the presence of IL-12
IL-19	IL-20R1/ IL-20R2	Monocytes, B cells, keratinocytes, epithelial cells, other cells	Enhancement of T_H2 cytokine production in keratinocytes; increase IL-6 and TNF-α from monocytes
IL-20	IL-20R1/ IL-20R2 and IL-22R1/ IL-20R2	Monocytes, epithelial cells, keratinocytes	Autocrine regulator of keratinocytes
IL-21	IL-21R	T_H9 cells, T_H17 cells, NKT cells	B cell proliferation and survival; NKT cell proliferation; T cell growth
IL-22	IL-22R	Activated T_H17 cells, T_H22 cells, NK cells, NKT cells, ILCs	Induction of antimicrobial peptides from keratinocytes; keratinocyte repair and healing; tissue reorganization
IL-23	IL-23R	Macrophages and DCs in peripheral tissues	T_H17 proliferation and maintenance; promotion of IL-17 production; NK cell activation; regulation of antibody production
IL-24	IL-20R1/ IL-20R2 and IL-22R1/ IL-20R2	Melanocytes, T cells, keratinocytes, other cells	Tumor suppression

(continued)

Table 1.1 (continued)

Cytokine/chemokine	Receptor	Produced by	Functions
IL-25 (IL-17E)	IL-17RA and IL-17RB	T_H2 cells, mast cells, eosinophils, basophils, epithelial cells	Alarmin cytokine; Induction of T_H2 responses; production of IgE, IL-4, IL-5, IL-13; inhibition of T_H1 and T_H17 responses
IL-26	IL-10R2 chain and IL-20R1 chain	Activated T_H17 cells, NK cells, memory T cells	Regulation of epithelial cells
IL-27	IL-27Rα and gp130	Activated macrophages, DCs, and epithelial cells	Control of differentiation of helper T cell subsets; T_H1 differentiation; induction of T-bet; inhibition of T_H17 responses; upregulation of IL-10
IL-28A/B/IL-29	IL-28R1/ IL-10R2	DCs and other nucleated cells in response to viral infections	Induction of T_H1 and T_{reg} responses; induction of tolerogenic DCs
IL-30 (p28 subunit of IL-27)			Prevention and treatment of cytokine-induced liver injury
IL-31	IL-31RA/ OSMRβ[a]	T_H2 cells, CD8 T cells, macrophages, DCs, keratinocytes, mast cells, other cells	Induction of chemokines from eosinophils and keratinocytes; itching during atopic dermatitis
IL-32	Unknown	Monocytes, macrophages, activated NK cells, activated T cells, epithelial cells	Induction of IL-6, CXCL8, TNF-α in macrophages and other cells; prevention of eosinophil apoptosis
IL-33	ST2	Epithelial cells, endothelial cells, necrotic cells, fibroblasts, stromal cells	Alarmin cytokine; induction of T_H2, mast cell, eosinophil, and ILC2 responses
IL-34	Colony stimulating factor (CSF)-1 receptor	Spleen, heart, brain, liver, kidney, thymus, testes, ovary, small intestine, prostate, colon	Regulation of myeloid lineage and microglial proliferation
IL-35	IL-12Rβ2/ gp130; IL-12Rβ2/ IL-12Rβ2; gp130/gp130	T_{reg} cells, monocytes, epithelial cells, endothelial cells, smooth muscle cells	T_{reg} proliferation; increased IL-10 production; inhibition of effector T cell function
IL-36	IL-36Ra	Endothelial cells, macrophages	Promotion of keratinocyte, DC, and T cell responses to tissue injury or infection
IL-37	IL-18Rα and IL-18BP	Monocytes, tonsil plasma cells, breast carcinoma, lung carcinoma, colon carcinoma, melanoma	Inhibition of IL-18 activity; inhibition of DCs and NK cell activity
IL-38	IL-1R1 with low affinity, IL-36R	Basal epithelia of skin, spleen, fetal liver, placenta, thymus, proliferating B cells of the tonsils	Inhibition of T_H17 responses; inhibition of IL-36
B-cell activating factor (BAFF) or B Lymphocyte Stimulator (BLyS)	TACI,[a] BCMA,[a] BAFF-R	Monocytes, dendritic cells, follicular dendritic cells, bone marrow stromal cells	B cell activation and maturation
Granulocyte colony-stimulating factor (G-CSF or CSF3)	G-CSF receptor	Bone marrow cells, endothelial cells, macrophages, other immune cells	Hematopoiesis; stimulates HSCs to produce neutrophils

(continued)

Table 1.1 (continued)

Cytokine/chemokine	Receptor	Produced by	Functions
Granulocyte-macrophage colony-stimulating factor (GM-CSF or CSF2)	GM-CSF receptor	Macrophages, mast cells, T cells, NK cells, endothelial cells, fibroblasts	Hematopoiesis; stimulates HSCs to produce granulocytes and myeloid cells
IFN-α and IFN-β	IFNAR	All nucleated cells in response to viral infections; plasmacytoid DCs	Antiviral response; interferon response; activation of NK cells; stimulation of DCs; stimulation of ADCC; apoptosis of tumor cells
IFN-γ	IFNGR1/ IFNGR2	T_H1 cells, CD8 T cells, NK cells, NKT cells, macrophages, B cells	Antiviral response; cytotoxic activity; upregulation of MHC II; enhancement of immunoproteasome
Macrophage colony-stimulating factor (M-CSF)	M-CSF receptor	Bone marrow cells, fibroblasts	Acts on HSCs to promote myeloid lineage
Thymic stromal lymphopoietin (TSLP)	CRLF2[a] and IL-7Rα chain	Fibroblasts, epithelial cells, stromal cells	Stimulates DCs and T_H2 responses
Transforming growth factor (TGF)-β	TβR I and TβR II	Epithelial cells, fibroblasts, macrophages, eosinophils, T cells, T_{reg} cells, other cells	Immune tolerance; induction of T_{reg} cells; decreased growth of immune precursors; mesenchymal cell transition; development of cardiac system and bone formation
Tumor Necrosis Factor (TNF)-α	TNFR1 and TNFR2	Macrophages, monocytes, DCs, T cells, mast cells, NK cells, NKT cells, fibroblasts, endothelial cells, other cells	Proinflammatory cytokine; vasodilation; vascular permeability; upregulation of adhesion molecules on endothelial cells; tumorigenesis
TNF-β or Lymphotoxin (LT)-α and LT-β	LT-β receptors	Lymphocytes	Formation of secondary lymphoid organs; anti-proliferative activity; destruction of tumor cell lines; innate immune regulation; pro-carcinogenic activity when upregulated

Adapted and modified from Akdis et. al. Interleukins (from IL-1 to IL-38), interferons,transforming growth factor β, and TNF-α: Receptors, functions, and roles in disease. J Allergy Clin Immunol 2016;138:984–1010

[a]*BCMA* B-cell maturation antigen, *CRLF2* cytokine receptor-like factor 2, *OSMRβ* oncostatin M specific receptor subunit beta, *SEF* similar expression to fibroblast growth factor genes, *TACI* transmembrane activator and calcium modulator and cyclophilin ligand interactor

Overview of the Immune Response

The primary purpose of the immune system is to defend the host against infectious organisms that may compromise the integrity of the host, leading to cellular damage and possible death of the host. Immune responses against pathogens can be compartmentalized into five stages: pathogen detection, acute inflammation, antigen presentation, adaptive immunity, and pathogen destruction (Fig. 1.1). As discussed throughout this book, various cell types are involved at each stage, with their function regulated by cell-to-cell interactions, surface receptors, and cytokines. Many of these receptors and cytokines (which include various **interleukins**) are therapeutic targets for patients with inflammatory diseases.

Infection with a pathogenic organism can lead to three possible outcomes: elimination of the

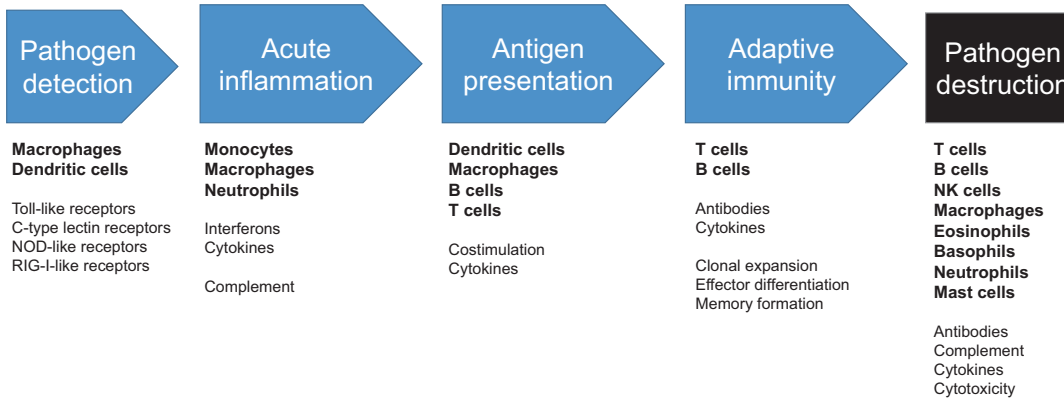


Fig. 1.1 Immune responses against pathogenic microorganisms occur in five stages, culminating in pathogen destruction. Examples of cell types, receptor interactions and/or immune checkpoints are indicated for each stage (figure contributed by Jeremy P. McAleer)

organism by the immune system, chronic infection that is held in check by the immune system, or death of the host due to a failure of the immune system to eliminate the pathogen. Most infections are successfully eliminated by the immune system, resulting in tissue healing and cellular memory of the infectious pathogen. A small number of pathogens may cause chronic infections that are not cleared, leading to latency of the infectious organism within the host and subsequent periods of reactivation by environmental or other stimuli. Although these infections are not completely eradicated, they are usually held in check by the immune system for long periods of time, until the immune system is either compromised or completely damaged. In the absence of treatment to restore the immune system or control the infection, this usually results in death of the host.

The immune system is also critical for human survival. In the absence of a functional immune system, the host is unable to protect itself against common environmental microorganisms, ultimately succumbing to various infections that often result in death. Severe cases of this are observed in patients born with primary immunodeficiencies, as exemplified by **Severe combined immune deficiency (SCID).** In this primary immunodeficiency, patients are unable to produce the T and B cells of the adaptive immune system, and survival is not possible, unless therapy is initiated with **hematopoietic stem cell transplantation** (bone marrow transplantation) to restore the immune system.

In addition to initiating and propagating immune responses, the cells of the immune system play important roles in several other organ systems. Various resident and migrating populations of immune cells such as macrophages and mast cells are present in almost every organ of the body, where they contribute to the integrity of tissues and participate in maintaining organelle function.

Hematopoiesis and Cells of the Immune System

The cells of the immune system are derived and transported via blood, and hence are referred to as hematopoietic cells. The process of formation of blood cells is termed as **hematopoiesis**. All the populations of blood cells are derived from common progenitors termed **hematopoietic stem cells (HSCs)**. These cells are present throughout the adult bone marrow and are long-lasting and self-renewing. They divide in the presence of growth factors and other instructions from stromal cells into several types of progenitor populations, eventually leading to the generation of distinct lineages of red and white blood cells. Thus, HSCs are also said to be pluripotent with the ability to differentiate into many different cell types.

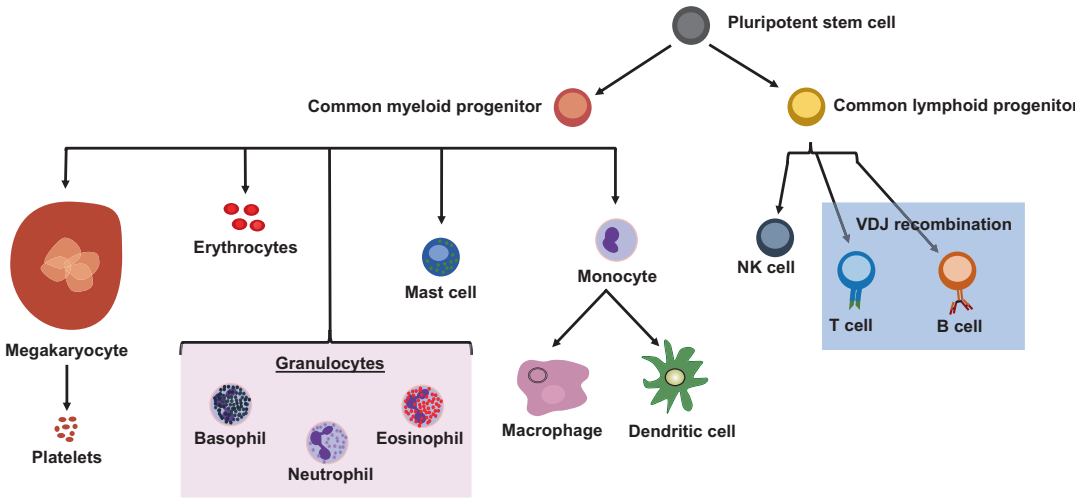


Fig. 1.2 The development of immune cells through hematopoiesis. Pluripotent stem cells are self-renewing and give rise to daughter progeny with a more limited developmental potential. Hematopoiesis occurs in the bone marrow and is guided by growth factors and cell to cell interactions. The common myeloid progenitor gives rise to several innate immune cell types including granulocytes, mast cells, and monocytes. The common lymphoid progenitor gives rise to lymphocytes (T cells, B cells, NK cells) (figure contributed by Jeremy P. McAleer)

In the developing embryo, hematopoiesis begins in the yolk sac. This later shifts to the fetal liver and then the spleen during the third to seventh months of fetal life. During the fourth to fifth months, hematopoiesis is initiated in the fetal bone marrow, and this continues throughout the life of the host. In adults, the major sites of hematopoiesis are the skull, sternum, vertebral column, femurs, pelvis, and ribs.

Hematopoietic cells are divided into two major categories: red blood cells or **erythrocytes** and white blood cells or **leukocytes** (Fig. 1.2). Immune cells are classically referred to as white blood cells, although erythrocytes also participate in the immune response. Two distinct lineages of leukocytes are derived from hematopoiesis: the **myeloid** lineage, which gives rise to **granulocytes**, **monocytes**, **macrophages**, **dendritic cells**, and **mast cells**; and the **lymphoid** lineage which gives rise to **natural killer (NK) cells**, B cells, and various populations of T cells.

Red blood cells and megakaryocytes (which give rise to platelets) are derived from the erythroid progenitor, which is derived from a common myeloid precursor. The primary purpose of erythrocytes is to transport oxygen throughout blood. However, they also participate in the removal of immune complexes containing antibodies bound to their target proteins. Platelets maintain the integrity of blood vessels and initiate and maintain clotting reactions to promote wound healing and prevent blood loss.

The Myeloid Lineage

The myeloid progenitor gives rise to three major cell types: granulocytes, monocyte-derived cells, and mast cells. The granulocytes consist of three major populations of cells: **neutrophils**, **eosinophils**, and **basophils**. They are characterized by the presence of cytoplasmic granules, which house a number of toxic mediators and enzymes that are involved in immune reactions. In addition, they possess many irregular, multi-lobed nuclei, leading to the use of the term **polymorphonuclear (PMN) leukocytes** to describe them.

Neutrophils Are Rapidly Mobilized to Tissues During an Infection

Neutrophils are the most abundant leukocyte present in blood, accounting for up to 70% of the

total leukocyte population. Their granules do not stain with acidic or basic dyes, forming the basis for the nomenclature *neutro*phils. Neutrophils are highly specialized cells that are adept in the capture, phagocytosis, and killing of infectious organisms. In addition, they also secrete a number of mediators that enhance inflammation. Neutrophils act as first responders during infections and are rapidly mobilized from the blood to sites of infection. Here, they help initiate and coordinate the capture and killing of microorganisms that have entered the tissue, thriving in the anaerobic conditions present in damaged tissues. Despite their intense activity, neutrophils are short-lived cells that die after their granular contents have been released, resulting in the formation of pus.

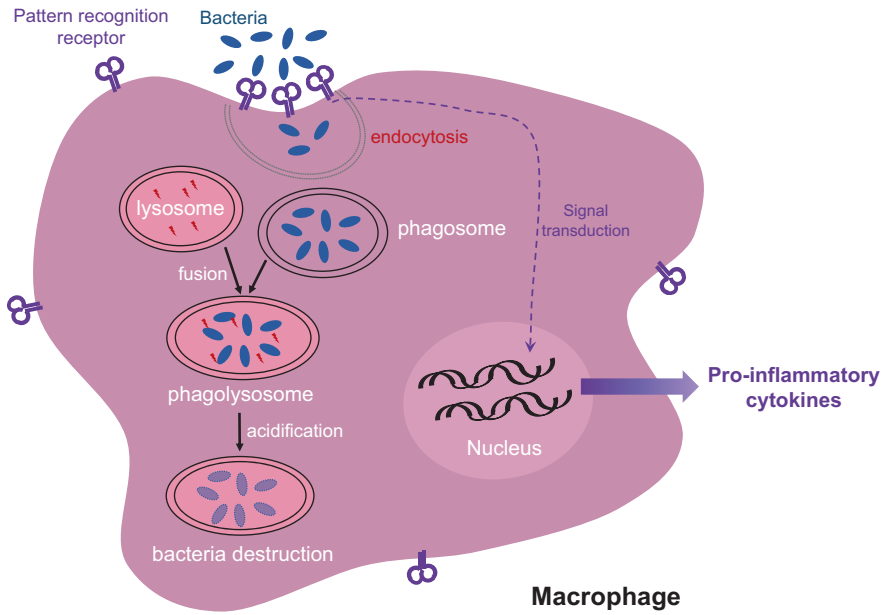
Eosinophils and Basophils Protect the Host from Parasitic Infections

Eosinophils derive their name from the pink staining of their granules when stained with the acidic dye eosin. The major function of eosinophils is to initiate defense against parasitic organisms such as helminth worms. These effects are primarily mediated in concert with parasite-specific **IgE antibodies** produced by the B cells of the adaptive immune system. Eosinophils are generated in the bone marrow under the control of stromal cells and several growth factors, including the interleukins **(IL)-3** and **IL-5**. During a parasitic infection, these cytokines, as well as chemokines such as **eotaxin** produced by T cells, induce their migration to tissues, where they promote their differentiation and survival. Once they reach the site of parasitic infection, eosinophils upregulate the high affinity receptor for IgE antibodies, **FcεRI**, and mediate antigen-induced inflammatory reactions resulting in degranulation and the release of toxic mediators such as major basic protein and eosinophil peroxidases which destroy the parasitic organism. In addition to their role in anti-parasitic responses, eosinophils are a major contributor to the development of allergic disease.

Basophils stain with the basic dye hematoxylin. They are a rare granulocyte population that like eosinophils and mast cells have been implicated in IgE-mediated reactions, but have recently been found to also contribute to other types of immune responses. Basophils are mostly present in circulation, where they constitutively express the IgE receptor, FcεRI, and participate in the development of anti-parasitic and allergic responses. Like mast cells and eosinophils, they also depend on growth factors such as IL-3 and **granulocyte-macrophage colony stimulating factor (GM-CSF)** for their differentiation and survival. They are prolific producers of the cytokine **IL-4**, and have been hypothesized to provide the initial source of IL-4 that is required for the differentiation and activation of **helper CD4 T cells** of the T_H2 phenotype. In addition, they have been found to express ligands for costimulatory molecules that activate T cells and have been postulated to act as antigen-presenting cells under some conditions.

Monocytes, Macrophages, and Dendritic Cells Capture and Destroy Pathogens and Alert the Immune System

The second group of myeloid cells consists of monocytes, macrophages, and dendritic cells. Monocytes are a distinct group of cells with indented nuclei that are present throughout the circulation. From the blood, monocytes migrate to tissues where they mature into macrophages or dendritic cells under the control of growth factors such as GM-CSF and IL-4. Macrophages are long-lasting cells that are present in all bodily tissues. Here, they not only perform functions that are unique to the tissue such as the capture of antigens by skin-resident cells or the maintenance of bone homeostasis and integrity by bone-resident **osteoclasts**, but are also involved in the initiation and propagation of immune responses. A primary immune function of macrophages in tissues is to act as sentinel cells that sense and alert the immune system to the presence of infection or danger. Macrophages are well-equipped to do this by virtue of possessing a number of receptors that are adept at both capturing pathogens and initiating an inflammatory signal transduction cascade. Pathogen capture is mediated by various receptors on the surface of macrophages including C-type



1-3. Bacterial phagocytosis and destruction

Fig. 1.3 Bacterial phagocytosis and destruction. Macrophages detect microbes including bacteria through pattern recognition receptors. This elicits receptor-mediated endocytosis as well as a signal transduction pathway leading to the expression of pro-inflammatory cytokines. Fusion of the phagosome with a lysosome results in acidification within the intracellular compartment and bacterial destruction (figure contributed by Jeremy P. McAleer)

lectin receptors (such as dectins and mannose binding receptors) as well as scavenger receptors. This is subsequently followed by the initiation of **phagocytosis** or receptor-mediated **endocytosis** (Fig. 1.3). This involves pathogen transport via a vesicular pathway that comprises of a series of vesicles that terminate in the cellular phagosome. Here, changes in cellular pH induce the fusion of the phagosome with the lysosome, giving rise to the phagolysosome, where the pathogen is destroyed and degraded. Pathogenic peptides derived from this process may be subsequently used as antigens to induce the activation of T cells during adaptive immune responses.

In addition to receptors for antigen capture, macrophages also express receptors that initiate signal transduction pathways. A vast majority of these belong to the **Toll-like receptor (TLR) family**, which may be expressed either on the plasma membrane or intracellularly. Examples include the TLR4 homodimer, which binds to **lipopolysaccharide**, an endotoxin found in the cell wall of gram-negative bacteria. Similarly, TLR5 binds bacterial flagellin, while TLR3 binds viral nucleic acids. Binding of ligands by TLRs results in the induction of signaling cascades that culminate in the activation of various transcription factors including **nuclear factor of kappa B (NF-κB)**, a potent transcription factor involved in the activation of a number of immune cytokine genes such as **IL-2**, **TNF-α**, **IL-1**, and **IL-6**.

Dendritic cells also derive from the monocyte lineage and perform similar functions as macrophages in various tissues. In addition, they are equipped with the unique ability to induce the activation of naïve T cells in secondary lymphoid organs, serving as a link between the innate and adaptive immune responses. Once they have captured antigens in peripheral tissues such as the skin, dendritic cells migrate to secondary lymphoid organs such as the draining lymph nodes, where they activate naïve T cells and induce their differentiation into various sub-types.

Mast Cells Protect Against Parasites and Also Promote Inflammation

The third category of myeloid cells, mast cells, are present throughout vascularized tissues, where they sense the presence of pathogens and initiate immune responses. Like eosinophils and basophils, they also possess large numbers of granules containing preformed mediators such as histamine, which are released upon activation and degranulation. Mast cells also constitutively express the IgE receptor, FcεRI, and participate in IgE-mediated anti-parasitic and allergic responses. However, they are highly versatile cells that are also implicated in many other types of immune reactions, and express several other receptors including the TLRs and complement receptors.

The Lymphoid Lineage

The lymphoid lineage of cells gives rise to NK cells, T cells, and B cells. NK cells are a heterogeneous group of innate lymphocytes that express several receptors that are involved in recognizing and attacking tumors or virus-infected cells. NK cells also produce a variety of cytokines that can modulate the function of other cell types such as dendritic cells, macrophages, and T cells.

T cells are the main drivers of the adaptive immune response. They are derived from lymphoid progenitors in the bone marrow, following which they travel to the thymus, where they complete their development and maturation. In the thymus, T cells are educated to recognize the difference between host and foreign antigens under the control of thymic epithelial cells, macrophages, and dendritic cells. T cells derived their name due to their maturation in the thymus gland. Following maturation, naïve T cells exit the thymus and enter circulation, where they are poised to interact with antigens presented by antigen presenting cells such as dendritic cells. Two major types of T cells have been described: **CD4 T cells**, which consist of **helper T cells** and **regulatory T cells** ($\mathbf{T_{reg}}$), and **CD8 T cells**, also referred to as **cytotoxic T cells**.

Helper T cells can be differentiated into many diverse sub-types including the $\mathbf{T_H1}$, $\mathbf{T_H2}$, $\mathbf{T_H9}$, $\mathbf{T_H17}$, $\mathbf{T_H22}$, and $\mathbf{T_{FH}}$ subsets depending on their phenotype. The differentiation of helper T cells is coordinated by both antigen presenting cells and other innate cell types through the release of distinct cytokines which promote their differentiation. Each type of helper T cell is associated with the expression and activation of transcription factors unique to that particular cell type. Helper T cells are critical to the immune system and perform diverse functions including the coordination of immune responses against intracellular and extracellular bacteria, viruses, parasites, and fungi. The depletion of helper T cells leads to severely compromised immune functions and death, as occurs during the development of **Acquired Immune Deficiency Syndrome (AIDS)**. Regulatory T cells play an important role in regulating or suppressing other cells in the immune system. They suppress unwanted responses to self or foreign antigens and prevent the development of autoimmunity.

In contrast, CD8 T cells are uniquely equipped to mediate adaptive immunity to viral infections. They kill virally-infected cells and may also enhance immune responses to other pathogens. Additionally, these cytotoxic T cells are the adaptive immune system's primary defense against tumors and the development of cancer.

B cells also arise from lymphoid progenitors in the bone marrow and complete their maturation and development there. The origin of their name comes from where they were first discovered, the Bursa of Fabricius, a specialized hematopoietic organ which is only found in birds. The primary function of B cells is the production and secretion of various immunoglobulins or antibody isotypes. Upon maturation, B cells express the **IgM** antibody, which is the first antibody isotype produced during immune responses. Under the direction of T cells, B cells can be further activated to produce various other antibody isotypes such as **IgG**, **IgA**, and **IgE**.

The Education and Shaping of Immune Cells

Regulation of Immune Cells by Commensal Microbiota

Immune cells are conditioned by their microenvironment. Signals received during infection or other types of host injury have the potential to modulate the functions of immune cells, leading to their activation or suppression. Similarly, several environmental factors have also been shown to modulate the development of immune responses. The host microbiota in particular has an enormous influence on the immune system. During fetal development, fetal cells have no interactions with microorganisms as a result of protection provided by maternal IgG antibodies and the mother's immune cells. This vastly changes as soon as a newborn is exposed to environmental bacteria. Upon birth, each individual is colonized by a host of **commensal** microorganisms, which constitute the normal microflora of the host. These bacteria reside in various mucosal tissues including the gastrointestinal tract, oral cavity, vagina, and skin. Here, they are in constant interaction with immune cells and modulate their activity and function, providing the necessary experience that is required for fighting infections. As such, the immune cells in mucosal tissues remain ever-ready to prevent the development of infection, actively monitoring the microbial population and preventing infection by opportunistic pathogens. This sentinel activity is performed in a manner that minimizes host cellular damage and prevents the development of chronic inflammation.

Commensal microorganisms perform many functions including aiding in digestion, providing metabolites and cofactors for cells, preventing the growth of opportunistic pathogens, and shaping the immune system. The interactions of immune cells with the commensal microflora play a pivotal role in providing the education and experience that is needed for future defense against infections with pathogenic organisms. Exposure to infections, especially during early life, can further modulate the development of the immune system, ensuring that immune cells develop in a healthy fashion that is geared towards host defense and not the development of unnecessary responses. For example, exposure to intracellular bacteria such as mycobacteria in early life may help to prevent a T_H2 bias of the immune system, while exposure to helminth worms is thought to reduce IgE-mediated allergic sensitization.

The diversity and composition of the commensal population is determined by a host of factors including exposure to dietary components and competing species of bacteria. When changes in the microbial composition occur, either due to illness, a change in diet, or treatment with antibiotics, further modulation of the immune system may also occur. In elderly or immunocompromised patients, antibiotic treatment can disrupt the normal microbial composition and allow for the growth of opportunistic pathogens such as *Clostridium difficile*, which are normally held in check by the immune system and by competing bacteria such as enterobacteria.

T and B Cell Education in Primary Lymphoid Organs

Adaptive immune cells gain specific experience in **primary lymphoid organs** such as the **thymus** and **bone marrow,** where they develop and mature. In the thymus, T cells are taught to differentiate between 'self' and 'non-self' antigens. Under the careful coordination of thymic epithelial cells and dendritic cells, they learn to tolerate self-tissues and mediate immune responses against foreign antigens. This selection process ensures that naïve T cells will only be activated against non-self antigens that are presented by host antigen presenting cells, thereby preventing the development of autoimmunity. Immature T cells which have the potential to recognize self-antigens are eliminated and undergo death by apoptosis. In a similar manner, B cells also undergo selection processes in the bone marrow and secondary lymphoid organs. These processes ensure that self-reactive B cells with the potential to bind autoantigens are eliminated from the immune repertoire and only those that can react against non-self antigens are retained. Further selection processes in secondary lymphoid organs such as the lymph node ensure the differentiation and

survival of mature B cells that have the potential to react with high affinity against specific antigens and make effective antibodies of various isotypes. Once mature naïve B and T cells enter the circulation, they are held in check by a number of regulatory processes, which are aimed at further preventing the development of autoimmunity.

Upon activation, all immune cells are programmed to differentiate into activated effector cells. Depending on the particular type of injury or antigenic trigger, effector cells mediate the active immune response to pathogens or other foreign agents, inducing the development of inflammation and destroying the foreign organism. The functions of effector cells are further conditioned by the release and activity of various cytokines, which modulate the behavior of the particular immune cell. Various types of effector cells exist depending on the type of cell and the particular immune response. In addition to giving rise to effector cells, adaptive immune cells also differentiate into memory cells. These are long-lasting cells that remember the particular antigenic exposure and are readily stimulated on antigenic re-exposure resulting in a rapid and potent immune response against the specific antigen.

The Innate Immune Response

The vast majority of infectious organisms are rapidly eliminated by the immune system soon after exposure without causing significant host damage and/or the induction of clinical symptoms. This response is mediated by a combination of both ubiquitously present anti-microbial proteins and molecules as well as the microbicidal activity of cells such as neutrophils and macrophages. This type of response is termed as the **innate immune response**, since it can be mobilized as soon as infection occurs, does not recognize specific antigens, and does not require a prolonged induction phase as in the case of T and B cells (Fig. 1.4).

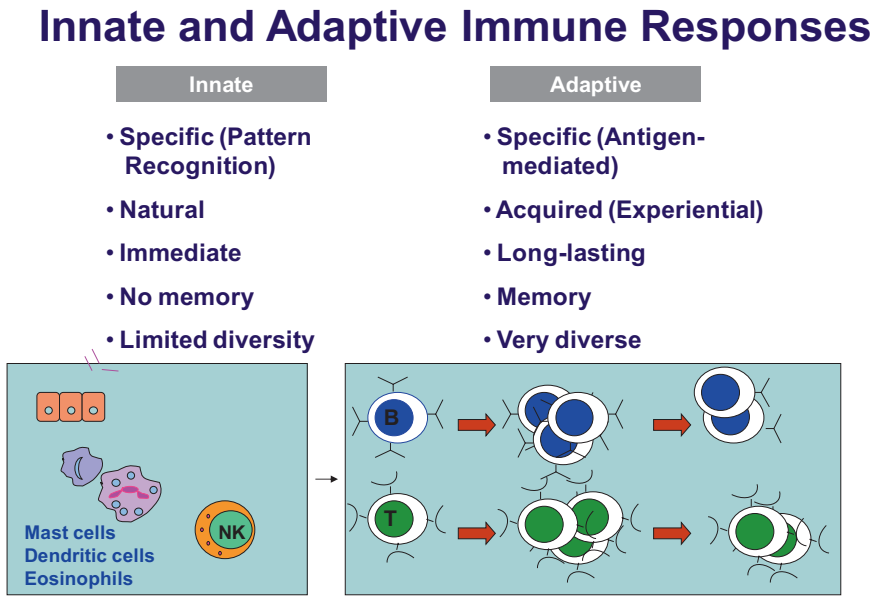


Fig. 1.4 Distinguishing characteristics of the innate and adaptive immune systems. Both innate and adaptive immune cells evolved to recognize foreign antigens. However, they differ with respect to their specificity and capacity to mediate long-lasting immune responses. Innate cells express a variety of receptors for the recognition of pathogen-associated molecular patterns. In contrast, adaptive cells are equipped with the unique ability to recognize distinct antigens by virtue of a single specific surface receptor. The effects of activated innate cells occur immediately. However, adaptive cells must go through a process of clonal selection and clonal expansion prior to activation. Activated adaptive cells can differentiate into effector and memory populations that mediate a tailored and life-long response to antigens

Pre-formed Molecules Provide an Immediate Defense Against Infectious Agents

A number of molecules present in blood and tissues possess anti-microbial activity. These include protease inhibitors such as α2-macroglobulins in the blood, acids in various tissues, lysozyme which degrades peptidoglycan, and **defensins** which are anti-microbial peptides. In addition to these, a unique family of serine proteases play a critical role in the elimination of pathogens and the facilitation of immune responses. These heat-labile proteins, which act on each other during the immune response, are collectively referred to as the **complement system**. The molecules of the complement system are constitutively produced by the liver. Upon antigenic exposure, whether due to changes in the physiological environment or the engagement of receptors, the complement pathway is activated. This results in the activation of key complement molecules such as **C3b**, the primary function of which is to tag pathogens for destruction and facilitate complement-initiated phagocytosis. This is referred to as **complement fixation** or **opsonization**. In addition to opsonization, complement components can directly lyse pathogenic cell membranes, mediating their destruction. They can also act as alarmin molecules, alerting the rest of the immune system to the presence of danger. **C3a** and **C5a**, formed during the cleavage of complement components can bind receptors on mast cells, basophils, and neutrophils, enhancing their recruitment and activation in tissues. A major trigger of the complement system during adaptive immune responses is antigen-specific antibody. Both IgM and IgG antibodies are very effective at complement fixation, binding complement components and inducing the phagocytosis of the pathogen. During the course of inflammation, large numbers of antigen-antibody immune complexes can be formed. Binding of these to the complement component C3b can facilitate the removal of **immune complexes** by erythrocytes which express receptors for C3b.

The Initial Response to Infection

In addition to immunity mediated by the complement system and other molecules, a number of leukocytes play key roles in the initial response to infection. Depending on the type and the site of infection, distinct immunological pathways are activated aimed at terminating the infection.

Early on, cells such as macrophages play a critical role in limiting the numbers of pathogens and alerting other immune cells. Damage to cells of the connective tissue such as a wound, burn, trauma, bite, or other type of injury to the skin induces the rapid activation of macrophages, which perform phagocytosis and release proinflammatory cytokines (Fig. 1.5). Of these, the cytokine, TNF-α, is a potent vasodilator, causing blood vessels to expand and inducing vascular permeability. As a result, endothelial cells lining blood vessels become leaky, allowing the exit of blood constituents including cells and other molecules. TNF-α also upregulates the expression of adhesion molecules on blood vessels, facilitating the migration of neutrophils and other cells that express corresponding ligands to tissues. The arrival of cells and other molecules to the infected tissue can cause localized swelling, resulting in the development of edema. Histamine produced by mast cells at sites of infection is also a potent vasoactivator and can act in a similar manner. Similarly, mast cells also produce high levels of TNF-α. Another important molecule produced by macrophages is the chemokine **CXCL8**. This molecule acts as a chemoattractant for neutrophils, driving their migration to the site of infection. Depending on the type of infection, additional cytokines may be produced by cells such as macrophages and mast cells. Most extracellular bacteria such as *Staphylococcus aureus* or other **pyogenic (pus-inducing) bacteria** are captured *via* phagocytosis. On the other hand, intracellular bacteria and viruses often cause infection by directly infecting the macrophages. Macrophages can also phagocytose other cells that have been infected by the pathogen. In response to viral infections, macrophages make the cytokine IL-12, which can serve to coactivate both dendritic cells and natural killer cells to the pathogen.

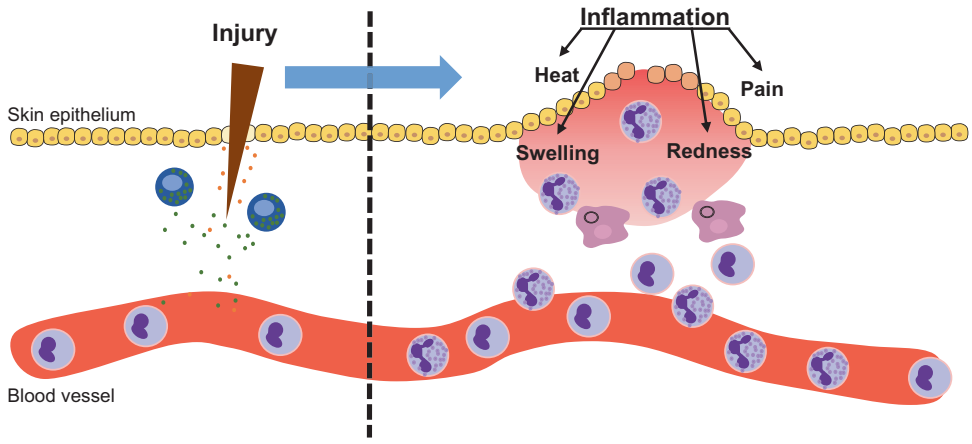


Fig. 1.5 Hallmarks of Inflammation. Injury to a body tissue such as the skin results in the immediate production of cytokines by epithelial cells, which serve to recruit neutrophils and other inflammatory cells from the blood. Release of TNF-α and other cytokines by tissue macrophages make blood vessels permeable, enhancing the migration of leukocytes to the injured area. The dilation of blood vessels and increased leukocyte infiltration at the injured site contributes to the redness, heat, and swelling associated with inflammation. The increase in edema causes pinching of the nerves attached to blood vessels, resulting in the induction of pain (figure contributed by Jeremy P. McAleer)

The Development of Inflammation Gives Rise to the Acute Phase Response

Signaling cascades induced by the engagement of pattern recognition receptors including TLRs on macrophages further enhance inflammation by inducing the activation of transcription factors such as NF-κB and the production of cytokines such as IL-1β and IL-6. Along with TNF-α, IL-1β and IL-6 are considered to be some of the most prominent proinflammatory cytokines produced during the innate immune response. Together, the three cytokines exert both localized and systemic effects to enhance the inflammatory response. IL-1β like TNF-α also acts on endothelial cells and promotes vasodilation. IL-6, and to a lesser effect IL-1β and TNF-α, promotes the **acute phase response**. This refers to a dynamic change in the profile of dozens of serum proteins that are secreted by hepatocytes in the liver. The concentrations of these proteins changes significantly, with proteins such as albumin (which is the most abundant plasma protein) decreasing while those of others such as **C-reactive protein (CRP)** and serum amyloid A increasing over a hundred-fold. The latter are referred to as acute phase proteins and their levels can be directly correlated to the intensity of inflammation. One of these, CRP, is also a trigger of the classical pathway of complement activation.

IL-1β, IL-6, and TNF-α also exert systemic effects. One of these effects includes actions on the temperature control sites of the hypothalamus as well as on fat and muscle cells, with the net effect of altering energy mobilization and raising the body temperature. These cytokines are therefore also referred to as pyrogens. The raised body temperature not only inhibits the growth of pathogens, but also enhances the effects of adaptive immunity.

Macrophages and Neutrophils Destroy Pathogenic Bacteria via Phagocytosis

Phagocytosis of extracellular bacteria by macrophages induces the release of CXCL8 and the eventual recruitment of neutrophils to the infected site. Neutrophils act as first responders and are extremely effective at killing and destroying extracellular bacteria. The responding neutrophils secrete a battery of toxic mediators and degradative enzymes stored in their granules which are extremely destructive to pathogens. The process of pathogen destruction begins with phagocytosis, subsequent to which pathogens are subjected to granule contents of many different types (Fig. 1.6).

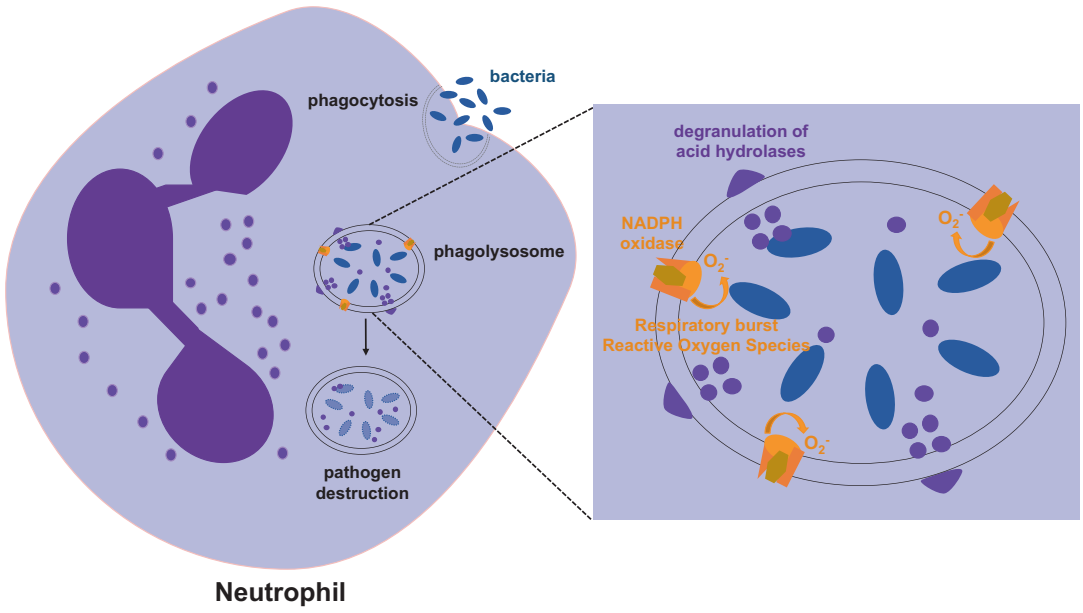


Fig. 1.6 Neutrophil microbicidal functions. Bacterial endocytosis in neutrophils results in activation of the NADPH oxidase, leading to the production of reactive oxygen species in phagolysosomes and ultimately resulting in bacterial cell death (figure contributed by Jeremy P. McAleer)

One hallmark of pathogen destruction by neutrophils is the induction of the respiratory burst. This involves the activity of enzymes such as NADPH oxidase which raises the pH in the cell and induces the release of a number of toxic oxides and superoxides. These reactive oxygen species enhance the activity of several degradative enzymes and antimicrobial peptides, which cause the death of the pathogen. Eventually the pathogen is completely degraded in the phagolysosome by the action of acid hydrolases. Once the pathogen is destroyed, the neutrophil is spent and also dies. The accumulation of dead neutrophils leads to the formation of pus.

Innate Immunity to Viruses Is Mediated by Natural Killer Cells

In contrast to bacterial infections, infection of cells with viruses induces the recruitment and activation of natural killer cells. Macrophages release **IL-12**, which together with TNF-α, has the ability to activate natural killer cells. However, the most potent activators of NK cells are **type I interferons** which are produced by all cells when infected with viruses, and produced prodigiously by epithelial cells and **plasmacytoid dendritic cells**. The latter, which are different from conventional dendritic cells, are also referred to as **interferon producing cells,** since they can produce a thousand times more type I interferon compared with epithelial cells.

The two main types of type I interferons are **IFN-α** and **IFN-β**. These are produced as soon as a cell is infected and promote what is termed as the **interferon response**. The net effect of the interferon response is to enhance viral resistance in infected cells, upregulate the expression of ligands that bind receptors on NK cells, and promote the activation of NK cells.

NK cells are potent killers of virally-infected cells. They are large granular lymphocytes which circulate throughout blood in a partially active state, where they are prevented from attacking the body's cells via a delicate balance of engagement of activating and inhibitory receptors present on the NK cell surface. These receptors are stochastically expressed on the surface of NK cells, and different NK cell subsets express different combinations of receptors. Under normal conditions, inhibitory receptors on NK cells bind **major**

histocompatibility class (MHC) I molecules which are expressed on every nucleated cell in the body. This signals the NK cell to not engage its activating receptors and prevents killing of uninfected cells. On the other hand, virally-infected cells downregulate MHC I and upregulate ligands for activating receptors on NK cells. These include **stress proteins** such as MHC Class I related polypeptide sequences A and B (**MIC-A** and **MIC-B**), as well as Rae 1. This alters the delicate balance of receptor engagement on NK cells and triggers their activation. Once activated, NK cells are induced to kill the virally infected cells, through a dedicated program of apoptosis mediated by perforin, granzymes, and caspases. In addition to killing, NK cells also produce a host of cytokines which have deleterious effects on infected cells as well as activate other immune cells. One of these is a potent cytokine called **IFN-γ**, which not only exerts anti-viral effects, but also promotes the degradation of the pathogen in antigen presenting cells, and enhances their ability to stimulate the activation of T cells. Depending on the type of response, other cytokines are also produced by specific subsets of NK cells, mimicking the types of cytokines produced by T cell subsets during the adaptive immune response.

Dendritic Cells Initiate the Development of Adaptive Immune Responses

While the major effect of cells such as macrophages, neutrophils, and NK cells is to terminate the pathogen at the site of infection and amplify the effects of the innate immune response, another innate immune cell serves a dual purpose, which is to initiate the activation of the adaptive immune response.

Like macrophages, dendritic cells (DCs) at sites of infection also conduct phagocytosis and release proinflammatory cytokines. However, their major function in immunity is to initiate the activation of naïve or uncommitted T cells to the particular pathogen. Immature DC at sites of infection phagocytose the pathogen and degrade it in either the proteasome or the phagolysosome depending on the type of infection. This results in the production of a number of peptides which may serve as antigenic triggers to activate naïve T cells. Loaded with this cargo of peptides, immature DC travel from infected sites to the draining lymph nodes or the spleen, where they encounter circulating naïve T cells that are moving through the organs. In the process of migration, DCs undergo a change in phenotype, acquiring and upregulating ligands that enhance their ability to activate a naïve T cell. Upon reaching the **lymph node** or **spleen**, the DC is now said to be a mature DC that is capable of initiating T cell activation.

The Adaptive Immune Response

While the primary purpose of the innate immune response is to limit the spread of the infection as much as possible while also paving the way for the adaptive immune response, the goal of the adaptive immune response is to mount a specific, targeted response that completely destroys the pathogen and ensures that the host is never again subjected to infection with the same pathogen (Fig. 1.7).

Principles of the Adaptive Immune Response

The adaptive immune response is mediated by T cells, B cells, and their various mediators such as cytokines and antibodies. The first time an adaptive immune response is mounted against a specific pathogen, it is called the **primary immune response**. Subsequent responses are termed as **secondary responses**. The secondary response is mediated by **memory** T cells and B cells which have formed a memory of the pathogen through the first encounter. The memory response is of much greater magnitude than the primary response, often resulting in termination of the infection without the development of any clinical symptoms.

The development of the adaptive response hinges on the principle of clonal selection and the expansion of T cells and B cells to the specific pathogen. Unlike innate cells, these cell types do not simply recognize the presence of patterns on pathogen surfaces. Rather, every single activated T or B cell is committed to the recognition of a unique **antigen** or **epitope** that is

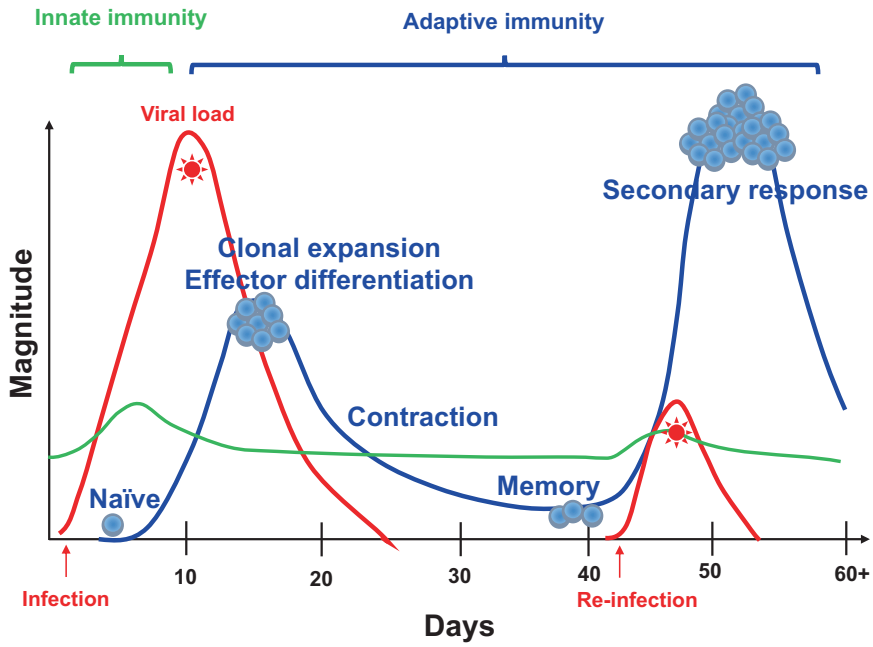


Fig. 1.7 Kinetics of anti-viral immune responses. This diagram outlines the time course of a virus infection and the relative magnitude of subsequent immune responses. Once viruses breach epithelial barriers, there is an incubation period in which symptoms from the infection have not yet occurred. During the next few days, viruses will undergo replication in host cells and begin to infect neighboring cells. The peak of viral replication may occur 7–10 days following initial exposure (red line), with levels declining over the next week or so, until the infection is cleared. The innate immune system is the first line of defense and includes macrophages, neutrophils, dendritic cells, NK cells and complement. The innate immune system can respond within hours following infections to initiate a type I interferon response. While this is important for controlling pathogen load, the magnitude of the innate response is not sufficient to clear the infection (green line). Adaptive immune responses take about a week to develop because they depend on the outgrowth of a single antigen-specific lymphocyte (T cell, B cell; blue line). Lymphocytes that have not yet encountered their antigen in lymph nodes are referred to as naïve. Following their activation by virus antigens, lymphocytes undergo a phase of clonal expansion in which one cell proliferates several times to become a population of thousands of lymphocytes that all recognize the same antigen. Clonal expansion is linked to their effector differentiation, in which lymphocytes acquire the ability to inhibit viral replication and/or dissemination, as described in Chap. 3. Therefore, clonal expansion coincides with the initial decrease observed in viral loads. Following expansion, there is a contraction phase in which most of the effector lymphocytes undergo apoptosis. A small population of memory cells persists, capable of mounting a rapid response to a second infection with the same virus. Memory cells live for several years within the individual (figure contributed by Jeremy P. McAleer)

derived from the pathogen. Recognition of this antigen allows the T or B cell to recognize the entire pathogen and mount a targeted response. The only antigens recognized by T cells are peptides that have been derived from degradation of a pathogen in an antigen presenting cell. In contrast, B cells recognize all sorts of antigens including peptides, glycoproteins, polysaccharides, and other types of pathogen components. Clonal selection refers to the process by which naïve T cells or B cells are selected to become specific to the particular pathogen. Once a naïve cell is activated to the specific antigen, it then divides into hundreds of similarly activated clones which now act against the pathogen and mediate its destruction.

The Lymphatic System

The first step in the initiation of the adaptive immune response is the antigen-specific activation of a naïve T cell to the offending pathogen. **Naïve** T cells along with naïve B cells circulate

throughout lymphoid organs, carried by a complex network of vessels connecting the blood and lymphatic system. The lymphatic system consists of an anastomosing network of lymphatic vessels which originate in connective tissues and collect the extracellular plasma or fluid that leaks out of blood vessels, returning it to the heart. This fluid is called the **lymph** and consists of a number of leukocytes which traverse throughout the lymphatic system, making regular stops at lymph nodes situated at intervening junctions in the lymphatics. At any given time, lymphocytes represent the largest population of leukocytes in the lymph, although they are only a fraction of the total lymphocyte population in the body. The vast majority of lymphocytes are present in the lymphoid organs which serve various areas of the body. Of these, the thymus and bone marrow are referred to as primary or central lymphoid organs since this is where T and B cells develop and mature. Activation of naïve lymphocytes typically occurs in the secondary or peripheral lymphoid organs, of which the lymph nodes and the spleen are the most prominent (Fig. 1.8). The lymph nodes collect the fluid draining from an infected site such as the skin or the respiratory tract and serve as an ideal location for the encounter between pathogen and naïve T and B cells. Similarly, the spleen acts as a reservoir for the filtration of blood, removing any damaged or senescent red blood cells. It is therefore uniquely poised to handle the activation of lymphocytes to blood-borne pathogens that directly enter the blood stream or eventually reach the blood. Several other organs can also act as secondary lymphoid organs including the tonsils, adenoids, Peyer's patches, and appendix. In addition, less organized lymphoid tissues referred to as tertiary lymphoid organs are present throughout the respiratory, gastrointestinal and urogenital tracts.

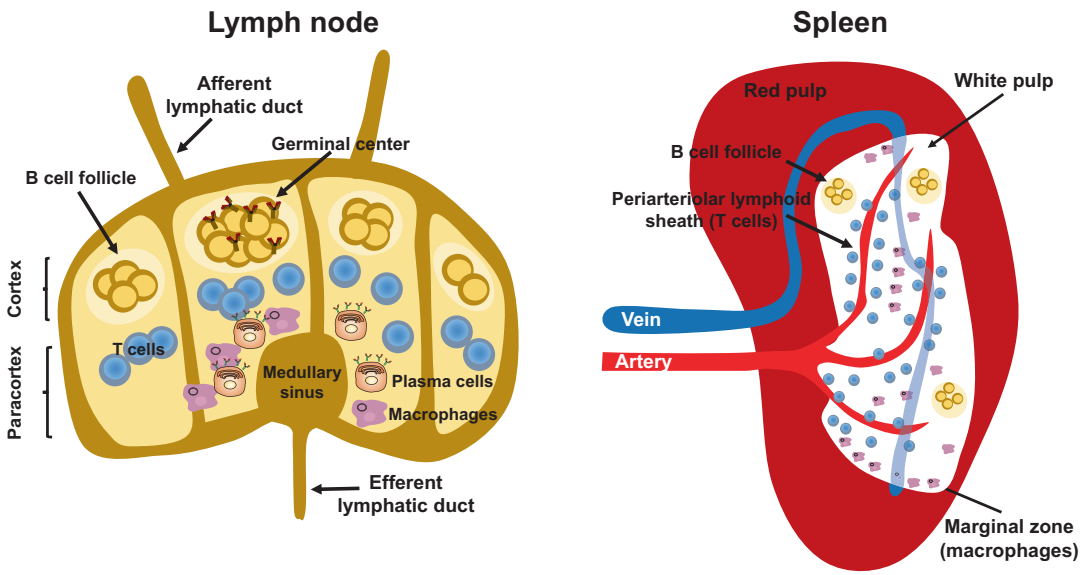


Fig. 1.8 Secondary lymphoid organs. Adaptive immune responses against microorganisms are initiated in lymph nodes and the spleen. These tissues contain organized regions that facilitate interactions between dendritic cells, T cells and B cells, promoting lymphocyte activation against antigens collected in peripheral tissues. In lymph nodes, the paracortical region is populated by T cells, while the outer cortex contains B cells, including germinal centers of activated B cells undergoing clonal expansion. The inner medulla of lymph nodes contains antibody-producing plasma cells and macrophages. Fluid enters lymph nodes through afferent lymphatic vessels, exits through efferent ducts, and ultimately drains into the thoracic duct where it enters the bloodstream. The spleen filters blood and has organized regions termed red pulp and white pulp. The red pulp is a site of red blood cell disposal, while the white pulp contains immune cells. Immune functions of the spleen are similar to that of lymph nodes, with the primary difference being that the spleen collects cells and antigens from blood rather than lymph fluid (figure contributed by Jeremy P. McAleer)

The Activation of Naïve Lymphocytes Occurs in Secondary Lymphoid Organs

In the absence of infection or other immune triggers, naïve lymphocytes constantly traverse the lymphatic system, surveying the lymph nodes for the presence of antigen. Antigen is detected by lymphocytes via a single unique receptor expressed on the surface of T cells and B cells. In T cells, this receptor is simply referred to as the T cell receptor or **TCR**. On B cells, the B cell receptor or **BCR** is the **immunoglobulin** molecule. Every T or B cell will only express one type of receptor, which is constrained by the specific antigen to which it binds, thus ensuring that activated T and B cells will only recognize the specific antigen to which it is activated.

Activation of lymphocytes is initiated in the secondary lymphoid organ. Once an infection has ensued, immature dendritic cells at the site of infection capture the offending pathogen and begin the process of pathogen destruction and migration to the secondary lymphoid organ. Depending on the type of pathogen, peptides are generated from pathogen breakdown in either the endoplasmic reticulum or the vesicular system. **Intracellular pathogens** such as viruses are degraded in the immunoproteasome, while **extracellular pathogens** such as pyogenic bacteria are destroyed in the phagolysosome. The process of pathogen destruction and the generation of peptides is termed as **antigenic processing**. Depending on the site of destruction, peptides generated from pathogen breakdown are eventually loaded onto the surface of ubiquitous molecules present in every nucleated cell of the body, called **major histocompatibility complex** or MHC molecules. Two types of MHC molecules are involved in the activation of T cells: MHC Class I molecules, which are required for the activation of CD8 T cells and **MHC Class II molecules** which are required for the activation of CD4 T cells. As the immature DC migrates toward the secondary lymphoid organ such as a lymph node, it begins to downregulate receptors for antigen capture and upregulate receptors that enhance activation of T cells. Of these, the upregulation of MHC molecules loaded with peptides is paramount for T cell activation to occur. In addition, a number of other receptors for ligands on naïve T cells are also highly expressed. The primary purpose of these is to costimulate the naïve T cell to the specific antigen on MHC molecules. Once the mature DC reaches the lymph node, it is now ready to make contact with a naïve T cell.

The Activation and Differentiation of T Lymphocytes Requires Costimulation and Direction from Cytokines

Three steps are involved in the activation of naïve T cells. First, the TCR on naïve T cells makes contact with the peptide antigen on the surface of MHC molecules on the antigen presenting cell. This is an essential first step which commits the naïve T cell to the specific antigen and provides specific identifying information regarding the nature of the pathogen. It can only effectively be carried out by professional **antigen presenting cells** (APCs) such as dendritic cells, macrophages, and B cells and is referred to as **antigen presentation**. A fundamental criterion of antigen presentation is that the TCR on a T cell will only engage the peptide antigen in the context of an MHC molecule on the surface of an APC. In the absence of the MHC molecule, naïve T cells cannot be activated to the peptide antigen. Furthermore, presentation of MHC and peptide on the surface of an APC is critical, since only these cells can provide the necessary **costimulation** to fully activate the naïve T cell. The engagement of costimulatory molecules on the surface of APCs and naïve T cells serves as the second critical step in the process of activation, conveying the sense of potential danger represented by the presented antigen, and gearing the T cell to initiate a program of clonal expansion in response to the antigen. It also ensures that naïve T cells will never be activated in the absence of costimulation, thus preventing the inadvertent activation of T cells to self-antigens expressed by other cells of the body. The most important costimulatory interaction for the activation of naïve T cells occurs between **CD28** on T cells and **B7 family** molecules such as **CD80** or **CD86** expressed on the surface of APCs. In addition, interactions between other costimulatory molecules play a role in the activation of effector or memory

T cells. These include OX40 (CD134) and OX40 ligand (CD252) as well as ICOS (inducible costimulator on T cells) and ICOS ligand. Engagement of the TCR and costimulatory molecules is facilitated by a tight zone of contact called the **immunological synapse** that is established between the APC and T cell. This allows the binding of a number of other receptors that strengthen the interaction between these molecules. The provision of costimulation initiates a signaling cascade that culminates in the activation of the transcription factor **nuclear factor of activated T cells (NFAT)**, which activates the gene for the cytokine IL-2. In the presence of IL-2, the activated T cell is now stimulated to divide and expand, thus completing the third step involved in T cell activation.

Depending on the type of MHC molecule presenting the antigen, activation results in the initiation of either a cytotoxic or helper T cell response. MHC I molecules present to CD8 T cells initiating a cytotoxic response to viral and tumor antigens. MHC II molecules present to CD4 T cells initiating a helper T cell response to bacterial, viral, fungal, parasitic, and other antigens. The helper T cell response is further delineated by the type of helper T cell activated. In general, T_H1 cells are activated to intracellular bacteria, T_H2 cells to parasitic antigens, and T_H17 cells to extracellular bacteria and fungi. However, in addition to their specified roles in host defense, these subsets exhibit a great degree of versatility and may be induced to perform overlapping and complementary functions depending on the type of antigenic stimulus and the cytokine microenvironment. Additional T helper subsets include follicular helper T cells (T_{FH}) which play a critical role in the secondary lymphoid organs in initiating the activation of naïve B cells. Regulatory T cells (T_{regs}), another type of CD4 T cell, suppress inflammatory responses once the infection is terminated.

Activation of Naïve B Cells

The second step in the development of the adaptive immune response is the activation of naïve B cells to the respective antigen. The recognition of antigen by B cells occurs via the immunoglobulin receptor expressed on its surface. The initial process of recognition involves binding via IgM and other coreceptors expressed on the surface of a B cell, resulting in receptor-mediated endocytosis of the pathogen. Unlike T cells, B cells are not constrained by the recognition of a specific peptide antigen and can recognize various types of macromolecules. Further activation of the B cell requires interactions between the antigen-specific B cell and a similarly activated antigen-specific helper T cell in the secondary lymphoid organ. The B cell presents a peptide antigen on the surface of MHC II to the CD4 T cell and costimulation is provided in the form of **CD40** molecules on the B cell which bind to CD40 ligands **(CD40L)** on the responding T cell. This causes the helper T cell to secrete the cytokines IL-4, IL-5, and IL-6, which stimulate the differentiation and division of B cells into effector, memory, and antibody-producing **plasma B cells**. Helper T cell cytokines also cause B cells to go through a program of antibody refinement, wherein B cells are induced to enhance the quality of their antibodies through repetitive mutations (**somatic hypermutation**), switch their antibody isotype to IgG, IgA or IgE (**isotype switching**), and increase the affinity of their antibodies to the antigen (**affinity maturation**). This ensures that activation results in the production of high affinity antibodies that are aimed at completely destroying the pathogen and terminating the infection. This is accomplished via three distinct mechanisms: **neutralization**, **opsonization**, and **antibody-dependent cellular cytotoxicity (ADCC)**.

Antibodies Are the Highly Specialized Weapons of Adaptive Immunity

Neutralization involves binding of antibodies to the respective antigen or pathogen, prior to cellular entry, thus preventing it from infecting or damaging the cell (Fig. 1.9). An example of neutralization is the binding of antibodies to bacterial toxins preventing their attachment and entry into a target cell. In opsonization, antigen-binding antibodies initiate phagocyte-mediated destruction by binding to antibody or complement receptors on the surfaces of macrophages, dendritic cells, or neutrophils. Lastly, ADCC is mediated by immune

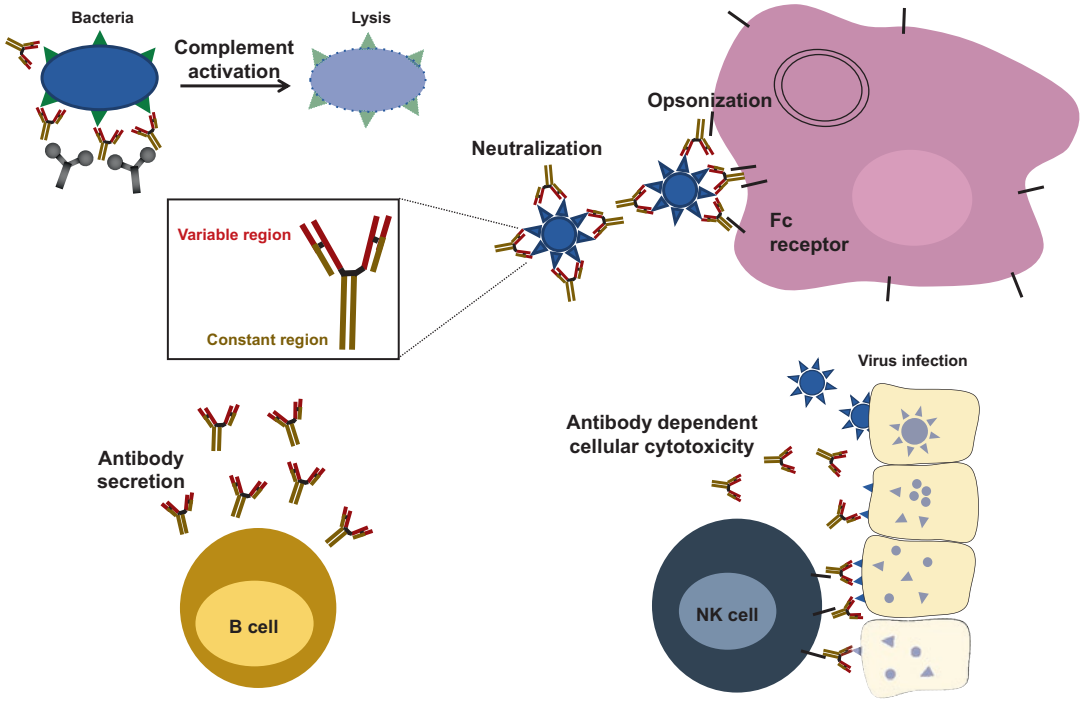


Fig. 1.9 Role of antibodies in host defense. Antibodies produced by B cells have a variable region for antigen binding and constant region that determines antibody function. Antibodies can neutralize pathogens or toxins by preventing their attachment to host cell surfaces. Antibodies attached to bacteria can activate the classical complement pathway, leading to lysis. Macrophages and NK cells, among other cell types, express Fc receptors that recognize constant regions of antibodies. This facilitates the uptake of antibody-coated pathogens by macrophages (opsonization) and the attack of virus-infected cells by NK cells (antibody-dependent cellular cytotoxicity) (figure contributed by Jeremy P. McAleer)

complexes of antigen and IgG molecules bound to IgG receptors on NK cells, triggering their activation and cytotoxic activity. Depending on the type of antigen, different types of antibodies are produced. IgM is the first antibody to be produced during an adaptive response. It is secreted as a pentamer and is very effective at complement activation. However, because of its large size, it is unable to enter many tissues. IgG is the most abundant antibody isotype present in circulation. It is very effective at neutralization, opsonization, and complement activation. Dimeric IgA is the most abundant antibody produced at mucosal surfaces and plays a critical role in mucosal immunity. Lastly, high levels of IgE are produced during infection with parasites such as helminth worms.

The production of high quality antibodies aimed at terminating the infection represents the peak of the adaptive immune response and typically occurs approximately 1 week after the onset of infection. At this time, elevated numbers of antibodies may be found in the sera of infected individuals. Depending on the type of dominating helper T cell response, some types of antibodies may predominate over others. For example, IgG1 and IgE antibodies are typically by-products of a T_H2-type response, whereas in T_H1-mediated responses, IgG2a antibodies predominate.

As the immune response progresses, the quality of antibodies continues to improve. This is a result of numerous changes in the antigen-binding portion or variable region of the antibody molecule, and its primary purpose is to increase the overall binding and effectiveness of the antibody. One process called somatic hypermutation involves the generation of successive mutations in the complementarity determining regions (CDR)s of the antigen-binding site. The purpose of this mutation is to increase the binding of the antibody for the antigen. Similarly,

transcriptional changes in IgM molecules result in switching of the IgM isotype of antibody to either the IgG, IgA, or IgE isotype. Lastly, processes such as affinity maturation increase the individual affinity of the antibody molecule and contribute to the strength or avidity of the overall binding. As such, successive exposures with the antigen exponentially increase the overall number and quality of the antibodies produced.

The Successful Outcome of the Adaptive Immune Response Results in Termination of the Infection

The combined actions of antibodies as well as effector T and B cells serves to eventually clear the infection from the patient. This changes the dynamics of the infection from one in which the pathogen predominates to one controlled by the immune system. As the numbers and effects of the pathogens subside, a dramatic improvement in the patient's condition occurs and the patient begins to experience relief from infection-associated symptoms. Control of the infection is also accompanied by the induction of several populations of regulatory cells, whose purpose is to aid in the resolution of inflammation, prevent inadvertent responses, and spur on the process of healing. Of these, CD4-positive regulatory T cells play a pivotal role in the suppression of unwanted T cell responses and the resolution of inflammation. Similarly, as the populations of effector T cells and B cells dwindle, subsets of antigen-specific memory T and B cell populations continue to persist and clones of these cells are retained interminably, poised to encounter a repeated strike by the same pathogen. When such a strike does occur, these cells are readily activated, mounting a rapid, potent memory T or B cell response that completely eliminates the pathogen before it has had a chance to initiate the process of infection.

Pharmacological Approaches to Treating Inflammation

Although the singular purpose of inflammation is to target and eliminate a perceived threat such as a pathogen, injury, or danger to the host, at the height of inflammation, most individuals are left feeling utterly feeble and helpless. In the midst of a high fever, patients often experience weakness, lethargy, fatigue and other symptoms that are geared toward encouraging the patient to rest so that the body's resources and energy may be expended toward the goal of eliminating the infection. This is also accompanied by other symptoms such as chills, muscle weakness, shivering, and organ-associated symptoms that contribute to the deterioration of the patient's health and overall malaise. In the presence of chronic inflammation, inflammation often continues to persist at a subclinical level, and contributes to fibromyalgia, pain, and decline in health of the patient. As such, a number of drugs have been developed with the aim of subduing inflammation or reducing some of the symptoms associated with it, without sacrificing the overall effectiveness of the immune response.

Drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, ibuprofen, and naproxen have been used for quite some time to bring about an overall reduction in pains and aches all over the body. These drugs act by typically targeting intermediaries in the inflammatory pathways such as enzymes that act on nerve cells and induce pain. Similarly, other drug classes such as **corticosteroids** mediate an overall suppression of the immune response, resulting in attenuation of inflammation-associated pain and pathology. More recently, advances in basic science research have resulted in fundamental breakthroughs regarding our understanding of the immunologic basis of many diseases, elucidating several new and selective targets for therapeutic purposes. These include among others cytokines, chemokines and their receptors, signaling molecules, mediators involved in leukocyte trafficking, and cellular targets such as activated T and B cells. Similarly, a number of drugs that can stimulate the immune response have also been developed for some diseases. A short description of the different types of drugs is provided below. Table 1.2 summarizes the present list of immunotherapeutic drugs approved by the Food and Drug Administration (FDA) for the treatment of many diseases.

Table 1.2 Currently available drugs used in the treatment or modulation of inflammation (table contributed by Doreen E. Szollosi, Jeremy P. McAleer and Clinton B. Mathias)

Drug	Target/action	Chapter(s)
Abatacept (Orencia®)	CTLA-4 fusion protein, Selective T-Cell Costimulation inhibitor	3, 7
Adalimumab (Humira®)	Anti-TNF-α monoclonal antibody	2, 5–7
Aldesleukin (Proleukin®)	Recombinant Interleukin-2	3, 10
Alefacept (Amevive®)	CD2 inhibitor, discontinued	5
Alemtuzumab (Lemtrada®)	Anti-CD52 monoclonal antibody, leukocyte depletion	7, 8
Anakinra (Kineret®)	IL-1 receptor antagonist	2, 7
Antithymocyte globulin (Thymoglobulin®)	Polyclonal rabbit anti-thymocyte globulin	7, 8
Apremilast (Otezla®)	Phosphodiesterase (PDE) 4 inhibitor	5
Atezolizumab (Tecentriq®)	Anti-PD-L1 monoclonal antibody, checkpoint inhibitor	3, 10
Avelumab (Bavencio®)	Anti-PD-L1 monoclonal antibody, checkpoint inhibitor	10
Axicabtagene ciloleucel (Yescarta™)	CAR-T cell therapy	10
Azathioprine (Imuran®, Azasan®)	Purine analog, anti-proliferative agent	5–8
Balsalazide (Colazal®)	5-aminosalicylate, anti-inflammatory	6
Baricitinib (Olumiant®)	Janus kinases (JAK) inhibitor	7
Basiliximab (Simulect®)	Anti-IL-2 receptor monoclonal antibody	3, 7, 8
Belatacept (Nulojix®)	CTLA-4 fusion protein, Selective T cell costimulation inhibitor	3, 8
Belimumab (Benlysta®)	Anti-B lymphocyte stimulator (BLyS; BAFF) monoclonal antibody	3, 7
Benralizumab (Fasenra®)	Anti-IL-5R monoclonal antibody	3, 4
Bevacizumab (Avastin®)	Anti-VEGF monoclonal antibody	10
Blinatumomab (Blincyto®)	Anti-CD19/CD3 monoclonal diabody	10
Brentuximab vedotin (Adcetris®)	Anti-CD30 monoclonal antibody conjugated to an antineoplastic agent	10
Brodalumab (Siliq™)	Anti-IL-17 receptor monoclonal antibody	3, 5, 7
Budesonide (Entocort)	Glucocorticoid receptor activation, anti-inflammatory	4, 6
Canakinumab (Ilaris®)	IL-1 receptor antagonist	2, 7
Certolizumab pegol (Cimzia®)	Anti-TNF-α antibody fragment	2, 5, 7
Cetuximab (Erbitux®)	Anti-EGFR monoclonal antibody	10
Cromolyn sodium	Inhibitor of mast cell degranulation	4
Cyclophosphamide (Cytoxan®, Procytox®)	Alkylating agent of the nitrogen mustard type	7, 8
Cyclosporine (Neoral®, Sandimmune®)	Calcineurin Inhibitor	3, 5–8
Daclizumab (Zenapax®, Zinbryta®)	Anti-IL-2 receptor monoclonal antibody, both brands discontinued	3, 8
Daratumumab (Darzalex®)	Anti-CD38 monoclonal antibody	10
Darbepoetin (Aranesp®)	Erythropoietin (long-acting)	10
Denosumab (Xgeva®, Prolia®)	Anti-RANKL monoclonal antibody	10
Dimethyl fumarate (Tecfidera®)	Immunomodulatory	7
DTaP vaccine (Daptacel®, Infanrix®)	Inactivated vaccine, diphtheria, tetanus, acellular pertussis	9
Dupilumab (Dupixent®)	Anti-IL-4Rα monoclonal antibody	3–5
Durvalumab (Imfinzi®)	Anti-PD-L1 monoclonal antibody	10
Elotuzumab (Empliciti)	SLAMF7-directed immunostimulatory antibody	10
Eltrombopag (Promacta®)	Thrombopoietin receptor agonist	10
Epoetin (Epogen®, Procrit®)	Erythropoietin	10
Etanercept (Enbrel®)	Anti-TNF-α fusion protein	2, 5–8
Everolimus (Afinitor®)	mTOR inhibitor, anti-proliferative agent	8
Filgrastim (Neupogen®)	G-CSF	10
Fingolomod (Gilenya®)	Immunomodulatory	7

(continued)

Table 1.2 (continued)

Drug	Target/action	Chapter(s)
Fluticasone	Glucocorticoid	4, 7
Glatiramer acetate (Copaxone®)	Immunomodulatory	7
Golimumab (Simponi®)	Anti-TNF-α monoclonal antibody	2, 5–7
Guselkumab (Tremfya®)	Anti-IL-23 monoclonal antibody	5, 7
Hepatitis A vaccine (Havrix®)	Inactivated (Viral) Vaccine	9
Hepatitis B vaccine (Recombivax Hb®, Engerix-b®, Heplisav-B®)	Inactivated (Viral) Vaccine	9
Hepatitis A, Hepatitis B combo vaccine (Twinrix®)	Inactivated (Viral) Vaccine	9
Herpes zoster vaccines (Zostavax®, Shingrix®)	Live attenuated vaccine (Zostavax®)	9
	Recombinant (Shingrix®)	
HPV vaccine (Gardasil-9®)	Inactivated (viral) vaccine	9
Hydrocortisone	Glucocorticoid	4, 5, 7
Hydroxychloroquine (Plaquenil®)	Anti-protozoan Agent + Anti-rheumatic (immunosuppressant, exact mechanism unknown)	7
Ibritumomab tiuxetan (Zevalin®)	Anti-CD20 monoclonal antibody + radioimmunotherapy	10
Imiquimod (Aldara®, Zyclara®)	TLR7 agonist	10
Infliximab (Remicade®)	Anti-TNF-α monoclonal antibody	2, 5–7
Influenza vaccines (various brands)	Inactivated influenza virus vaccine	9
	Live attenuated influenza vaccine, or	
	Recombinant influenza vaccine	
Interferon alfa-2b (Intron A®)	Interferon	6, 10
Interferon beta-1a (Avonex®, Rebif®) pegylated (Plegridy®)	Type 1 Interferon	2, 6, 7
Interferon beta-1b (Betaseron®)	Type 1 Interferon	6, 7
Interferon gamma-1b (Actimmune®)	Type 2 Interferon	7
Intravenous immune globulin, IVIG (Gammagard®), SCIG (Vivaglobin®)	Polyclonal IgG Immune Globulin, for antibody reconstitution or suppressing hyperacute organ rejection	6–8
Ipilimumab (Yervoy®)	CTLA-4 antagonist	10
Ixekizumab (Taltz®)	Anti-IL-17 monoclonal antibody	3, 5, 7
Leflunomide (Arava®)	Pyrimidine synthesis inhibitor	7
Lenalidomide (Revlimid®)	IMiD[a]/immunomodulator	10
MMR/MMRV vaccines	Live attenuated vaccines for measles, mumps, and rubella. MMRV includes varicella	9
Meningococcal vaccines	Conjugate, polysaccharide, or protein vaccine	9
Mepolizumab (Nucala®)	Anti-IL-5 monoclonal antibody	3, 4
6-Mercaptopurine	Purine analog, anti-proliferative agent	5, 6
Mesalamine (Asacol®, Canasa®, Lialda®, Pentasa®, Rowasa®)	5-aminosalicylate, anti-inflammatory	6
Methotrexate (Rheumatrex®)	Purine and pyrimidine synthesis inhibitor, anti-proliferative agent	5–7
Methoxy polyethylene glycol-epoetin beta (Mircera®)	Erythropoietin (long acting)	10
Methylprednisone	Glucocorticoid	4, 5, 7
Mitoxantrone (Novantrone®)	Immunomodulatory	7
Moxetumomab pasudotox (Lumoxiti®)	Anti-CD22 monoclonal antibody	10
Muromonab (Orthoclone OKT3®)	Anti-CD3 monoclonal antibody, discontinued	3, 8
Mycophenolate mofetil (CellCept®)	Inhibitor of inosine-5′-monophosphate dehydrogenase, anti-proliferative agent	7, 8

(continued)

Table 1.2 (continued)

Drug	Target/action	Chapter(s)
Natalizumab (Tysabri®)	Anti-$\alpha_4\beta_1$ integrin monoclonal antibody	2, 6, 7
Necitumumab (Portrazza®)	Anti-EGFR monoclonal antibody	10
Nivolumab (Opdivo®)	Anti-PD1 monoclonal antibody, checkpoint inhibitor	3, 10
Obinutuzumab (Gazyva®)	Anti-CD20 monoclonal antibody	3, 10
Ocrelizumab (Ocrevus®)	Anti-CD20 monoclonal antibody	3, 7
Ofatumumab (Arzerra®)	Anti-CD20 monoclonal antibody, B cell death	3, 10
Olsalazine (Dipentum)	5-aminosalicylate, anti-inflammatory	6
Omalizumab (Xolair®)	Anti-IgE monoclonal antibody	4
Oprelvekin (Neumega®)	Recombinant IL-11	10
Palivizumab (Synagis®)	Respiratory syncytial virus monoclonal antibody	1
Panitumumab (Vectibix®)	Anti-EGFR monoclonal antibody	10
PCV (Prevnar 13®)	Pneumococcal conjugate vaccine	9
Pegfilgrastim (Neulasta®)	Pegylated G-CSF	10
Peginterferon alfa-2a, 2b (Pegasys®, Pegintron®, Sylatron®)	Covalent conjugate of recombinant alfa-2a, 2b interferon	2, 10
Pembrolizumab (Keytruda®)	Anti-PD-1 monoclonal antibody, checkpoint inhibitor	3, 10
Pentostatin (Nipent®)	Adenosine deaminase inhibitor, anti-proliferative agent	8
Pertuzumab (Perjeta®)	Anti-HER2 monoclonal antibody	10
Pimecrolimus (Elidel®)	Calcineurin inhibitor	5, 6
Pomalidomide (Pomalyst®)	IMiD[a]/Immunomodulatory	10
PPSV23 (Pneumovax 23®)	Pneumococcal polysaccharide vaccine	9
Prednisone/prednisolone	Glucocorticoid/anti-inflammatory	4–7
Ramucirumab (Cyramza®)	Anti-VEGFR1 monoclonal antibody	10
Rh_o(D) Immune Globulin (Rhogam®)	Anti-D (Rho) immunoglobulin, prevents maternal sensitization against fetal Rho(D) antigens	3, 8
Reslizumab (Cinqair®)	Anti-IL-5 monoclonal antibody	3, 4
Rilonacept (Arcalyst®)	IL-1 receptor inhibitor	2, 7
Rituximab (Rituxan®)	Anti-CD20 monoclonal antibody	3, 7, 8, 10
Romiplostim (Nplate®)	Thrombopoietin analog	10
Sargramostim (Leukine®)	GM-CSF	10
Sarilumab (Kevzara®)	Anti-IL-6 receptor monoclonal antibody	7
Secukinumab (Cosentyx®)	Anti-IL-17A monoclonal antibody	3, 5, 7
Siltuximab (Sylvant®)	Anti-IL-6 monoclonal antibody	2, 7
Sipuleucel-T (Provenge®)	Dendritic cell-based prostate cancer vaccine	10
Sirolimus (Rapamune®)	mTOR kinase inhibitor, anti-proliferative	3, 8
Sulfasalazine (Azulfidine®, Sulfazine®)	5-Aminosalicylic Acid Derivative, anti-inflammatory	6, 7
Tacrolimus (Prograf®, Protopic®)	Calcineurin Inhibitor	3, 5–8
Talimogene laherparepvec (Imlygic®)	Modified *Herpes simplex virus-1* therapy	10
Tdap (Boostrix,® Adacel®)	Toxoid, acellular pertussis vaccine	9
Teriflunomide (Aubagio®)	Immunomodulatory	7
Thalidomide (Thalomid®)	IMiD[a]/Immunomodulatory	6, 10
Tildrakizumab (Ilumya®)	Anti-IL-23 monoclonal antibody	5, 7
Tisagenlecleucel (Kymriah®)	CAR-T cell therapy	10
Tocilizumab (Actemra®)	Anti-IL-6 receptor monoclonal antibody	2, 7, 8
Tofacitinib (Xeljanz®)	Janus kinases (JAK) inhibitor	7
Trastuzumab (Herceptin®)	Anti-HER2 monoclonal antibody	10
Ustekinumab (Stelara®)	Anti-IL-12/IL-23p40 monoclonal antibody	2, 5, 7
Varicella zoster (Varivax®)	Live attenuated varicella zoster virus vaccine	9
Vedolizumab (Entyvio®)	Anti-$\alpha_4\beta_7$ integrin monoclonal antibody, inhibits leukocyte migration	2, 6, 7

[a]*IMiD* immune modulatory imide drug

Inhibitors of Inflammation

Glucocorticoids

Glucocorticoids (corticosteroids) have remained the mainstay of immunotherapy for several decades and are widely prescribed for the treatment of many chronic inflammatory diseases such as asthma and rheumatoid arthritis. They work by inducing a general suppression of the immune system and thereby preventing inflammation-associated pathology. The mechanism of action of glucocorticoids is described in detail in Chaps. 4 and 6. Since glucocorticoids are broadly effective, long-term treatment with systemic corticosteroids is not recommended and is associated with several adverse effects including susceptibility to infections and the development of cancer. However, the use of selective formulations such as inhaled corticosteroids for chronic asthma have proven to be extremely beneficial and effective in the treatment of inflammatory conditions.

Anti-histamines (Histamine Receptor Antagonists)

These are widely available over the counter and used in the symptomatic treatment of diverse conditions including allergies, acidity, sleeplessness and anxiety. They include both competitive inhibitors of histamine as well as inverse agonists of histamine receptors and work primarily by targeting histamine produced by cells such as mast cells, preventing its binding to one of four types of histamine receptors. Induction of histamine signaling can result in the development of vasodilation, vascular permeability and smooth muscle constriction, resulting in symptoms such as coughing, sneezing or itching. Thus, antihistamines provide a temporary resolution of these symptoms by curtailing histamine-induced effects. The mechanism of action of antihistamines is described in Chap. 4.

Anti-eicosanoids

Derivatives of the arachidonic acid pathway such as **prostaglandins** and **leukotrienes** play a vital role in inflammation, inducing a variety of physiological responses such as vasodilation, vascular permeability, smooth muscle reactivity, recruitment of immune cells, thrombosis and gastrointestinal secretion. These derivatives along with other arachidonate metabolites such as thromboxane A_2, lipoxins, and hepoxilins are collectively referred to as eicosanoids. In addition to the above effects, eicosanoids such as prostaglandins contribute to the development of inflammation by inducing both pyrogenic and neurological effects such as fever and pain. A number of widely available agents have been developed to target the effects of both prostaglandins and leukotrienes. These include inhibitors of the enzymes that are necessary for their derivation from arachidonic acid as well as specific leukotriene receptor antagonists. Prostaglandins are synthesized via the cyclooxygenase (COX) pathway of arachidonic acid metabolism, whereas leukotrienes are derived via the 5-lipoxygenase pathway. Both COX 1 and COX2 inhibitors as well as selective COX2 inhibitors are widely available as over-the-counter agents. These include several NSAIDs such as aspirin, ibuprofen, acetaminophen and COX2 inhibitors such as celecoxib (Celebrex®). The NSAIDS and COX2 inhibitors are not discussed further in this book. Inhibitors of leukotriene synthesis and function are also available and are commonly prescribed for the treatment of chronic inflammatory diseases such as asthma. The mechanism of action of leukotriene antagonists is described in detail in Chap. 4.

Calcineurin Inhibitors (Specific Inhibitors of T Cell Function)

The **calcineurin inhibitors cyclosporine** and **tacrolimus** revolutionized the treatment of solid organ and hematopoietic stem cell or bone marrow transplantation. In fact, the advent of cyclosporine in the therapeutics of transplantation is referred to as the cyclosporine era of transplantation. Both cyclosporine and tacrolimus act by suppressing the proliferation of T cells via the inhibition of NFAT activation and the blockade of IL-2 release. Cyclosporine is a peptide antibiotic that binds to cyclophilin, a member of a class of intracellular proteins termed as immunophilins. The cyclosporine-cyclophilin complex then

inhibits the phosphatase calcineurin, which is required for the activation of the T cell specific transcription factor NFAT (nuclear factor of activated T cells). Tacrolimus (FK 506), a macrolide antibiotic, produced by *Streptomyces tsukubaensis*, acts in a similar manner by binding to the immunophilin, FK binding protein. Calcineurin inhibitors are widely used in solid organ and hematopoietic stem cell transplantation and along with glucocorticoids remain the mainstay of therapy. Topical calcineurin inhibitors are also used in the treatment of dermatologic diseases such as atopic dermatitis and psoriasis. The mechanism of action of calcineurin inhibitors is described in Chaps. 5, 7, and 8.

Inhibitors of Proliferation

Sirolimus (Rapamycin) and Everolimus

These drugs also inhibit T cell activation and block the release of IL-2 and other T cell-derived cytokines. Although, like the calcineurin inhibitors, they also complex with an immunophilin, FK506-binding protein 12, their mechanism of action is dependent on the inhibition of the protein kinase, mTOR (molecular target of rapamycin), which is essential for cell growth, proliferation, and metabolism. Both these drugs are mainly used in transplantation therapy.

Mycophenolate Mofetil (MMF)

MMF is semisynthetic derivative of mycophenolic acid (MPA), which is produced by the mold *Penicillium glaucus*. It is a pro-drug that is converted to its active metabolite MPA *in vivo*, which selectively and reversibly inhibits inosine monophosphate dehydrogenase, an enzyme required for the synthesis of guanine nucleotides in T and B cells. The inosine monophosphate dehydrogenase-dependent *de novo* pathway of guanine synthesis is essential for T and B cell proliferation and function, due to the absence of alternative salvage pathways which exist in other cell types. As a result, inhibition of this enzyme by MPA leads to the suppression of T and B cell proliferation and function. MMF is mainly used in transplantation therapy, but is also being considered for therapeutic purposes in rheumatoid arthritis, inflammatory bowel disease, and lupus nephritis.In addition, it is also commonly prescribed off-label for the treatment of systemic lupus erythematosus.

Azathioprine

Azathioprine is a cytotoxic drug that is mainly used for the treatment of solid-organ transplantation. It is a pro-drug that is converted in vivo to 6-mercaptopurine, which is subsequently converted to other derivatives that inhibit *de novo* purine synthesis. This results in the death of stimulated lymphocytes, dampening the induction of T and B cell mediated immunity. Due to its cytotoxic effects, the major toxicity associated with azathioprine is bone marrow suppression resulting in leukopenia, thrombocytopenia, and/or anemia. It is used for the maintenance of renal allografts, and also sometimes in the treatment of rheumatoid arthritis, Crohn's disease, and acute glomerulonephritis associated with systemic lupus erythematosus.

Other Anti-proliferative Drugs

Other anti-proliferative and cytotoxic drugs include **thalidomide**, which inhibits angiogenesis, has anti-inflammatory effects, and is used in the treatment of multiple myeloma and other cancers; **cyclophosphamide**, a cytotoxic agent, which destroys immune cells by alkylating resting and proliferating cells and is used in the treatment of some autoimmune disorders; and pyrimidine synthesis inhibitors such as **leflunomide** and **teriflunomide**, which inhibit the mitochondrial enzyme dihydroorotate dehydrogenase required for pyrimidine synthesis and immune cell function, and are used in the treatment of rheumatoid arthritis and relapsing-remitting multiple sclerosis. In addition, other cytotoxic drugs such as **methotrexate** are also commonly used for various therapeutic purposes.

Biologics

Over the last few decades, revolutionary advances in the understanding of the immunological basis of diseases and molecular and cell biology techniques,

have resulted in the development of several new biologics that specifically target components of immune-mediated pathways such as immune cells, cytokines, cell signaling molecules, and various receptors and their associated ligands. These classes of drugs include monoclonal antibodies, small molecule inhibitors, fusion proteins, and various receptor antagonists.

Monoclonal Antibodies

Since the advent of recombinant DNA technology, various monoclonal antibodies are now therapeutically used for the treatment of a number of diseases. Based on whether they incorporate the variable and/or **complementarity-determining regions (CDRs)** of mouse antibodies, they are referred to as **chimeric** (composed of mouse variable chains), **humanized** (composed of mouse CDR sequences), or **fully human** (consisting of no mouse chains or sequences). The first monoclonal antibodies were produced using **hybridomas** derived from myeloma cell lines, although they are now frequently produced commercially using recombinant DNA technology. The different classes of therapeutic monoclonal antibodies are described more extensively in Chap. 3. Examples of prototypic antibodies belonging to the different classes include **rituximab (Rituxan®)**, a chimeric anti-CD20 antibody used in the treatment of non-Hodgkin's lymphoma, **omalizumab (Xolair®)**, a humanized anti-IgE antibody used in the treatment of asthma, and **adalimumab (Humira®)**, a fully human anti-TNFα antibody used in the treatment of rheumatoid arthritis.

In addition to treatment of inflammatory diseases, a number of monoclonal antibodies targeting various cell surface molecules and pathways have also been developed for the treatment of diverse types of cancers. These include inhibitors of angiogenesis, proliferation, and cell signaling. Examples include **alemtuzumab**, an anti-CD52 antibody that depletes B and T cells and is used for the treatment of B-cell chronic lymphocytic leukemia, **bevacizumab**, which inhibits vascular endothelial growth factor (VEGF) and blocks angiogenesis in tumors, and **trastuzumab**, which blocks the extracellular domain of HER-2/*neu* in breast cancer patients and prevents signaling in HER-2/*neu*-positive tumors. Several monoclonal antibodies are also used to specifically deliver toxins and radioisotopes to tumor cells.

Similarly, monoclonal antibodies that target infectious organisms have also been approved by the FDA. **Palivizumab (Synagis®)** is a humanized neutralizing IgG antibody that is used to prevent respiratory syncytial virus (RSV) infections in children at increased risk of severe disease. This includes children who were born prematurely and are under 6 months of age, and children who may be at high risk of RSV infection due to bronchopulmonary dysplasia or congenital heart disease. The drug is given once a month during RSV season and provides protection by binding an epitope in the F protein subunit of RSV. This results in the inhibition of viral fusion and the prevention of syncytia within the lungs, which are necessary for the intercellular spread of the virus.

T Cell Checkpoint Inhibitors

More recently, a number of T cell specific inhibitors have been developed that selectively inhibit or enhance the activation of T cells for the treatment of non-immune cell cancers. Checkpoint inhibitors such as **anti-PD1** (**pembrolizumab** and **nivolumab**) and **anti-CTLA-4** (**ipilimumab**) enhance T cell activity against tumors by presumably increasing their costimulatory activity (Figs. 10.2 and 10.3). In contrast, the fusion proteins **abatacept** and **belatacept**, which consist of the extracellular domain of human **CTLA-4** fused with the constant regions of IgG, inhibit the costimulation of T cells and dampen T cell activity. The 2018 Nobel Prize in Physiology or Medicine was awarded to Drs. James P. Allison and Tasuko Honjo for their work on T cell checkpoint inhibitors. In addition to the drugs mentioned above, several others have been approved by the FDA for the treatment of various cancers and inflammatory diseases, and others are currently in development.

Cytokine Inhibitors

Insights into immune signaling mechanisms and the cross-talk between various immune cells have led to the development of several drugs that block

cytokine function by inhibiting their binding, signaling, or activity. The first cytokine antagonists to be developed included both monoclonal antibodies and fusion proteins targeting the pro-inflammatory cytokine, TNF-α. These include **infliximab**, **etanercept**, and **certolizumab pegol**. More recently, a number of other cytokine antagonists have been developed targeting various cytokines including IL-1, IL-2, IL-5, IL-6, IL-12 and IL-23, and IL-17. In addition, inhibitors that target the JAK-STAT pathway of cytokine signaling have also been approved by the FDA and others are currently in development. It is also anticipated that several new drugs targeting various cytokines and their signaling pathways will be approved by the FDA in the near future. Presently FDA-approved drugs targeting various cytokines are described throughout this textbook.

Immune Cell Recruitment Inhibitors

The migration of immune cells to various organs is a critical component of inflammatory reactions during chronic inflammatory diseases. As such, a number of drugs have been developed that inhibit the expression or function of adhesion molecules on leukocytes or blood vessels and prevent the migration of effector cells to target tissues. Examples of these drugs include the integrin inhibitors **natalizumab** and **vedolizumab** used in the treatment of multiple sclerosis and Crohn's diseases as well as leukocyte function-associated antigen-1 (LFA-1) inhibitors such as **efalizumab**, which was previously used for the treatment of Crohn's disease, but was subsequently withdrawn.

Immunomodulatory Drugs

Recombinant Cytokines

Interferons

Interferons have been used for therapeutic purposes since as early as the 1980s. While initially studied mainly in the context of anti-viral responses, increasing evidence suggests that they have a number of immunomodulatory effects. These include the enhancement of antigen presentation, phagocytosis, upregulation of MHC Class I and II, and the induction of the immunoproteasome. They are also potent inducers of the antiviral cytotoxic response by both NK cells and cytotoxic T cells. The two main types of interferon that have been extensively studied in humans are both used for immunotherapeutic purposes. These include the type I interferons IFN-α and IFN-β as well as the type II interferon, IFN-γ. The type I interferons are produced by cells such as epithelial cells and plasmacytoid dendritic cells soon after infection and both activate NK cells as well as increase the intensity of anti-viral resistance through a series of molecular and cellular events, which are collectively termed as the interferon response. IFN-γ is produced by both activated NK cells and T cells (T_H1 and CD8 T cells) and further contributes to the antiviral response by inhibiting viral replication and activating various immune cells such as phagocytes. A number of interferon drugs comprising of all three types have been developed for the treatment of several diseases. While their mechanism of action is not always clear, they are therapeutically effective.

IFN-α is used for the treatment of a variety of cancers. These include hairy cell leukemia, malignant melanoma, follicular lymphoma, and Kaposi's sarcoma (seen in patients with AIDS). It is also used for the treatment of chronic hepatitis B and until recently, was also commonly used in conjunction with ribavirin for the treatment of chronic hepatitis C. IFN-β is currently FDA-approved for the treatment of relapsing multiple sclerosis and is used to reduce the frequency of clinical exacerbations. IFN-γ is currently used to reduce the frequency and severity of infections associated with chronic granulomatous disease, which is an immune deficiency resulting in defective phagocytic function due to the absence of NADPH oxidase activity.

Adverse effects associated with interferon therapy include flu-like symptoms such as fever, chills and headaches, gastrointestinal reactions, rash, myalgia, and injection site reactions.

Interleukin-2

IL-2 is a cytokine that is critical for the proliferation and division of T cells and induces their function and activity. Human recombinant IL-2

(**aldesleukin** or **Proleukin®**) is used for the treatment of metastatic renal cell carcinoma and melanoma. It stimulates lymphocytes and enhances their activity against the tumor. Adverse effects include flu-like symptoms as well as a serious but uncommon cardiovascular toxicity resulting from capillary leak syndrome.

Immunization

Immunization used in the prevention of various diseases can be classified as active or passive. **Active immunization** involves the induction of systemic immune responses to specific antigens, and often results in the acquisition of life-long immunity. The most commonly utilized application of active immunization has been the **vaccination** of a population against prevalent infectious pathogens. A number of vaccines described in Chap. 9 are currently in use against a wide variety of bacterial and viral infections. These include diphtheria, pertussis, tetanus, measles, mumps, polio, meningitis (bacterial and viral), chicken pox, shingles, rota viruses, influenza, and human papilloma virus, among others. In addition to protection from infectious organisms, therapeutic vaccines have also been developed or are being considered for other types of diseases. This includes cancer vaccines that utilize various types of cancer antigens (as described in Chap. 10) and vaccines to prevent the development of allergic disorders (as described in Chap. 4).

Passive immunization has also been used for the treatment of diseases and historically has included the transfer of antibodies from both animals and humans to patients. The passive transfer of antibodies is indicated when individuals are unable to make antibodies due to a congenital or acquired deficiency, when exposed to lethal doses of an infectious or toxic agent such as venoms and there is no time for the development of adaptive immunity, or when a particular disease can be ameliorated with the passive transfer of antibodies. Depending on the disease, both non-specific and highly-specific immunoglobulins may be used. Protection typically lasts for 1–3 months, by which time many immune-competent individuals should be able to generate adaptive immune responses. Specific immunoglobulin preparations are available for several diseases including rabies, tetanus, botulism, and respiratory syncytial virus. **Rho(D)** is a specific IgG preparation given to Rh-negative pregnant women for the prophylaxis of hemolytic disease of the newborn in the developing fetus.

Intravenous Immunoglobulin (IVIG)

Non-specific immune globulin is derived from the pooled plasma of thousands of adults and is used for the treatment of a variety of diseases. It mainly consists of IgG molecules and its initial application was primarily for the treatment of antibody deficiencies such as **agammaglobulinemia**. However, more recently, it has been considered for the treatment of several autoimmune diseases, both FDA-approved and off-label. The effects of IVIG are thought to be mediated through a combination of factors. This includes the saturation of both activating and inhibitory **Fc receptor**s for IgG as well as the **FcRn receptor** which enhances the half-life of IgG in serum. This prevents autoantibodies from engaging Fc receptors and inducing phagocytosis. The pooled preparation is also thought to contain anti-idiotypic antibodies, *i.e.* antibodies that bind to other antibodies such as the autoantibodies that exist within the patient. In addition, they may also contain helpful antibodies against B cell proliferation and survival factors, thus shutting down the production of autoantibodies. Lastly, they are thought to downregulate antigen presentation and complement activation.

Allergen Immunotherapy

Allergen immunotherapy or allergen desensitization is an immunotherapeutic procedure that has existed since the early 1900s. It is mostly used in the treatment of allergic diseases with the aim of shifting the immunologic response from a pathologic IgE-dominated response to a protective IgG4-dominant response. The induction of the tolerogenic response is thought to be dependent on the production of immunoregulatory cytokines such as IL-10.

The Adverse Effects Associated with Immunotherapy

As in the case of any type of pharmacological treatment, there exists the potential for the development of both minor and serious, or even life-threatening adverse effects. The development of adverse effects is often correlated with the dose, duration, and route of therapy, but other factors also play a role such as age, gender, and the immune status of the patient. Short-term treatment often results in minimal side effects, which are reversible after the end of treatment. However, long-term treatment may be associated with longer-lasting adverse effects. The immune specificity of the drug is also an important factor. For example, short term treatment with the glucocorticoid, oral prednisone, may result in weight gain, insomnia, fluid retention, and mood changes. However, long-term treatment is associated with osteoporosis, hypertension, weight gain, glaucoma, diabetes, muscle weakness and Cushing syndrome. In contrast, the major effect associated with long-term treatment with calcineurin inhibitors is the development of irreversible nephrotoxicity and impaired renal function. The route of treatment is also an important factor. For example, topical treatment with calcineurin inhibitors is associated with limited toxicities such as the development of rashes associated with herpes simplex virus infections. Similarly, one adverse effect of inhaled corticosteroids is the potential for development of oral candidiasis.

Inhibition of specific types of immune cells or their mediators such as cytokines is often associated with adverse effects relative to the functions of the specific target. For example, inhibition of TNF-α may result in the activation of latent tuberculosis, while the inhibition of IL-17 may result in the occurrence of upper respiratory tract infections or fungal infections. Similarly, enhancement of T cell costimulation for cancer treatment may be associated with the risk for developing autoimmunity. Chronic treatment with almost all immunosuppressive drugs is associated with the risk of development of infections. This is further enhanced in the case of transplantation recipients receiving long-term treatment with a wide variety of immunosuppressive drugs. As such, patients are often advised about the potential for developing infections and closely monitored throughout the duration of therapy. Long-term treatment over several years can also increase the risk of development of cancers such as carcinomas of the skin and genital tract and Kaposi's sarcoma. Transplantation recipients in particular are two to four times more likely to develop these cancers compared to the general population.

Hypersensitivity Reactions to Drugs

Drug hypersensitivities are immune-mediated reactions to drugs. Depending on the type of drug, they may be mediated by IgE or IgG antibodies and often involve the activation of T cells, B cells and phagocytes. Symptoms may range from mild to severe, and may include the development of rash, serum sickness, or in rare cases anaphylaxis.

Many drugs act as haptens that bind to cell-surface molecules, resulting in the formation of immunogenic peptides that stimulate the immune system. For example, in some individuals, penicillin can conjugate with erythrocytes resulting in the production of modified epitopes that stimulate T_H2 cells and induce the production of IgE antibodies. Subsequently treatment with penicillin can induce severe IgE-mediated anaphylactic reactions (**type I hypersensitivity** reactions) that can have fatal consequences. Conversely, the induction of IgG antibodies can trigger the complement-mediated phagocytic destruction of erythrocytes resulting in anemia (**type II hypersensitivity** reactions). Recent findings implicate a single, specific receptor, MrgprX2, on mast cells that is often involved in pseudo-allergic reactions to various drugs.

Some drugs such as large proteins or therapeutic monoclonal antibodies can directly stimulate antibodies resulting in **type III hypersensitivity** reactions and the development of serum sickness. This is often accompanied by fever, chills, rash and vasculitis in the target tissues. The reactions are mediated by immune

complexes of the drug with IgG antibodies and subside when the immune complexes are cleared.

Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a severe reaction to some types of drugs that induces skin necrosis and detachment. The mucus membranes of the eyes, mouth, and genitals are often affected. The onset of SJS/TEN is a significant medical emergency and is life-threatening. The first symptoms include fever and flu-like symptoms, which is followed 1–3 days later by various rashes leading to blistering and peeling of the skin, starting with the face and spreading to other areas of the body. The reaction is triggered by certain medications such as **allopurinol**, anti-epileptics, cancer therapies, and antibiotics and often occur 1–3 weeks after therapy. It may also be triggered by infections. People with a weakened immune system, HIV, a family history of SJS/TEN, and certain polymorphisms in HLA-B are particularly at risk. The reaction is thought to be mediated by activated CD8 T cells which cause the blistering and is considered a **type IV hypersensitivity** reaction. Treatment includes supportive therapy and treatment with cyclosporine, IVIG, plasma exchange, and corticosteroids.

Summary

The immune system plays a critical role in host defense and is required for human survival. The cells of the immune system are generated through the process of hematopoiesis in the bone marrow. Innate immune responses are triggered immediately after infection, injury, or other trauma and involve the activity of various cell types including myeloid cells, granulocytes, and mast cells. These cells in coordination with a number of proinflammatory cytokines initiate host defense and alert the immune system. Neutrophils are efficient defenders of the host against bacterial infections, while NK cells are quick to respond to viral infections. Dendritic cells survey the infectious site for pathogens and act as an important link between the innate and adaptive immune responses. Adaptive immune responses are established several days after infection and mediate specific, potent, and long-lasting responses against pathogenic antigens. Helper CD4 T cells drive the adaptive immune response and differentiate into various subsets depending on the specific type of pathogen. Cytotoxic CD8 T cells are activated against viral and tumor antigens. The activation of T cells and their effector function is dependent on dendritic cells, other antigen presenting cells, and cytokines, which regulate their function. B cells are also activated to pathogenic antigens and produce various antibodies, which can destroy the pathogen. When the infection begins to clear, the adaptive immune response wanes, and memory lymphocytes are generated that persist during life and provide protection against future attacks.

Recent advances in immunology research have significantly enhanced our understanding of the immunological basis of many diseases. Immune cells and their mediators are not only involved in host defense against foreign pathogens, but also play a vital role in maintaining homeostatic integrity and participate in reactions that contribute to the development of either immunity or tolerance. Further investigation of the mechanisms involved in these processes have resulted in the elucidation of several new immune-mediated targets for therapeutic purposes, leading to the development of novel drugs that target the immune system. These drugs belong to various classes inducing immunosuppression, inhibiting proliferation of immune cells, and modulating immune activity. The latter category includes several monoclonal antibodies and other biologics that target specific immune cells and molecules. In addition, several types of drugs also stimulate the immune system. These include various vaccines as well as recombinant cytokines that can activate immune activity against specific targets. It is anticipated that in future years, the complexity of the various interactions between immune cells and their mediators will be further uncovered, leading to the development of even more immunotherapeutic drugs.

Practice Questions

1. Provide three examples each of an innate and an adaptive immune cell and list at least one function of each cell type.

2. Provide examples of how microbiota influence the development of the immune response.
3. Describe the cardinal characteristics of inflammation and explain the immunological mechanisms underlying their development.
4. _____ is a cytokine produced by macrophages that causes the dilation of blood vessels and promotes the recruitment of leukocytes to injured tissues.
   (a) TNF-α
   (b) IL-6
   (c) IL-1β
   (d) IL-5
5. _____ is a chemokine produced by macrophages that enhances the recruitment of neutrophils to injured tissues.
   (a) CXCL8
   (b) Eotaxin
   (c) TNF-α
   (d) IL-5
6. Which of the following represent examples of innate cells that are involved in IgE-mediated immune responses to parasites? Select all that apply.
   (a) T_H2 cells
   (b) Eosinophils
   (c) Basophils
   (d) Neutrophil
7. The_____ is involved in the phagocytosis-mediated killing of bacterial cells by neutrophils.
   (a) activation of NF-κB
   (b) respiratory burst
   (c) release of cytokines
   (d) induction of costimulation
8. _____ is a growth factor required for the generation of eosinophils in the bone marrow. Select all that apply.
   (a) IL-3
   (b) IL-6
   (c) IL-1β
   (d) IL-5
9. What do you mean by the interferon response? How does it affect the activation of NK cells?
10. Explain how cell surface receptors contribute to the NK cell-mediated killing of virally-infected cells.
11. Explain the process involved in the activation of naïve T cells to a novel antigen.
12. Which of the following molecules is expressed by dendritic cells as they migrate towards draining lymph nodes after capture of an antigen?
   (a) CD80
   (b) MHC I
   (c) IL-6 receptor
   (d) CD28
13. The engagement of _____ molecules is a critical second step in the activation of naïve T cells to an antigen.
   (a) TLR
   (b) adhesion
   (c) costimulatory
   (d) inhibitory
14. Describe the various subsets of helper T cells and give one example of their immunological function.
15. Explain the mechanisms by which antibodies combat infectious organisms.
16. _____ is a costimulatory molecule expressed on B cells required for the induction of isotype switching in antibody molecules.
   (a) CD28
   (b) CD40
   (c) ICOS
   (d) PD-1
17. How does somatic hypermutation contribute to the development of the B cell repertoire?
18. _____ is an example of an eicosanoid produced by mast cells after IgE-mediated activation.
   (a) Histamine
   (b) Leukotriene
   (c) Tryptase
   (d) IL-6
19. Which of the drugs below complexes with FK506BP12 and inhibits the actions of mTOR?
   (a) Tacrolimus
   (b) Everolimus
   (c) Cyclosporine
   (d) Abatacept
20. _____ is a drug that inhibits purine synthesis *via* derivatives of 6-mercaptopurine.

(a) Azathioprine
(b) Methotrexate
(c) Cyclophosphamide
(d) IL-5

21. _____ is an example of a drug that inhibits T cell-mediated responses by inhibiting T cell costimulation.
(a) Abatacept
(b) Ipilimumab
(c) Pembrolizumab
(d) Nivolumab

22. _____ is a chimeric monoclonal antibody used in the treatment non-Hodgkin's lymphoma.
(a) Rituxan
(b) Xolair
(c) Humira
(d) Cosentyx

23. Which of the following are examples of inhibitors of TNF-α? Select all that apply.
(a) Etanercept
(b) Infliximab
(c) Adalimumab
(d) Secukinumab

24. Which of the following is an example of an immunotherapeutic drug used in the treatment of metastatic renal carcinoma?
(a) Rituximab
(b) Aldesleukin
(c) Nivolumab
(d) Alemtuzumab

25. _____ is a receptor on mast cells that is involved in pseudo-allergic reactions to drugs
(a) MrgprX2
(b) FcεRI
(c) TLR
(d) Leukotriene receptor D4

26. _____ is an example of a severe hypersensitivity reaction that can develop in some people who are treated with allopurinol.
(a) Type II hypersensitivity reactions
(b) Anaphylaxis.
(c) Steven Johnson syndrome
(d) Serum sickness

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[1]The suggested reading list below was created with the aim of highlighting classic papers in immunology that describe seminal findings in the field of immunology. Many of these discoveries have advanced our current understanding of immunology and medicine and several have resulted in the receipt of the Nobel Prize.

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