

Clinton B. Mathias · Jeremy P. McAleer
Doreen E. Szollosi

Pharmacology of Immunotherapeutic Drugs

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 Springer

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ISBN 978-3-030-19921-0 ISBN 978-3-030-19922-7 (eBook)
<https://doi.org/10.1007/978-3-030-19922-7>

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This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The human immune system is an intricate network of cells and molecules that is critical for our survival and protects our bodies from damage by pathogens, toxins, and other foreign substances. Protection from infection and other injuries prolongs the life of individuals and contributes to their overall health. In contrast, dysregulated immune responses that attack self-antigens or react to harmless substances cause damage to host tissues and induce the development of disease.

Work done by immunologists over the last few decades has revealed a remarkable complexity underlying the mechanisms by which the immune system protects us from infectious organisms while simultaneously avoiding collateral tissue damage. These studies suggest new and hitherto unappreciated roles for many immune cells and molecules in both host protection and disease development, providing novel insights into the mechanisms by which immune cells modulate physiological functions. 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.

These insights and developments have led to the investigation of a number of immune system components as drug targets for therapeutic purposes. Over the years, this has resulted in the approval by the Food and Drug Administration of several immune-modulating drugs for the treatment of diverse diseases ranging from asthma to cancer. These treatments include general immunosuppressants and antiproliferative agents as well as targeted therapies aimed at modulating specific components of the immune system. This latter category includes various biologics, such as monoclonal antibodies, small molecules, and recombinant cytokines. The immunological principles underlying the activity of these drugs as well as their mechanisms of action is increasingly becoming an important component of health sciences education, including professions such as medicine, pharmacy, and nursing.

We wrote *The Pharmacology of Immunotherapeutic Drugs* in order to bridge the gap between basic science and medical education related to disorders of the immune system. While most pathophysiology and pharmacology textbooks aimed at health science students focus on disease pathogenesis and treatments, there is a dearth of textbooks that are devoted to the immunological mechanisms of disease development and their therapeutic treatment. This is important considering the multitude of immunotherapeutic drugs that have

been recently approved for the treatment of a wide variety of diseases. Our book is intended to be a reference for both basic immunologists and clinicians, including medical doctors, pharmacists, and nurses, with the goal of enhancing our understanding of the complexity of the interactions between the immune system and disease. We are not only authors but also teachers, scientists, and lifelong students of immunology who desire to share our passion for immunology with others in the health sciences.

The book opens with a general overview of the immune system, examining the link between inflammation and the onset of disease and providing a synopsis of various pharmacological targets in the context of immunotherapy. While we do cover the basic principles and concepts involved in immunology wherever applicable, it is presupposed that the student will have had prior instruction in basic immunology. A unique feature of this chapter is the inclusion of a comprehensive table listing the various classes and types of immunotherapeutic drugs that are currently approved for the treatment of diseases. Another highlight is a table containing a list of all currently known cytokines and their roles in immune development and function. Lastly, the suggested reading list at the end of Chap. 1 highlights major discoveries in the field of immunology during the last two centuries that have advanced our current understanding of immunology and medicine.

In Chaps. 2 and 3, we build on the preliminary concepts introduced in Chap. 1 and discuss the principles of both innate and adaptive immune processes and their therapeutic modulation. Following this in Chaps. 4, 5, and 6, we focus on inflammatory diseases affecting the major organ systems, such as the respiratory system, the skin, and the gastrointestinal system, and discuss the immunopharmacology of drugs used in their treatment. Similarly, in Chaps. 7 and 8, we cover the basic principles and immune mechanisms involved in autoimmunity and transplantation and discuss the roles of various immunotherapeutic drugs. Lastly, in Chaps. 9 and 10, we discuss the role of immunomodulatory agents in fighting infectious diseases and cancers.

Our book is structured to easily navigate through drug information related to the diseases. Each chapter begins with a table summarizing the drugs discussed in the chapter and their classification. This is followed by a summary of the role of the immune system in health and disease and mechanistic information on how the medications work to treat each disease. In order to provide a historical perspective on drug development, including serendipitous discoveries, trials, and tribulations, “From Bench to Bedside” sections are included at the end of each chapter. Finally, several clinical applications are highlighted in case studies and practice questions that have been added to the chapters.

The development of this textbook has been a long process, and we are grateful to everyone who has played a role in seeing it through completion. We are especially grateful to our family members, who encouraged and supported us in this endeavor throughout the last 2 years. We are also thankful to our colleagues and co-workers, many of whom were willing to review material and provide suggestions and ideas. We are particularly thankful for our coauthors who contributed to chapter material, including Chaps. 7, 9, and 10. A number of students and fellows were willing to read the chapters and make figures and tables. We are grateful for their assistance. We are also thankful to

our colleagues who provided materials for case studies, bench to bedside, and practice questions. Lastly, we are thankful to our editors at Springer, who have provided guidance and direction throughout the process.

Immunology is an important subject, not only for the basic science researchers but also for the clinicians. We hope our book helps to illuminate the therapeutic principles behind immunomodulatory drugs for individuals working in health-care fields across several disciplines.

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Acknowledgments

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Hector Garcia, PharmD
Yamilia Garcia, PharmD
Ana Gomes, PharmD
Ernest Agyemang, PharmD
Christina Petrelis, PharmD
Zara Saqab, PharmD
Heather DeMar

The authors would like to thank the following reviewers for their thoughtful feedback:

Mohammed Manzoor, PharmD
Alexander Levine, PharmD, BCPS
Swetha Rudraiah, PhD
Junjiang Sun, MD
A.R.M. Ruhul Amin, PhD
Thomas Wadzinski, MD, PhD
Morgan Reynolds, PharmD, CDE
James Knittel, PhD
Diptiman Bose, PhD

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Overview of the Immune System and Its Pharmacological Targets

1

Clinton B. Mathias

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

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-1 α and IL-1 β	IL-1R type 1 and type 2	Macrophages, lymphocytes, neutrophils, keratinocytes, fibroblasts, other cells	Proinflammatory cytokine; can act as pyrogen; involved in T _H 17 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 _H 2 cells, basophils, mast cells, eosinophils, NKT cells, $\gamma\delta$ T cells	T _H 2 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 _H 2 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 _H 2 cells, T _H 9 cells, T _H 17 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 _H 2 cells, T _{reg} cells, T _H 1 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-11R α 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-12R β 1 and IL-12R β 2	Macrophages, neutrophils, DCs, B cells, other cells	Development and maintenance of T _H 1 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-13R α 1 and IL-4R α) and type II (IL-13R α 2)	T _H 2 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 $\gamma\delta$ 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 _H 17 cells, CD8 T cells, $\gamma\delta$ 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 _H 2 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 _H 9 cells, T _H 17 cells, NKT cells	B cell proliferation and survival; NKT cell proliferation; T cell growth
IL-22	IL-22R	Activated T _H 17 cells, T _H 22 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 _H 17 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 _H 2 cells, mast cells, eosinophils, basophils, epithelial cells	Alarmin cytokine; Induction of T _H 2 responses; production of IgE, IL-4, IL-5, IL-13; inhibition of T _H 1 and T _H 17 responses
IL-26	IL-10R2 chain and IL-20R1 chain	Activated T _H 17 cells, NK cells, memory T cells	Regulation of epithelial cells
IL-27	IL-27R α and gp130	Activated macrophages, DCs, and epithelial cells	Control of differentiation of helper T cell subsets; T _H 1 differentiation; induction of T-bet; inhibition of T _H 17 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 _H 1 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/OSMR β^a	T _H 2 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 _H 2, 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-12R β 2/gp130; IL-12R β 2/IL-12R β 2; 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-18R α 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 _H 17 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 _H 1 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-7R α chain	Fibroblasts, epithelial cells, stromal cells	Stimulates DCs and T _H 2 responses
Transforming growth factor (TGF)- β	T β R I and T β R 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

^aBCMA B-cell maturation antigen, CRLF2 cytokine receptor-like factor 2, OSMR β 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 presenta-

tion, 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

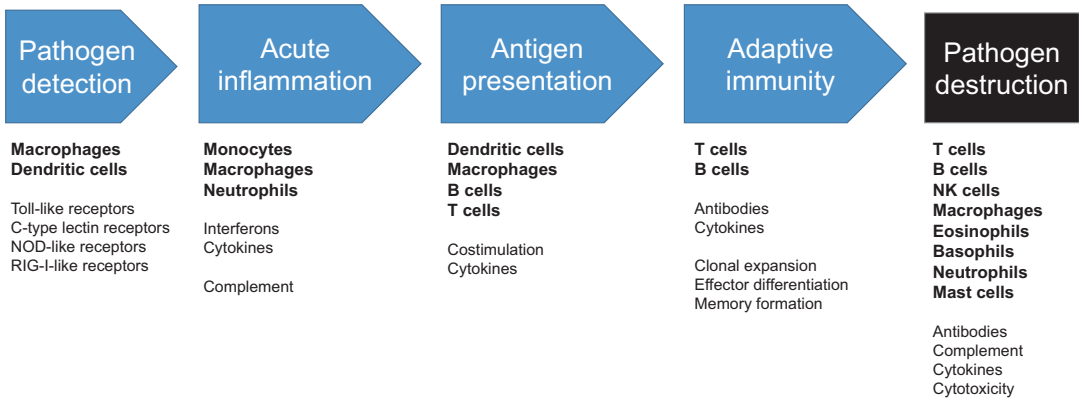


Fig. 1.1 Immune responses against pathogenic microorganisms occur in five stages, culminating in pathogen destruction. Examples of cell types, receptor interactions and/or immune checkpoints are indicated for each stage (figure contributed by Jeremy P. McAleer)

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.

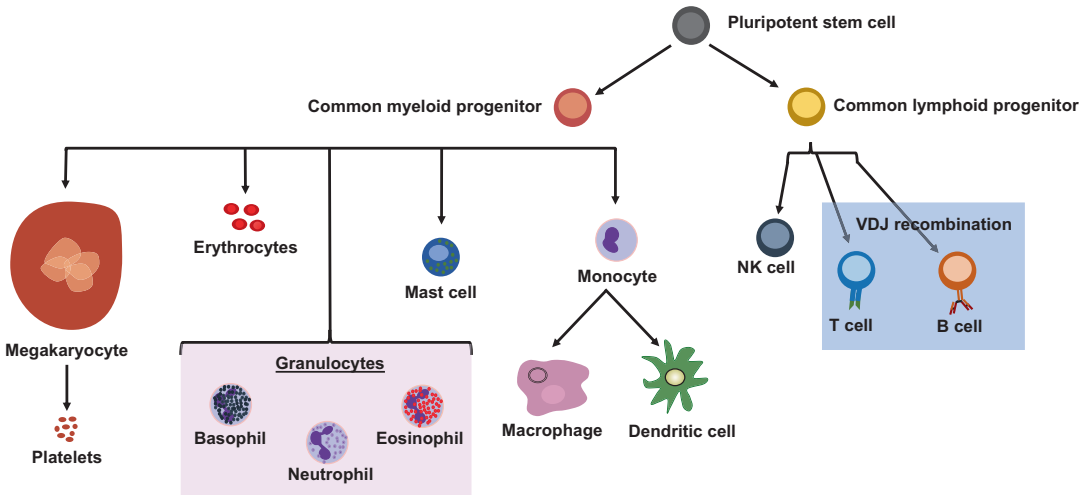


Fig. 1.2 The development of immune cells through hematopoiesis. Pluripotent stem cells are self-renewing and give rise to daughter progeny with a more limited developmental potential. Hematopoiesis occurs in the bone marrow and is guided by growth factors and cell to cell interactions. The common myeloid 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 the body. 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