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医学免疫学

Medical Immunology

Tenth Edition

Tristram G.Parslow
Daniel P.Stites
Abba I.Terr
John B.Imboden

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Preface

With this tenth edition, *Medical Immunology* marks its 25th year as the leading textbook of immunology written specifically for both health care students and practitioners. By combining a state-of-the-art overview of basic immunologic science with a detailed compendium of human immune disorders and their treatments, the book is intended to help busy professionals remain current in this rapidly advancing field. The emphasis is on human immunology throughout, with reference to key experiments or animal models only when they illuminate important aspects of human physiology or pathology. The organization of the book proceeds logically, building from a foundation of cellular and molecular immunology, through clinical laboratory methods, to clinical disorders and their treatment. Every chapter and section emphasizes broad, general principles, but coverage of each specific topic is designed to stand alone for easy reference or review. The authors and editors have made every effort to write in a lucid, readable style without sacrificing important details. As in the past, our goal has been to provide a well-integrated, practical, and accessible survey of basic and clinical immunology.

The book is arranged in four sections that deal, respectively, with Basic Immunology, Immunologic Laboratory Tests, Clinical Immunology, and Immunologic Therapy.

Section I, Basic Immunology, presents a concise but thorough overview of the science of immunology. Designed to be both authoritative and accessible, it can serve as either a textbook for preclinical courses or a timely review and reference book for practicing clinicians, immunologists, and scientists from other fields. The section opens with a chapter that reviews the key molecular processes governing intercellular communication, signal transduction, mitosis, and cell death as they apply to blood cell biology. Chapter 2 then summarizes the humoral and cellular agents of innate immunity, including the vascular inflammatory response and the role of phagocytic cells. This is followed, in Chapters 3 through 9, by progressively sophisticated explorations of acquired immunity, beginning with an introduction to lymphocyte biology and the immune response, followed by discussions of immunogenicity and antigen presentation, and culminating in detailed analyses of B- and T-cell functions. Chapters 10 through 14 then comprehensively review the cytokines, chemokines, inflammatory mediators, and other key aspects of immune function. A list of references is provided at the end of each chapter for readers wishing to explore these subjects further.

Section II, Immunologic Laboratory Tests, serves as a bridge between basic immunology and the clinical sections that follow. The methods used to evaluate various aspects of human immunologic function are described, as are tests that employ immunologic reagents and procedures. Chapter 18 introduces the emerging field of molecular diagnostics in immunology, and other chapters explore the important areas of blood banking, histocompatibility, and immunohematology. A succinct chapter on the evaluation of immune competence in patients brings this section to a close.

Section III, Clinical Immunology, surveys broad categories of human immunologic diseases, organizing them either by organ systems or by common mechanisms of pathogenesis. Chapters 21 through 25 focus on congenital disorders of immunity, highlighting the latest information about their underlying genetic defects. The allergic disorders are reviewed authoritatively in Chapters 26 through 30, followed by detailed coverage of rheumatic disorders in Chapter 31, of major organ system pathologies in Chapters 32 through 41, and of neoplastic diseases in Chapters 42 and 43. The section closes with a se-

ries of six chapters on infectious diseases, including a thorough and timely discussion of the acquired immune deficiency syndrome (AIDS).

Section IV, Immunologic Therapy, reviews immunization, allergy desensitization, and treatment modalities currently used in transplantation and immunologic diseases. This section also discusses the available strategies for manipulating immune function, particularly in clinical transplantation or for treating autoimmunity.

New features included in this tenth edition:

- The section on basic immunology has been updated throughout and now includes expanded coverage of innate immunity, apoptosis, dendritic cells, natural killer cells, and other key topics; a new chapter devoted entirely to the chemokines; and the most comprehensive, authoritative review of cytokines available in a textbook of this kind.
- In the section on clinical laboratory methodology, the chapters covering clinical tests for humoral immunity, cell-mediated immunity, histocompatibility, and immunocompetence have each been rewritten by new expert authors, with an emphasis on the molecular diagnostic assays now in widespread clinical use.
- All of the chapters in the section on Clinical Immunology have been revised, streamlined, and updated, many of them under the guidance of a new editor, Dr. John Imboden. The chapters on vasculitis, renal disease, and spirochetal infections have been rewritten by new authors who are experts in these fields.
- Coverage of AIDS, Lyme disease, asthma, reproductive disorders, inflammatory bowel disease, neurologic syndromes, and other important clinical entities have been expanded and updated to reflect the latest research on pathogenesis and treatment.
- Discussions of treatment options incorporate the newest drugs and therapeutic regimens, immunization protocols, immunosuppressive therapies, and approaches to allergy desensitization.
- The Appendix includes a concise table listing the most important hematopoietic cell-surface markers (the CD classification) encountered in clinical medicine or research.

ACKNOWLEDGMENTS

The editors are sincerely grateful to Janet Foltin for her wise counsel and kind indulgence during the preparation of this edition. The book has also benefited immeasurably from the meticulous and painstaking copyediting by Linda Davoli and from the artistry of Charissa Baker. We also thank Dr. Steve Rosen for his expert advice regarding some of the material in Section I.

Recommendations about diagnosis and treatment of disease are based on the best scientific and clinical information currently available. These are intended, however, as guidance to the clinician and not necessarily as recommendations for specific cases. Furthermore, we recognize that we may have overlooked errors despite our best efforts. We would be grateful if our readers would point these out so that they may be corrected in the next edition.

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John B. Imboden, MD

Contents

Section I.
Basic Immunology

Fundamentals of Blood Cell Biology 1

Clifford Lowell, MD, PhD

Immunology is the study of the ways in which the body defends itself from infectious agents and other foreign substances in its environment. Broadly defined, the field encompasses many layers of defense, including physical barriers like the skin, protective chemical substances in the blood and tissue fluids, and the physiologic reactions of tissues to injury or infection. But by far the most elaborate, dynamic, and effective defense strategies are carried out by cells that have evolved specialized abilities to recognize and eliminate potentially injurious substances. Some of these defensive cells circulate continually through the body in search of foreign invaders; others are stationary sentinels that lie in wait in solid tissues or at body surfaces. Because of their central roles in host defense, these cells are the major focus of contemporary immunology and are the principal subjects of this book.

Virtually all of the specialized defensive cells have two things in common: They all spend at least part of their lives in the bloodstream, and they are all ultimately derived from cells produced in the bone marrow. We therefore begin, in this chapter, by considering the processes involved in cell formation and maturation in the bone marrow—one of the most prolific sites of cell replication in the human body and one that is indispensable for health and even for survival. Investigating these processes provides an opportunity to introduce many of the individual cell types involved in host defense, as well as several regulatory factors that govern their lives. We will also examine the fundamental molecular mechanisms by which cells receive signals from their environments and how these signals control whether cells proliferate, migrate, and carry out specific functions, and even when they die.

HEMATOPOIESIS

Origins of Cells in the Blood & Bone Marrow

The process by which blood cells grow, divide, and differentiate in the bone marrow is called **hematopoiesis.** Three general classes of cells are produced: (1) red blood cells (erythrocytes), responsible for oxygen transport; (2) platelets, responsible for the control of bleeding; and (3) white blood cells **(leukocytes),** the vast majority of which are involved in host defense. All three classes are ultimately derived from a pool of pluripotent **hematopoietic stem cells (HSCs),** which reside in the marrow and have the unique ability to give rise to all of the different mature blood cell types, under the appropriate conditions. The HSCs are **self-renewing** cells: When they proliferate, at least some of their daughter cells remain as HSCs, so that the pool of stem cells does not become depleted.

The other daughters of HSCs, however, can each commit to any of several alternative differentiation pathways that lead to the production of one or more specific types of blood cells (Figure 1–1). A typical pathway involves several cycles of cell division (five or more) and proceeds in stages, with cells at each stage progressively acquiring features of one particular mature cell type while losing the capacity to form any others. Because progression along these pathways is coupled to cell division, the more mature forms greatly outnumber their less differentiated precursors. As the cells differentiate, however, their capacity for replication and self-renewal declines. Indeed, most types of hematopoietic cells lose replicative capacity altogether by the time they are fully mature, and so are said to be **terminally differentiated.** Thus, in general, the less differentiated

cells in a given pathway are rare but replicate actively, whereas the mature cells are more numerous but mitotically inert.

The progeny of HSCs initially commit to one of three main alternative differentiation pathways (or **lineages**) that yield erythrocytes, lymphocytes, or myeloid cells, respectively. The most primitive cells in each lineage, called **lineage-committed progenitors,** cannot be identified morphologically; however, their existence and some of their properties can be inferred from their ability to generate particular types of mature cells in biologic assay systems (see later discussion). Erythrocyte development is outside the scope of this book and will not be considered further, but both myeloid cells and lymphocytes are critical to host defense. The mature cells of the myeloid lineage* include neutrophils, monocytes, mast cells, eosinophils, basophils, and megakaryocytes (the cells that produce platelets). All these cells descend from a common myeloid progenitor through a series of intermediate stages, only one of which—the granulocyte–monocyte progenitor, a precursor to both neutrophils and monocytes—is shown in Figure 1–1. Mature cells of the lymphocyte lineage include B lymphocytes, T lymphocytes, and possibly also natural killer (NK) cells; the development and functions of these three cell types is discussed in great detail in later chapters. Altogether, the myeloid and lymphocyte lineages account for roughly 60% and 15%, respectively, of all marrow cells; the remainder are erythroid precursors.

Vast numbers of mature blood cells are produced daily in the marrow, but the rate of production of each cell type is precisely controlled and responsive to physiologic demands. For example, production of leukocytes often increases markedly during systemic infections, whereas red cell production can rise as a reaction to anemia. In addition, many mature leukocytes, particularly neutrophils, are stored in the marrow before being released into the bloodstream. This storage pool, which normally accounts for 10–20% of all marrow cells, provides a reservoir of mature defensive cells that can be mobilized rapidly in times of need. Thus, bone marrow hematopoiesis is precisely controlled at several levels in order to (1) maintain an available pool of HSCs; (2) regulate the commitment, proliferation, and differentiation of cells at all stages of each hematopoietic pathway; and (3) modulate the activity of each pathway in response to physiologic demands. As we shall see, much of this regulation is achieved through physical interactions of the hematopoietic cells with other cells and with soluble factors in the surrounding tissues.

* The term *myeloid* means "of the bone marrow." As a group, cells of the myeloid lineage are the most abundant cells in the marrow.

Ontogeny of Hematopoiesis

HSCs arise in the mesoderm of the yolk sac during the first weeks of embryonic life (Figure 1–2). Within 2 months following conception, most HSCs have migrated to the fetal liver, and it is here that the bulk of hematopoiesis occurs during fetal development. Most embryonic and fetal hematopoiesis is devoted to the production of red cells; platelet production first becomes apparent at 3 months of gestation, and leukocytes do not appear until the fifth month. Later in gestation, HSCs begin to colonize the developing bone marrow cavities throughout the skeleton, which contain a network of epithelial cells (called the **bone marrow stroma**) that provide the necessary environment for growth and differentiation of HSC and their progeny. By birth, virtually all of the marrow space is occupied by developing hematopoietic cells, giving the newborn child about the same hematopoietic capacity as his or her adult parents. Hematopoietic activity in the long bones then declines with age, so that after puberty it is largely confined to the axial skeleton—the pelvis, sternum, ribs, vertebrae, and skull. If the bone marrow is injured by infection or malignancy, however, hematopoiesis can resume in the liver and spleen of an adult to maintain the supply of blood cells.

Hematopoietic Cell Growth & Differentiation

Our understanding of hematopoiesis has advanced greatly in recent years with the isolation and characterization of HSCs and the identification of many of the factors that influence the production and differentiation of lineage-committed progenitors (Figure 1–3). HSCs are defined by their abilities to self-renew throughout life and to give rise to committed progenitors that can differentiate along all of the possible hematopoietic lineages. They were first purified from mice as a tiny subpopulation of marrow cells that could completely reconstitute the hematopoietic systems of other mice, whose own marrows had been destroyed by inherited mutations or by radiation. Although similar experiments cannot, of course, be done with human beings, presumptive human HSCs have since been identified that, under certain conditions, are able to repopulate the marrows of mice.

Human HSCs express a characteristic surface protein, **CD34.*** Though CD34 is not unique to HSCs (it

* Many of the cell surface proteins important to immunology are referred to by the initials **CD** (which stand for **cluster of differentiation**) followed by a unique identifying number. This CD system of nomenclature was originally developed for membrane proteins or protein complexes that could be identified by their physical properties (eg, molecular weight) or by other means, but whose biologic functions had not yet been determined. Most CD proteins are not related to one another, either structurally or functionally. The CD nomenclature is most often used for proteins expressed on hematopoietic cells, although many are also expressed on one or more nonhematopoietic cell types. A partial listing of CD proteins appears in the Appendix.

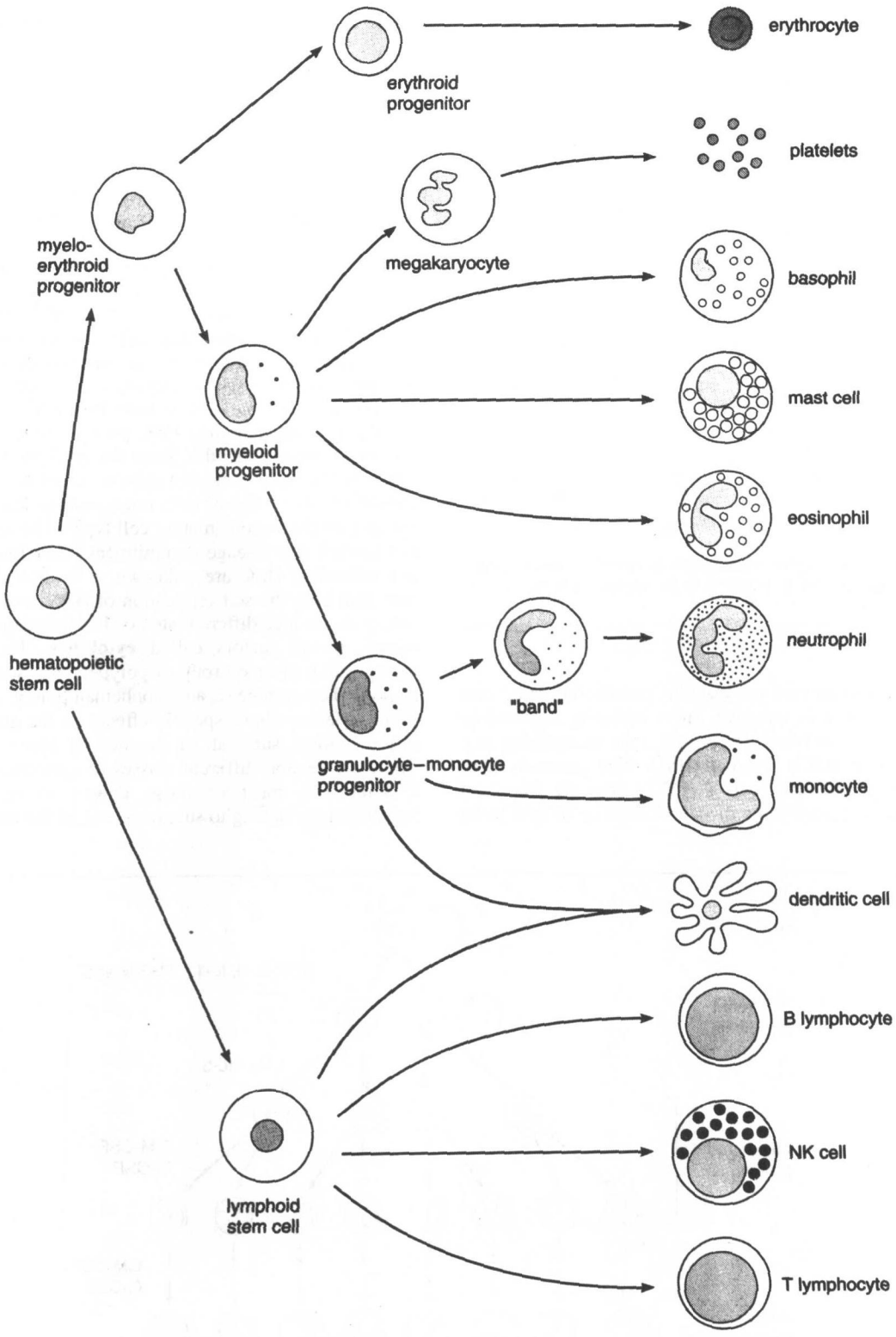

Figure 1–1. Schematic overview of hematopoiesis, emphasizing the erythroid, myeloid, and lymphoid pathways. This highly simplified depiction omits many recognized intermediate cell types in each pathway. All of the cells shown here develop to maturity in the bone marrow, except T lymphocytes, which develop from marrow-derived progenitors that migrate to the thymus (see Chapter 3). A common lymphoid stem cell serves as the progenitor of T and B lymphocytes and of natural killer (NK) cells. Dendritic cells arise from both the myeloid and lymphoid lineages.

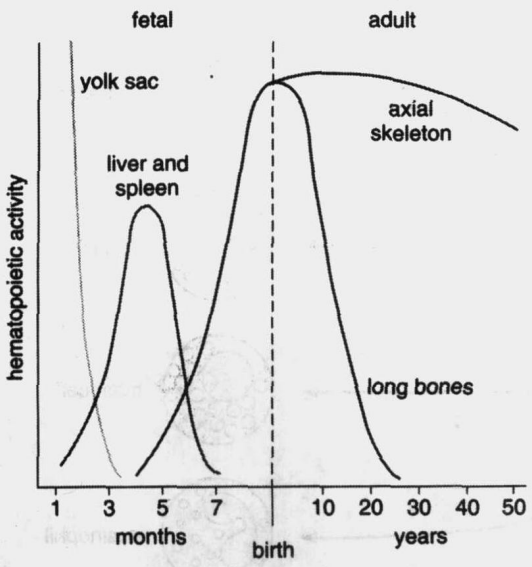

Figure 1–2. Tissue localization of hematopoiesis at various phases of prenatal and postnatal development in humans.

is also expressed on vascular endothelial cells) and its function is unknown (it is probably involved in cell–cell adhesion), it is useful in recognizing and isolating HSCs. Purified HSCs also generally lack surface proteins, such as CD38, that are found on mature marrow cells; hence HSCs can be said to be $CD34^+CD38^-$. HSCs make up only 0.01% of total marrow cells in adults but are more abundant in fetal liver and in umbilical cord blood. In adults, HSCs can be induced to leave the bone marrow and enter the peripheral circulation by treatment with certain hormones; these "mobilized" peripheral blood HSCs are being extensively studied for use in clinical bone marrow transplantation.

HSCs are small, morphologically nondescript cells with round nuclei and scant cytoplasm. They vary markedly in their ability to proliferate and differentiate into mature hematopoietic cells (Figure 1–4). At any given moment, about 25% are actively progressing through mitosis, but at varying rates—adult marrow HSCs proliferate slowly, fetal liver HSCs do so rapidly. The entire human HSC pool probably turns over every several months. Since the total number of HSCs in the body normally remains constant, some portion of their daughter cells must undergo differentiation into the various mature cell types. The factors that control this lineage commitment "decision" for any individual HSC are unknown. It is clear, however, that both the self-replication of HSCs and their ability to produce differentiated cells depend on hormonal growth factors called **cytokines.** The cytokines are a diverse group of polypeptides, secreted by both hematopoietic and nonhematopoietic cells. Many cytokines have specific effects on the growth, differentiation, survival, or function of blood cells. There are several different classes of cytokines (see Chapter 10); most of those known to regulate hematopoiesis belong to subgroups called the **colony-**

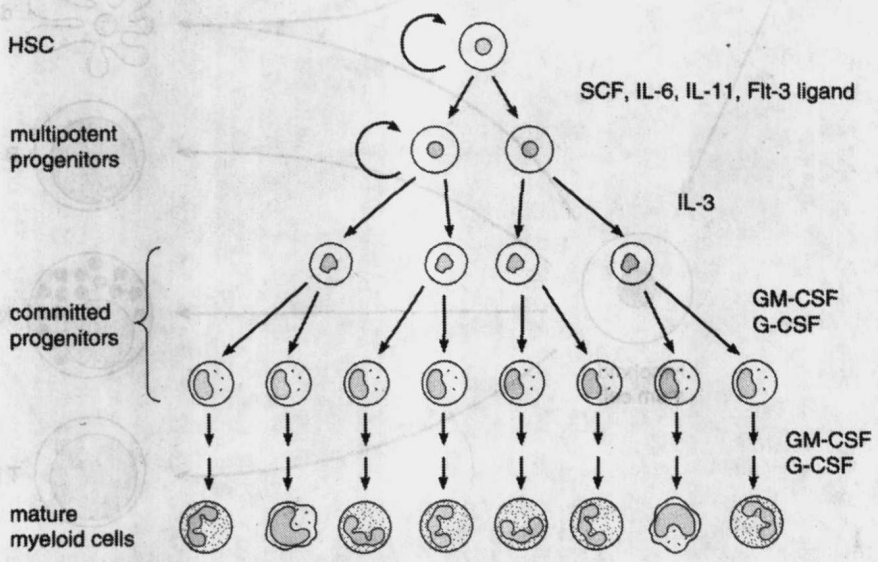

Figure 1–3. Proliferation and differentiation of cells in the myeloid lineage. Early cells are capable of self-renewal and proliferation; later cells are committed to differentiation only. Cytokines required for survival and progression through each stage are indicated at the right. *Abbreviations:* HSC = hematopoietic stem cell; SCF = stem cell factor; IL = interleukin; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte–monocyte colony-stimulating factor.