3rd Edition

HARRISON'S™

HEMATOLOGY AND ONCOLOGY

DAN L. LONGO

3rd Edition

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HEMATOLOGY AND ONCOLOGY

Derived from Harrison's Principles of Internal Medicine, 19th Edition

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PREFACE

Harrison's Principles *of* Internal Medicine has a long and distinguished tradition in the field of hematology. Maxwell Wintrobe, whose work actually established hematology as a distinct subspecialty of medicine, was a founding editor of the book and participated in the first seven editions, taking over for Tinsley Harrison as editor-in-chief on the sixth and seventh editions. Wintrobe, born in 1901, began his study of blood in earnest in 1927 as an assistant in medicine at Tulane University in New Orleans. He continued his studies at Johns Hopkins from 1930 to 1943 and moved to the University of Utah in 1943, where he remained until his death in 1986. He invented a variety of the measures that are routinely used to characterize red blood cell abnormalities, including the hematocrit, the red cell indices, and erythrocyte sedimentation rate, and defined the normal and abnormal values for these parameters, among many other important contributions in a 50-year career.

Oncology began as a subspecialty much later. It came to life as a specific subdivision within hematology. A subset of hematologists with a special interest in hematologic malignancies began working with chemotherapeutic agents to treat leukemia and lymphoma in the mid-1950s and early 1960s. As new agents were developed and the principles of clinical trial research were developed, the body of knowledge of oncology began to become larger and mainly independent from hematology. Informed by the laboratory study of cancer biology and an expansion in focus beyond hematologic neoplasms to tumors of all organ systems, oncology developed as a separable discipline from hematology. T is separation was also fueled by the expansion of the body of knowledge about clotting and its disorders, which became a larger part of hematology.

In most academic medical centers, hematology and oncology remain connected. However, conceptual distinctions between hematology and oncology have been made. Differences are reinforced by separate fellowship training programs (although many joint training programs remain), separate board certification examinations, separate professional organizations, and separate textbooks describing separate bodies of knowledge. In some academic medical centers, oncology is not merely a separate subspecialty division in a Department of Medicine but is an entirely distinct department in the medical school with the same standing as the Department of Medicine. Economic forces are also at work to separate hematology and oncology.

Perhaps I am only ref ecting the biases of an old dog, but I am unenthusiastic about the increasing fractionation of medicine subspecialties. T ere are now invasive and noninvasive cardiologists, gastroenterologists who do and others who do not use endoscopes, and organ- or individual disease-focused subspecialists (diabetologists, thyroidologists) instead of organ system–focused subspecialists (endocrinologists). T is fractionation has also begun within hematology and oncology. Some oncologists specialize in a single type of cancer and divisions of hematology have designated experts in clotting. At a time when the body of knowledge that must be mastered is increasing dramatically, the duration of training has not been increased to accommodate the additional learning that is necessary to become highly skilled. Extraordinary attention has been focused on the hours that trainees work. Apparently, the administrators are more concerned about undocumented adverse effects of every third night call on trainees than they are about the well-documented adverse effects on patients of frequent handoffs of patient responsibility to multiple caregivers.

Despite the sub-sub-subspecialization that is pervasive in modern medicine, students, trainees, general internists, family medicine physicians, physicians' assistants, nurse practitioners, and specialists in nonmedicine specialties still require access to information in hematology and oncology that can assist them in meeting the needs of their patients. Given the paucity of single sources of integrated information on hematology and oncology, the editors of Harrison's Principles *of* Internal Medicine decided to pull together the chapters in the "mother book" related to hematology and oncology and bind them together in a subspecialty themed book called Harrison's Hematology and Oncology. T e first edition of this book appeared in 2010 and was based on the 17th edition of Harrison's Principles *of* Internal Medicine. A second edition based on 18th edition of Harrison's Principles *of* Internal Medicine appeared in 2013. T is third edition is derived from the 19th edition of Harrison's Principles *of* Internal Medicine. T e book contains 57 chapters organized into 12 sections: (I) T e Cellular Basis of Hematopoiesis, (II) Cardinal Manifestations of Hematologic Diseases, (III) Anemias, (IV) Myeloproliferative Disorders, (V) Hematologic Malignancies, (VI) Disorders of Hemostasis, (VII) Biology of Cancer, (VIII) Principles of Cancer Prevention and Treatment, (IX) Neoplastic Disorders, (X) Endocrine Neoplasia, (XI) Remote Effects of Cancer, and (XII) Oncologic Emergencies and Late Effects and Complications of Cancer and Its Treatment.

T e chapters have been written by physicians who have made seminal contributions to the body of knowledge in their areas of expertise. T e information is authoritative and as current as we can make it, given the time requirements of producing books. Each contains the relevant information on the genetics, cell biology, pathophysiology, and treatment of specific disease entities. In addition, separate chapters on hematopoiesis, cancer cell biology, and cancer prevention ref ect the rapidly growing body of knowledge in these areas that are the underpinning of our current concepts of diseases in hematology and oncology. In addition to the factual information presented in the chapters, a section of test questions and answers is provided to reinforce important principles. A narrative explanation of what is wrong with the wrong answers should be of further value in the preparation of the reader for board examinations.

T e bringing together of hematology and oncology in a single text is unusual and we hope it is useful. Like many areas of medicine, the body of knowledge relevant to the practice of hematology and oncology is expanding rapidly. New discoveries with clinical impact are being made at an astounding rate; nearly constant effort is required to try to keep pace. It is our hope that this book is helpful to you in the struggle to master the daunting volume of new findings relevant to the care of your patients.

We are extremely grateful to Kim Davis and James Shanahan at McGraw-Hill for their invaluable assistance in the preparation of this book.

Dan L. Longo, MD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. T e authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. T is recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). Harrison's Self-Assessment and Board Review, 19th ed. New York, McGraw-Hill, 2017, ISBN 978-1-259-64288-3.

T e global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

T e genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

THE CELLULAR BASIS OF HEMATOPOIESIS

CHAPTER 1

HEMATOPOIETIC STEM CELLS

David T. Scadden ■ Dan L. Longo

All of the cell types in the peripheral blood and some cells in every tissue of the body are derived from hematopoietic (hemo: blood; poiesis: creation) stem cells. If the hematopoietic stem cell is damaged and can no longer function (e.g., due to a nuclear accident), a person would survive 2–4 weeks in the absence of extraordinary support measures. With the clinical use of hematopoietic stem cells, tens of thousands of lives are saved each year **(Chap. 31)**. Stem cells produce hundreds of billions of blood cells daily from a stem cell pool that is estimated to be only in the tens of thousands. How stem cells do this, how they persist for many decades despite the production demands, and how they may be better used in clinical care are important issues in medicine.

T e study of blood cell production has become a paradigm for how other tissues may be organized and regulated. Basic research in hematopoiesis includes defining stepwise molecular changes accompanying functional changes in maturing cells, aggregating cells into functional subgroups, and demonstrating hematopoietic stem cell regulation by a specialized microenvironment; these concepts are worked out in hematology, but they offer models for other tissues. Moreover, these concepts may not be restricted to normal tissue function but extend to malignancy. Stem cells are rare cells among a heterogeneous population of cell types, and their behavior is assessed mainly in experimental animal models involving reconstitution of hematopoiesis. T us, much of what we know about stem cells is imprecise and based on inferences from genetically manipulated animals.

CARDINAL FUNCTIONS OF HEMATOPOIETIC STEM CELLS

All stem cell types have two cardinal functions: self-renewal and differentiation **(Fig. 1-1)**. Stem cells exist to generate, maintain, and repair tissues. T ey function successfully if they can replace a wide variety of shorter-lived mature cells over prolonged periods. T e process of self-renewal (see below) assures that a stem cell population can be sustained over time. Without self-renewal, the stem cell pool would become exhausted and tissue maintenance would not be possible. T e process of differentiation leads to production of the effectors of tissue function: mature cells. Without proper differentiation, the integrity of tissue function would be compromised and organ failure or neoplasia would ensue.

In the blood, mature cells have variable average life spans, ranging from 7 h for mature neutrophils to a few months for red blood cells to many years for memory lymphocytes. However, the stem cell pool is the central, durable source of all blood and immune cells, maintaining a capacity to produce a broad range of cells from a single cell source, yet keeping itself vigorous over decades of life. As an individual stem cell divides, it has the capacity to accomplish one of three division outcomes: two stem cells, two cells destined for differentiation, or one stem cell and one differentiating cell. T e former two outcomes are the result of symmetric cell division, whereas the latter indicates a different outcome for the two daughter cells—an event termed asymmetric cell division. T e relative balance for these types of outcomes may change during development and under particular kinds of demands on the stem cell pool.

DEVELOPMENTAL BIOLOGY OF HEMATOPOIETIC STEM CELLS

During development, blood cells are produced at different sites. Initially, the yolk sac provides oxygen-carrying red blood cells, and then the placenta and several sites of intraembryonic blood cell production become involved. T ese intraembryonic sites engage in sequential order, moving from the genital ridge at a site where the aorta, gonadal tissue, and mesonephros

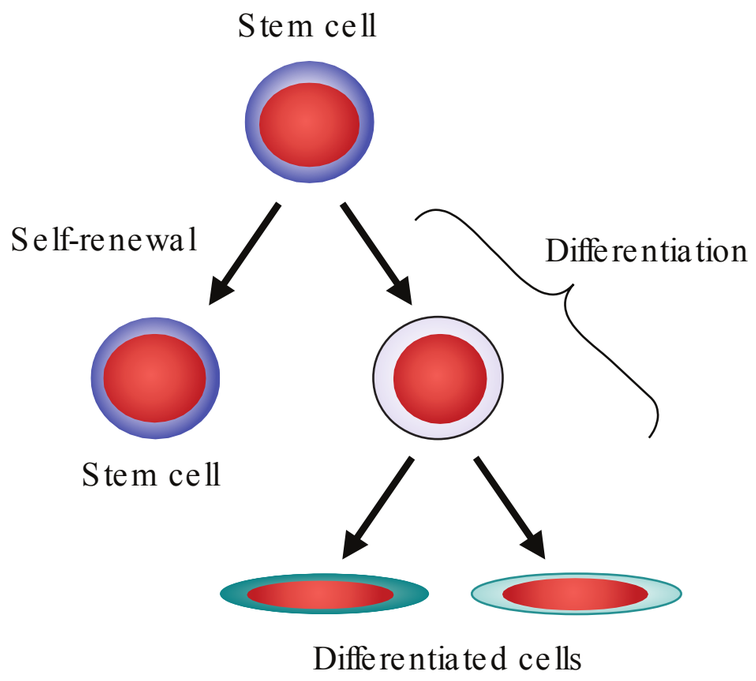

FIGURE 1-1
Signature characteristics of the stem cell. Stem cells have two essential features: the capacity to differentiate into a variety of mature cell types and the capacity for self-renewal. Intrinsic factors associated with self-renewal include expression of Bmi-1, Gf-1, PTEN, STAT5, Tel/Atv6, p21, p18, MCL-1, Mel-18, RAE28, and HoxB4. Extrinsic signals for self-renewal include Notch, Wnt, SHH, and Tie2/Ang-1. Based mainly on murine studies, hematopoietic stem cells express the following cell surface molecules: CD34, Thy-1 (CD90), c-Kit receptor (CD117), CD133, CD164, and c-Mpl (CD110, also known as the thrombopoietin receptor).

are emerging to the fetal liver and then, in the second trimester, to the bone marrow and spleen. As the location of stem cells changes, the cells they produce also change. The yolk sac provides red cells expressing embryonic hemoglobins while intraembryonic sites of hematopoiesis generate red cells, platelets, and the cells of innate immunity. The production of the cells of adaptive immunity occurs when the bone marrow is colonized and the thymus forms. Stem cell proliferation remains high, even in the bone marrow, until shortly after birth, when it appears to dramatically decline. The cells in the bone marrow are thought to arrive by the bloodborne transit of cells from the fetal liver after calcification of the long bones has begun. The presence of stem cells in the circulation is not unique to a time window in development; however, hematopoietic stem cells appear to circulate throughout life. The time that cells spend freely circulating appears to be brief (measured in minutes in the mouse), but the cells that do circulate are functional and can be used for transplantation. The number of stem cells that circulate can be increased in a number of ways to facilitate harvest and transfer to the same or a different host.

MOBILITY OF HEMATOPOIETIC STEM CELLS

Cells entering and exiting the bone marrow do so through a series of molecular interactions. Circulating stem cells (through CD162 and CD44) engage the lectins (carbohydrate binding proteins) P- and E-selectin on the endothelial surface to slow the movement of the cells to a rolling phenotype. Stem cell integrins are then activated and accomplish firm adhesion between the stem cell and vessel wall, with a particularly important role for stem cell VCAM-1 engaging endothelial VLA-4. The chemokine CXCL12 (SDF1) interacting with stem cell CXCR4 receptors and ionic calcium interacting with the calcium sensing receptor appear to be important in the process of stem cells getting from the circulation to where they engraft in the bone marrow. This is particularly true in the developmental move from fetal liver to bone marrow.

However, the role for CXCR4 in adults appears to be more related to retention of stem cells in the bone marrow rather than the process of getting them there. Interrupting that retention process through either specific molecular blockers of the CXCR4/CXCL12 interaction, cleavage of CXCL12, or downregulation of the CXCR4 receptor can all result in the release of stem cells into the circulation. This process is an increasingly important aspect of recovering stem cells for therapeutic use as it has permitted the harvesting process to be done by leukapheresis rather than bone marrow punctures in the operating room. Granulocyte colony-stimulating factor and plerixafor, a macrocyclic compound that can block CXCR4, are both used clinically to mobilize marrow hematopoietic stem cells for transplant. Refining our knowledge of how stem cells get into and out of the bone marrow may improve our ability to obtain stem cells and make them more efficient at finding their way to the specific sites for blood cell production, the so-called stem cell niche.

HEMATOPOIETIC STEM CELL MICROENVIRONMENT

The concept of a specialized microenvironment, or stem cell niche, was first proposed to explain why cells derived from the bone marrow of one animal could be used in transplantation and again be found in the bone marrow of the recipient. This niche is more than just a housing site for stem cells, however. It is an anatomic location where regulatory signals are provided that allow the stem cells to thrive, to expand if needed, and to provide varying amounts of descendant daughter cells. In addition, unregulated growth of stem cells may be problematic based on their undifferentiated state and self-renewal capacity. Thus, the niche must also regulate the number of stem cells produced. In this manner, the niche has the dual function of serving as a site of nurture but imposing limits for stem cells: in effect, acting as both a nutritive and constraining home.

The niche for blood stem cells changes with each of the sites of blood production during development, but for most of human life it is located in the bone marrow. Within the bone marrow, the perivascular space

particularly in regions of trabecular bone serves as a niche. T e mesenchymal and endothelial cells of the marrow microvessels produce kit ligand and CXCL12, both known to be important for hematopoietic stem cells. Other cell types, such as sympathetic neurons, nonmyelinating Schwann cells, macrophages, osteoclasts, and osteoblasts, have been shown to regulate stem cells, but it is unclear whether their effects are direct or indirect. Extracellular matrix proteins like osteopontin also affect stem cell function. T e endosteal region is particularly important for transplanted cells, suggesting that there may be distinctive features of that region that are yet to be defined that are important mediators of stem cell engraftment. T e functioning of the niche as a supportive context for stem cells is of obvious importance for maintaining hematopoiesis and in transplantation. An active area of study involves determining whether the niche is altered in disease and whether drugs can modify niche function to improve transplantation or normal stem cell function in hematologic disease.

EXCESS CAPACITY OF HEMATOPOIETIC STEM CELLS

In the absence of disease, one never runs out of hematopoietic stem cells. Indeed, serial transplantation studies in mice suggest that sufficient stem cells are present to reconstitute several animals in succession, with each animal having normal blood cell production. T e fact that allogeneic stem cell transplant recipients also never run out of blood cells in their life span, which can extend for decades, argues that even the limiting numbers of stem cells provided to them are sufficient. How stem cells respond to different conditions to increase or decrease their mature cell production remains poorly understood. Clearly, negative feedback mechanisms affect the level of production of most of the cells, leading to the normal tightly regulated blood cell counts. However, many of the regulatory mechanisms that govern production of more mature progenitor cells do not apply or apply differently to stem cells. Similarly, most of the molecules shown to be able to change the size of the stem cell pool have little effect on more mature blood cells. For example, the growth factor erythropoietin, which stimulates red blood cell production from more mature precursor cells, has no effect on stem cells. Similarly, granulocyte colony-stimulating factor drives the rapid proliferation of granulocyte precursors but has little or no effect on the cell cycling of stem cells. Rather, it changes the location of stem cells by indirect means, altering molecules such as CXCL12 that tether stem cells to their niche. Molecules shown to be important for altering the proliferation, self-renewal, or survival of stem cells, such as cyclin-dependent kinase inhibitors, transcription factors like Bmi-1, or microRNA-processing enzymes like Dicer, have little or different effects on progenitor cells. Hematopoietic stem cells have governing mechanisms that are distinct from the cells they generate.

HEMATOPOIETIC STEM CELL DIFFERENTIATION

Hematopoietic stem cells sit at the base of a branching hierarchy of cells culminating in the many mature cell types that compose the blood and immune system **(Fig. 1-2)**. T e maturation steps leading to terminally differentiated and functional blood cells take place both as a consequence of intrinsic changes in gene expression and niche-directed and cytokine-directed changes in the cells. Our knowledge of the details remains incomplete. As stem cells mature to progenitors, precursors, and, finally, mature effector cells, they undergo a series of functional changes. T ese include the obvious acquisition of functions defining mature blood cells, such as phagocytic capacity or hemoglobin synthesis. T ey also include the progressive loss of plasticity (i.e., the ability to become other cell types). For example, the myeloid progenitor can make all cells in the myeloid series but none in the lymphoid series. As common myeloid progenitors mature, they become precursors for either monocytes and granulocytes or erythrocytes and megakaryocytes, but not both. Some amount of reversibility of this process may exist early in the differentiation cascade, but that is lost beyond a distinct stage in normal physiologic conditions. With genetic interventions, however, blood cells, like other somatic cells, can be reprogrammed to become a variety of cell types.

As cells differentiate, they may also lose proliferative capacity **(Fig. 1-3)**. Mature granulocytes are incapable of proliferation and only increase in number by increased production from precursors. T e exceptions to the rule are some resident macrophages, which appear capable of proliferation, and lymphoid cells. Lymphoid cells retain the capacity to proliferate but have linked their proliferation to the recognition of particular proteins or peptides by specific antigen receptors on their surface. Like many tissues with short-lived mature cells such as the skin and intestine, blood cell proliferation is largely accomplished by a more immature progenitor population. In general, cells within the highly proliferative progenitor cell compartment are also relatively short-lived, making their way through the differentiation process in a defined molecular program involving the sequential activation of particular sets of genes. For any particular cell type, the differentiation program is difficult to speed up. T e time it takes for hematopoietic progenitors to become mature cells is ~10–14 days in humans, evident clinically by the

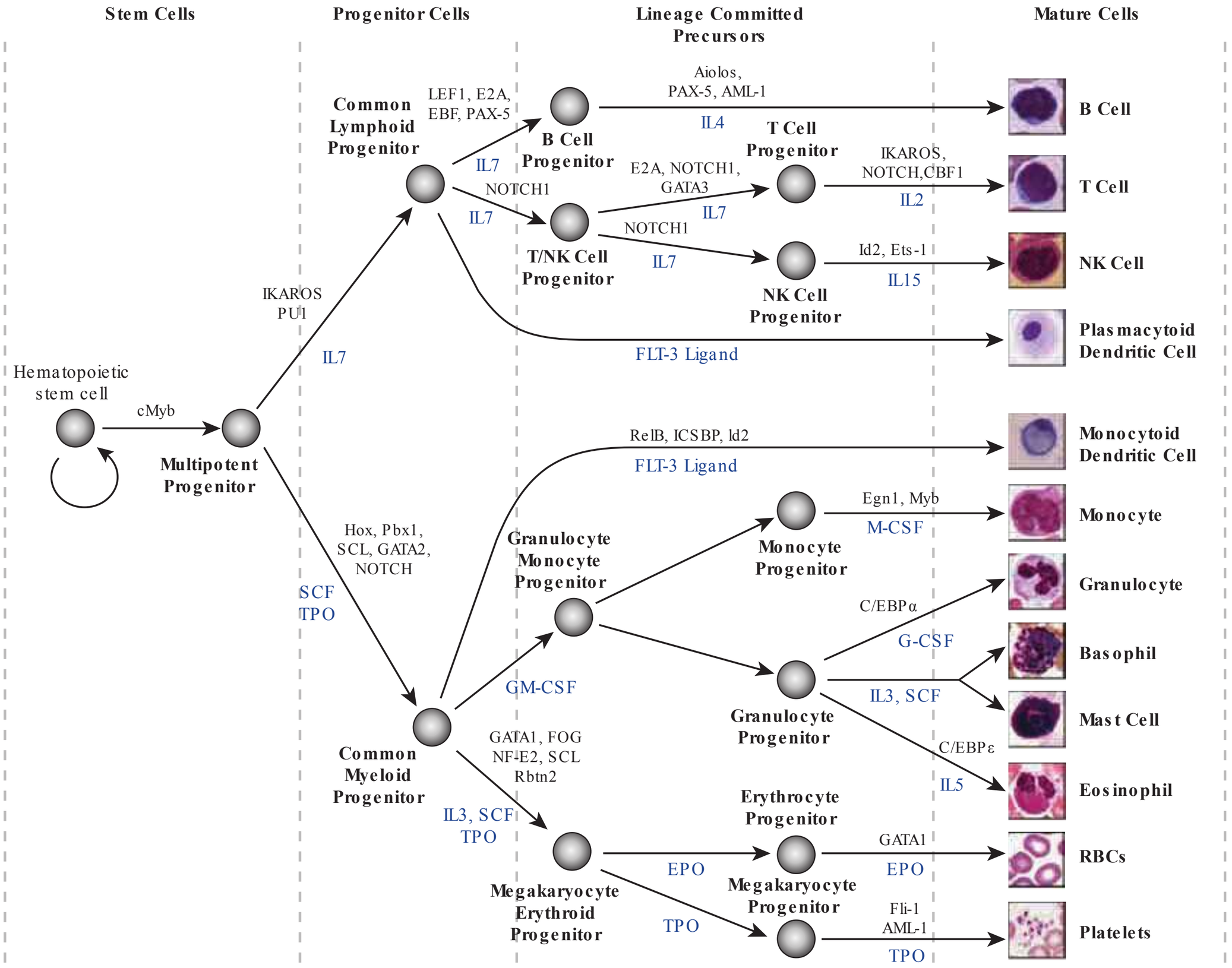

FIGURE 1-2

Hierarchy of hematopoietic differentiation. Stem cells are multipotent cells that are the source of all descendant cells and have the capacity to provide either long-term (measured in years) or short-term (measured in months) cell production. Progenitor cells have a more limited spectrum of cells they can produce and are generally a short-lived, highly proliferative population also known as transient amplifying cells. Precursor cells are cells committed to a single blood cell lineage but with a continued ability to proliferate; they do not have all the features of a fully mature cell. Mature cells are the terminally differentiated product of the differentiation process and are the effector cells of specific activities of the blood and immune system. Progress through the pathways is mediated by alterations in gene expression. The regulation of the differentiation by soluble factors and cell-cell communications within the bone marrow niche are still being defined. The transcription factors that characterize particular cell transitions are illustrated on the arrows; the soluble factors that contribute to the differentiation process are in blue. This picture is a simplification of the process. Active research is revealing multiple discrete cell types in the maturation of B cells and T cells and has identified cells that are biased toward one lineage or another (rather than uncommitted) in their differentiation. EPO, erythropoietin; RBC, red blood cell; SCF, stem cell factor; TPO, thrombopoietin.

interval between cytotoxic chemotherapy and blood count recovery in patients.

Although hematopoietic stem cells are generally thought to have the capacity to form all cells of the blood, it is becoming clear that individual stem cells may not be equal in their differentiation potential. That is, some stem cells are "biased" to become mature cells of a particular type. In addition, the general concept of cells having a binary choice of lymphoid or myeloid differentiation is not entirely accurate. A cell population with limited myeloid (monocyte and granulocyte) and lymphoid potential is now added to the commitment steps stem cells may undergo.

SELF-RENEWAL

The hematopoietic stem cell must balance its three potential fates: apoptosis, self-renewal, and differentiation.

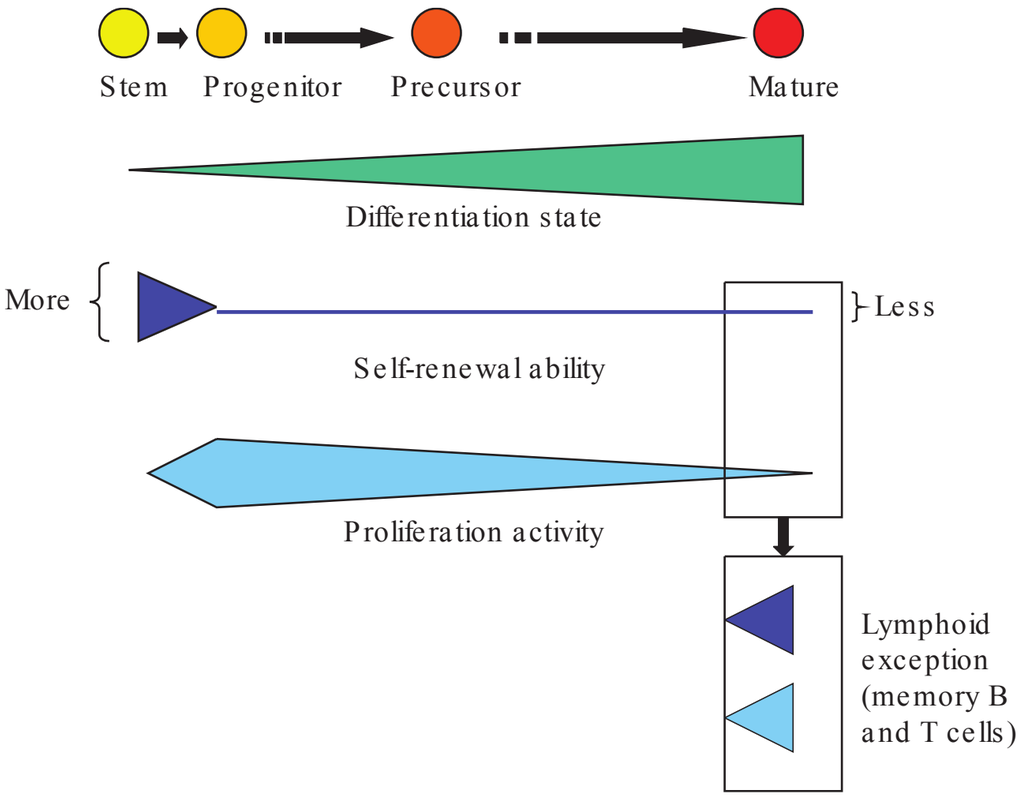

FIGURE 1-3
Relative function of cells in the hematopoietic hierarchy. The boxes represent distinct functional features of cells in the myeloid (upper box) versus lymphoid (lower box) lineages.

The proliferation of cells is generally not associated with the ability to undergo a self-renewing division except among memory T and B cells and among stem cells. Self-renewal capacity gives way to differentiation as the only option after cell division when cells leave the stem cell compartment, until they have the opportunity to become memory lymphocytes. In addition to this self-renewing capacity, stem cells have an additional feature characterizing their proliferation machinery. Stem cells in many mature adult tissues may be heterogeneous with some being deeply quiescent, serving as a deep reserve, whereas others are more proliferative and replenish the short-lived progenitor population. In the hematopoietic system, stem cells are generally cytokine-resistant, remaining dormant even when cytokines drive bone marrow progenitors to proliferation rates measured in hours. Stem cells, in contrast, are thought to divide at far longer intervals, measured in months to years, for the most quiescent cells. This quiescence is difficult to overcome in vitro, limiting the ability to effectively expand human hematopoietic stem cells. The process may be controlled by particularly high levels of cyclin-dependent kinase inhibitors like p57 or CDKN1c that restrict entry of stem cells into the cell cycle, blocking the G_1-S transition. Exogenous signals from the niche also appear to enforce quiescence, including the activation of the tyrosine kinase receptor Tie2 on stem cells by angiopoietin 1 on niche cells.

The regulation of stem cell proliferation also appears to change with age. In mice, the cyclin-dependent kinase inhibitor p16INK4a accumulates in stem cells in older animals and is associated with a change in five different stem cell functions, including cell cycling. Lowering expression of p16INK4a in older animals improves stem cell cycling and capacity to reconstitute hematopoiesis in adoptive hosts, making them similar to younger animals. Mature cell numbers are unaffected. Therefore, molecular events governing the specific functions of stem cells are being gradually made clear and offer the potential of new approaches to changing stem cell function for therapy. One critical stem cell function that remains poorly defined is the molecular regulation of self-renewal.

For medicine, self-renewal is perhaps the most important function of stem cells because it is critical in regulating the number of stem cells. Stem cell number is a key limiting parameter for both autologous and allogeneic stem cell transplantation. Were we to have the ability to use fewer stem cells or expand limited numbers of stem cells ex vivo, it might be possible to reduce the morbidity and expense of stem cell harvests and enable use of other stem cell sources. Specifically, umbilical cord blood is a rich source of stem cells. However, the volume of cord blood units is extremely small, and therefore, the total number of hematopoietic stem cells that can be obtained in any single cord blood unit is generally only sufficient to transplant an individual of <40 kg. This limitation restricts what would otherwise be an extremely promising source of stem cells. Two features of cord blood stem cells are particularly important. (1) They are derived from a diversity of individuals that far exceeds the adult donor pool and therefore can overcome the majority of immunologic cross-matching obstacles. (2) Cord blood stem cells have a large number of T cells associated with them, but (paradoxically) they appear to be associated with a lower incidence of graft-versus-host disease when compared with similarly mismatched stem cells from other sources. If stem cell expansion by self-renewal could be achieved, the number of cells available might be sufficient for use in larger adults. An alternative approach to this problem is to improve the efficiency of engraftment of donor stem cells. Graft engineering is exploring methods of adding cell components that may enhance engraftment. Furthermore, at least some data suggest that depletion of host NK (natural killer) cells may lower the number of stem cells necessary to reconstitute hematopoiesis.

Some limited understanding of self-renewal exists and, intriguingly, implicates gene products that are associated with the chromatin state, a high-order organization of chromosomal DNA that influences transcription. These include members of the polycomb family, a group of zinc finger–containing transcriptional regulators that interact with the chromatin structure, contributing to the accessibility of groups of genes for transcription. One member, Bmi-1, is important in enabling hematopoietic stem cell self-renewal through modification of cell cycle regulators such as the cyclin-dependent kinase inhibitors. In the absence of Bmi-1 or of the transcriptional regulator, Gfi-1, hematopoietic

stem cells decline in number and function. In contrast, dysregulation of Bmi-1 has been associated with leukemia; it may promote leukemic stem cell self-renewal when it is overexpressed. Other transcription regulators have also been associated with self-renewal, particularly homeobox, or "hox," genes. T ese transcription factors are named for their ability to govern large numbers of genes, including those determining body patterning in invertebrates. HoxB4 is capable of inducing extensive self-renewal of stem cells through its DNA-binding motif. Other members of the hox family of genes have been noted to affect normal stem cells, but they are also associated with leukemia. External signals that may inf uence the relative self-renewal versus differentiation outcomes of stem cell cycling include specific Wnt ligands. Intracellular signal transducing intermediates are also implicated in regulating self-renewal. T ey include PTEN, an inhibitor of the AKT pathway, and STAT5, both of which are downstream of activated growth factor receptors and necessary for normal stem cell functions including self-renewal, at least in mouse models. T e connections between these molecules remain to be defined, and their role in physiologic regulation of stem cell self-renewal is still poorly understood.

CANCER IS SIMILAR TO AN ORGAN WITH SELF-RENEWING CAPACITY

T e relationship of stem cells to cancer is an important evolving dimension of adult stem cell biology. Cancer may share principles of organization with normal tissues. Cancer cells are heterogeneous even within a given patient and may have a hierarchical organization of cells with a base of stem-like cells capable of the signature stem cell features: self-renewal and differentiation. T ese stem-like cells might be the basis for perpetuation of the tumor and represent a slowly dividing, rare population with distinct regulatory mechanisms, including a relationship with a specialized microenvironment. A subpopulation of self-renewing cells has been defined for some, but not all, cancers. A more sophisticated understanding of the stem cell organization of cancers may lead to improved strategies for developing new therapies for the many common and difficult-to-treat types of malignancies that have been relatively refractory to interventions aimed at dividing cells.

Does the concept of cancer stem cells provide insight into the cellular origin of cancer? T e fact that some cells within a cancer have stem cell–like properties does not necessarily mean that the cancer arose in the stem cell itself. Rather, more mature cells could have acquired the self-renewal characteristics of stem cells. Any single genetic event is unlikely to be sufficient to enable full transformation of a normal cell to a frankly malignant one. Rather, cancer is a multistep process, and for the multiple steps to accumulate, the cell of origin must be able to persist for prolonged periods. It must also be able to generate large numbers of daughter cells. T e normal stem cell has these properties and, by virtue of its having intrinsic self-renewal capability, may be more readily converted to a malignant phenotype. T is hypothesis has been tested experimentally in the hematopoietic system. Taking advantage of the cell-surface markers that distinguish hematopoietic cells of varying maturity, stem cells, progenitors, precursors, and mature cells can be isolated. Powerful transforming gene constructs were placed in these cells, and it was found that the cell with the greatest potential to produce a malignancy was dependent on the transforming gene. In some cases, it was the stem cell, but in others, the progenitor cell functioned to initiate and perpetuate the cancer. T is shows that cells can acquire stem cell–like properties in malignancy.

WHAT ELSE CAN HEMATOPOIETIC STEM CELLS DO?

Some experimental data have suggested that hematopoietic stem cells or other cells mobilized into the circulation by the same factors that mobilize hematopoietic stem cells are capable of playing a role in healing the vascular and tissue damage associated with stroke and myocardial infarction. T ese data are controversial, and the applicability of a stem cell approach to nonhematopoietic conditions remains experimental. However, reprogramming technology offers the potential for using the readily obtained hematopoietic stem cell as a source for cells with other capabilities.

T e stem cell, therefore, represents a true dual-edged sword. It has tremendous healing capacity and is essential for life. Uncontrolled, it can threaten the life it maintains. Understanding how stem cells function, the signals that modify their behavior, and the tissue niches that modulate stem cell responses to injury and disease are critical for more effectively developing stem cell–based medicine. T at aspect of medicine will include the use of the stem cells and the use of drugs to target stem cells to enhance repair of damaged tissues. It will also include the careful balance of interventions to control stem cells where they may be dysfunctional or malignant.

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SECTION II

CARDINAL MANIFESTATIONS OF HEMATOLOGIC DISEASE