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traditionally been performed by oncologists, but the magnitude of the problem mandates that primary care providers and preventive medi cine specialists be trained in the follow-up of treated cancer patients in remission or undergoing chronic therapy. All former cancer patients should undergo surveillance for recurrence and second malignancies and be monitored for long-term effects of treatment; however, nearly all recurrences are detected because of symptoms. Health promotion and disease prevention with age- and sex-specific routine screening tests (e.g., colonoscopy, Pap smears, mammography, human papillo mavirus vaccination, dual-energy x-ray absorptiometry scans) should be a focus of survivorship care along with psychosocial well-being. Annual mammography should start no later than 10 years after breast radiation. Patients receiving radiation fields encompassing thyroid tis sue should have regular thyroid examinations and TSH testing. Local ized pain or palpable abnormality in a previously radiated field should prompt radiographic evaluation. Patients treated with alkylating agents or topoisomerase inhibitors should have a complete blood count every 6–12 months, and cytopenias, abnormal cells on peripheral smear, or macrocytosis should be evaluated with bone marrow biopsy and aspi rate and include cytogenetics, flow cytometry, or fluorescence in situ hybridization (FISH) studies as appropriate.

As the population of cancer survivors increases and patients live longer, cancer survivorship has become increasingly important, and the Institute of Medicine and National Research Council have pub lished a monograph entitled From Cancer Patient to Cancer Survivor: Lost in Transition. The monograph proposes a plan that would inform clinicians caring for cancer survivors of the complete details of patients’ previous treatments, complications thereof, signs and symptoms of late effects, and recommended screening and follow-up procedures. PART 4 Oncology and Hematology OUTLOOK Survivorship care is a burgeoning problem facing oncologists today. The challenge is to develop cancer treatments that maximize clini cal benefit including cure of disease while also mitigating the risks of long-term toxicity. As cancer treatments continue to improve, the prevalence of cancer survivors increases along with an increase in life expectancy. Further, since emerging therapies often have improved tolerability profiles, a greater number of patients with advanced age or comorbid medical conditions will become cancer survivors with per sistent treatment-related toxicities. As treatment paradigms continue to evolve, the nature and biologic basis for toxicities will change and phar macovigilance of new therapies is critical. Advances in genomic medi cine may allow for more risk-stratified personalized care. The choice of therapy needs to be tailored to the type of cancer, expected outcomes, and patient-related risk factors for both acute and long-term toxicities. After therapy is complete, longitudinal monitoring of the health and health-related

quality of life of cancer survivors is critical since the inci dence of late effects of treatment does not appear to plateau over time. Acknowledgment We would like to acknowledge the contribution of Carl E. Freter who coauthored a previous version of this chapter; material from his chapter was retained in this version. ■ ■FURTHER READING Armenian SH et al: Cardiovascular disease in survivors of childhood cancer: Insights into epidemiology, pathophysiology, and prevention. J Clin Oncol 36:2135, 2018. Brinkman TM et al: Psychological symptoms, social outcomes, socioeconomic attainment, and health behaviors among survivors of childhood cancer: Current state of the literature. J Clin Oncol 36:2190, 2018. Chow EJ et al: New agents, emerging late effects, and the development of precision survivorship. J Clin Oncol 36:2231, 2018. Ehrhardt MJ et al: Health care transitions among adolescents and young adults with cancer. J Clin Oncol 42:743, 2024. Lustberg MB et al: Mitigating long-term and delayed adverse events associated with cancer treatment: Implications for survivorship. Nat Rev Clin Oncol 20:527, 2023.

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Hematopoietic Stem

Cells All of the cell types in the 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. 119). Stem cells produce hundreds of billions of blood cells daily from a stem cell pool that is estimated to be only 20,000–200,000. 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. The study of blood cell production has become a paradigm for how other tissues may be organized and regulated. Basic research in hema topoiesis 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 and offer models for other tissues. Moreover, these con cepts may not be restricted to normal tissue function but extend to malignancy. CARDINAL FUNCTIONS OF HEMATOPOIETIC STEM CELLS All stem cell types have two cardinal functions: self-renewal and dif ferentiation (Fig. 101-1). Stem cells exist to generate, maintain, and repair tissues. They function successfully if they can replace a wide variety of shorter-lived mature cells over prolonged periods. The pro cess 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. The 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 hours 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. The former two outcomes are the

Stem cell Self-renewal Differentiation Stem cell Differentiated cells FIGURE 101-1 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, Gfi-1, PTEN, STAT5, Tel/Atv6, p21, p18, MCL-1, Mel-18, RAE28, and HoxB4. Extrinsic signals for self-renewal include Notch, Wnt, SHH, angiogenin, 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). result of symmetric cell division, whereas the latter indicates a different outcome for the two daughter cells—an event termed asymmetric cell division. The 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 many of the macrophage-like cells that are resident in tissues: cells like microglia in the brain. The placenta and several sites of intraembryonic blood cell production then become involved in sequential order. These move from the genital ridge at a site where the aorta, gonadal tissue, and mesonephros are emerging to the fetal liver and then, in the sec ond 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 and tissue-resident mac rophages. Intraembryonic sites of hematopoiesis generate stem cells, red cells, platelets, and the circulating cells of innate immunity. The production of the cells of adaptive immunity occurs then as well but becomes robust as the thymus forms and the bone marrow is colonized in the second trimester. Stem cell proliferation remains high, even in the bone marrow, until shortly after birth, when it appears to dramati cally 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, as hemato poietic stem cells circulate throughout life. The time that stem cells spend freely circulating appears to be brief (measured in minutes in the mouse), but the stem 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 their 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 are 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.

In the adult, the role for CXCR4 is in retention of stem cells in the bone marrow as well as getting them there. Interrupting that retention process through specific molecular blockers of the CXCR4/CXCL12 interaction, cleavage of CXCL12, or downregulation of the CXCR4 receptor can 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 mac rocyclic compound that can block CXCR4, are both used clinically to mobilize marrow hematopoietic stem cells for transplant. ■ ■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 regula tory 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 also regulates 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. CHAPTER 101 Hematopoietic Stem Cells 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. The mesenchymal and endothelial cells of the marrow microvessels pro duce kit ligand and CXCL12, both known to be important for hema topoietic stem cells. Other cell types, such as sympathetic neurons, nonmyelinating Schwann cells, macrophages, megakaryocytes, osteo clasts, and osteoblasts, have been shown to regulate stem cells, some by direct and others by indirect effects. Extracellular matrix proteins like osteopontin and heparan sulfates also affect stem cell function. The endosteal region appears to be particularly important for transplanted cells, in part because many of the mesenchymal cells and sinusoidal blood vessels of the central marrow are disrupted by the conditioning regimens used to prepare a patient for transplantation. The function ing 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 as experimental models have shown that mutations in niche cells can lead to myeloid malignancies. ■ ■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 suf ficient stem cells are present to reconstitute several animals in succes sion, with each animal having normal blood cell production. The fact that allogeneic stem cell transplant recipients also never run out of blood cells over decades argues that even the limiting numbers of stem cells provided to them are sufficient. How stem cells respond to dif ferent 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 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. Mole cules 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, microRNA-processing enzymes like Dicer, or even metabolic regulators like pyruvate kinase isoforms, 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. 101-2). The maturation steps leading to terminally differentiated and functional blood cells take place both as a consequence of intrinsic changes in gene expression and external, Stem Cells Progenitor Cells Lineage Committed PART 4 Oncology and Hematology LEF1, E2A, EBF, PAX-5 Common Lymphoid Progenitor B-Cell Progenitor IL7 NOTCH1 IL7 T/NK Cell Progenitor IKAROS PU1 IL7 Lymphomyeloid Potent Progenitor Hematopoietic stem cell cMyb Multipotent Progenitor Hox, Pbx1, SCL, GATA2, NOTCH Granulocyte Monocyte Progenitor SCF TPO GM-CSF GATA1, FOG NF-E2, SCL Rbtn2 Common Myeloid Progenitor IL3, SCF TPO Megakaryocyte Progenitor Megakaryocyte Erythroid Progenitor FIGURE 101-2 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 shorter-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.

niche-directed or cytokine-directed changes in the cells. Our knowl edge of the details remains incomplete. As stem cells mature to pro genitors, precursors, and, finally, mature effector cells, they undergo a series of functional changes. These include the acquisition of functions defining mature blood cells, such as phagocytic capacity or hemoglobin synthesis. They also include the progressive loss of plasticity (i.e., the ability to become other cell types). For example, some myeloid progeni tors can make all cells in the myeloid series but none in the lymphoid series. As common myeloid progenitors mature, they become precur sors for either monocytes and

granulocytes or erythrocytes and mega karyocytes, 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. As cells differentiate, they may also lose proliferative capacity (Fig. 101-3). Mature granulocytes are incapable of proliferation and only increase in number by increased production from precursors. The exceptions to the rule are some tissue-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 Mature Cells Precursors Aiolos, PAX-5, AML-1 B Cell IL4 T-Cell Progenitor IKAROS, NOTCH,CBF1 E2A, NOTCH1, GATA3 T Cell IL2 IL7 NOTCH1 Id2, Ets-1 IL7 NK Cell IL15 NK Cell Progenitor Plasmacytoid Dendritic Cell FLT-3 Ligand Monocytoid Dendritic Cell RelB, ICSBP, ld2 FLT-3 Ligand Egn1, Myb Monocyte M-CSF Monocyte Progenitor Granulocyte C/EBPα G-CSF Basophil IL3, SCF Granulocyte Progenitor Mast Cell C/EBPε IL5 Eosinophil Erythrocyte Progenitor GATA1 RBCs EPO EPO Fli-1 AML-1 TPO Platelets TPO

Stem Precursor Progenitor Mature Differentiation state More Less Self-renewal ability Proliferation activity Lymphoid exception (memory B and T cells) FIGURE 101-3 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. 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 differentia tion 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. The time it takes for hematopoietic progenitors to become mature cells is ~10–14 days in humans, evident clinically by the interval between cytotoxic chemo therapy and blood count recovery in patients. Although hematopoietic stem cells are generally thought to have the capacity to form all cells of the blood, individual stem cells are hetero geneous in their differentiation potential. That is, some stem cells are “biased” to become mature cells of a particular type. In addition, indi vidual stem cells may respond differently to proliferation or cell death signals. Therefore, the stem cell population is an aggregate of cells with somewhat distinctive properties that have the collective characteristics ascribed to hematopoietic stem cells. ■ ■SELF-RENEWAL AND CLONAL DYNAMICS Self-renewal is the ability to divide while preserving an undifferentiated state. This stem cell characteristic is generally not seen in progenitor or mature cells where proliferation is coupled with progressive differen tiation. Stem cells being able to asymmetrically divide, such that one daughter cell is the product of self-renewal and the other enters into the differentiating progenitor pool, enables the hematopoietic system to have a modestly sized pool of stem cells yet produce seven orders of magnitude greater numbers of mature blood cells each day. Self-renewal has its risks, however. Genetic mutations that occur in a stem cell will durably persist in stem cells because of self-renewal. In contrast, mutations in progenitors will largely be lost as the cells terminally differentiate and die. It is the stem cell then that has greater potential to accumulate genetic mutations, a setting that can lead to cancer. Countering this risk is the small number of stem cells, the radioprotective environment of their bone localized niche, and the relative quiescence of stem cells. Stem cells have distinctive cell cycle regulation. Some are deeply qui escent, serving as a deep reserve, whereas others are more proliferative and replenish the short-lived progenitor population. Hematopoietic 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 abil ity 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 by blocking the G1-S transition. Exogenous signals from the niche also appear to enforce quiescence, including angio genin, interleukin 18, and perhaps angiopoietin 1.

Individual stem cells may vary in their proliferation and self-renewal features. This can lead to distortions in the representation of any given clone of stem cells, a feature commonly seen with aging and often associated with acquired somatic mutations. Hematopoietic stem cells are estimated to acquire 17 somatic mutations with each year of life based on deep sequencing studies. Some of these appear to provide a fitness advantage to the stem cell as the presence of mutated or “variant” alleles contributing to >1% of blood cells is virtually uniform by age 70. Furthermore, it is estimated that 10–20 such clones exist in individuals by 70, and in aggregate, those clones provide between 30 and 60% of the blood cells. Thus, the diversity of active stem cell clones declines with age with a likely accompanying reduced diversity of functions that each clone provides. Whether this contributes to immune alterations or other aspects of aging is to be determined. However, some expanded clones are associated with “driver” mutations observed in myelodys plasia and myeloid leukemias. These clones do have a low frequency of progression to overt neoplastic disease, and at least one of them, an inactivating mutation of TET2, can also increase adverse outcomes from a number of chronic inflammatory conditions. CHAPTER 101 The most common mutations associated with clonal hematopoiesis are of epigenetic regulatory genes. For example, inactivating mutations of the DNA methyl transferase DNMT3a or the dioxygenase involved in DNA demethylation, TET2, are commonly found, as are mutations in ASXL1, a member of the polycomb family of genes whose products alter chromatin structure, a high-order DNA organization that affects transcription. Therefore, epigenetic control appears to be critical for homeostasis of the hematopoietic stem cell pool and constraining the outgrowth of potentially pathogenic stem cell clones. Hematopoietic Stem Cells THE RELATIONSHIP OF STEM CELLS TO CANCER Some cancers have been shown to have a cellular hierarchy similar to normal tissues, with stem-like cells having the capacity to self-renew and differentiate. These stem-like cells can be experimentally trans planted into immunodeficient animals and initiate a new cancer. It is hypothesized that these stem-like cells may be the basis for disease relapse after therapy as they have distinctive molecular features from other cells in the cancer that may render them less vulnerable to therapies. Myeloid leukemias have been experimentally shown to be consistent with this model. Focusing therapies on the stem-like cells as opposed to the bulk population of the cancer cells as a means to improve cure rates is an active area of investigation. Given that hematopoietic stem cells can accumulate genetic muta tions by virtue of their self-renewal, it is logically appealing to regard them as the likely cell source of leukemias. Experimental testing of this hypothesis has shown that stem cells are more likely to result in malignancy following an oncogenic mutation. However, some more mature populations with less well-defined self-renewal capability can also be transformed to malignancy. Therefore, self-renewal may also be acquired by mutation, and cancer stem-like cells need not have originated in normal stem cells. STEM CELLS AS TARGETS OF GENE THERAPY OR GENE EDITING The hematopoietic stem cell is the ideal cell target for genetic therapies intended to durably change the genome of blood cells. Because stem cells can persist for the lifetime of an individual, genetically modify ing them can provide curative

therapies for genetic disorders such as hemoglobinopathies or congenital immunodeficiencies. The extensive cell proliferation with limited or no self-renewal among progenitor populations makes them less able to provide durable benefit if they are genetically modified. Therefore, modification of stem cells is criti cal and requires integration of the genetic therapy into the host cell’s

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