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Review

Role of key regulators of the cell cycle in maintenance of hematopoietic stem cells ☆

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ABSTRACT

Background: Hematopoietic stem cells (HSCs) are characterized by pluripotentiality and self-renewal ability. To maintain a supply of mature blood cells and to avoid HSC exhaustion during the life span of an organism, most HSCs remain quiescent, with only a limited number entering the cell cycle.
Scope of review: The molecular mechanisms by which quiescence is maintained in HSCs are addressed, with recent genetic studies having provided important insight into the relation between the cell cycle activity and stemness of HSCs.
Major conclusions: The cell cycle is tightly regulated in HSCs by complex factors. Key regulators of the cell cycle in other cell types—including cyclins, cyclin-dependent kinases (CDKs), the retinoblastoma protein family, the transcription factor E2F, and CDK inhibitors—also contribute to such regulation in HSCs. Most, but not all, of these regulators are necessary for maintenance of HSCs, with abnormal activation or suppression of the cell cycle resulting in HSC exhaustion. The cell cycle in HSCs is also regulated by external factors such as cytokines produced by niche cells as well as by the ubiquitin–proteasome pathway.
General significance: Studies of the cell cycle in HSCs may shed light on the pathogenesis of hematopoietic disorders, serve as a basis for the development of new therapeutic strategies for such disorders, prove useful for the expansion of HSCs in vitro as a possible replacement for blood transfusion, and provide insight into stem cell biology in general. This article is part of a Special Issue entitled Biochemistry of Stem Cells.

1. Introduction

Hematopoiesis is a tightly regulated process that involves self-renewal of stem cells, expansion of lineage-committed progenitor populations, and maturation of terminally differentiated cell types (Fig. 1) [1]. Once established, the hematopoietic system supplies an organism with the various blood cell lineages in a regulated manner. Regulation of the cell cycle plays a key role at each step of hematopoiesis: a low proliferation rate or quiescence is thought to be necessary for the maintenance and self-renewal of primitive stem cells, a high cycling rate is required for effective expansion of the progenitor populations, and withdrawal from the cell cycle is associated with and sometimes a prerequisite for the various functions of terminally differentiated cells [2]. Moreover, most differentiated hematopoietic cells retain the ability to reenter the cell cycle on stimulation. Such control of the cell cycle is thus important throughout the life span of an organism, given that the half-life of mature hematopoietic cells ranges from several hours to years. It underlies the continuous production of differentiated cells from hematopoietic stem cells (HSCs) as well as serves as a check on uncontrolled proliferation that might lead to carcinogenesis.

2. Molecular mechanisms of cell cycle regulation

Progression of the cell cycle is controlled by pairs of cyclins and cyclin-dependent kinases (CDKs). Progression through G_1 phase of the cell cycle is thus dependent on the cyclin D–CDK4 (or CDK6) complex, whereas cyclin E–CDK2 is required for the G_1–S transition and cyclins A and B together with CDK1 are required for G_2–M progression (Fig. 2A) [3].

Members of the retinoblastoma protein (Rb) family associate with the cellular transcription factor E2F and negatively regulate E2F-dependent transcription. Phosphorylation of Rb by cyclin–CDK complexes results in activation of E2F through relief of the inhibitory effect of Rb. E2F activity is fundamental to cell cycle progression as it regulates the transcription of genes that contribute to such key processes as DNA replication and mitosis (Fig. 2B) [4].

Cell cycle progression is also under the control of negative regulators, the CDK inhibitors (CKIs), which belong to either the Ink4 or Cip/Kip families. Members of the Ink4 family—such as $p16^{Ink4a}$ (p16),

Abbreviations: APC/C, anaphase-promoting complex/cyclosome; BM, bone marrow; CDK, cyclin-dependent kinase; CKI, cyclin-dependent kinase inhibitor; CXCL12, chemokine (C-X-C motif) ligand 12; HSC, hematopoietic stem cell; Hsc70, heat shock cognate protein 70; LAP, latency-associated protein; LLC, large latent complex; LTBP-1, latent transforming growth factor-β binding protein-1; Rb, retinoblastoma protein; SCF, Skp1–Cul1–F-box protein; TPO, thrombopoietin; TGF-β, transforming growth factor-β

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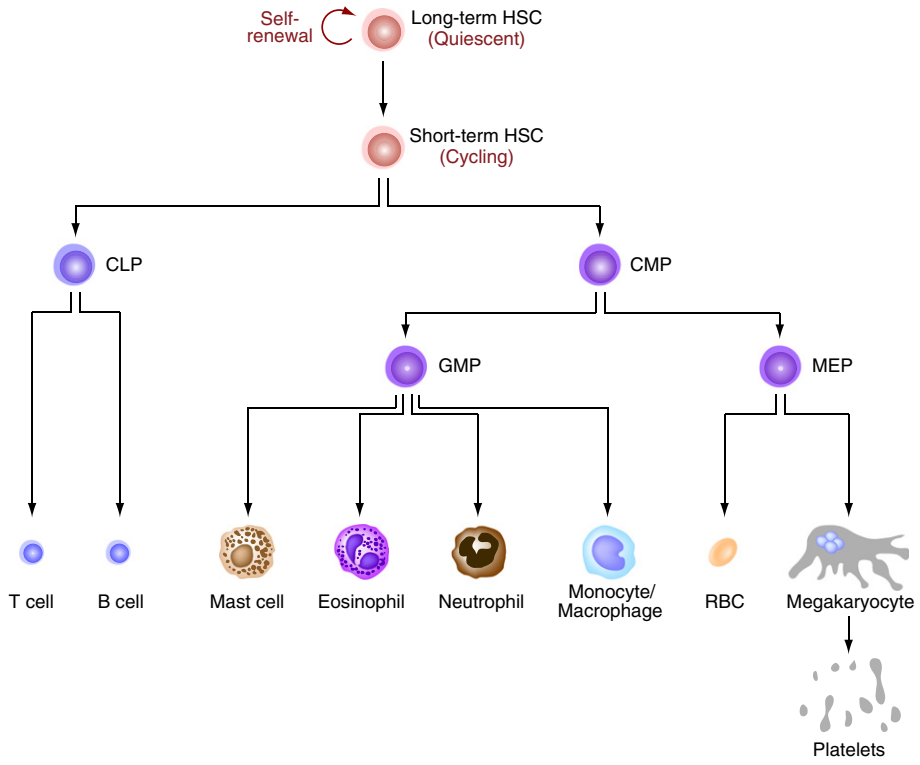

Fig. 1. Hematopoietic development. Hematopoietic stem cells (HSCs) give rise to progenitor cells that become increasingly lineage restricted and ultimately differentiate into mature blood cells of all lineages. Most HSCs, referred to as long-term HSCs, are quiescent, and they enter the cell cycle only infrequently to undergo self-renewal. Such quiescence is thought to be essential for HSC longevity and function, perhaps in part by minimizing stress associated with cellular respiration and genome replication. The transition from long-term to short-term HSCs is characterized by cell proliferation and subsequent differentiation. Common lymphoid progenitors (CLP) give rise to T cells and B cells. Common myeloid progenitors (CMP) give rise to granulocyte–macrophage progenitors (GMP) and megakaryocyte–erythroid progenitors (MEP).

$p15^{Ink4b}$ (p15), $p18^{Ink4c}$ (p18), and $p19^{Ink4d}$ (p19)—are inhibitors specific for CDK4 or CDK6, whereas those of the Cip/Kip family, including $p21^{Cip1}$ (p21), $p27^{Kip1}$ (p27), and $p57^{Kip2}$ (p57), mainly target CDK2 and CDK4/CDK6 (and CDK1 in some situations) for inhibition [5].

Regulation of the cell cycle is thought to be integral to the maintenance and function of HSCs. Mutant mice with deletions in genes encoding various cell cycle regulators thus manifest a variety of defects in HSC maintenance and function (Fig. 3).

3. Key regulators of the cell cycle in HSCs

3.1. Cyclins

3.1.1. Cyclin D

Three D-type cyclins (cyclins D1, D2, and D3) operate in mammalian cells [3,5]. These three proteins are encoded by different genes but show substantial similarity in their amino acid sequences [6,7]. The levels of D-type cyclins are controlled largely by the extracellular environment: their expression is thus induced by mitogens, and their abundance declines after the removal of such mitogens or exposure to antimitogens [8]. D-type cyclins are therefore regarded as sensors of the extracellular environment that link mitogenic signaling pathways to the core machinery of the cell cycle.

Mice deficient in individual D-type cyclins manifest only limited developmental abnormalities. The phenotype of cyclin D1-deficient mice is characterized by a reduced body size, retinal hypoplasia, a spastic leg-clasping reflex, and a slightly increased frequency of premature mortality within the first 3 weeks of life [9,10]. Female mice lacking cyclin D2 are sterile, as a result of the inability of ovarian granulosa cells to proliferate normally in response to follicle-stimulating hormone, whereas cyclin D2-deficient males, although fertile, display hypoplastic testes [11]. In addition, the proliferation of peripheral B lymphocytes is impaired in cyclin D2-deficient animals [12,13]. Cyclin D3-deficient mice are also viable but manifest defects in the maturation of T cells, B cells, and granulocytes. In contrast, the expansion of HSCs and lineage-committed myeloid progenitors appears relatively normal in mice lacking cyclin D3, suggesting that cyclin D3 is required at later stages of hematopoietic development [14–16].

Mice lacking both cyclins D2 and D3 (cyclin D1-only mice) develop severe megaloblastic anemia, those lacking both cyclins D1 and D3 (cyclin D2-only mice) manifest neurological abnormalities, and those lacking both cyclins D1 and D2 (cyclin D3-only mice) show defective development of the cerebellum. The remaining D-type cyclin in each of these double-knockout mice thus fails to compensate for the loss of the other two cyclins with regard to these specific impairments [17].

Mice lacking all three D-type cyclins (cyclin D-null mice) manifest a pronounced reduction in the number of HSCs and hematopoietic progenitor cells associated with a loss of reconstitution capacity. These animals develop severe anemia and die in utero [18].

3.1.2. Cyclin E

The two E-type cyclins in mammals, cyclin E1 (formerly termed cyclin E) and cyclin E2, show marked similarity in amino acid sequence (75% identity within the cyclin box domain; 47% overall) and are thought to be coexpressed in virtually all proliferating cells [3,5]. Cyclin E1-deficient mice manifest no obvious abnormalities and have a normal life span. Mice lacking cyclin E2 also are viable, but the mutant males display a reduced fertility as a result of defective testicular development. Endoreplication of megakaryocytes and trophoblast giant cells is severely impaired in the absence of cyclin E1 and cyclin E2, however [19,20]. Although HSCs lacking both cyclins E1 and E2 have not been fully analyzed, hematopoiesis appears relatively normal in cyclin E-null mice.

Phosphorylation within NH_2- and COOH-terminal degrons independently controls the binding of cyclin E1 to the SCF^{Fbw7} ubiquitin ligase complex, which mediates the ubiquitylation and thereby promotes the proteasomal degradation of cyclin E1 [21]. Cyclin $E1^{T74A/T393A}$

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