Review

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Special Focus – Metabolism

Surviving change: the metabolic journey of hematopoietic stem cells

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Hematopoietic stem cells (HSCs) are a rare population of somatic stem cells that maintain blood production and are uniquely wired to adapt to diverse cellular fates during the lifetime of an organism. Recent studies have highlighted a central role for metabolic plasticity in facilitating cell fate transitions and in preserving HSC functionality and survival. This review summarizes our current understanding of the metabolic programs associated with HSC quiescence, self-renewal, and lineage commitment, and highlights the mechanistic underpinnings of these changing bioenergetics programs. It also discusses the therapeutic potential of targeting metabolic drivers in the context of blood malignancies.

Hematopoiesis: an ever-changing developmental system

The blood system is one of the most dynamic tissues in mammals, with an extremely high cellular turnover on a daily basis. Given that most mature blood cells have short lifespans, the onus of maintaining blood homeostasis rests almost entirely on the self-renewal and differentiation capabilities of a long-lived but rare population of somatic stem cells, the HSCs. HSCs can maintain themselves and generate all types of mature blood cells through the production of a series of increasingly committed progenitor cells [1]. It is now recognized that the biological properties of HSCs are not constant throughout life but vary temporally to meet the shifting demands of an evolving organism [2]. During embryonic development, fetal HSCs emerge from various hemogenic endothelia and are programmed to be highly proliferative. This cycling state allows rapid production of mature blood cells to meet the immediate requirements of a developing embryo, while simultaneously building a reservoir of expanding fetal HSCs to colonize the emerging sites of adult hematopoiesis. In adults HSCs are mainly found in specialized niches in the bone marrow (BM) cavity and are programmed for enforced quiescence. This dormancy state allows adult HSCs to stay poised for quick and massive production of blood cells in emergency situations, while simultaneously limiting their proliferation to homeostatic production of blood cells. Hence, at steady-state, adult HSCs divide only rarely to maintain low production of committed progenitor cells and renew the HSC pool. In mice, although the majority of adult HSCs divide on average once every 30 days [3], a small subset of deeply quiescent HSCs has been found to cycle on average once every 145–193 days [4,5]. However, HSCs can rapidly respond to cues produced by the environment following stress or damage, and exit from quiescence to replenish the injured blood system. Finally, with age, HSCs increase in numbers but show severe functional decline [6]. This reduced functionality of old HSCs leads to impaired blood production, with characteristic anemia and immunosenescence features, and increased age-dependent incidence of diverse blood disorders including BM failure, myeloproliferative neoplasms (MPN), and leukemia [7]. Therefore, one of the most striking features of HSCs is their ability to adapt to the changing needs of the blood system. In addition, each of the different cellular states in HSCs (i.e., quiescence, proliferation, and differentiation) imposes a unique set of bioenergetic demands [8]. This review focuses on describing the unique bioenergetic properties of HSCs and the signaling networks that act as metabolic sensors in HSC regulation. It also highlights the major metabolic regulators that have emerged as potential therapeutic targets in blood malignancies.

HSC biology: a dynamic metabolic landscape

Cellular metabolism involves a tug-of-war between energy-producing catabolic processes and energy-consuming anabolic processes [9]. Transitioning between different cellular states requires HSCs to depend on a flexible balance among these energy processes. Therefore, one of the defining features of HSCs is their metabolic plasticity, and this underlies the successful transitions of HSCs from dormancy to activity.

Quiescence – the anaerobic bias

Quiescence provides an effective barrier against the onset of blood disorders by preserving the integrity and function of HSCs via limitation of cellular damage from mitochondria respiration and cytotoxic agents, and by preventing HSC exhaustion due to uncontrolled cell cycle entry and excessive proliferation [10,11]. Accumulating evidence indicates that although HSCs carry higher levels of mitochondria relative to other primitive blood cell types, they are less active, as determined by lower mitochondrial membrane potential and ATP levels, and by greater reliance on anaerobic glycolysis relative to oxidative

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phosphorylation and the tricarboxylic acid (TCA) cycle [12–14]. In fact, isolation techniques based on low mitochondrial activity and high endogenous NADH fluorescence can enrich for engrafting HSCs [12], and a recent metabolomic study demonstrating elevated levels of glycolytic intermediates and byproducts such as fructose 1,6-bisphosphate and pyruvate, and a relative absence of TCA cycle-related metabolites, in quiescent HSCs [14] further supports the idea of a glycolytic bias in HSCs. Anaerobic glycolysis, where pyruvate (the glycolytic end-product) is directed towards lactate production, is not an efficient energy-producing process because it generates only two ATPs per molecule of glucose – as opposed to oxidative phosphorylation where pyruvate enters the mitochondrial TCA cycle and generates 36 ATPs per glucose molecule [9]. However, it likely suffices for a quiescent population that has relatively low energy demands and a greater need to prevent the production of reactive oxygen species (ROS) as byproducts of active mitochondria [15]. Understanding whether enforcement of anaerobic glycolysis in HSCs is the product of niche regulation or the result of cell intrinsic wiring is currently the topic of active research in the field. A series of publications have inspired a model where anaerobic glycolysis is driven by the residence of HSCs in low oxygen pockets in the BM, and adaptation to these 'hypoxic niches' remodels the metabolic profile of postnatal HSCs and induces quiescence [12,16–18]. This idea is supported by several lines of evidence including mathematical modeling of the BM cavity, which suggests that HSCs reside in areas of low oxygen supply [19]; the enhanced incorporation of pimonidazole (Pimo), which forms adducts with cellular proteins under low oxygen states, in HSCs [12,16,20]; the stable expression of the α subunit of hypoxia-inducible transcription factor 1 (HIF-1α), which undergoes proteasomal degradation when oxygen levels exceed 5% in HSCs [12,20]; and the *in vivo* loss of HSCs following injection of tirapazamine, a toxin selective for hypoxic cells [16]. However, comprehensive mapping of the spatial distribution of HSCs in femoral BM cavities using laser scanning cytometry demonstrates that the hypoxic profile of HSCs, based on Pimo incorporation and HIF-1α expression levels, is not related to the localization of HSCs in regions of minimal oxygen supply [21]. This study raises the possibility that HSCs can stabilize HIF-1α through oxygen-independent mechanisms [22,23], and this highlights the need for caution when directly correlating these assays with oxygen defects. It also indicates that the glycolytic profile of HSCs is not merely a product of their BM microenvironment but relies heavily on cell intrinsic mechanisms. In turn, this idea is supported by the fact that HSCs strongly express the CRIPTO protein, an extracellular factor essential for early vertebrate development, which induces the expression of many glycolytic enzymes [24]; and, that HIF-1α actively promotes anaerobic glycolysis in HSCs by preventing pyruvate from entering the TCA cycle via upregulation of several pyruvate dehydrogenase kinases (PDKs) including PDK2 and PDK4 [14]. In addition, HIF-1α levels are regulated by the homeobox transcription factor MEIS1 (myeloid ecotropic viral integration site 1 homolog), and deletion of either *Hif1a* or *Meis1* results in loss of quiescence and HSC dysfunction [12,25]. Together, these studies point towards the active cooperation of an array of cell extrinsic/niche-related and cell intrinsic mediators to cement a strong glycolytic bias in HSCs. However, it remains to be established whether HSCs solely rely on anaerobic glycolysis for maintenance of quiescence, and how this anaerobic bias is relieved when HSCs shift to a more energy-consuming active state. Recent findings summarized below have started to provide insights into these outstanding questions.

Commitment – burning fat to determine fate

As HSCs exit quiescence and re-enter the cell cycle, the choice between asymmetric and symmetric divisions constitutes one of the first important decision points governing their fate. Asymmetric division generates two cells with different fates, and this allows maintenance of the HSC pool and the generation of differentiating progeny during homeostatic blood production. By contrast, symmetric division generates two cells with equivalent fates, and can either expand the HSC pool or increase the number of differentiating cells in conditions of emergency hematopoiesis. A shifted balance between asymmetric and symmetric HSC divisions is also often associated with disease conditions including BM failures and leukemic transformation [26]. Strikingly, fatty acid oxidation (FAO) has emerged as a crucial determinant of these fate decisions in HSCs. FAO consists of a series of biochemical reactions that result in the progressive shortening of fatty acids and the production of acetyl CoA, which can enter the TCA cycle and generate, via β-oxidation, both NADH and $FADH_2$, and twice as much ATP as carbohydrate metabolism [27]. Members of the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors are important regulators of FAO [28], and PPARδ deletion or direct pharmacological inhibition of FAO results in HSC loss and concomitant accumulation of committed progenitor cells [29]. This progenitor expansion is due to a decrease in the number of asymmetric divisions with a concomitant increase in differentiation-inducing symmetric divisions, thereby impairing HSC self-renewal activity and promoting HSC exhaustion. The promyelocytic leukemia (PML) tumor-suppressor protein, which is also implicated in HSC maintenance [30], is one of the key regulators of the FAO pathway in HSCs [29]. However, the mechanism by which the PML/PPARδ/FAO metabolic axis normally promotes HSC self-renewal and opposes HSC commitment still remains largely unknown. Based on the observation that both PML and FAO can sustain ATP levels in breast epithelial cells that have lost contact with the extracellular matrix [31], it is proposed that the PML/PPARδ/FAO metabolic axis might support asymmetric divisions by supplying enough ATP molecules to HSCs when they lose contact with the BM niche during cell division [29]. However, this possibility remains to be tested directly. Interestingly, PML has also been implicated in the onset of p53-dependent aging through induction of premature senescence [32]. Although cellular senescence is not a readily accepted feature of aged HSCs [33,34], a p53-dependent proliferation decline is actually observed in the expanded but functionally deficient pool of old HSCs [35], hence reinforcing the idea of a functional link between PML,

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