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Metabolic Plasticity and Hematopoietic Stem Cell Biology

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Abstract

Purpose of review—Hematopoietic stem cells (HSCs) residing in the hypoxic niches can both self-renew and give rise to progeny. Multiple regulatory mechanisms for these cellular processes have been identified. Emerging evidence has revealed that metabolism and bioenergetics play important roles in determining stem cell fate in concert with other regulatory networks. In this review, we will discuss recent advances in this field.

Recent findings—Recent studies have helped define and redefine metabolic regulation of HSCs. Resting quiescent stem cells use primarily anaerobic glycolysis for energy production and this metabolic program is required to maintain a functional quiescent state. However, when they exit this state and rapidly proliferate and differentiate into different blood cell types, a robust upregulation of energy metabolism is expected to meet the quickly rising energy demand. Dysregulation of metabolism in HSCs results in various blood disorders, including leukemia.

Summary—Energy metabolism and HSC activity influence and interlink each other in a highly sophisticated and orchestrated manner. Understanding metabolic regulation of HSC function has significant implications for HSC-based therapies and leukemogenesis research.

Keywords

Hematopoietic stem cell; Self-renewal and differentiation; Mitochondria; Metabolism; Bioenergetics

Introduction

Mammalian hematopoietic stem cells (HSCs) are maintained in a resting quiescent state in specialized hypoxic niches within the bone marrow [1, 2]. In response to changes in the microenvironment, they can exit this state and rapidly proliferate and differentiate into different blood cell types. Many regulatory mechanisms have been found to coordinate these cellular processes. In addition to environmental cues and the intracellular signaling pathways activated by these signals, cell intrinsic mechanisms such as genetic and epigenetic regulations are also critical in determining stem cell behavior. Emerging evidence has suggested that metabolism and bioenergetics also cooperatively coordinate HSC maintenance and lineage differentiation with other regulatory mechanisms. Bioenergetics and HSC activity influence and interlink each other in a highly sophisticated and

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orchestrated manner. In this review, we will summarize recent studies regarding energy metabolism associated with HSCs at different stages and various signaling pathways affecting HSC metabolism.

Self-renewal vs. Differentiation

HSCs are a rare population of hematopoietic cells that are early precursor cells responsible for maintenance of hematopoietic homeostasis. These cells reside in hypoxic niches and they have unlimited capacity for self-renewal, producing new stem cells [1, 2]. Stem cells can also give rise to various lineage-committed progenitors, a process known as differentiation. These progenitors can then further expand and divide to maintain and replenish all of the blood cell lineages throughout the lifetime of an organism. Stem cell self-renewal and differentiation are highly regulated in response to physiological and disease conditions.

HSC self-renewal and differentiation are fundamentally linked to cell division that appears to be associated with cell metabolism. HSC maintenance relies on their asymmetric division [3], which produces two distinct populations of daughter cells varying in the amount of mitochondria [4, 5]. It has been suggested that such an asymmetric division of stem cells allows one group to lose the undesired mitochondria, thus minimizing production of reactive oxygen species (ROS), a byproduct of mitochondrial respiration during energy production, and become the stem group, while the other group to accumulate activated mitochondria and commit to differentiation. The notion that HSC division is coupled with metabolism is strongly supported by the recent study showing that fatty acid oxidation is critical for the asymmetric division of HSCs. Disturbance to the PML-PPAR- δ -fatty acid oxidation pathway results in excessively symmetric daughter cells after division, negatively impacting HSC maintenance [6*].

Quiescence vs. Cycling

Hematopoietic cells are generally classified as quiescent or cycling, with quiescence also defined as slow-cycling and cycling classically considered as fast-cycling. Ample evidence suggests that long-term HSCs are dormant/quiescent and reside in the hypoxic niches within the bone marrow [7, 8]. Quiescence is regarded as a mechanism to minimize accumulation of cellular damage due to physiological or oxidative stress as well as to potentiate life-long self-renewal capacity [8, 9]. In terms of molecular morphology and functionality, there are some marked distinctions between quiescent stem cells and actively-cycling progenitors. Recent studies have demonstrated that the mitochondrial content in HSCs is lower than that in progenitors from later stages [4, 5] and mitochondrial activities in these HSCs are relatively inactive [10]. In addition, in comparison to fast-cycling stem cells and progenitors, slow-cycling (quiescent) HSCs possess long-term reconstitution activity and are characterized by lower mitochondrial membrane potential, lower endogenous NADH fluorescence, lower oxygen consumption, lower ATP levels, and greater need for glycolysis [10–12].

It is well known that although detrimental when in excess, at physiological levels, ROS serve as signaling molecules for various biological responses necessary for cellular functionality [13]. Physiological induction of ROS in stem and progenitor cells is regulated by many factors. Recent studies have demonstrated that developmentally regulated, moderately high ROS levels prime hematopoietic stem/progenitor cells for differentiation whereas those cells with low levels of ROS retain their long-term self-renewal capability [14–17]. ROS levels are associated with the microenvironment that HSCs reside in. There are two proposed microenvironments within the bone marrow that are thought to give rise to the unique niche of HSCs, one being the endosteal niche and the other one as the vascular

niche, both being low-oxygen which limit ROS production and thus confer long-term protection for HSCs from oxidative stress [8, 18].

Multiple regulators of ROS involved in HSC function have been studied. Elevated levels of ROS in HSCs result in severe defects in stem cell maintenance. For example, lack of polycomb repressor Bmi1 results in impaired mitochondrial function, reduced ATP, markedly increased ROS, and DNA damage in HSCs [19]. Loss of ATM (ataxia telangiectasia mutated) leads to progressive bone marrow failure resulting from a defect in HSC function that was associated with elevated ROS, demonstrating that the self-renewal capacity of HSCs depends on ATM-mediated inhibition of oxidative stress [14]. The FoxO transcription factors that are important for the expression of antioxidant enzymes also protect HSCs against oxidative stress. Defective self-renewal of HSCs associated with a marked increase in ROS is observed following depletion of FoxOs [16].

Glycolysis vs. Mitochondrial oxidative phosphorylation

Cells from different stages require different, yet specific, metabolic flexibility in order to support the intrinsic and unique bioenergetic demands, a process that involves meticulous calibration between anabolic and catabolic needs. Therefore, as cells transition from quiescence to an actively-cycling state, they alter their metabolism accordingly. Mitochondria are highly dynamic organelles that serve to regulate and generate energy depending on the intrinsic metabolic demand within a specific cell type where glucose-derived pyruvate, fatty acids, and amino acids are used as substrates for ATP synthesis via oxidative phosphorylation. Compared to mitochondrial oxidative phosphorylation, glycolysis is a low efficiency energy producing pathway where pyruvate is shunted to the cytosol to generate lactate. In embryonic stem cells (ESCs), metabolism must be reprogrammed during maintenance and differentiation. It has been observed that pluripotent ESCs rely heavily on glycolysis for energy metabolism [9, 20]; they require a high flux of glucose uptake and lactate production, even under aerobic conditions outside of the hypoxic blastocysts. In contrast, differentiating cells often require lower rates of aerobic glycolysis and shunt most of their cytosolic pyruvate into the mitochondria where it is oxidized for ATP synthesis via the Krebs cycle and electron transport chain.

Recent evidence suggests that mitochondrial spare respiratory capacity, defined as the extra capacity a cell has to produce energy or to induce mitochondrial biogenesis, is crucial for T cell survival, maintenance, and functionality or efficiency [21]. Activation of T lymphocytes from a resting quiescent state triggers a dramatic increase in glucose transport and metabolism. Quiescent lymphocytes derive most of their ATP from oxidative phosphorylation [22]. In contrast, activated lymphocytes depend heavily on glucose to serve as a carbon source and provide the needed ATP for biosynthesis and secretion. In HSCs, requirements of energy and reducing cofactors must not occur at the expense of exhaustion of biosynthesis of cell building blocks. Therefore, in addition to providing ATP and NADPH, increased expression of glycolytic enzymes and glycolysis serve to fuel anabolism for stem cell maintenance and self-renewal, prolonging cellular lifespan [23, 24]; this enriched glycolysis-dependent pathway along with reduced oxidative capacity and lower mitochondrial activity have all been proposed as markers of stemness [5, 9, 11, 25]. Similar to pluripotent ESCs, HSCs rely mainly on glycolysis and increase oxidative phosphorylation as they differentiate. HSCs, unlike their progeny, have high levels of pyruvate kinase and accumulate high levels of fructose-1,6-bisphosphate, a metabolite of cytosolic glycolysis [26*]. However, due to quiescence, a high cell replication rate does not seem to be the main reason for which HSCs preferentially employ glycolysis as their energy source. Rather, such behavior seems to stem from the adaptation of HSCs to their hypoxic niche [8]. One obvious advantage of this relative dependence on glycolysis versus oxidative phosphorylation has to

do with the reduction of ROS production. As previously mentioned, ROS, mainly generated from the mitochondria, aid in various signaling pathways necessary for normal HSC functions at physiological levels. However, excessive ROS can damage macromolecules such as DNA, proteins, and lipids, contributing to aging and cell death. Therefore, stemness seems to be directly related to low levels of ROS in HSCs. When HSCs undergo differentiation, the metabolic reprogramming from glycolysis to mitochondrial oxidative phosphorylation must occur in order to fulfill the robust energy demand. Depletion of PTPMT1, a PTEN-like mitochondrial phosphatidylinositol phosphate phosphatase required for mitochondrial aerobic metabolism, causes hematopoietic failure due to a block in the differentiation of HSCs, suggesting that mitochondria must be primed for the rapid metabolic transition during HSC differentiation [27*].

Cancer cells are on the same spectrum but at the opposite pole from HSCs. Therefore, though extremely interesting, it should not be a surprise that dysregulation of stem cell metabolism is indeed leukemogenic [28]. In fact, gain-of-function mutations in the IDH1 and IDH2 genes, which encode isocitrate dehydrogenases, are commonly found in both glioblastomas and acute myeloid leukemias [28, 29]. In vivo and in vitro studies have both been able to demonstrate that, via elevated conversion of α -ketoglutarate into 2-hydroxyglutarate (2-HG), an oncometabolite, epigenetic regulations are altered and multiple cellular processes are disrupted, leading to increased hematopoietic progenitor cells and impaired myeloid differentiation [30*, 31, 32]. IDH1 mutation knock-in mice manifest increased numbers of early hematopoietic progenitors associated with bone marrow dysfunction and extra-medullary hematopoiesis [30]. In short, 2-HG inhibits TET1/2, JmJc-HDs, C-P4H1-3, PLOD1-3, and PHDs, leading to hypermethylation profiles seen in IDH1/IDH2 mutant acute myeloid leukemia and dysfunctional angiogenesis in the brain [32].

Additionally, emerging evidence also indicates that mitochondrial substrate accessibility and utilization can influence HSC activities, and cellular differentiation may be intimately tied to the balance between glucose and fatty acid oxidation. Remarkable differences are observed in terms of nutritional sources and usage in cells cycling at various rates. It has been found that activated proliferating T cells mainly use glucose as their energy source, whereas quiescent naïve and memory T cells break down glucose, amino acids, and fatty acids interchangeably for energy [22, 33]. Glucose oxidation is required for activation of T cells from quiescent naïve state to proliferating state, whereas increased fatty acid oxidation promotes the switch from growth to quiescent survival and markedly enhanced memory T cell development [22, 33]. In HSCs or ESCs, while mitochondrial fatty acid oxidation promotes maintenance of stemness [6], glucose-derived pyruvate oxidation in the mitochondria is required for anabolism and energy demand during the fast cycling differentiation. This notion is supported by recent findings that ectopic expression of mitochondrial uncoupling protein 2 (UCP2) blocks ESC differentiation by perturbing the metabolic transition from glycolysis to mitochondrial aerobic metabolism required for ESC differentiation [34] and that enhanced UCP2 activity by the accumulation of phosphatidylinositol phosphate substrates of the mitochondrial phosphatase PTPMT1 is associated with a differentiation block of PTPMT1 knockout HSCs [27]. UCP2 may regulate cellular bioenergetics by controlling mitochondrial substrate utilization. Specifically, increased UCP2 activity inhibits pyruvate entering into the mitochondria for Krebs cycle utilization while facilitating the oxidation of alternative carbon sources, such as fatty acids and glutamine [35, 36].

Signaling pathways regulating bioenergetics

Several pathways have been studied in attempts to better define metabolism and bioenergetics in HSCs. Aside from cell signaling pathways involved in self-renewal and

maintenance of HSCs, recent research advances have also furthered our understanding in cell signaling that connects mitochondrial biogenesis, changes in the levels of ROS, and HSC behavior. A key hypoxia response machinery in regulating HSC maintenance and differentiation is HIF-1 α [37]. HIF-1 α , a transcription factor highly expressed in long-term HSCs, mediates cellular and systemic responses to reduced oxygen availability via anaerobic-biased energy metabolism rather than oxidative phosphorylation, promoting hematopoietic maintenance by reducing production of ROS [8, 37]. HIF-1 α deletion in mice results in a loss of stem cell quiescence associated with decreased long-term reconstitution ability in transplantation assays [37]. Recent studies demonstrate that HIF-1 α regulates energy metabolism through upregulation of pyruvate dehydrogenase kinases (PDK) 2 and 4, which inactivate pyruvate dehydrogenase that is required to convert pyruvate to acetyl-CoA to feed the Krebs cycle and engage in oxidative phosphorylation [26]. In addition, many other transcriptional factors play important roles in HSC metabolism through interacting with HIF-1 α . For example, loss of Meis1 results in downregulation of HIF-1 α and HIF-2 α , leading to increased ROS production, loss of hematopoietic quiescence, and apoptosis [38].

Of equal importance as the HIF-1, the TSC-mTOR pathway maintains HSC quiescence via repression of mitochondrial biogenesis, therefore reducing the production of ROS and is implicated in leukemogenesis, though the exact mechanisms seem to be different in adult versus neonatal HSCs [39, 40*, 41]. Lack of TSC, an mTOR inhibitor, drives HSCs from quiescence into rapid cycling via increased mitochondrial biogenesis [39]. However, not all regulators downstream of TSC affect ROS [42]. AKT kinase that phosphorylates and inhibits TSC promotes HSC transition from quiescence to myeloid-biased commitment in a ROS-dependent fashion and evidence has revealed that constitutively active AKT leads to hematopoietic stem cell exhaustion, bone marrow failure, myeloproliferative disease, and/or acute myeloid leukemia [43, 44]. In addition, LKB1, a tumor suppressor that phosphorylates and activates the energy sensor AMPK in response to a decline in the ATP/AMP ratio [45], maintains HSC quiescence. LKB1 inactivation leads to a loss of HSC quiescence followed by rapid depletion of all hematopoietic subpopulations, mitochondrial defects, elevated long-chain fatty acids and nucleotide metabolites, and reduced PGC1 α/β expression [46–48]. Interestingly, the hematopoietic effects are also found to be AMPK- and mTOR-independent, raising the possibility that LKB1 restricts HSC entry into cell cycle also through a novel metabolic checkpoint [46–48].

Knowing that anaerobic glycolysis is necessary for the maintenance of a functional quiescent HSC population and that dysregulation of anaerobic glycolysis results in the loss of HSC functional quiescent state and self-maintenance, mitochondrial bioenergetics appears to be selectively important for differentiation versus self-renewal in stem cells. However, how does the coordination and regulation of mitochondrial metabolism ultimately affect HSC function? The bioenergetic stress-induced differentiation checkpoint seems to be a reasonable and promising hypothesis. This concept is supported by recent evidence showing that mitochondrial metabolic defect in PTPMT1 knockout HSCs causes a differentiation block by inducing cell cycle changes [27]. Though differentiation of PTPMT1 knockout HSCs is completely blocked and they are delayed in the G1 phase, these cells are found to be still cycling in vivo as the percentage of S/G₂/M cells is comparable to that of control cells; since the stem cell pool in knockout mice is drastically expanded, these cell cycle changes appear to mainly affect the differentiation but not self-renewal-associated cell division. The mitochondrial bioenergetic stress signal elicited by PTPMT1 ablation appears to be propagated and amplified through the p53-p21/p57 pathway, similar to the DNA damage-induced cell cycle checkpoint [49]. As the energy stress sensor AMPK is highly activated in the PTPMT1 knockout stem cells and activation of AMPK has been demonstrated to induce p53-dependent cell cycle arrest [50], it is likely that the mitochondrial metabolic stress caused by PTPMT1 deficiency is sensed by AMPK and then

relayed to the cell cycle machinery through the p53-p21/p57 axis [27]. It remains to be determined whether or not a similar pathway is activated by mitochondrial energetic stress in other models.

Conclusion

In this review, we have summarized recent studies regarding HSC quiescence, mitochondrial bioenergetics, and signaling pathways affecting HSC metabolism and thereby self-renewal and differentiation (Figure 1). Though our knowledge has greatly advanced in these fields, many interesting questions still remain. For example, in quiescence, is the relative dependence on glycolysis an adaptive strategy to the hypoxic niche or is it an intrinsic criterion for stemness? How is energy metabolism so quickly switched between glycolysis and mitochondrial oxidative phosphorylation during HSC self-renewal and differentiation? Finally and importantly, can we improve normal stem cell therapies or target cancer stem cells by manipulating the metabolic pathways? In addressing these and other questions, future research will help shape the path of stem cell research as well as therapeutic considerations in various diseases.

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Key Points

1. Metabolism plays an essential role in determining hematopoietic stem cell behavior.
2. While glycolysis is essential for stem cell maintenance, mitochondrial oxidative phosphorylation is required for stem cell differentiation.
3. Dysregulation of metabolism in hematopoietic stem cells leads to blood disorders.

Figure 1. Metabolic plasticity in hematopoietic stem cells

Hematopoietic stem cells (HSCs) residing in the hypoxic niches use primarily glycolysis for energy production. Also, fatty acid metabolism is required for the self-renewal associated asymmetric division in HSCs. Upon differentiation of HSCs, cellular metabolism must be switched to mitochondrial oxidative phosphorylation in order to meet the robust energy demand required for this cellular process. The metabolic reprogramming to mitochondrial aerobic metabolism leads to increased levels of cellular reactive oxygen species that prime HSCs for differentiation.