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Review Article

Hypoxic Niche of Glycolytic Stem and Progenitor Cells

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Abstract

Stem cells are crucial for tissue homeostasis and repair. They maintain themselves by self-renewal in an undifferentiated state while generating differentiated cells. Adult stem cells including hematopoietic stem cells (HSCs) reside in their respective hypoxic niche, which protects them from oxidative damage. However, survival in this low-oxygen microenvironment requires some significant metabolic adaptations, such as utilization of glycolytic metabolism instead of mitochondrial respiration, which is regulated by the transcription factors Hif-1α and Meis1.In addition to HSCs, glycolytic cardiac progenitors (GCPs) expressing Hif-1α havealso been shown to reside in a hypoxic niche and share similar metabolic properties with HSCs. This review provides insights into hematopoietic and cardiac hypoxic niche and Meis-Hif axis in the regulation of stem cell metabolism and function.

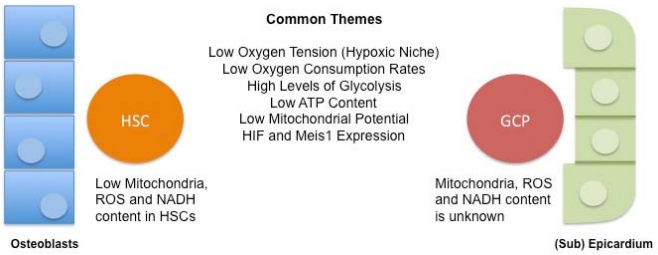
ABBREVIATIONS

HSCs: Hematopoietic Stem Cells; **HIF**: Hypoxia-Inducible Factor; **GCP**: Glycolytic Cardiac Progenitors.

HIGHLIGHTS

- Hypoxia plays a major role in the determination of stem cell and progenitor niche
- Metabolic adaptation to hypoxic environment is essential for stem cell survival and self-renewal
- Transcriptional regulation of HIF family by Meis1 is crucial for bona fide glycolytic metabolism and stem cell function in the hypoxic microenvironment.

GRAPHICAL ABSTRACT



INTRODUCTION

Tissue homeostasis and repair are dependent on stem cells, which maintain themselves in an undifferentiated state by undergoing self-renewal while generating required differentiated cells [1-3]. Stem cells have been extensively studied for treatment of a wide range of diseases including neurological disorders, heart failure, diabetes, spinal cord injury, leukemia and so on. Hematopoietic stem cells (HSCs) are among the most widely studied adult stem cells due to their incredible potential [4]. They are generally kept quiescent, maintained at G_0 phase of cell cycle and divide only in response to stimulus to replenish blood components. Their maintenance during the life of an organism requires complex interplay between extrinsic and intrinsic factors such as growth factors, transcription factors and cell cycle regulators [5,6].

One of the most critical areas of research is regulation of cell cycle, as it has wide implications in regenerative biology and cancer [7]. Cell cycle regulation is a highly complex process that involves hundreds of genes that regulates cell cycle progression through cell cycle checkpoints, namely G1, G2 and Metaphase checkpoints [8]. Lessons learned from the cancer field indicate that dysregulation of cell cycle checkpoints and metabolism occur hand in hand [9]. Cancer cells preferentially metabolize glucose at higher rates using glycolysis, which is known as Warburg effect [1,10,11]. This provides a short cut to produce enough ATP to meet energy demand. One accepted reason for preferential use of glycolysis by cancer cells *in vivo* is the lack of adequate supply of oxygen [12,13]. The use of anaerobic glycolysis confers survival advantage to cancer cells in this hypoxic environment. Similarly, several stem cells have been reported to reside in hypoxic niches, which suggest presence of unique metabolic adaptations in stem cells [14-16]. However, until recently metabolic phenotype of stem cells and how metabolism of stem cells is linked to their cell cycle was unknown [17-20]. This review summarizes recent studies on metabolic phenotype of stem cells and how this is related to stem cell niche, and stem cell function.

Stem Cell Niche

Stem cells are distinguished by their ability to remain undifferentiated and capacity to undergo self-renewal, which allow them to proliferate during fetal development and to be maintained throughout adult life [2,8,21-23]. An emerging hallmark of stem cell function relies on the specialized microenvironments, called niche. Stem cell niches are initially described in worms and flies, and later in mammals and defined as a microenvironment that supports the function and maintenance of stem cells trough integration of local and systemic factors (Doetsch et al., 1999a; Doetsch et al., 1999b; Kimble and White, 1981; Mohyeldin et al., 2010; Spradling et al., 1997; Xie and Spradling, 1998). Several adult stem cells has been suggested to reside in niches which show low partial pressure of oxygen, namely hypoxia [9,15,24-28]. Neuronal stem cell niches, for instance, demonstrate characteristics of hypoxic niche, where neuronal stem cells located in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus[1,29]. Mesenchymal stem cells (MSCs), however, are located in almost all tissues in relatively hypoxic perivascular niches [12,26] (Crisan et al., 2008; Pasarica et al., 2009). Moreover, hematopoietic stem cells, which are among the most widely studied adult stem cells, have been show to reside in the hypoxic endosteal regions of bone marrow[14,30].

Hypoxic Hematopoietic Stem Cell Niche

HSCs are classified by their repopulation ability in lethally irradiated recipients. The cells that can repopulate and maintain hematopoietic system for rest of the life are defined as Long-term HSCs (LT-HSCs) (Figure 1). While HSC isolation relies on the expression of surface antigens or transporters[17,26,31], functional properties of HSCs remains to be determined for HSC enrichment protocols.

HSC are known to reside in specialized niches within the bone marrow[21,32]. Previous studies suggest that the HSC niche in the endosteal regions of the bone marrow has limited perfusion and low levels of partial pressure of oxygen(PO_2) (average fifty-five mmHg) [24,26,28,33,34]. In addition, cells away from capillaries have been estimated to show 10-fold lower levels of PO_2[29,35-37]. Moreover, perfusion studies, using a Hoechst staining technique, demonstrated that HSCs predominantly reside in low perfusion compartments in the bone marrow[26,38]. However, a recent study revealing perivascular localization of hematopoietic progenitors indicates that hypoxic phenotype of HSCs may not be reflect their residency in the endosteal compartments [30,35,39,40]. On the other hand, HSCs are sensitive to hypoxic cytotoxintirapazamine and show staining of hypoxia probe pimonidazole *in vivo*[26,41]. *In vitro* studies also indicate that HSC function and reconstitution ability are well preserved upon culturing in hypoxic conditions[32,42] [10,33,34,43].Finally, several reports also support the role of hypoxia inthe maintenance of HSCsquiescence(Goodell et al., 1996; Hermitte et al., 2006; Kim et al., 2002; Scharenberg et al., 2002; Shima et al., 2010). These findings suggest that HSCs reside in a hypoxic microenvironment and indicate the importance of hypoxia signaling in HSCs.

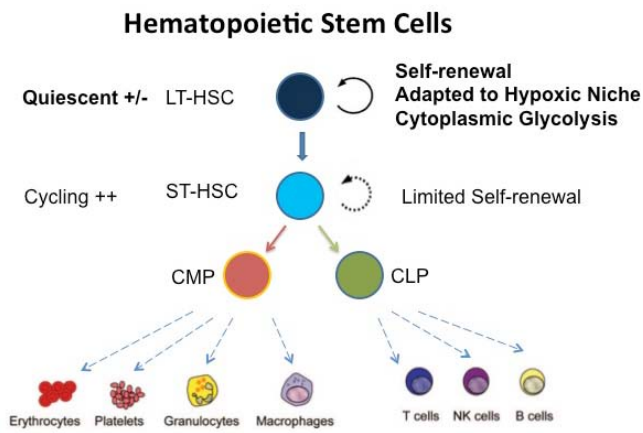


Figure 1 Hematopoietic Stem Cells. Long-Term HSCs (LT-HSCs) are known as true stem cells of the hematopoietic system and characterized by unlimited self-renewal, adaptation to hypoxic niche and preferential utilization of cytoplasmic glycolysis rather than mitochondrial oxidative phosphorylation. LT-HSCs give rise to short-term HSCs (ST-HSCs), which are followed by increased proliferation and differentiation into common myeloid progenitors (CMP) or common lymphoid progenitors (CLP) and other blood lineages.

Hypoxia Signaling

All mammals express a highly conserved transcriptional complex that responds to decreased oxygen levels, namely hypoxia inducible factor (HIF)[35-37,44]. Hif-1 belongs to PER-ARNT-SIM subfamily of the basic helix-loop-helix (bHLH) family of transcription factors. It is composed of oxygen regulated Hif-1α subunit and constitutively expressed Hif-1β subunit. Hif-1α initially discovered as the transcriptional regulator of erythropoietin gene (EPO) that controls the erythrocyte production. Hif-1α activity is inherently dependent on oxygen levels and is unstable at normoxia (20% oxygen) such that its half-life is shorter than five minutes[38]. In normoxia, Hif-1α is hydroxylated by prolyl-hydroxylases (PHDs) and degraded through the ubiquitin-proteasome pathway following interaction with the von Hippel-Lindau (VHL) protein[35,39,40]. PHDs use oxygen and α-ketoglutarate as substrates to undergo enzymatic reactions to modify two proline residues (P402 and P564) of Hif-1α[41]. Hydroxylation of Hif-1α recruits VHL protein, which interacts with ElonginBC/E3 ubiquitin-protein ligase for ubiquitination and degradation by proteasome complex. Under hypoxia, however, hydroxylation of prolyl residues is inhibited, which results in stabilization, formation of the Hif-1 complex,nuclear translocation, and transactivation of downstream genes.

Hif-1, which has hundreds of downstream target gene, plays a crucial role in cellular metabolism [42]. Hif-1 induces expression of glucose transporters and glycolytic enzymes such as hexokinase, aldolase, enolase, and lactose dehydrogenase A [10,43]. Moreover, Hif-1 inhibits mitochondrial activity by repressing key enzymes in the Krebs cycle and preventing production of NADH and FADH2 delivered to the electron transport chain [44]. In addition to preferential induction of glycolysis and inhibition of mitochondrial respiration, Hif-1 inhibits mitochondrial biogenesis, which results in a metabolic shift from oxidative phosphorylation to anaerobic cytoplasmic

glycolysis [2,36,45]. This metabolic shift may have significant consequences unrelated to metabolism, primarily related to the production of reactive oxygen species (ROS) by the mitochondria, which is a major mediator of cellular oxidative stress.

Oxidative Stress

Mitochondrial oxidative phosphorylation is a major source of ROS production. It is estimated that about 2% of all electrons flowing through the respiratory chain, through premature transfer of electrons, result in generation of ROS [4,46,47]. ROS can lead to wide spread cellular damage by oxidizing proteins, lipids, and nucleic acids. Regulation of ROS is important for HSC function [6,16,48,49]. HSCs located in the low ROS flow cytometry compartment show selective repopulation capacity[7,49]. In addition, high levels of ROS is associated with loss of HSC function[8,48]. Cells residing in hypoxic microenvironment gain protection against harmful effects of ROS through inhibition of mitochondrial metabolism by Hif-1α [9,35,44,50] or induction of antioxidant genes by Hif-2α [10,11,51].

Hif-2α (EPAS1)has many similarities with Hif-1α but demonstrates distinct functional roles [13,51-53]. While Hif-1α is expressed ubiquitously, expression of Hif-2α limited to certain tissues [15,52,54]. Hif-2α knockout mice show a number of defects in hematopoiesis, metabolism, and regulation of reactive oxygen species. Increased ROS in Hif-2α knockout mice was associated with lower expression of antioxidant genes such as *Cat*, *Gpx1*, *Sod1* and *Sod2*[18-20,51,52]. Moreover, Hif-2α is associated with cardioprotection through transcriptional activation of Abcg2 in cardiac side population progenitors[2,22,23,55].

Hematopoietic Stem Cell Metabolism

Hematopoietic stem cells (HSCs) are characterized by their ability to self-renew and provide lifelong supply of blood cells. They reside primarily in the endosteal regions of the bone marrow described as "hypoxic niche" of HSCs[15,25-27]. While this hypoxic niche provides protective mechanisms against oxidative damage, HSCs require certain metabolic adaptations for self-renewal and survival in this microenvironment.

Flow cytometry has been extensively used for HSC isolation, which mostly relies on the expression of combination of a number of surface markers or transporters[2,6,56]. We developed a flow cytometry protocol that allows us to enrich HSCs based on their metabolic profile. We demonstrated thatmouse LT-HSCs are localized to a distinct population of cells characterized by low mitochondrial potential (MP)[4,19,57]. This population represents only a small fraction of the total bone marrow but contains the vast majortiy of HSCs. We showed that separation of cells solely based on this metabolic footprint markedly enriches HSCs as determined by *in vitro* colony forming assays and *in vivo* long-term repopulation assays.

Following flow cytometric isolation of HSCs and Low MP cells, we determined rates of glycolysis, oxygen consumption and ATP content. We showed that both HSCs and Low MP cellshave lower rates of metabolism (low ATP content and lower rates of oxygen consumption) and utilize glycolytic metabolism instead of mitochondrial respiration. This unique metabolic profile of HSCs and low MP cells is associated with upregulation of Hif-1α and Meis1. As mentioned above, Hif-1 is the key transcription factor for response to the hypoxia and mediates metabolic switch from mitochondrial oxidative phosphorylation to glycolysis[6,16,35,36,40,58]. Hif-1 consist of oxygen regulated Hif-1α and constitutively expressed Hif-1β subunits. Hif-1α could be regulated either by protein stabilizationor transcriptional activation. Our studies showed Meis1 as a transcriptional regulator of Hif-1α in HSCs.

Meis1-HIF axis in the Regulation of Metabolism

Meis1, myeloidecotrophic insertion site 1, was first identified in a spontaneous mouse leukemia model (BXH-2) as a common integration site of B-ecotropic provirus (Moskow et al., 1995). Meis1 belongs to three-amino-acid loop extension (TALE) class transcriptions factors, which specifically bind and activate transcription via TGACAG motifs [7,59,60]. High levels of Meis1 expression were found in bone marrow of acute myeloid leukemia patients and in the primitive hematopoietic cells [8,61,62]. Meis1 expression is crucial to suppress differentiation of hematopoietic cells by G-CSF stimulated differentiation, whereas Meis1 expression decreases in differentiated [9,61,63]. Mice lacking Meis1 shows various hematopoietic and cardiac defects and die around E11.5-14.5 [10,11,64]. Meis1$^{-/-}$ embryos have decreased number of colony-forming cells. In addition, fetal liver cells fail to radioprotect following transplantation into irradiated host and show poor competition in repopulation assays.

Meis1 represents an important cofactor for Pbx1 and HoxA9 [13,62,65,66]. Meis1 and other TALE family proteins cooperate and form dimeric or trimeric complexes with Hox proteins thus increase DNA binding specificity and affinity. Meis1-Pbx-Hox trimer demonstrate higher stability suggesting the role of Meis1 in stabilization of DNA bound complex[15,67]. In addition, the Pbx interaction domain, the homeodomain and transactivating C-terminal domain of Meis1 are required for interaction with Pbx proteins and HoxA9 [18-20,68]. Pbx1 knockdown in Zebra fish show similar hematopoietic defects with Meis1 knockdown [2,22,23,69]. Moreover, Pbx1 regulates self-renewal of mouse HSCs by maintaining their quiescence [15,25,27,70]. Additional characterization on how cofactors of Meis1 such as Pbx and Hox family of proteins are involved in the regulation of Hif-1α gene awaits further studies.

HSC fate is tightly regulated between self-renewal, quiescence, apoptosis and differentiation. Growing evidence indicates that not only environmental cues provided by the HSC niche but also intrinsic stem cell factors govern HSC fate decision[1,71]. Conditional and tissue specific deletion of *Hif-1α* and *Meis1* in HSCs *in vivo* showed that Hif-1α and Meis1 are required for proper HSC function and metabolism. Similarly, studies by Takubo et al. (2010) also demonstrated that conditional deletion of Hif-1α in bone marrow leads to loss of HSC quiescence, increased HSC cycling and loss of long-term repopulation [12,72].Interestingly, Hif-1α expression has been shown to remain stable in both cycling and non-cycling hematopoietic stem and progenitor cells (HSPCs), which indicates that the hypoxic phenotype of HSPCs is not specific to quiescent cells and it is maintained throughout the cell cycle as well[14,30].Despite the importance of Hif-1α, which is consideredthe master regulator of metabolism, the role of Hif-1α and its upstream regulators in HSC metabolism

just started to emerge. HSCs lacking *Hif-1α*or *Meis1*show a metabolic shift from cytoplasmic glycolysis to mitochondrial oxidative phosphorylation with markedlyhigher rates of oxygen consumption, lower rates of glycolysis, and increased ROS, which results in loss of HSC quiescence and apoptosis.

In addition, Meis1 regulates not only HSC metabolism but also oxidative stress response through transcriptional regulation of Hif-2α [17,18,31,57]. While Hif-1α and Hif-2α are highly homologous and target similar genes such as GLUT1 and VEGF, they have distinct targets. For instance, Hif-1α uniquely stimulates glycolytic enzymes (PGK, LDHA) while Hif-2α regulates expression of antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxide [21,51]. Mitochondrial oxidative phosphorylation is accompanied by the generation of ROS and if excessive, it could lead to senescence or apoptosis. Hif-2α null mice demonstrate increased oxidative stress with multiorgan dysfunction including cardiac hypertrophy, hepatic steatosis, defects in spermatogenesis and hematopoiesis [24,26,28,51-53]. Deletion of Meis1 in HSCs results in downregulation of Hif-2α and increased ROS in HSCs [18,29]. Moreover, adverse effects of ROS in Meis1 KO mice can bereversed by treatment of N-acetyl-L-cysteine (NAC), a ROS scavenger. These findings highlight an important transcriptional network that regulates HSC metabolism, ROS and HSC function, which Meis1 at its core. Intriguingly, Meis1 is expressed in the heart and shown to be involved in neonatal cardiac regeneration [26,57,73,74]. This raises the question whether Meis-Hif axis applies to regulation of cardiac stem cell/progenitor metabolism.

Cardiac Stem/Progenitor Cells

Recent reports indicate that the adult mammalian heart is capable of limited, but measurable, cardiomyocyte turnover [30,75-77].While the lineage origin of the newly formed cardiomyocytes is not entirely understood, mounting evidence suggest thatthey may be derived from an unidentified cardiac progenitor population [26,77]. A number of resident cardiac progenitorcells are identifiedbased on the expression of surface markers such as c-kit, Scal-1 and Isl-1, epicardial localization, dye exclusion or in vitro culture [32,78-81]. Many of these cardiac progenitor cells demonstrate capacity for self-renewal, clonogenicity, can differentiate into cardiomyocyte and vascular lineages *in vitro* and express cardiac genes such as GATA-4, Nkx2.5 and MEF2, which are important for cardiac development. Wilms` tumor 1 gene (WT1)is another important transcription factor that has been identified in cardiac progenitors [33,34,82]. Lineage tracing studies demonstrate that WT1 expressing epicardial cells differentiate into cardiomyocytes during cardiac development and contribute to *de novo* cardiomyocytes following injury in adult mouse hearts[35-37,82]. Intriguingly, Hif-1 has been shown to play an important role in the regulating WT1 expression *in vitro* and *in vivo* [38,83,84].

Several studies suggested presence of cardiac progenitor cell niches based on the staining of surface marker Isl-1 [35,39,40,85,86]. However, recent studies on lineage of Isl-1+ cells in adult heart demonstrated that Isl-1+ cells are a marker of adult sinoatrial node rather than cardiac progenitors or cardiac stem cell niche[41,87]. Hypoxia could be considered as common theme for adult stem cell niches, where stem cells preferentially utilize cytoplasmic glycolysis to meet their energy demands. However, it was unclear until recently if the heart harbors similar hypoxic regions, or whether these regions house metabolically distinct cardiac progenitor populations.

Hypoxic Cardiac Stem Cell Niche

Knowledge from HSC biology has been extensively used for the identification of cardiac progenitor and stem cells, which lead to discovery of a number of resident cardiac progenitor and stem cells [42,81]. Metabolic profiling of hematopoietic stem cells provided with a functional approach to assess if there is any resident cardiac progenitor and stem cell population that can be isolated based on metabolic footprint without the use of surface markers. Metabolic profiling based approach led us to identifyglycolytic cardiac progenitors (GCPs) that mainly use glycolysis, express Hif-1α and display a multilineage differentiation potential (Figure 2) [10,43,57,88]. Furthermore, similar to HSCs, Hif-1α regulates the metabolic phenotype, differentiation and proliferation of GCPs (Table 1). These findings raised an obvious question: Is there a hypoxic niche that GCPs are maintained?

Quest to find where GCPs might reside in adult mouse heart led to identify the epicardium and subepicardium as the cardiac hypoxic niche. Epicardium and subepicardiumshow lower capillary densities and house Hif-1α expressing cells, including numerous cardiomyocytes. Further evidence is provided by thecolocalization of epicicardial marker expressing GCPs with the lowest Hoechst perfusion in the heart. Future studies are needed whether these hypoxic epicardial and subepicardial cells give rise to all cardiac lineages *in vivo* after myocardial injury. This will require generation of an inducible Hif-1α reporter mouse line, which is technically challenging since Hif-1α is regulated by protein stabilization and is ubiquitously transcribed in all cells.Interestingly, some of the Hif-1α+ cells in the epicardium/

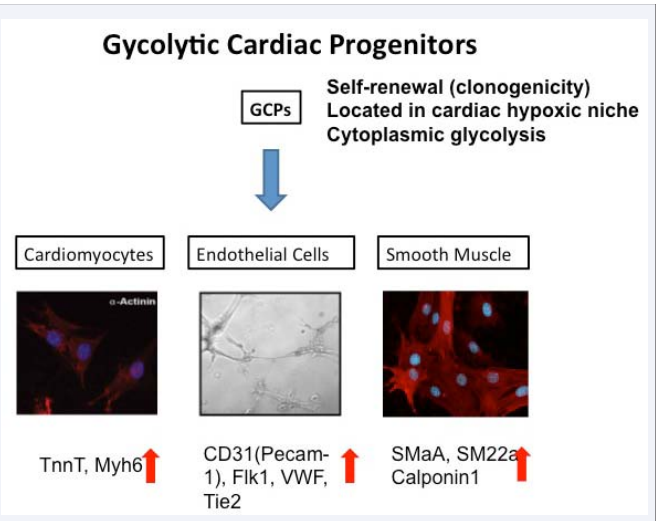


Figure 2 Glycolytic Cardiac Progenitors. Glycolytic cardiac progenitors are characterized by unlimited in vitro expansion (clonogenicity, self-renewal), adaptation to cardiac hypoxic niche of (sub)epicardium and preferential utilization of cytoplasmic glycolysis rather than mitochondrial oxidative phosphorylation. GCPs demonstrate ability to differentiate into cardiomyocytes, endothelial cells and smooth muscle cells.

subepicardium show patterns of cardiomyocytes as this is evident by staining with cardiac troponin.It is intriguing to ponder whether these Hif-1α$^+$ cardiomyocytes/cardiac progenitors differ from other cardiomyocytes reside in well-perfused myocardium. For example, are these cardiomyocyte mononucleated or bi-nucleated? Are they arrested in G_0/G_1 phase of cell cycle like the majority of cardiomyocytes in the adult heart? Or are they able to cycle in response to injury? Further studies are also required to determine the role of Meis1 and hypoxia signaling in the cell fate decision of cardiac progenitors as well as for cell cycle regulation of cardiomyocytes that reside in the cardiac hypoxic niche.

Meis1 in Reactivating Cardiomyocyte Proliferation and Differentiation

Neonatal heart differs from adult heart in virtue of ability to regenerate following injury at P1 with a profound and global cardiomyocyte proliferation [44,89-91]. Meis1 expression pattern in the postnatal heart corresponded with postnatal cell cycle arrest [36,45,73,74]. Knockdown or cardiomyocyte specific deletion of Meis1 in the cardiomyocytes ledto profound cardiomyocyte proliferation. More importantly, inducible Meis1 KO in the adult heart is associated with reactivation of cardiomyocyte cell cycle. Finally, *in vitro* and *in vivo* studies demonstrated that Meis1 regulates all three checkpoints of cardiomyocyte cell cycle by transcriptional activation of synergisticcyclin-dependent kinase inhibitors; $p15^{INK4B}$, $p16^{INK4A}$, $p19^{ARF}$ and $p21^{CIP1}$. Further studies to understand how Meis1 cardiomyocyte expressionis regulated could provide new approaches to cardiac regeneration therapies following myocardial infarction. It is attracting to find out inhibitors of Meis1 and how microRNAs involved in the regulation of Meis1 transcript levelsin the heart. Intriguingly, a recent study on conversion of human fibroblasts into cardiomyocytes showed that induction of cardiomyocyte differentiation depends on introduction of myogenic microRNAs [46,47,92,93]. It would be interesting to find out if inhibition or down regulation of Meis1 in cardiac fibroblasts or cardiac progenitors involves in cardiomyocyte differentiation.

Table 1: Comparison of HSC and GCP niches.

Hematopoietic Stem Cell Niche	Cardiac Hypoxic Niche
Localization of HSCs to endosteal regions of bone marrow[21,24,26,28,35,44,50] [14,26,51]	Localization of GCPs to epicardium and subepicardum of the heart [51-53,88,97]
Low Oxygen Tension [15,34,52,54]	Low capillary density [51,52,57,88,97]
Low oxygen consumption rates by HSCs [19,55,57,98]	Low oxygen consumption rates by GCPs [26,88,97]
High glycolysis rates in HSCs [19,98-100]	High glycolysis rates in GCPs [88,97]
Low ATP content in HSCs [19,98-100]	Low ATP content in GCPs (Kocabas et al, JCTR, 2012)[97]
Hif-1a expression and stabilization in HSCs [19,72,99]	Hif-1a expression and stabilization in GCPs [88,97]
Low Mitochondrial content in HSCs Low ROS levels in HSCs Low NADH content in HSCs [19,49,72,100-103]	Mitochondria, ROS and NADH content is unknown

Table 2: Pending Issues.

PENDING ISSUES
What is metabolic profile of other adult stem cells?
What are the components of hypoxic microenvironments for other adult stem cells?
Hypoxia map of the tissues and types of cells they house
Studies directed to the use of metabolic regulators for the treatment of stem cell associated diseases
Other metabolic adaptations in stem cells in their respective hypoxic microenvironments
Characterization of human HSC metabolism

Final remarks

Analysis of HSC and cardiac progenitor metabolism provide new insights into the interplay between metabolism and cell cycle regulation. These findings can have far reaching impacts on regenerative medicine as well as cancer biology. Meis1 and its cofactors are overexpressed in a wide variety of leukemia [48,49,94,95] and found to modulate maintenance of leukemia cells [49,61,68,96]. In addition, it has been reported that cancer cells demonstrate metabolic adaptations and preferential use of glycolysis[13,48]. Although the clear association of metabolic adaptation and overexpression of Meis1 in cancer cells, the involvement of Meis1 and its cofactors in the transformation and regulation of cancer cell metabolism remain to be determined (Table 2). Since stem cells could be enriched solely based on metabolic profiling, similarly, metabolic profiling of cancer cells could provide novel approaches to identify cancer stem cells. While these studies clearly demonstrate that Meis-Hif axis is an integral part of the transcriptional network that regulates metabolism and cell cycle, we have only begun to understand how these complex processes may be linked. It is crucial for future studies to determine other links between metabolism and cell cycle regulation, and more importantly, understand how these master transcription factors are regulated, either by epigenetic, systemic, or environmental factors.

Glossary

Glycolysis: A metabolic pathway that converts glucose into pyruvate to generate ATP and NADH under anaerobic reaction.

Hematopoietic Stem Cells (HSCs): Main blood cell type that give rise to all the other blood cells. They give rise to the myeloid and lymphoid lineages.

Hypoxia-inducible factor (HIF): Main transcription factor that respond to oxygen changes in the cellular environment and is upregulated and stabilized under low levels of oxygen, or hypoxia.

Quiescence: A cellular state in which cells are arrested at a postmitotic stage, and usually characterized by G_0/G_1 phase of the cell cycle.

Stem Cell Niche: The microenvironment where stem cells are located in tissues.

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