Review Article

# The cardiac hypoxic niche: emerging role of hypoxic microenvironment in cardiac progenitors

**Wataru Kimura, Hesham A. Sadek**

Department of Internal Medicine, Division of Cardiology, UT Southwestern Medical Center, Dallas, TX, USA

*Corresponding to:* Hesham A. Sadek. Department of Internal Medicine, Division of Cardiology, UT Southwestern Medical Center, Dallas, TX, USA. Email: hesham.sadek@utsouthwestern.edu.

**Abstract:** Resident stem cells persist throughout the entire lifetime of an organism where they replenishing damaged cells. Numerous types of resident stem cells are housed in a low-oxygen tension (hypoxic) microenvironment, or niches, which seem to be critical for survival and maintenance of stem cells. Recently our group has identified the adult mammalian epicardium and subepicardium as a hypoxic niche for cardiac progenitor cells. Similar to hematopoietic stem cells (LT-HSCs), progenitor cells in the hypoxic epicardial niche utilize cytoplasmic glycolysis instead of mitochondrial oxidative phosphorylation, where hypoxia inducible factor 1α (Hif-1α) maintains them in glycolytic undifferentiated state. In this review we summarize the relationship between hypoxic signaling and stem cell function, and discuss potential roles of several cardiac stem/progenitor cells in cardiac homeostasis and regeneration.

**Key Words:** Hypoxic microenvironment; cardiac progenitors; hypoxia inducible factor 1a (Hif-1a); hematopoietic stem cells (LT-HSCs)

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## Hifs and hypoxia response

In aerobic organisms, cells require the supply of oxygen ($O_2$) for generating intracellular ATP through oxidative phosphorylation. $O_2$ availability profoundly affects almost all biological processes, and therefore, the response to hypoxia, is critical for all organisms. During hypoxia, cells activate a number of adaptive physiological responses, which directly influence metabolism, redox homeostasis, vascular remodeling etc. Hypoxia inducible factors (Hifs) are key modulators of the hypoxia-induced transcriptional program designed to counteract the reduced $O_2$ availability at both cellular and systemic levels (1). Hifs are heterodimeric factors consisting of an $O_2$-regulated alpha subunit and constitutively expressed beta subunit. Three isoforms of Hifα have been identified in mammals. Hif-1α and Hif-2α are highly related in their amino acid structures, and molecular and biological roles of them are well characterized. Hif-1α is expressed ubiquitously, but Hif-2α and Hif-3α, in contrast, are selectively expressed in certain tissues, including vascular endothelial cells (2) and peritubular interstitial cells in the kidney (3). Hif-1α expression induces a switch from the oxygen-dependent oxidative metabolism in the mitochondria to anaerobic glycolytic metabolism in the cytoplasm, whereas Hif-2α is believed to be a master regulator of oxidant stress response (4). The function of Hif-3α is not entirely understood, but it is known to possess a variety of splicing isoforms and some of them act as dominant negative forms of Hif-1α and Hif-2α (5-10).

Regulation of Hif activity by $O_2$ tension has been demonstrated at transcriptional, translational and post-transcriptional levels. $O_2$-dependent control of Hifα protein stability is one of the classic and best characterized regulatory mechanism (*Figure 1A*). Under normal $O_2$ tension, or normoxic conditions, Hifα subunits are hydroxylated at conserved proline residues in the oxygen dependent degradation (ODD) domain (9). These modifications are mediated by three prolyl hydroxylase domain-containing enzymes (PHD1-3), which require $O_2$

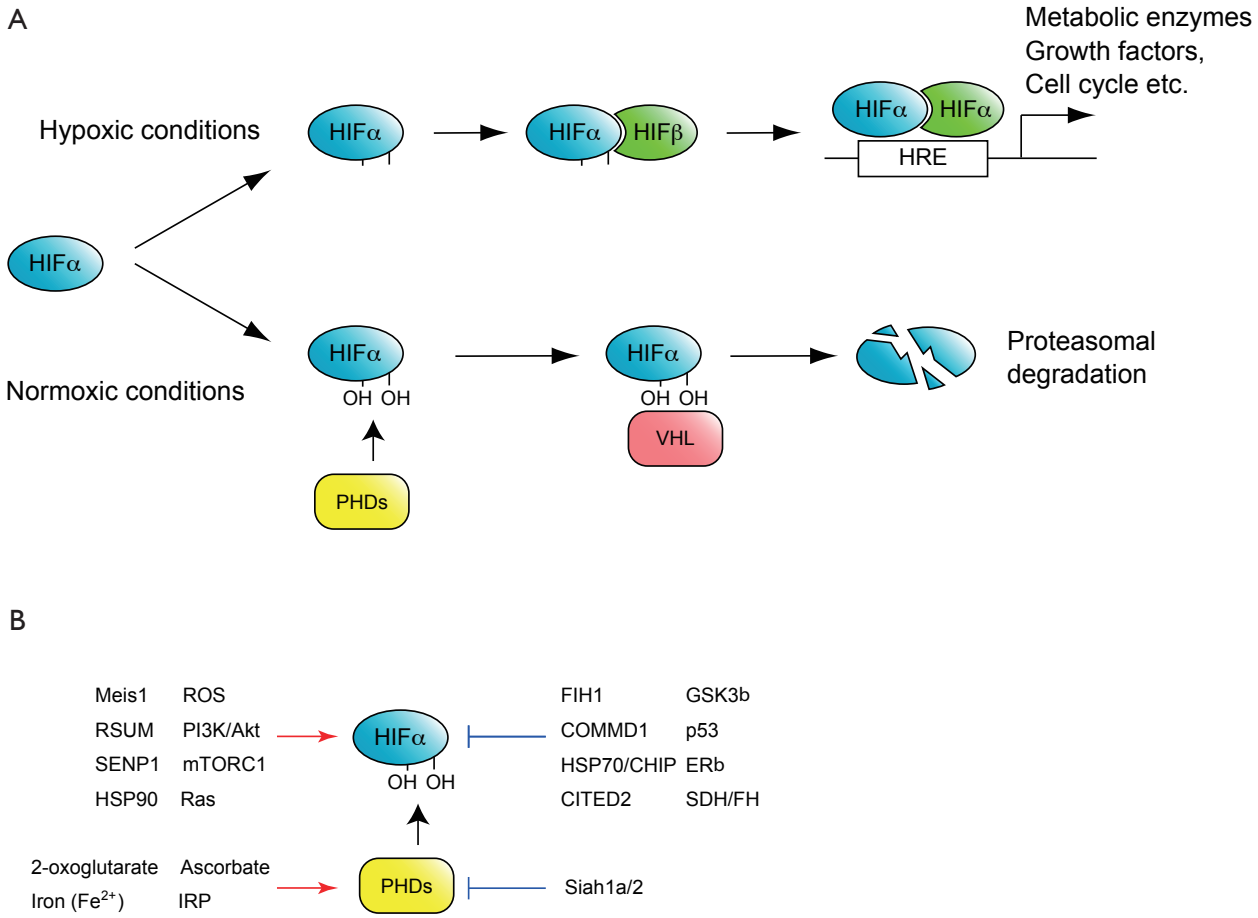


**Figure 1** $O_2$ dependent HIF regulation. A. One of the classic and well-studied mechanisms regulating HIF activity by $O_2$. Under normoxic conditions HIFα is hydroxylated by prolyl hydroxylase domain-containing enzymes (PHDs), and recognized by the E3-ubiquitin-ligase, von Hippel-Lindau (VHL) to be subjected to proteasome-mediated degradation. Under hypoxic conditions HIFα is stable and together with constitutive HIFβ, binds to hypoxia response element (HRE) to activate hundreds of target genes; B. Factors activate or repress HIF activity. Note that these factors modulate HIF at several different levels. For example Meis1 activates the transcription of HIFα mRNA, whereas RSUME and SEMP1 mediate SUMOylation of HIFα proteins

for their enzymatic activity (9). Prolyl-hydroxylated Hifα is then recognized by the E3-ubiquitin-ligase, von Hippel-Lindau (VHL) complex and degraded by the ubiquitin-mediated proteasome pathway. Under hypoxic conditions, Hifα prolyl hydroxylation is suppressed due to the lack of oxygen as a substrate of hydroxylation reaction and consequently Hifα proteins stabilization.

Recently more factors which regulate Hif protein activity have been reported, such as factor-inhibiting Hif-1α (FIH1) an asparaginyl hydroxylase, histone deacetylases Sirtuins, several oncogenes and tumor suppressor factors, as well as a number of transcriptional regulators [reviewed by Majmundar *et al*. (11) and Semenza (12)], suggesting more complex and precise regulation of Hif complexes in several different cellular contexts (*Figure 1B*).

During hypoxia, Hifα is stabilized and forms heterodimers with Hifβ, which causes conformational change in Hif-α that allows the HIF heterodimer to bind to hypoxia response elements (HREs) (13) scattered throughout the genome and activate the transcription of several hundreds of target genes (14,15). Typical examples of the target genes of Hif heterodimers include erythropoietin (16,17) and vascular endothelial growth factor receptor (18,19), which activate erythropoiesis and angiogenesis, respectively. Hif complexes also regulates genes that activate glycolysis, which include glucose transporters [such glucose transporter 1 (GLUT1)], glycolytic regulatory enzymes like 6-phospho-2-kinase/fructose 2, 6-biphosphatase (PFKFB1-4),

 

hexokinase II (HKII) and lactate dehydrogenase A (LDHA), as well as activating genes which diminish mitochondrial oxidative metabolism, including pyruvate dehydrogenase kinase 1 (PDK1) [reviewed by Iyer *et al.* (20), Bartrons and Caro (21), and Wheaton and Chandel (22)]. The net result is a metabolic switch from mitochondrial phosphorylation to glycolysis. These Hif complex mediated transcriptional programs regulate many biological processes including embryonic development, tumor progression and also stem cell properties such as maintenance, self-renewal and differentiation.

## Hypoxia signaling in adult stem cells

Hematopoietic stem cells (HSCs), which have capacities for both self-renewal and multi-lineage differentiation, continue to replenish all blood cells throughout the entire life span of an organism (23,24). The bone marrow microenvironment which house HSCs, known as niches, provide HSCs with regulatory signals essential for their maintenance, proliferation and differentiation. One of the hallmarks of the HSC niche is its low oxygen tension, hence the term "hypoxic niche" (25). A number of studies revealed that this hypoxic environment is required for HSC quiescence. Moreover, colony-forming ability and transplantation capacity increases when bone marrow cells are cultured under low oxygen tension (26-28). Therefore, this low oxygen environment is not only tolerated by HSCs, but is also essential to maintain their function (26,29,30). Our group, as well as others, recently reported that Hif-1α mRNA and protein are highly expressed in LT-HSCs where it plays a crucial role in role in the maintenance of HSC quiescence and stress resistance (31-33).

Since HSCs are sustained for a long time, they have to evolve mechanisms to diminish, and resist many stressors including oxidative stress. Our group revealed that LT-HSCs utilize cytoplasmic glycolysis, instead of mitochondrial respiration for their energy production (32), thereby minimizing mitochondrial derived reactive oxygen species (ROS). We showed that HSC-specific deletion of Hif-1α results in increased rates of mitochondrial respiration and decreased glycolytic flux (33). Interestingly, Hif-1α appears to be regulated at multiple levels in HSCs. We recently reported that homeodomain transcription factor Meis1 plays an essential role in the maintenance of LT-HSC through transcriptional activation for Hif-1α (32,33) (*Figure 2*). Meis1 also regulates Hif-2α transcription, where loss of Meis1 results in downregulation of Hif-2α levels, and increased ROS levels. Intriguingly, systemic administration of ROS scavengers rescues the Meis1$^{-/-}$ phenotype in HSCs. These results strongly support the central role of hypoxia signaling and redox regulation in HSC maintenance and survival (32,33).

In addition to the hematopoietic system, hypoxia and Hif genes also play important roles in other adult stem cell populations. The subventricular zone of the hippocampus, known as a neural stem cell (NSC) niche, shares low oxygen tension properties with the hypoxic HSC niche (34), where loss of Hif-1α decreases NSC proliferation, differentiation and neural maturation (34). Moreover, Hifs are upregulated in several cancer stem cells and play roles in their survival and differentiation [reviewed by Semenza (12), Kobayashi and Suda (35), Heddleston *et al.* (36), and Li and Rich (37)]. For example, Hif-1α and Hif-2α is expressed in glioma stem cells and are essential for their self-renewal and tumorigenic capacity (38,39). In addition, the Hif-1α inhibitor echinomycin eradicates lymphoma and acute myeloid leukemia by eliminating cancer stem cells (40). Thus, hypoxia and Hif-1α upregulation appears to be a features shared by various types of stem cells and an important regulator of their stem cell properties.

## Tissue specific cardiac progenitors

It has been long thought that cardiomyocyte turnover does not occur in the adult mammalian hearts, because myocardial injury invariably results in irreversible scar formation (41-43). However, recent evidence suggests that the adult mammalian heart does in fact undergo some degree of cardiomyocyte renewal during normal aging (44-48) and disease (45,46,48-50). Unfortunately, this modest myocyte renewal is insufficient for restoration of contractile function following injury. In contrast, some species of fish (51,52) and amphibians (53-56), as well as fetal (57) and neonatal mammals (58) have a remarkable ability to regenerate damaged myocardium, which is mainly achieved by proliferation of pre-existing cardiomyocyte (58-61). Interestingly, current evidence suggests that the adult mammalian heart derives the small number of new cardiomyocytes from an unknown stem or progenitor cell source (62).

Several reports indicate that the adult rodent and human myocardium harbors populations of stem/progenitor cells, which appear to have the potential to generate cardiomyocytes *in vitro* (63-65). These cells are potentially an attractive source for cardiac repair and therefore, over the past decade, extensive studies have examined their use for

 

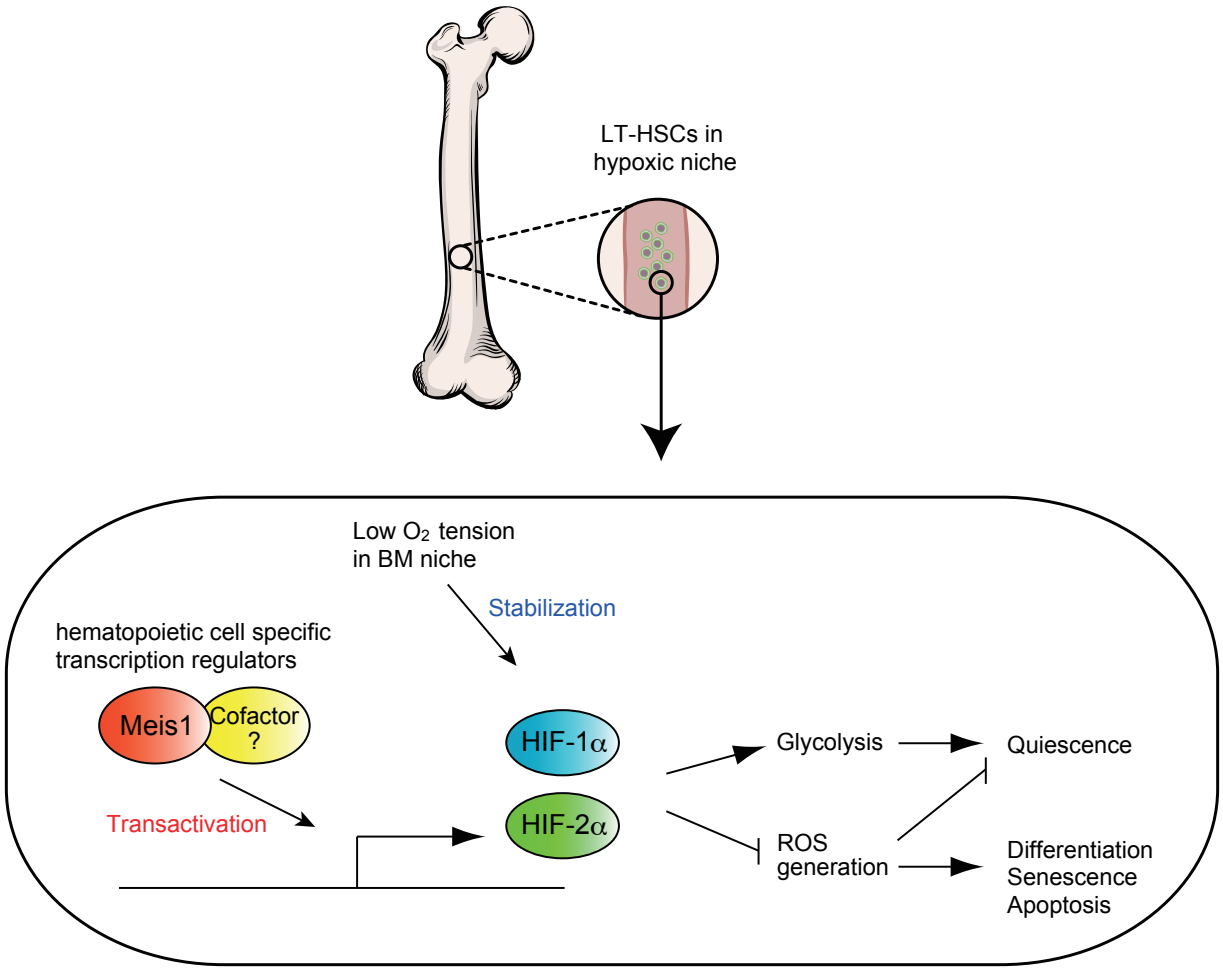


**Figure 2** In LT-HCSs, Meis1 (and its cofactor) upregulate both HIF-1α and HIF-2α. This transcriptional activation is essential for maintaining the glycolytic metabolic phenotype and preventing ROS mediated senescence and apoptosis

cardiac regeneration [reviewed by Laflamme and Murry (49), Hansson *et al*. (66), and Choi and Poss (67)]. In mice, cells expressing the stem cell factor receptor c-kit, (68), stem cell antigen-1 [Sca-1, (69)], the transcription factor islet-1 [Isl-1, (70)], and side population (SP) cells (71) have been identified as cardiac resident progenitor cells due to their ability to acquire a cardiomyocyte lineage *in vivo*. Moreover, progenitor cells in the postnatal human hearts have been also identified by the expression of c-kit, Sca-1, Isl-1 (72-77) or SP profile (78). Even though SP cells, c-kit+ cells, Sca-1+ cells and Isl1+ cells all have a capacity to differentiate into smooth muscle cells, endothelial cells and cardiomyocytes, they are clearly distinct cell population in several aspects. For example, Isl1 positive progenitor cells do not express c-kit as oppose to SP, Sca-1 positive and c-kit positive progenitor cells [reviewed by Guan and Hasenfuss (79), and Bollini *et al*. (80)]. In addition, their localization within the heart appears to be distinct, where SP cells, Sca-1+ cells and c-kit+ cells are mostly enriched in the atria (73,74), Isl1+ cells are found widely in ventricles and atria (70). It is therefore critical to determine which lineages these cells contribute to during normal cardiac homeostasis, ageing and after injury. However, definitive genetic fate mapping studies are still underway to conclusively determine which of these diverse cell populations are true cardiac stem or progenitor cells.

## The epicardium as a source of cardiac progenitor cells

Another type of resident cardiac progenitors has been identified based on anatomical localization to the epicardium, and expression of epicardial markers. In zebrafish, the

 

epicardium is activated within 1-2 days after injury (60,81,82), where it proliferates, expresses embryonic epicardial genes, and undergoes epithelial-mesenchymal transition (82-84). The adult mammalian epicardial cells are activated similarly by myocardial infarction and/or Thymosin β4 stimulation (85), where they proliferate, start to express embryonic epicardial genes (86), and secrete paracrine factors that modified the myocardial injury response (83,87-90).

In the past few years, increasing evidences suggested that the epicardium also contains distinct progenitor cells during normal development and upon injury (reviewed by Schlueter and Brand (91,92). Epicardial derived cells contribute to cardiac fibroblast, vascular smooth muscle cells and cardiomyocytes during embryogenesis by lineage tracing with WT1-Cre (93) and Tbx18-Cre (94) lines [although the epicardial origin of cardiomyocyte remains controversial because it was revealed that the Tbx18 is not only expressed in epicardium, but also in developing cardiomyocytes (95)]. Moreover, Chong *et al*. showed that the adult epicardium contains multipotent stem cells, which have the capacity to differentiate into cardiomyocytes, vascular endothelial and smooth muscle cells (96). Moreover, taking advantage of the upregulation of WT1 in epicardium in the adult heart upon injury, Zhou *et al*. revealed by lineage tracing that adult epicardium-derived cells contribute to fibroblasts and perivascular smooth muscle cells, without contribution to the cardiomyocyte pool (83), except after priming with thymosin beta 4 (85). These studies support the role of epicardial cells as cardiac progenitors, although fate-mapping studies that unequivocally demonstrate that the epicardium is the source of turnover of cardiomyocytes are still lacking.

## Hypoxic cardiac progenitor cells

These studies reviewed above identify the epicardium as a potential source of cardiac progenitors, however whether the epicardium is the true cardiac progenitor/stem cell niche, and whether it shares the hypoxic properties with other stem cell niches in the adult organism is not clear. To answer this question, we recently sought to identify hypoxic regions in the uninjured adult mammalian heart, and we found that the epicardium and subepicardium represent the cardiac hypoxic niche (97). The epicardial and subepicardium (within three-cell layer from the epicardium) have the lowest capillary density across the ventricle, with over 50% of epicardial cells and less than 10% of the subepicardial cardiomyocytes express Hif-1α protein. Moreover, non cardiomyocytes isolated from this region and expanded in culture, are clonogenic, self-renewing, express cardiac progenitor and epicardial markers, and are capable of acquiring different cardiac lineages *in vitro* including endothelium, smooth muscle and cardiomyocyte lineages. These results provide proof that the epicardium and subepicrdium represent the hypoxic niche of adult heart which, like other hypoxic niches in the adult organism, houses a population of cardiac progenitor cells (*Figure 3*).

In support of the link between the metabolic phenotype and stem or progenitor cell phenotype, we found that these hypoxic cardiac niche cells mainly rely on cytoplasmic glycolysis, rather than mitochondrial oxidative phosphorylation (and therefore we named them glycolytic cardiac progenitors, or GCPs). Not surprisingly, knockdown of Hif-1α in these cells resulted in metabolic shift from glycolysis to mitochondrial oxidative phosphorylation, which was associated with decreased in their rate of proliferation and spontaneous differentiation. These findings suggest that similar to LT-HSCs, Hif-1α is required for maintaining self-renewing stem/progenitor cells within the hypoxic niche by regulating their glycolytic phenotype (97).

A number of questions regarding hypoxic cardiac progenitor cells still remain unanswered. For example, do they contribute to the cardiomyocyte turnover during normal aging and after myocardial injury? To answer this question conclusively, fate-mapping studies are necessary. However lineage tracing of GCPs is currently not technically feasible, in part because there are no known specific marker of GCPs or of cardiac hypoxic niche cells. In addition, what is the relationship between the hypoxic response (for example which occurs after myocardial infarction) and proliferation, migration and differentiation of GCPs *in vivo*? It is known that high ROS levels force other types of stem cells (such as HSCs) to exit from quiescence, spontaneously differentiate, and lose their self-renewal capacity (98-100). ROS levels markedly increase in the myocardium following an acute myocardial infarction (101,102), at the time of ischemia/reperfusion (103-105) and in chronic heart failure (106-108), where they play a major role in mediating cardiomyocyte injury and death [reviewed by (109-111)]. Taking the similarities between HSCs and GCPs into consideration, it is important to determine how an *in vivo* ROS-rich environment would affect GCPs, and whether this plays a role in the deleterious effects of ROS on the myocardium. Another important question is the potential mechanism of migration of epicardial/subepircardial cells toward the injured myocardium. It is thought that epicardial/subepicardial cells can migrate into myocardial wall and

 

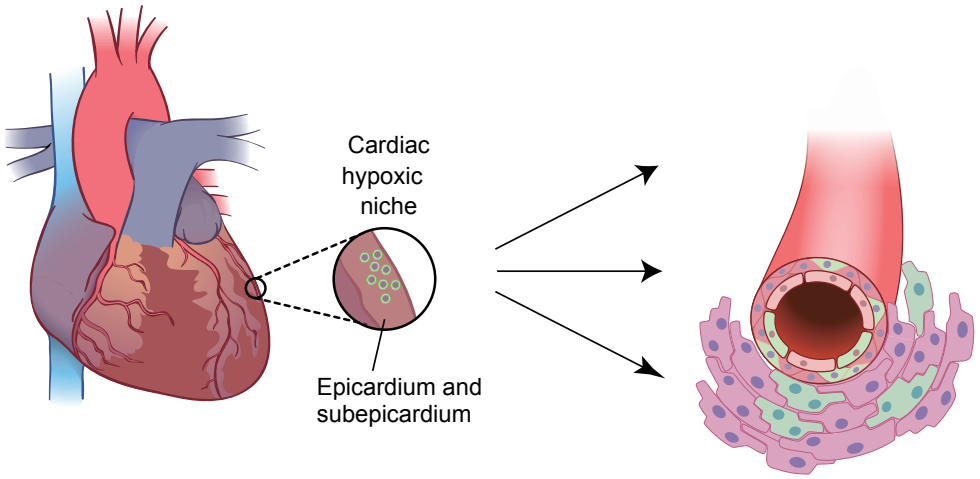


**Figure 3** Cardiac hypoxic niche in epicardium and subepicardium. The hypoxic microenvironment houses metabolically distinct population of glycolytic cardiac progenitor cells (GCPs). Epicardial GCPs isolated based on low mitochondrial content are c-kit-; Sca-1-; Nkx2.5+ and can differentiate into endothelial cells, smooth muscle cells and cardiomyocytes *in vitro*

differentiate into cardiomyocyte (85), however, factors that control their migration remain still unknown. One possible mechanism is the hypoxia itself that occurs as the result of injury (112,113). Hypoxia is known to promote stem cell recruitment, for example HSC homing into hypoxic bone marrow niche, via Hif-1α mediated production of chemokine SDF-1/CXCL12 [reviewed by Shiozawa *et al*. (114), Kavanagh and Kalia (115), Suárez-Álvarez *et al*. (116), and Schulz *et al*. (117)]. Chemokines including SDF-1 are also upregulated in the heart after acute myocardial infarction and attract various progenitor cell populations, which possess cardioprotective properties [reviewed by Ghadge *et al*. (118), and Smart and Riley (119)]. Moreover, in zebrafish SDF-1/CXCL12 is reported to regulate cardiomyocyte migration after injury (120). Therefore, it is plausible that hypoxia plays a dual role in maintenance as well as recruitment of epicardial cells after injury. However, a full understanding of the mechanisms that govern homing and migration of epicardial cells is still lacking.

## Concluding remarks

One important question that presents itself is whether there is a true cardiac stem cell in the adult mammalian heart. While other adult tissues, like the hematopoietic system, certainly have true stem cells, it is unclear if this is the case in the heart, especially if one takes clues from cellular origin of the heart during development. A true adult heart stem cell, from the differentiation perspective, would have to give rise to all cells within the heart including endothelial cells, smooth muscle cells, fibroblasts and cardiomyocytes, however these cells are actually quite distinct developmentally. During embryonic heart formation, two different major sources in splanchnic mesoderm provide cardiac progenitor cells: one is heart field mesoderm, and the other is proepicardium [reviewed by Dyer and Kirby (121); Abu-Issa and Kirby (122); Lie-Venema *et al*. (123) and Ishii *et al*. (124)]. Heart field mesoderm mainly contributes to cardiomyocytes (Nkx2.5+ cells), endocardium and vascular endothelium (Flk1+ cells) (125-127). However, most of the cardiac vascular endothelial cells are descendants of pre-existing endothelial cells in sinus venosus (128) with some contribution from the endocardium (129) from which cells sprout out and migrate within the myocardial wall. On the other hand, the proepicardium gives rise to epicardial cells, cardiac fibroblasts, part of vascular endothelium and vascular smooth muscle cells (93,94,130-132) [coronary smooth muscle cells are also derived from cardiac neural crest (133)]. Therefore, while the concept of a true cardiac stem cell is highly appealing, there is no definitive proof (by genetic fate mapping) to indicate that this type of cell exists and contributes to cellular turnover as in case of HCSs. In fact, the current evidence suggests that turnover of cells in the post-natal heart resembles that during development (*Table 1*). For example, fibroblasts and vascular smooth muscle cells are derived from the epicardium (93,94), vascular endothelial cells are descendants of proliferating and migrating endothelial cells originated from adjacent

 

**Table 1** Origins of cardiac tissues during embryonic development and postnatal turnover

| | Embryonic development | Postnatal turnover |
|---|---|---|
| Cardiomyocyte | Heart field mesoderm (121,122)<br>[Nkx2.5+ cells (126,127)]<br>Epicardium? (93-95) | Neonate: cardiomyocyte (58)<br>Adult: unidentified progenitor cells (or cardiomyocyte?) (44,62,134,135)<br>Epicardium with thymosin-β4 priming (85) |
| Endocardial cells | Heart field mesoderm (113) | ? |
| Vascular endothelial cells | Pre-existing endothelial cells from sinus venosus (128), endocardium (129) and in part from epicardium (64) | Pre-existing endothelial cells (136-139)<br>Circulating bone marrow- or peripheral endothelium-dericed precursors? (140-146) |
| Vascular smooth muscle cells | Epicardium (93,94,130-132)Neural crest (133) | Epicardium (83,147) |
| Epicardial cells | Proepicardium (148,149) | Epicardium (83,147) |
| Cardiac fibroblasts | Epicardium (93,94,130-132) | Epicardium (83,147) |

endothelium (136-139) and/or circulating progenitor cells of bone marrow or peripheral endothelium (140-143) [although recently it has been questioned that these circulating progenitor cells really contribute to newly generated endothelial cells after the injury (144-146)]. Moreover, post-natal cardiomyocytes appear to be derived from pre-existing cardiomyocytes (58,134,135), the epicardium [only after thymosin beta 4 priming (85)] or unknown progenitor cells (44,62). It is perhaps intriguing that these cell lineages, which replenish the adult heart, appear to recapitulate their developmental origin, and very rarely cross the boundary of major developmental lineage sources.

It is important to remember that even if there is currently no irrefutable evidence of a "true" adult cardiac stem cell that carries out the function of replenishing all cell lineages in the heart during ageing and disease, this does not mean that many of the cell populations described above have no therapeutic value. On the contrary, mounting evidence suggests that cell therapy may in fact induce a measurable regenerative response in the adult myocardium, unrelated to their transdifferentiation capacity. An elegant example of a regenerative role of C-Kit cells was recently demonstrated by the Lee lab, where they clearly showed an increase in the number of newly formed cardiomyocytes, and improved systolic function after injection of C-Kit cells, although these cells were no longer present in the heart (150).

In this review we summarized recent findings that highlight the emerging role of hypoxia signaling in stem cell niches, including the newly identified cardiac hypoxic niche. We propose that better characterizing of the epicardial hypoxic niche cells, in terms of their lineage differentiation potential, and the role of hypoxia signaling in regulating their function, are important targets for modulating the capability of resident cardiac stem/progenitor cells for therapeutic applications.

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