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Stem cells, telomerase regulation and the hypoxic state

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1. ABSTRACT

The cellular response to a hypoxic environment is regulated by hypoxia inducible factors. Hypoxia inducible factor 1 alpha (Hif1alpha) in particular, is tightly regulated by the hypoxic environment in most cells, and plays an important role in regulating the stress response of cells to hypoxia. Interestingly, substantial observations are now emerging that point to an important role for Hif1alpha in stem cells, including embryonic stem cells, neuronal stem cells and hematopoietic stem cells. Notably, Hif1alpha has been shown to enhance self-renewal of stem cells, mediate a shift to glycolytic metabolism, and promote telomerase expression.

2. INTRODUCTION

A cell's available oxygen can dramatically change its metabolic profile. Oxygen is needed in order to drive oxidative phosphorylation and provide the Krebs cycle with nicotinamide adenine dinucleotide (NAD+). Both of these processes occur in the mitochondria and provide the large portion of ATP derived from cellular respiration. A hypoxic condition occurs when there is a decrease in oxygen partial pressure. Hypoxia, which results from injury or disease in complex multicellular organisms, can ultimately cause cell death. However, during development, cells in the embryo also encounter hypoxic microenvironments that facilitate cell differentiation. Moreover, these hypoxic niches are essential, since they trigger the vascular development of the organism and can maintain stem cell populations (1–3). Therefore, understanding the response to hypoxia can shed light on the factors triggered in cell death or pertinent to self-renewal of stem cells.

3. TELOMERASE AND CELLULAR LIFESPAN

It is now well established that the gradual shortening of telomeres ultimately causes cell senescence in proliferative normal somatic cells (4). The direct association of telomere shortening and cell senescence was first discovered in the single cell eukaryote Saccharomyces cerevisiae, wherein mutants that prevented stable maintenance of telomeres eventually caused cell senescence and limited lifespan. Telomere shortening was shown to be a general characteristic of proliferative human somatic cells *in vitro* and *in vivo* (5,6) over twenty years ago. However, there are rare populations of adult human cells, specifically certain stem cells and the male germ line, that are immune to telomere-induced cell senescence due to the presence of telomerase in these cells. Telomerase is a ribonucleoprotein complex that functions to complete telomere replication, and thereby maintain, or even extend, telomeres in proliferative cells. Indeed, human telomerase was first discovered in an immortal tumor cell line (7).

The active telomerase enzymatic complex requires 2 essential components, a catalytic component called telomerase reverse transcriptase (TERT), and an RNA moiety aptly called the telomerase RNA component. The telomerase RNA component is expressed more or

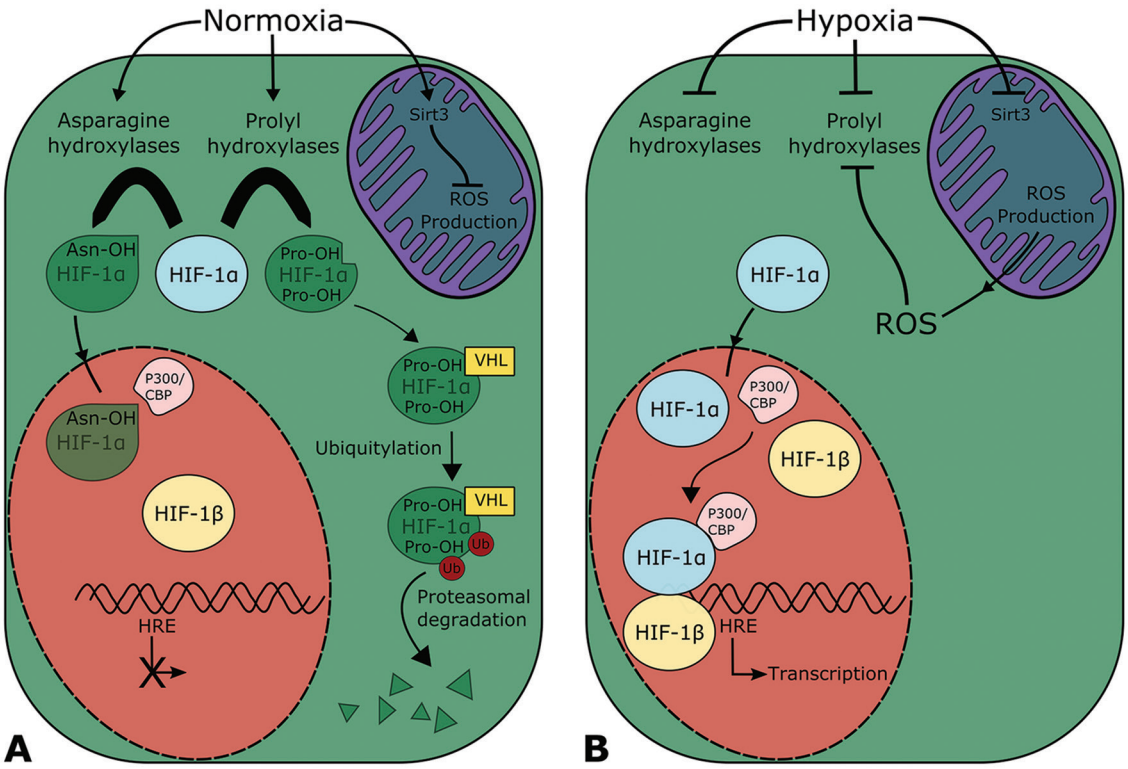

Figure 1. Regulation of HIF1 under hypoxic and normoxic conditions. During normoxic conditions HIF1alpha is inactivated and degraded by oxygen-dependent prolyl hydroxylases (e.g. PHD), allowing the binding of the von Hippel-Lindau protein that tags the HIF1alpha for ubiquitination and thus proteasomal degradation. Hydroxylation of HIF1alpha by an asparagine hydroxylase under normoxic conditions occurs at the transactivation domain and prevents the assembly of the transcriptional co-activator complex (HIF1alpha, p300/CBP, and HIF1beta) inside the nucleus. In the presence of oxygen SIRT3 regulates the production of ROS inside the mitochondria keeping cellular ROS levels low (A). Under hypoxic conditions the prolyl and asparagine hydroxylases are inhibited and active HIF1alpha translocates to the nucleus, forms the transactivation complex at HRE sites, and up-regulates the transcription of hypoxia-responsive genes. Inhibition of SIRT3 in the mitochondria permits an increase in ROS production under hypoxic conditions, which in turn inhibits the prolyl hydroxylation of HIF1alpha facilitating its stabilization (B).

less ubiquitously in adults. In most human somatic cells, telomerase activity is either very low or undetectable due to the lack of expression of TERT. Thus over expression of TERT is sufficient to reactivate telomerase activity in a variety of different somatic cell types (4). Furthermore, this reactivation is sufficient to prevent telomere shortening, and extend replicative lifespan indefinitely. The ability of over-expression of TERT to extend replicative lifespan has now been extended to somatic cells from other species as well (8–10).

4. HYPOXIA INDUCIBLE FACTOR 1 (HIF1) AND REGULATION OF HYPOXIA

Hypoxic-Inducible Factor 1 (HIF1) is the primary transcription factor that mediates the cellular response to hypoxia. HIF1, a heterodimer made up of HIF1alpha and HIF1beta and belongs to a family of basic helix-loop-helix/ Per-ARNT-Sim proteins (11). HIF1 was first discovered when studying the regulation of erythropoietin (EPO), a hormone that stimulates blood cell proliferation (12). The HIF1alpha subunit is inactivated and degraded under normoxic conditions by oxygen-dependent prolyl-4-hyrodxylase domain (PHD) proteins which bind to specific prolines and allow the binding of the von Hippel-Lindau protein and subsequent ubiquitination that results in proteasomal degradation (13–15). The other post-translational modification that is essential to activating HIF1alpha, is an oxygen-dependent asparagine hydroxylation carried out by factor inhibiting HIF1 that targets the transactivation domain located in the C-terminal forty amino acids (16) (Figure 1A). This hydroxylation interrupts the ability for the C-terminal forty amino acids to assemble a transcriptional co-activator complex with the cyclic AMP response element-binding protein-binding protein (CBP). CBP and E1A-binding protein p300 (p300/CBP) activate the transcriptional activity of HIF1 (17). Stability of the HIF1alpha protein at the bipartite nuclear localization signal is essential for the translocation of the subunit into the nucleus where it binds with HIF1beta and becomes transcriptionally active (18,19). HIF1beta, also known as aryl hydrocarbon receptor nuclear translocator, is constitutively expressed and, unlike HIF1alpha, is stable in normoxic environments (20).

In the nucleus, the HIF1 protein is capable of binding to hypoxia response elements and serves as an activator for a variety of proteins, including EPO, vascular endothelial growth factor, pyruvate dehydrogenase kinase 1, and enzymes involved in glucose uptake and utilization (21–24). The specific reaction to the hypoxic condition is variable for different cell types and is partly due to the differing amounts of PHDs available (25). The HIF1-mediated increase in glycolysis and the modification of mitochondrial function, allows some cells to reduce oxygen consumption by decreasing the number of mitochondria and diverting pyruvate towards lactate production to provide the cell with NAD+ (22,26). However, HIF1 can mediate cell cycle arrest or stimulation in different cell types (27).

Whether or not a cell is stimulated to divide or become quiescent under hypoxic conditions is intimately tied to the downstream targets of HIF1 in that specific cell (28). A sudden drop in oxygen can cause a redox imbalance within the mitochondrial electron transport chain that results in an increase in reactive oxygen species (ROS) (26). This increase in ROS is essential for HIF1 activation in hypoxic conditions but not anoxic (29). In lymphocytes, the reason for this difference is due to the inactivation of PHDs by ROS during hypoxia, which stabilizes HIF1alpha and allows a transcriptionally active HIF1 to increase levels of B-cell lymphoma 2 protein adenovirus E1B 19 kDa-interacting protein 3 and 3L (BNIP3 and BNIP3L) (30). During anoxic conditions ROS are not generated, so the lack of oxygen becomes the primary reason that PHDs cannot target HIF1alpha for hydroxylation and deactivation (29). BNIP3, up regulated by HIF1, competes with Beclin1 for binding to B-cell lymphoma 2 protein, resulting in excess levels of unbound Beclin1, which promotes autophagosome formation and results in mitophagy (31). However, in embryonic neural stem/progenitor cells, HIF1 increases the production of miR-210, this miRNA then directly suppresses the expression of BNIP3 and allows cell survival (28). Consistent with the study done by Wang *et al*, HIF1alpha activation has been found to increase cell proliferation in embryonic neural stem/progenitor cells (32). This proliferation occurs even though miR-210 represses the mitochondrial iron-sulfur cluster assembly proteins essential for tricarboxylic acid cycle enzyme aconitase and electron transport chain complex I (33). Reduced mitochondrial function and increased glycolysis has been observed in a variety of stem cells and in the developing embryo (34,35).

The downstream effect of HIF1 on mitochondria is also dependent on certain sirtuins. This family of proteins are NAD+-dependent histone deacetylases and under hypoxic conditions they are down-regulated due to the decrease in available NAD+ from the mitochondrial electron transport chain (36). Sirt3, localized in the mitochondria and responsible for activating many of the genes required for oxidative metabolism, destabilizes HIF1alpha by decreasing ROS production (36) (Figure 1B). Sirt6 deacetylates histone 3 lysine 9 (H3K9) causing a reduction in HIF1α expression (37) (Figure 2).

4.1. Oxygen-independent Regulation of Hif1

HIF1alpha is not only regulated by oxygen-dependent processes, but also by oxygen-independent processes. The phosphoinositol 3-kinase (PI3K) and mitogen activated protein kinase (MAPK) signaling cascades can increase expression and activation of HIF1alpha in certain conditions (38). In many cancers, loss of a functional phosphatase and tensin homolog tumor suppressor can increase the activity of the PI3K/Akt pathway resulting in increased cellular proliferation and expression of genes involved in glycolysis (39). It has been found that under normal serum conditions, Akt increases HIF1alpha translation in a way that is independent of the mammalian target of rapamycin (mTOR) (40). However, under low serum conditions, mTOR increases translation of HIF1alpha through the activation p70S6 kinase, which then activates the ribosomal S6 protein. This pathway results in the increased translation of mRNAs containing a 5'-terminal oligopyrimidine tract, which HIF1alpha possesses (41). Also important, is the effect that the MAPK pathway has on the formation of the HIF1-p300/CBP complex, allowing HIF1 to become transcriptionally active (42) (Figure 2).

4.2. Hypoxia and embryonic development

Mammalian embryogenesis is a complex process that depends on the hypoxic response to trigger vascularization, and mesenchymal cell development (43). At E8 and E8.5., murine embryos that are HIF1alpha null show a lack of cephalic vascularization, abnormal neural fold formation, and a reduction in the number of somites (2). Supporting this, another study showed that a lack of HIF1alpha expression by E11 results in developmental arrest and lethality due to cardiovascular malformations and cell death in the cephalic mesenchyme (44). Figure 3 shows the changes in oxygen availability as development progresses. Initially, prior to formation of the trophoblast shell and cell compaction at the blastocyst stage, the developing embryo is small enough that oxygen is capable of diffusing through the cellular mass. From the blastocyst stage until just prior to vascularization, the developing embryo grows in an increasingly hypoxic state, until it reaches a mass to surface area ratio that no longer allows simple diffusion of oxygen. This hypoxic state results in the stabilization of Hif1alpha and initiates vascularization and cardiac development. Interestingly, development of cardiac vascularization is dependent on a continued hypoxic state and it has been found that the oxygen partial pressure of fetal blood is at the same level as found in hypoxic adult tissues (45).

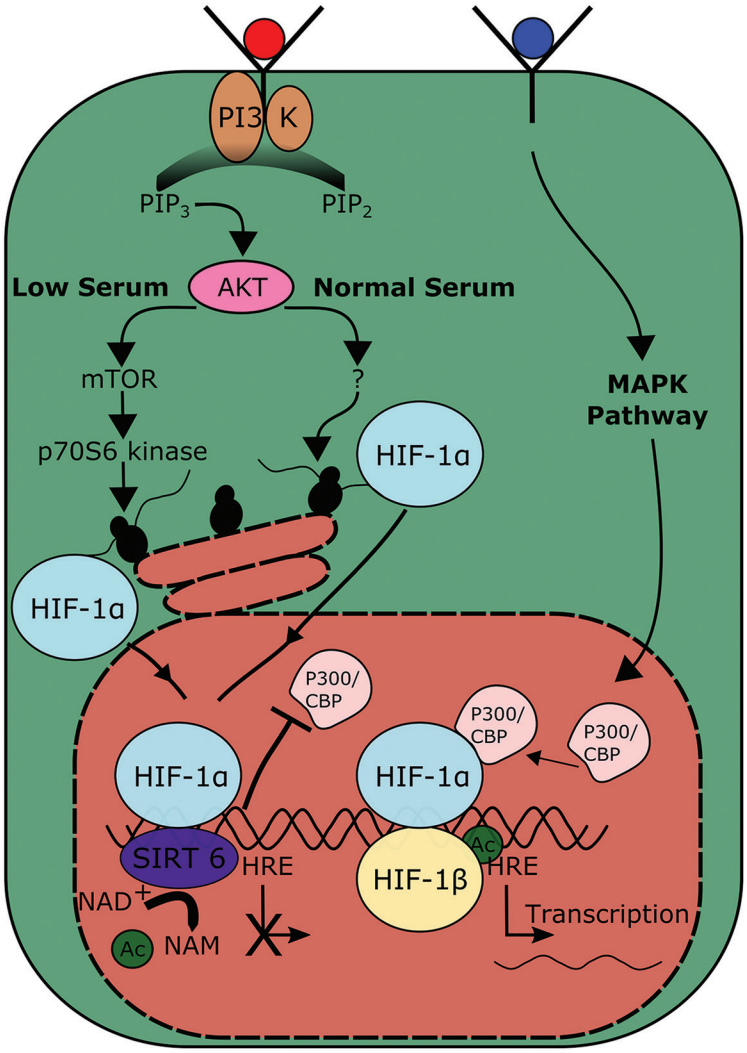

Figure 2. Oxygen-independent regulation of HIF1. HIF1 is regulated both by oxygen-independent mechanisms through the PI3K/AKT and MAPK pathways. AKT is activated by Phosphatidylinositol (3,4,5)-trisphosphate (PIP3), a product of the phosphorylation of Phosphatidylinositol (4,5)-bisphosphate (PIP2) by PI3K at the plasma membrane. Under normal serum conditions, Akt increases HIF1α translation independent of mTOR via and unknown mediator. However, under low serum conditions AKT activates mTOR which increases translation of HIF1alpha mRNA via p70S6 kinase activation of the ribosomal S6 protein. The MAPK signaling pathway up-regulates the transcription of HIF1alpha via its p300/CBP coactivator. In the nucleus, Sirt 6 deacetylates the histones in the HRE region of the promoter that HIF1alpha binds, repressing its transcriptional activity by preventing the formation of the transactivation complex with p300/CBP.

5. TELOMERASE FUNCTION IN STEM CELLS

5.1. Telomerase expression in stem cells

In the very early stages of embryonic development in mammals telomerase plays the critical role of extending the parentally-derived telomeres during the transition from morula to blastocyst stages (46). Embryonic stem (ES) cells, which are derived from mouse and human embryos in the blastocyst stage of development, express high levels of active telomerase (47). Stem cells in the tissues of adults are often characterized by the presence of telomerase, for example the bone marrow is comprised of niche environments that contain hematopoietic and mesenchymal stem cells. Telomerase activity has been found respectively in human and mouse hematopoietic stem cells (48,49), intestinal crypt cells (50,51), mesenchymal stem cells (52,53), cardiac stem cells (54), neural progenitor cells (55,56). Telomerase activity has also been detected in human epithelial regenerative keratinocytes (57), as well as adult human tissues requiring constant turn over of cells and known to contain stem cell populations including testis, ovaries, liver, lung, and skin (58). Similarly mouse female germ cells (59) and kidney stem cells (60) have also been shown to express active telomerase.

Telomerase activity is lower in adult stem cells and tissue than their embryonic counterparts, which

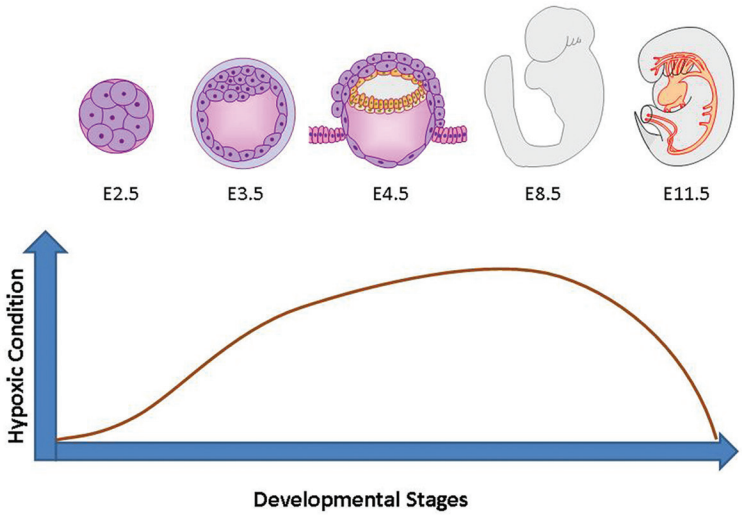

Figure 3. Change in the hypoxic environment during mammalian embryonic development.

in unsurprising given the critical nature of telomere maintenance and chromosomal stability during rapid growth and development in the embryo. Although telomerase activity has been demonstrated to be critical to slowing telomere attrition and extending the replicative potential of adult stem cells (61), in general the activity level of telomerase in adult stem cells is adequate only to slow the loss of telomere length relative to telomerase-negative somatic cells. It is likely that the level of telomerase activity in adult stem cells is an evolutionary-derived balance between the need to stave of critically short telomere-induced senescence in tissue renewing cells and the avoidance of neoplasia arising from telomerase-expressing cells.

5.2. Induction or elimination of telomerase expression

Much interest in telomerase, particularly its expression in stem cells, has derived from a desire to impede or reverse the affects of aging. Working towards that end and to help understand the role that telomerase plays, genetic models have been created in mice and in human and mouse cell lines. Increasing telomerase activity extended the replicative capacity of human somatic cells (4), and restored telomere length in serially transplanted T-cells from wild type mice but not telomerase RNA component knockout mice (62). However, increasing the expression of telomerase to restore age-shortened telomeres does not come without risks. For example, a study involving K5-mTERT mice that have increased telomerase activity in skin found augmented hair growth and skin stem cell proliferation, but also an increased risk of tumorigenesis (63). That being said, a recent study by DePinho and colleagues demonstrated that the promise of telomerase activation to combat aging is more than just hubris. They generated mice with an dysfunctional TERT allele that could have functionally active telomerase restored with exposure to a chemical and bred homozygous knockouts together for four generations (64). These mice showed signs telomere attrition, cellular proliferation, and tissue morphology associated with advanced age. Following restoration of telomerase in the fourth generation adults, tissue morphology in the highly proliferative organs testis, spleen, and intestine was restore to the appearance of wild type mice of the same age (64). Neural stem cell proliferation, brain size and olifactory function were also restored in telomerase-reactivated mice (64). Maria Blasco's group has shown that it was possible to reverse some of the effects of accelerated aging in a line of mice lacking the telomerase RNA component TERC by backcrossing them with mice carrying the wild type allele, thus partially restoring telomerase activity (65). The Blasco group then initially demonstrated that constitutive TERT expression could counter the effects of aging in mice, which also had been made cancer-resistant by the over-expression of tumor suppressor proteins (66). In an approach more closely modeling potential therapeutic intervention they then used viruses to deliver a TERT expressing vector into mice at the equivalent of middle and old age, and found a reduction in signs of age-related degeneration such as osteoporosis and an extension of lifespan without increased incidence of cancer in C57BL6 mice (67). A separate study by the Artandi group into the effects of induction of telomerase used a telomerase inducible mouse strain to specifically study the impact on hair follicles and hair growth (68). They found that induction of telomerase induction caused a transition from telogen phase to anagen phase and a consequent proliferation of the hair follicle stem cells, this in turn promoted new hair growth from the follicles (68). Findings such as these provide both useful insights into

the role of telomerase in adult tissue homeostasis and hope for those interested in utilizing telomerase as a tool to combat age-related loss of function and vitality. The case for employing telomerase in the extension of health span has been discussed elsewhere (69).

Telomere elongation has been previously been demonstrated to be unnecessary for the extension of the life-span of immortalized cells (70). However, ES cells derived from mice with and telomerase RNA component knockout phenotype do not exhibit active telomerase and show gradual attrition of telomere length and loss of growth rate with continuous passaging (71). In a transient comparison, short hairpin RNA knockdown of hTERT caused an reduction in TERT expression and telomerase activity that lead to loss of telomere length in telomerase-positive carcinoma cells (72). Likewise TERT knockout ES cells lack telomerase and show progressive telomere attrition when passaged in culture (73).

This accumulation of more than two decades of knowledge into the function, role, and necessity of telomerase in the maintenance of telomeres, and the self-renewal of stem cells throughout development highlights both the importance of this enzyme and the distance remaining in our understanding of it.

6. HYPOXIA AND STEM CELLS

Interestingly, hematopoietic stem cells (HSC) require HIF1alpha for efficient re-population potential and self-renewal (74). Indeed, circulating HSC, which reside in a normoxic environment, maintain expression of HIF1alpha (75). Recently, it has been shown oxygen partial pressure status of HSC and committed HSC progenitors is phenotype-dependent rather than localization-dependent (76). This has been backed by direct measurement of the partial oxygen pressure within mouse bone marrow which demonstrated that the HSC reside along arterial-like vessels, but that the oxygen in these vessels depletes rapidly upon entering the bone marrow cavity (77). It seems probable that this apparent localization contradiction can be accounted for by a specific population of pericytes found in association with quiescent HSC but not cycling HSC along these arteriolars (78).

Furthermore, hypoxic growth conditions enhance the self-renewal of pluripotent stem cells (embryonic stem cells) (79), as well as the Yamanaka factor driven reprogramming of somatic cells into induced pluripotent stem cells (80). Together, these observations support an important role for Hif1alpha in stem cell self-renewal.

6.1. HIF1 and telomerase regulation in stem cells

The maintenance of longevity of murine embryonic stem (mES) cells is also dependent on the ability of HIF1alpha to induce telomerase expression (81). Telomere dysfunction can trigger p53-mediated repression of peroxisome proliferator-activated receptor gamma, coactivator 1 alpha and beta, which in turn impairs mitochondrial biogenesis and leads to apoptosis or senescence (82). We have shown (81) in murine ES cells that long term short hairpin RNA mediated knock down of HIF1alpha leads to reduced expression of telomerase reverse transcriptase, the catalytic component of telomerase (83). This in turn causes reduction of telomerase activity and the inability of mES cells to maintain telomere length during proliferation (81). Hypoxia-elevated nuclear expression of TERT not accompanied by increases in telomerase activity is sufficient to maintain stemness in human embryonic stem cells (84). This suggests non-canonical roles for TERT expression that are related to cell survival and retention of phenotype in stem cells. However, it remains to be assessed whether HIF1 is also required to maintain active telomerase in other types of stem cells. It is known that different cancer cell lines do not present a consistent telomerase regulation response to hypoxia (85,86). The MAPK pathway was suggested to mediate the regulation of telomerase under hypoxia as demonstrated by the lack of telomerase activation under hypoxic conditions and in the presence of a Mitogen-activated protein kinase kinase 1-specific inhibitor in solid tumor cells (85). The MAPK pathway is involved in the activation of HIF1 expression (42), and HIF1 has been shown by chromatin immunoprecipitation assay to bind to the promoter region of hTERT (86), likely at the +1 hypoxia response element site in mTert (81). All of which implies that upregulation of telomerase under hypoxic conditions occurs through the MAPK-mediated activation of HIF1, and consequentially the direct transactivation of the TERT gene by HIF1.

In a survey of normal somatic tissue Hif1alpha expression was absent, with the exception of bone marrow (87). This does not come as a surprise since the bone marrow contains niches that maintain a low oxygen environment (77,88), something that is essential to maintenance of the hematopoietic and mesenchymal stem cells that reside there (89,90). The renal papilla, also noted to have a low oxygen tension, has been identified as a niche for adult kidney stem cells (91). Recent evidence suggests that despite extensive vasculature, portions of the brain supporting a neural stem cell niche are in fact functionally hypoxic and display Hif1alpha expression (92). Most adult stem cells express telomerase (93). We already know that regulatory relationship exists between telomerase and Hif1alpha in the earliest stages of embryonic development when telomerase activity is critically important and oxygen tension is low. We also know that low oxygen and telomerase activity are found together later in development in adult stem cell niches. These correlations suggest a strong link between Hif1alpha and telomerase,

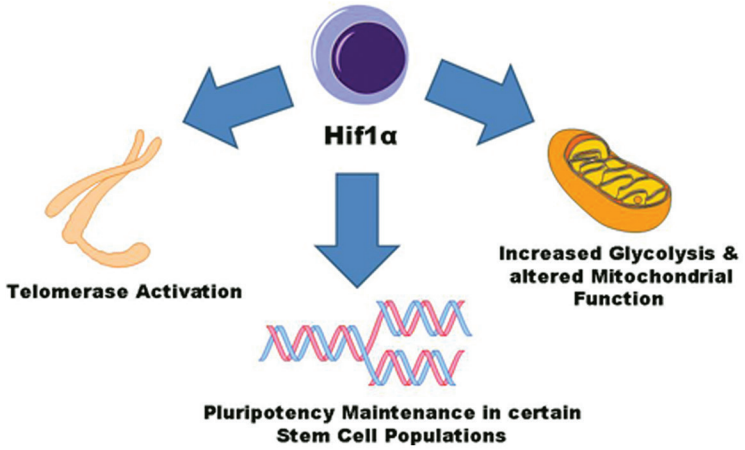

Figure 4. Emerging regulatory roles for Hif1alpha in stem cells.

and support the idea that hypoxia response elements may have a role in telomere maintenance throughout life.

In conclusion, a number of important roles for HIF1alpha in maintenance of stem cells are now emerging (Figure 4). First, evidence is emerging in support of a role for Hif1 in promoting a shift from oxidative metabolism to glycolytic metabolism in ES cells (34,35,80). Second, we have shown that Hif1alpha is essential for maintenance of telomerase activity and telomere length stability in ES cells (81). Third, studies have shown that hypoxic growth conditions promote self-renewal of ES cells (79). Furthermore, HSC require Hif1alpha for efficient re-population and self-renewal potential (74). In the future, it will be interesting to assess the extent to which different types of stem cells share these different roles for Hif1alpha.

7. ACKNOWLEDGEMENT

All authors contributed equally to this article.

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Abbreviations: HIF1alpha: Hypoxia Inducible Factor 1 alpha; HIF1beta: Hypoxia Inducible Factor 1 beta; NAD+: nicotinamide adenine dinucleotide; TERT: telomerase reverse transcriptase; PHD: prolyl-4-hyrodxylase domain; CBP: cyclic AMP response element-binding protein-binding protein; ROS: reactive oxygen species; PI3K: phosphoinositol 3-kinase; MAPK: mitogen activated protein kinase; mTOR: mammalian target of rapamycin; HSC: hematopoietic stem cells

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