Published in final edited form as:
Cancer Biol Ther. 2010 June 15; 9(12): 949–956.

Impact of the Hypoxic Tumor Microenvironment on the Regulation of Cancer Stem Cell Characteristics

Qun Lin and **Zhong Yun**
Department of Therapeutic Radiology, Yale University School of Medicine, P.O. Box 208040, New Haven, CT 06520-8040, USA

Abstract

Solid tumors often contain regions with insufficient oxygen delivery, a condition called hypoxia. Tumor hypoxia is an independent prognostic factor significantly correlated with advanced stages of malignancy, increased resistance to conventional therapy, and reduced disease-free survival. Hypoxic tumor cells exhibit poorly differentiated phenotypes resembling stem or progenitor cells. Studies have shown that hypoxia can inhibit tumor cell differentiation and promote maintenance of cancer stem cells. In addition, hypoxia also blocks differentiation of mesenchymal stem/progenitor cells, a potential source of tumor-associated stromal cells. Therefore, hypoxia may play a critical role during the evolution of the tumor stromal microenvironment and formation of the putative cancer stem cell niches. Conceptually, hypoxia may help create a microenvironment enriched both in poorly differentiated tumor cells and in undifferentiated stromal cells. Such an undifferentiated hypoxic microenvironment may provide essential cellular interactions and environmental signals for the preferential maintenance of cancer stem cells. This review will discuss the hypoxia-regulated stem cell pathways and their roles in the maintenance of cancer stem cell functions.

Keywords

Cancer stem cells; differentiation; hypoxia; niche; oxygen; tumor microenvironment

Introduction

The transformation from a benign to a malignant state is a rather slow process, often taking years to complete.[1, 2] During their malignant progression, tumor cells accumulate multiple mutations in oncogenes, tumor suppressor genes, as well as other epigenetic changes.[3, 4] The key to tumor progression is that these mutational events need to take place longitudinally in a linear fashion in a single tumor cell created by the initial oncogenic transformation. In order to complete this protracted journey, this tumor cell must be able to faithfully reproduce itself in order for previously acquired mutations to be inherited and be combined with newly acquired mutations in the daughter cell stages. In other words, this initially formed tumor cell must be capable of self-renewal and must remain in a stem cell-like state along the process toward increased malignancy (Figure 1).

Since being first identified from acute myeloid leukemia (AML) patients in 1997,[5] cancer stem cells or tumor-initiating cells have also been found in many commonly diagnosed solid tumors including breast cancers,[6] colon cancers,[7–9] cancers of the central nervous

Correspondence: Zhong Yun, Ph.D., Department of Therapeutic Radiology, Yale University School of Medicine, P.O. Box 208040, New Haven, CT 06520-8040, USA, Tel: 203-737-2183, Fax: 203-785-6309, zhong.yun@yale.edu.

Disclosure: The authors claim no conflicts of interest.

system,[10–12] head-and-neck cancers,[13] lung cancers, [14, 15] and pancreatic cancers.[16] It is worth noting that cancer stem cells are more or less defined by their biological functions, especially the ability for self-renewal or clonogenic growth and the potential to initiate a tumor upon transplantation in a new host. However, there is a lack of consensus on the cell surface markers that define the cancer stem cell population from a tumor.[17, 18] It is highly likely that a tumor may contain a heterogeneous population of cancer stem cells arising from differential clonal evolution or different developmental stages.

Studies using the euploid teratocarcinoma model strongly suggest that cancer could result from mis-regulated differentiation.[19] Therefore, cancer stem cells may share functional similarities with normal stem or progenitor cells. Gene expression profiling of gliomas has revealed that high-grade gliomas express neural stem cell markers, whereas low-grade gliomas possess lineage-specific markers of neuronal differentiation.[20] Furthermore, cancer stem cells can use many of the same mechanisms that regulate self-renewal of normal stem cells, such as Bmi-1, Notch, Wnt and Sonic Hedgehog.[18, 21–23].

Generally speaking, the microenvironment in normal tissues is ideal for differentiated cells to perform their biological functions and is permissive for lineage-specific differentiation of stem and progenitor cells. Therefore, uncommitted stem cells are often found in a unique microenvironment or niche where they can undergo self-renewal without premature or misguided differentiation.[24–27] By the same token, cancer stem cells may also rely on a specific microenvironment to protect their stem cell characteristics. Although cancer stem cell niches are still poorly understood, components of the tumor microenvironment have been shown to regulate stem cell functionalities. This review will discuss the potential role of tumor hypoxia in the regulation of cancer cell differentiation and formation of a niche environment that may facilitate cancer stem cell maintenance.

Hypoxia and Tumor Progression

Decreased oxygenation or hypoxia is a common feature of all solid tumors and is an independent prognostic factor for advanced disease progression and poor clinical outcome.[28–32] Hypoxia induces a wide range of biological changes that may contribute to the evolution of malignant tumor cells, such as decreased cell proliferation,[33] increased expression of drug-resistance gene,[34, 35] selection of apoptosis-resistant clones,[36] facilitation of tumor invasion and metastasis,[37, 38] reduced expression of DNA repair genes,[39–42] and increased genomic instability.[43, 44] During the last decade, a number of studies have shown that hypoxia has the potential to regulate cell differentiation, which has led to the emergence of a new paradigm that tumor hypoxia may facilitate the maintenance of cancer stem cell characteristics and thus allow a tumor cell with self-renewal potential to accumulate a multitude of genetic and epigenetic changes over a long period of time in order to become increasingly malignant.

Hypoxia-induced signaling is primarily mediated by the ubiquitous hypoxia-inducible factor-1 (HIF-1), a master regulator of O_2 homeostasis that consists of O_2-regulated HIF-1α and O_2-insensitive HIF-1β.[45] Genes induced by HIF-1 are involved in a wide range of cellular functions such as cell growth, survival, motility, angiogenesis, energy metabolism, and cellular differentiation.[45, 46] The second important member of the HIF family is HIF-2α, which is structurally similar to HIF-1α but appears to have non-overlapping functions.[47] In most cases, increased HIF activity is associated with tumor development. Elevated levels of HIF-1α protein are often detected by immunochemical staining in solid tumors, in contrast to normal non-ischemic tissues.[45, 48, 49] Clinical studies have shown that elevated levels of HIF-1α protein[50, 51] or HIF-2α protein[52] show significant statistical correlation with poor patient survival. Furthermore, nuclear accumulation of HIF-1α protein

is correlated with poor tumor differentiation in primary pancreatic cancers.[53] However, not all tumors benefit from increased HIF expression or activity. Tumors derived from HIF-1α$^{-/-}$ mouse embryonic stem (ES) cells exhibit accelerated growth, due in part to decreased hypoxia-induced apoptosis.[54] Similarly, elevated levels of HIF-2α have been shown to decrease growth of rat glioma tumors *in vivo*.[55] These contradicting observations may reflect the differences in the interaction between specific tumor cells and their microenvironment.

Nonetheless, recent studies have shown that increased expression of HIF-1α and/or HIF-2α has been found in the stem cell-like populations of neuroblastomas[56, 57] and gliomas.[58] Knocking down either HIF-1α or HIF-2α results in reduced tumor sphere growth and survival of glioma stem cells.[58] Compared to HIF-1α, HIF-2α appears to have a higher normoxic level of expression in glioma stem cells,[58] which might explain why HIF-2α exhibits stronger effects than HIF-1α does. In human neuroblastoma tumors, HIF-2α is preferentially expressed in the immature neural crest-like neuroblastoma cells *in vivo* and appears to be required for the maintenance of the undifferentiated neuroblastoma cells.[56, 57] These studies suggest that activation of the HIF pathway may potentially contribute to the maintenance of undifferentiated cancer stem cell phenotypes and thus facilitate malignant tumor progression.

Hypoxia-Activated Stem Cell Genes and Pathways in Tumor Cells

Several stem cell genes and/or pathways have been shown to be upregulated by hypoxia in tumor cells. However, we are still in the very early stages of understanding the mechanisms by which hypoxia regulates the maintenance or differentiation of cancer stem cells. Kim *et al.*[59] have recently identified the stem cell gene DLK1, or delta-like 1 homolog (Drosophila), as a new transcription target of the HIF pathway in neuronal tumor cells. DLK1, also known as pref-1 (preadipocyte factor 1) and fetal antigen 1 (FA1) among others, is a type I transmembrane protein with abundant expression in embryonic tissues and immature cells but not in differentiated adult tissues,[60] suggesting a role of DLK1 in the regulation of stem cells and progenitor cells. Elevated expression of DLK1 has also been reported in several tumor types.[61–66] Kim *et al.*[59] have found that DLK1 is robustly expressed in undifferentiated, but not differentiated, tumor cells. Inhibition of DLK1 enhances spontaneous neuronal differentiation, decreases clonogenicity or the colony-forming potential, and suppresses tumorigenicity *in vivo*. Overexpression of DLK1, on the other hand, inhibits differentiation, enhances clonogenicity, and increases tumorigenicity. The proximal 5′ promoter/enhancer region of the human DLK1 gene contains three putative hypoxia-responsive elements (HRE) with the conserved motif of 5′-ACGTG-3′[67] at −758, −402, and −248, respectively, from the transcription start site. Both HIF-1α and HIF-2α can bind to this promoter region under hypoxia, as demonstrated by chromosome immunoprecipitation.[59] Further investigation demonstrates that the DLK1 cytoplasmic domain, especially Tyrosine-339 and Serine-355, is required for maintaining both clonogenicity and tumorigenicity.[59] These observations demonstrate that HIF and DLK1 constitute an active signal transduction pathway that facilitates the maintenance or selection of cancer stem cells and increases their tumorigenic potential.

Chemokine receptor CXCR4 and its ligand CXCL12 or SDF-1 (stromal cell-derived factor-1) play a critical role during embryogenesis and regulate the functions of subsets of adult stem/progenitor cells.[68–70] Hypoxia, as well as activation of HIF pathways due to loss of pVHL tumor suppressor protein, strongly induces expression of *CXCR4* and *SDF-1* in both cancer cells and normal stem/progenitor cells.[71–76] CXCR4-mediated signal transduction plays an important role in homing of stem cells to hypoxic regions via the CXCL12 gradient.[71] Similarly, elevated CXCR4 expression in tumors has been found to be

associated with increased metastasis and poor patient survival.[77–80] Interestingly, the $CXCR4^+$ subpopulations of the $CD133^+$ human pancreatic cancer stem cells are essential for liver metastasis when orthotopically injected in immune-deficient mice,[81] suggesting that the $CXCR4^+$ cancer stem cells are the most likely source of tumor metastasis. However, it remains to be determined whether CXCR4-CXCL12 has the potential to regulate stem cell maintenance or cellular differentiation.

The POU family transcription factor POU5F1 (Oct3/4) has been shown to be one of the four to five critical genes that collectively transform adult somatic cells into pluripotent stem cells.[82–84] Elevated levels of *POU5F1* has been found in germ cell cancers and several types of somatic cancers including human cervical carcinomas, breast carcinomas and pancreatic cancers.[85–88] Using transgenic mice with doxycycline-inducible expression of *POU5F1*, Hochedlinger *et al.*[89] have shown that increased *POU5F1* expression results in inhibition of cellular differentiation and dysplastic growths in epithelial tissues, thus demonstrating a direct role of POU5F1 in tumorigenesis. Interestingly, the genetic *HIF-2α* "knock-in" study has shown that HIF-2α is directly involved in transcription of *POU5F1* in mouse embryonic tissues.[90] Loss of *POU5F1* results in decreased growth of mouse embryonal stem cell-derived teratomas.[90] Similarly, Forristal *et al.*[91] have found that reduced HIF-2α expression results in decreased expression of *POU5F1* and other stem cell genes in human ES cells cultured at 5% O_2. These observations strongly suggest that HIF-2α is an important regulator of cellular stemness. Nevertheless, it remains to be examined whether hypoxia increases *POU5F1* expression in common types of clinical cancers and whether hypoxia-dependent upregulation of *POU5F1* expression plays a role in the regulation of cancer stem cell characteristics.

The pentaspan transmembrane glycoprotein prominin-1 (CD133) has been widely used as a marker to isolate perspective cancer stem cells from a variety of tumors[18] although its functions remain to be investigated. Recent studies have shown that hypoxia (1% O_2) can increase *CD133* expression in human glioma cells and can promote the expansion of the $CD133^+$ tumor cell population.[92–94] Interestingly, the hypoxia-dependent induction of *CD133* expression is attenuated in glioma cells when expression of either HIF-1α[94] or HIF-2α[93] is knocked down. Contradictorily, Matsumoto *et al.*[95] have shown that *CD133* expression in several gastric, colorectal, and lung cancer cell lines with elevated basal *CD133* levels is down regulated upon exposure to hypoxic conditions (0.1% O_2 or deferoxamine). In addition to cell line differences, an important difference between these two experimental models is the degree of hypoxia, i.e. 1% O_2 for glioma cells versus 0.1% O_2 for other cell lines. Future investigation of the transcriptional regulation of *CD133* expression under hypoxia may shed light on the discrepancy between these two experimental models.

Impact of Hypoxia and Cancer Stem Cell Niches

Genetic studies have shown that differentiation status of niche stromal cells can exert strong impact on stem cell maintenance. In mouse bone marrow (BM), destruction of osteoblasts at the early stage of osteoblastogenesis results in severe decrease of hematopoietic stem cells.[96] In contrast, ablation of osteoblasts at later stages of differentiation has little effect on hematopoiesis.[97] Furthermore, $CD146^+$ osteoprogenitor cells are able to reconstitute the hematopoietic microenvironment in bone marrow.[98] These immature $CD146^+$ cells, but not the differentiated $CD146^-$ cells, can produce significant amounts of angiopoietin-1 to support the maintenance of hematopoietic stem cells.[98–100] These data suggest that immature stromal cells are preferentially suited for the maintenance of stem cells.[27] It can therefore be argued that cancer stem cells might also prefer being surrounded by poorly differentiated stromal cells.

With the initiation and progression of a tumor, the tumor stromal microenvironment also undergoes progressive changes characterized by loss of normal tissue structures and reduced numbers of well-differentiated stromal cells.[101–103] For example, breast carcinoma is predominantly rich in fibroblasts, whereas normal mammary tissues have abundant adipocytes and sparse connective tissue. Interactions between tumor cells and their microenvironment exert profound influence upon tumor development and progression toward malignancy.[101, 104, 105] As an excellent example, Pine *et al.* have shown that the decision to undergo symmetric or asymmetric cell division by a small population of human lung cancer cells is partially determined by hypoxia and cell-cell contact, among other environmental factors.[106]

Tumor-associated stromal cells appear to be developmentally immature. Mouse stromal cells isolated from human breast cancer xenografts have been shown to have the ability to form fibroblastoid colonies (CFU-F) *in vitro*, a hallmark of undifferentiated mesenchymal stem cells.[105, 107] In contrast, stromal cells prepared from control Matrigel plugs or from adjacent normal tissues do not form fibroblastoid colonies,[105] suggesting that tumor stroma contains higher populations of immature cells than normal stroma does. Interestingly, weakly metastatic human breast carcinoma cells become highly metastatic when injected subcutaneously as a mixture with human BM-derived mesenchymal stem cells.[105] Although it remains to be determined whether mesenchymal stem cells play a role in regulation of cancer cell differentiation, this study clearly demonstrates that immature stromal cells facilitate acquisition of aggressive tumor phenotypes.

It is not yet understood what causes the changes in the stromal microenvironment and what is the cellular origin of tumor-associated fibroblasts, although BM-derived mesenchymal stem cells and hematopoietic stem cells are among the likely sources of tumor stromal cells.[105, 108, 109] Also not clear is how the cell fate decision of these tumor-infiltrating mesechymal stem cells is regulated by tumor microenvironment. As discussed below, it is possible that tumor hypoxia regulates the cell fate decisions in these mesenchymal stem cells and thus affects the evolution of the tumor stromal microenvironment.

Mesenchymal stem cells are capable of differentiating into several cell types including adipocytes, chondrocytes, and myocytes in response to specific differentiation cues. Interestingly, it has been demonstrated that adipogenic differentiation by mesenchymal stem or progenitor cells is inhibited at physiologically relevant levels of hypoxia or 1–2% O_2.110–113 Ectopic expression of constitutively active *HIF-1α* mutants is sufficient to inhibit adipogenic differentiation under normoxic conditions.[112] On the other hand, knocking down *HIF-1α* by gene-specific siRNA rescues adipogenic differentiation under hypoxic conditions.[112] Mechanistically, hypoxia increases the expression of *DEC1/Stra13*, a putative transcription repressor with homology to the *Hairy* and *Enhancer-of-Split* (HES) family of transcription repressors that represses the expression *PPARγ2,* a critical differentiation-determination gene for terminal adipogenic differentiation.[112, 113] In addition, HIF-independent signaling pathways also appear to be involved in the inhibition of adipogenic differentiation by hypoxia. The Transforming Growth Factor β (TGFβ)-Smad pathway in human BM-derived mesenchymal stem cells is activated under hypoxia as shown by increasing levels of phosphorylated Smad2/3, which leads to inhibition of adipogenic differentiation of human BM-derived mesenchymal stem cells.[114] However, whether or how the HIF pathway is involved in activation of the TGFβ-Smad pathway remains to be determined. Nonetheless, it is worth noting that mesenchymal stem/progenitor cells remain undifferentiated and uncommitted under hypoxic conditions and can still undergo lineage-specific differentiation once they return to normoxic conditions.[112] Collectively, these data suggest that hypoxia has the ability to maintain mesenchymal stem cells in an undifferentiated state and to prevent them from committing to adipogenic

differentiation. These findings could provide a plausible mechanism underlying the stromal changes observed in breast cancers.[101]

Hypoxia also decreases the potential of mesenchymal progenitor cells to undergo myogenic differentiation.[115, 116] Nonetheless, the degree of inhibition is dose dependent on the level of hypoxia with strongest inhibition at nearly anoxic pO_2 level.[116] Interestingly, expression of the key myogenic transcription factor *MyoD* is only transiently repressed at 0.5–2% O_2 and gradually recovers even when the myogenic precursor C2C12 cells are continuously maintained under hypoxic conditions. This observation suggests that myogenic differentiation, in contrast to adipogenic differentiation, can adapt to persistent or chronic hypoxia.[116] The mechanisms underlying hypoxia adaptation remain to be fully understood.

There have been conflicting reports regarding the mechanisms of hypoxic inhibition of myogenesis. Yun *et al.*[116] have shown that ectopic expression of constitutively active HIF-1α does not affect myogenic differentiation under normoxia or hypoxia, suggesting that the HIF pathway does not play a significant role in the regulation of myogenic differentiation. Nonetheless, Gustafsson *et al.*[115] have reported that HIF-1α is involved in inhibition of myogenic differentiation via interaction with the Notch intracellular domain (NICD) and subsequently activation of Notch-regulated genes. In contrast, Yun *et al.*[116] have found that expression of *Notch* family genes, *Notch1*, *Notch2* and *Notch3,* is decreased at <0.01% O_2, but is insignificantly affected at 0.5–2% O_2, compared to the ambient (21% O_2) culture condition. Furthermore, pharmacological inhibition of Notch signaling by N-[N-(3,5-difluorophenylacetyl-L-alanyl)]-S-phenylglycine t-butylester (DAPT), a specific γ-secretase, has no significant effect on myogenic differentiation of C2C12 myoblasts under either normoxic or hypoxic conditions.[116]

A study by Sun *et al.*[117] may have provided a clue about the mechanism of hypoxic regulation of myogenic differentiation. Mice homozygous-null for *Stra13* (*BHLHB2* or *DEC1*) have defective muscle regeneration with degenerated myotube formation. Primary *Stra13*$^{-/-}$ myoblasts show elevated Notch activity, increased proliferation, and defective differentiation.[117] Interestingly, Stra13 can be co-immunoprecipitated with NICD, and ectopic expression of *Stra13* rescues the Notch-dependent inhibition of myogenesis.[117] Because *Stra13* is a HIF target gene,[113, 118, 119] the genetic study by Sun *et al.* does not support the HIF-dependent activation of Notch as reported by Gustafsson *et al.* Since myogenic differentiation is only transiently inhibited by moderate hypoxia,[116] it is tempting to hypothesize that the transient inhibition of myogenesis might be mediated by the HIF-Notch interaction; whereas the recovery of myogenic differentiation under prolonged hypoxia may potentially be mediated by the inhibition of Notch signaling by the hypoxia-induced gene *Stra13*.

As discussed above, hypoxia clearly has a profound impact on differentiation of mesenchymal stem cells. Tumor hypoxia undoubtedly plays a significant role in the composition of tumor-associated stromal cells and the evolution of tumor stroma. It is conceivable that hypoxic tumor stroma is enriched in undifferentiated stromal cells, which may provide a favorable microenvironment for maintaining tumor cells in a stem cell state (Figure 2).

A recent study has shown that human glioblastoma cells expressing a subset of stem cell genes can be found in the hypoxic perinecrotic regions with positive immunostaining for both HIF-1α and HIF-2α.[93] However, brain cancer stem cells can also be identified in perivascular zones.[93, 120, 121] Similarly, some immature neural crest-like neuroblastoma cells are reportedly found in a perivascular niche.[56] These latter findings seem to argue against the notion that stem cell niches are hypoxic; however, *in vitro* co-culture assays have

shown that endothelial cells promote growth or self-renewal of cancer stem cells, at least in part, via endothelial cell-derived paracrine factors.[120] This result suggests that endothelial cells directly regulate cancer stem cells independent of their blood-carrying or other vascular functions. As is widely known, tumor-associated blood vessels are often structurally and functionally abnormal, which results in tumor hypoxia.[122, 123] Consistent with this notion, some of the perivascularly located immature neuroblastoma cells express high levels of HIF-2α.[56] It will be interesting to determine whether cancer stem cells are preferentially associated with endothelial cells in hypoxic regions.

As suggested by current observations, cancer stem cells may exist in two types of niches: the hypoxic niche located distally from the functional blood vessels and the perivascular niche that may or may not be hypoxic. Nonetheless, there are at least three potential mechanisms by which tumor hypoxia may regulate maintenance and differentiation of cancer stem cells (Figure 2). First, hypoxia directly prevents cancer stem cells from undergoing differentiation. Second, hypoxia inhibits differentiation of niche stromal cells and maintains them in an undifferentiated state. Third, hypoxia may potentially regulate the expression of paracrine factors by endothelial cells for the maintenance of cancer stem cells located in the periendothelial niche.

Implications in Cancer Therapy

Stem cells seem to have superior survival potential. Among different subpopulations of hematopoietic stem cells, the most immature hematopoietic stem cells are more resistant to radiation than partially differentiated stem cells.[124] These immature stem cells seem to have robust repair capabilities, which may offer a partial explanation about therapy resistance by stem/progenitor cells. Similarly, as shown recently by Bao *et al.*[125], $CD133^+$ tumor stem cells isolated from both human glioma xenografts and clinical glioblastoma tumors display more robustly activated DNA damage checkpoints in response to ionizing radiation and repair radiation-induced DNA damage more effectively than $CD133^-$ tumor cells isolated from the same tumors. These findings indicate that poorly differentiated tumor cells or cancer stem cells are likely to be the source of resistance to conventional therapies such as radiotherapy and chemotherapy. Therefore, targeting cancer stem cells would offer a potentially highly effective approach for cancer therapy.

Despite the close similitude between cancer stem cells and normal stem cells in their gene expression profiles, it remains challenging to identify a marker that is specific to cancer stem cells only. Nonetheless, the distinctive tumor microenvironment, especially hypoxia, may offer unique opportunities for potentially effective targeting of cancer stem cells. As discussed above, HIF-α proteins, especially HIF-2α, are capable of facilitating cancer stem cell maintenance and expansion.[57, 58, 93] Inhibitors of the HIF pathway[126–128] would have the potential to decrease the self-renewal of cancer stem cells and sensitize them to undergo differentiation. This approach is likely to be useful for targeting both cancer stem cells located in the hypoxic regions and those $HIF\text{-}\alpha^+$ cancer stem cells residing around blood vessels.

Targeting the tumor microenvironment would be another promising strategy for effective control of cancer stem cells. Anti-angiogenesis compounds can strongly reduce tumor blood supply if tumor vasculature is severely destroyed, but can also improve tumor blood flow and oxygenation with partial vascular destruction.[129, 130] Because at least a subpopulation of cancer stem cells resides in perivascular niches[93, 120, 121] and endothelial cell-derived paracrine factors can promote cancer stem cell maintenance,[120] ablation of blood vessels would be detrimental to the perivascularly localized cancer stem cells. Furthermore, improved oxygenation after vascular normalization would have the potential to reduce the

expression of HIF-α proteins in cancer stem cells located in the hypoxic regions, thus rendering the niche environment permissive for these cancer stem cells to undergo differentiation. Another potential approach for controlling cancer stem cells is to therapeutically target the tumor-associated stromal cells. Altering the composition or differentiation of tumor-associated stromal cells would likely change the cancer stem cell niche from a microenvironment that supports stem cell maintenance to one that facilitates cell differentiation or loss of self-renewal. However, different types of cancer stem cell niches may exist in a typical solid tumor due to the heterogeneity in the tumor microenvironment. Effective control of tumor growth and improvement of disease-free survival will have to rely on a combination of therapeutic approaches that collectively targets different molecular pathways in both cancer stem cells and stromal cells located in different depots of tumor microenvironment.

Acknowledgments

The authors thank the present and past members of the Yun Laboratory for their contribution to the herein referenced work and Lisa Cabral for her excellent editorial assistance. ZY is partly supported by R01CA125021 and R01CA148996 from the National Institutes of Health.

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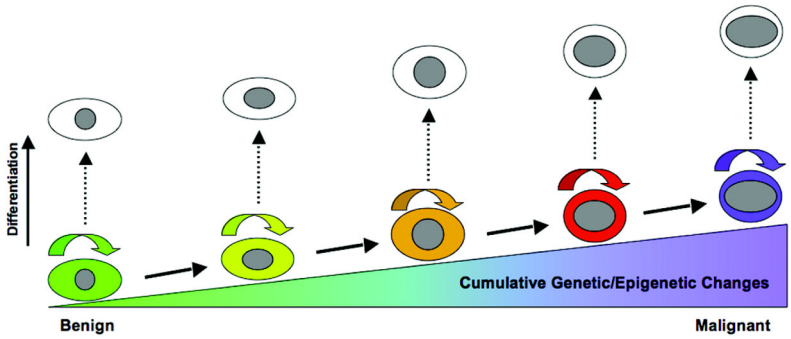

Figure 1. Cancer Cell Stemness is Essential for Tumor Progression

Tumor progression is accompanied by multiple genetic mutations and epigenetic changes that occur over a long period of time. Since these nuclear mutations and changes must be inherited in the same tumor cell or its identical clones, the capacity of self-renewal is absolutely required for malignant progression. Differentiation of a clonal population at any stage of this linear progression will effectively block the tumor progression.

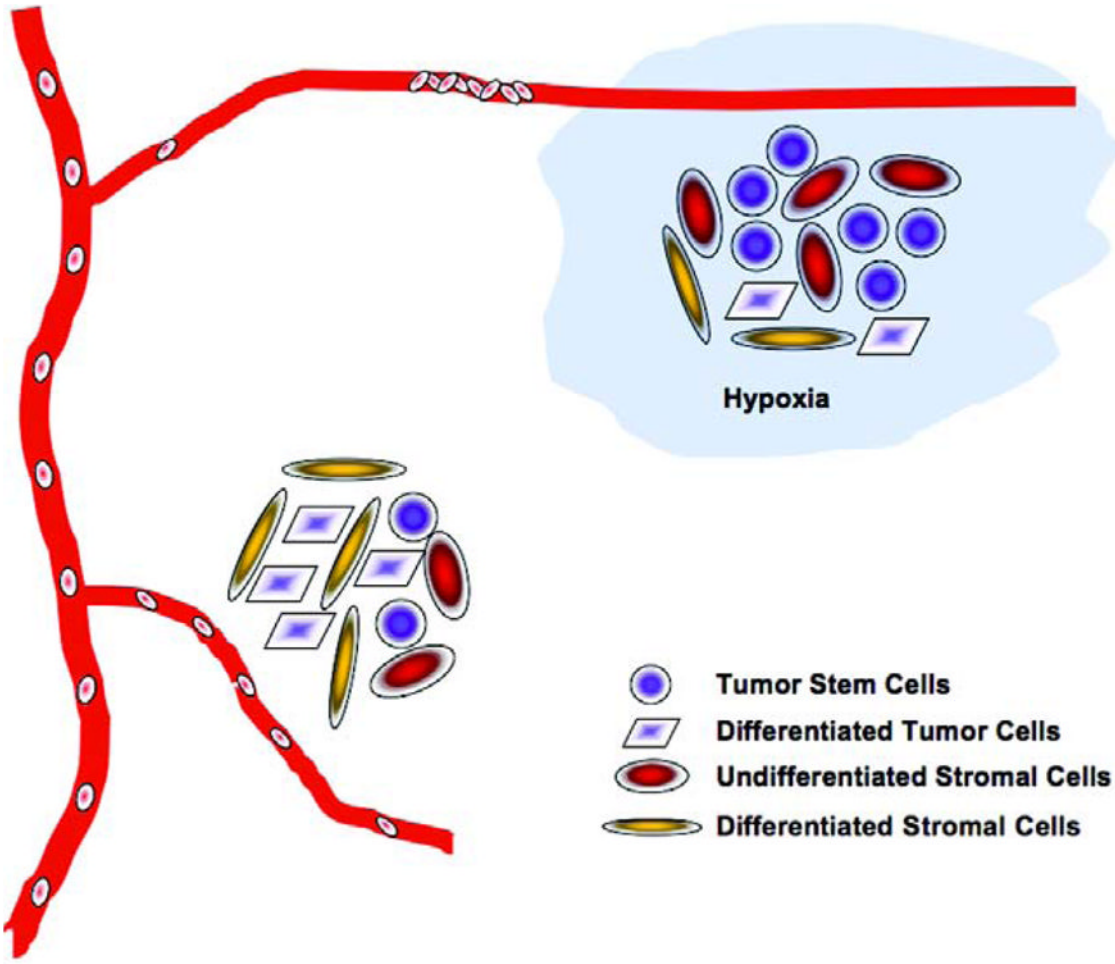

Figure 2. Hypoxia Facilitates the Evolution of Cancer Stem Cell Niche

Tumor hypoxia develops mainly due to the abnormal structures and functions of tumor-associated blood vessels. Three potential mechanisms by which hypoxia regulates maintenance and differentiation of cancer stem cells can be envisioned. First, hypoxia directly prevents cancer stem cells from undergoing differentiation by activating intracellular stem cell pathways. Second, hypoxia maintains niche stromal cells in an undifferentiated state to support the self-renewing cancer stem cells. Third, hypoxia may potentially regulate the expression of paracrine factors by endothelial cells for the maintenance of cancer stem cells located in the periendothelial niche.