

Normal Stem Cells and Cancer Stem Cells: The Niche Matters

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Abstract

Scientists have tried for decades to understand cancer development in the context of therapeutic strategies. The realization that cancers may rely on “cancer stem cells” that share the self-renewal feature of normal stem cells has changed the perspective with regard to new approaches for treating the disease. In this review, we propose that one of the differences between normal stem cells and cancer stem cells is their degree of dependence on the stem cell niche, a specialized microenvironment in which stem cells reside. The stem cell niche in adult somatic tissues plays an essential role in maintaining stem cells or preventing tumorigenesis by providing primarily inhibitory signals for both proliferation and differentiation. However, the niche also provides transient signals for stem cell division to support ongoing tissue regeneration. The balance between proliferation-inhibiting and proliferation-promoting signals is the key to homeostatic regulation of stem cell maintenance versus tissue regeneration. Loss of the niche can lead to loss of stem cells, indicating the reliance of stem cells on niche signals. Therefore, cancer stem cells may arise from an intrinsic mutation, leading to self-sufficient cell proliferation, and/or may also involve deregulation or alteration of the niche by dominant proliferation-promoting signals. Furthermore, the molecular machinery used by normal stem cells for homing to or mobilizing from the niche may be “hijacked” by cancer stem cells for invasion and metastasis. We hope this examination of the interaction between stem cells and their niche will enhance understanding of the process of cancer development, invasiveness, and metastasis and reveal possible targets for cancer treatment. (Cancer Res 2006; 66(9): 4553-7)

Is Cancer a Disease of Stem Cells?

In recent decades, biomedical research has revealed extraordinary diversity within the broad category of diseases known as cancers. This astounding variety confounds attempts to find common features among the many forms of cancer. However, all clinically significant cancers share at least one common characteristic: excessive proliferation of affected cells. As highly differentiated cells rarely divide, and rapidly proliferating cells have poorly differentiated phenotypes, two basic therapeutic approaches for combating cancers have developed: “differentiation therapy” (1) to induce differentiation and “destruction therapy” (2) to thwart malignant proliferation. Apart from limited success in some cases, neither of these approaches completely cures cancer.

In the early 1990s, clinical observations and genetic studies of a variety of cancers led to the hypothesis that six genetic mutations were required to convert a normal somatic cell into a cancer cell (3, 4). These six mutations included (a) self-sufficiency for growth signals, (b) insensitivity to antigrowth signals, (c) evasion of apoptosis, (d) limitless ability to replicate, (e) sustained angiogenesis, and (f) tissue invasion and metastasis.

However, not all cells in a given tissue are created equally in terms of their stage of development and their potential for proliferation and/or differentiation. Stem cells sit at the top of the developmental hierarchy, having the ability to self-renew and give rise to all the cell lineages in corresponding tissues. Stem cells divide to produce two daughter cells. One daughter remains a stem cell (self-renewal). The other daughter becomes a progenitor cell that undergoes expansion and further differentiation into mature cells. Stem cells have the highest potential for proliferation and a much longer life span compared with their progeny and therefore have a greater opportunity to accumulate genetic mutations (5). The realization that the adult body harbors small numbers of stem cells offered an alternative possibility for the origin of cancer. Perhaps only one or two mutations, such as self-sufficiency in growth or insensitivity to antigrowth signals, are needed for stem cells to initiate tumorigenesis rather than six mutations, a rare event in any type of cell.

The thought that cancer might originate in stem cells harkens back to the 19th century concept of “embryonal rest” (6, 7). Over a century later, one recognizes the similarity between the old belief that cancer arises from embryonal rests and the contemporary view that some forms of cancer originate in adult stem cells. In 1994, John Dick’s lab showed that leukemia-initiating stem cells present in the peripheral blood of acute myelogenous leukemia (AML) patients (1 of 250,000 cells) could induce AML when transplanted into severe combined immunodeficient (SCID) mice (8). Demonstration of tumorigenesis in SCID mice became convincing proof of the role of stem cells in perpetuating cancer in various organs. In 2003, Michael Clarke’s lab conclusively showed the presence of stem cells in breast cancer (9). The following year, Peter Dirks’ lab unequivocally proved stem cell involvement in brain cancer (10).

Within established tumors, the great majority of the cancer cells cannot sustain the lesion nor establish it elsewhere in the body. Only a few cells within the tumor, the cancer stem cells, are tumorigenic and possess the metastatic phenotype (5). This circumstance has implications for both therapy and research (11). It explains why treatments that substantially reduce the tumor mass by removing proliferating cells fail to cure patients with some types of cancer, because cancer stem cells are usually slowly cycling cells and thus insensitive to these treatments. It also introduces a note of caution among researchers seeking insight from analysis of a cross-section of the tumor cell population. Gene expression profiles obtained from samples of heterogeneous tumor tissue probably bear limited resemblance to those of the tumor stem cell population, which forms only a tiny fraction of the whole tumor (12).

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Anyone tempted to embrace the stem cell genesis of cancer too warmly should remember the accumulated frustrations of the two-century-long quest to find a unifying theory of how malignant tumors arise. Stem cell biology clearly holds critical insight for understanding and defeating many kinds of cancer, but not all cancers come from populations of self-renewing stem cells. Some forms of leukemia clearly come from true stem cells (13), but cancer can also arise from progenitor cells downstream of stem cells. For example, Weissman's lab recently found that a mutation that enhances nuclear β -catenin in granulocyte-macrophage progenitor cells causes a blast crisis in some patients with chronic myeloid leukemia (14). It seems these mutated progenitor cells have acquired the ability to self-renew, a feature thought to be specific to stem cells, and to undergo unlimited growth as cancer cells. In this sense, cancer may prove to be more of a stem cell disease than previously suspected (13, 15). This concept has immediately changed the perspective of the cancer field and shed light on new strategies for therapeutic treatment of cancers.

Homeostatic Regulation of Stem Cells by the Niche: a Balance between Self-renewal and Differentiation

In adults, stem cells reside in a physiologically limited and specialized microenvironment, or niche, that supports stem cells but varies in nature and location depending on the tissue type (16, 17). Remarkable progress has been made in studies regarding the interaction between stem cells and their surrounding microenvironment in flies, *Caenorhabditis elegans*, and mammals. By comparing the stem cell niches in these systems, features and functions common to all stem cell niches have emerged as follows (17–19):

- The stem cell niche is composed of a group of cells in a special location that functions to maintain stem cells.
- The niche is a physical anchoring site for stem cells, and adhesion molecules are involved in the interaction between stem cells and the niche and between stem cells and the extracellular matrix.
- The niche generates extrinsic factors that control stem cell number, proliferation, and fate determination. Many developmental regulatory signal molecules, including hh, Wnts, bone morphogenetic proteins (BMP), fibroblast growth factors, and Notch, have been shown to play roles in controlling stem cell self-renewal and in regulating lineage fate in different systems.
- The niche controls normal asymmetrical division of stem cells. This has been shown in invertebrates; whether it is conserved in the mammalian system is still an open question.

Normally, at least in the hematopoietic, intestinal, and hair follicle systems, the niche maintains stem cells primarily in a quiescent state by providing signals that inhibit cell proliferation and growth as evidenced by the ability of stem cells to retain bromodeoxyuridine labeling for a relatively long period of time (20–24). Only upon receipt of a stimulating signal does the stem cell become activated to divide and proliferate (Fig. 1). Therefore, stem cell proliferation depends on dynamic niche signaling. Maintaining a balance between the proliferation signal and antiproliferation signal is the key to homeostatic regulation of stem cells, allowing stem cells to undergo self-renewal while supporting ongoing tissue regeneration (25). Any genetic mutation that leads stem cells to become independent of growth signals, or to resist antigrowth signals, will cause the stem cells to undergo

uncontrolled proliferation and possible tumorigenesis (Fig. 1). In this review, we will use recent studies of signaling regulation of stem cells in bone marrow, intestine, and skin to show the importance of this balanced control of stem cells by both growth-promoting and growth-inhibiting signals.

In adults, hematopoiesis occurs in bone marrow in which hematopoietic stem cells (HSC) are primarily located in the osteoblastic niche on the bone surface (21, 22, 26, 27). Upon mobilization, HSCs and their progenitor cells are found adjacent to the sinusoid endothelial cells (vascular niche; refs. 28, 29). It has been proposed that a gradient of osteoblastic niche to vascular niche exists in bone marrow, with the osteoblastic niche providing a quiescent microenvironment, and the vascular niche favoring for proliferation and further differentiation (30).

In skin, stem cells are located in the bulge area of the hair follicle (24). Wnt signaling has been reported to play a role in promoting stem cell activation and expansion in skin (31, 32). However, Wnt inhibitors, including Dkk, sFRP, and Wif, have been found to be dominantly present in the stem cell niche in the hair follicle bulge, providing an environment of cell growth inhibition (20). The Wnt molecules are primarily expressed in dermal papilla, separate from the bulge region, and only when the bulge area is close to the dermal papilla during the early anagen phase can stem cells be activated in response to Wnt signals emanating from the dermal papilla (33). Likewise, Wnt signaling can also promote HSC proliferation (34), but which Wnt signal, if any, is expressed in the osteoblastic or vascular niche is thus far unknown.

In intestine, intestinal stem cells (ISC) are located between differentiated Paneth cells and proliferating progenitor cells (35–37). Wnt signaling is known to promote crypt cell proliferation (38); however, sFRP5, a Wnt inhibitor, has also been shown to be predominantly expressed in ISCs (39). In contrast, active Wnt signaling is widely seen in the proliferating crypt cells (37, 38). Overall, Wnt signaling is most likely only transiently active in the ISC niche (25).

On the other hand, signals, including transforming growth factor- β (TGF- β) and BMP, provide proliferation-inhibition signals to inhibit stem cell activation and proliferation (37, 40, 41), but whether they are expressed in each or all of the niches described above is not clear, apart from BMP4, which has been shown to be expressed in the intestinal stem cell niche (37).

Wnt signaling, known to promote cell growth (42), is activated when Wnt binds its receptor Frizzled and sends a signal to inhibit a negative complex formed by adenomatous polyposis coli (APC) and glycogen synthase kinase-3 β , which controls the phosphorylation and subsequent degradation of β -catenin. Abnormal activation of the Wnt signaling pathway causes cells to receive a continuous signal for proliferation due to accumulation of β -catenin in the nuclei, thereby leading to the development of APC in intestine, hair follicle tumors in skin, and leukemia in bone marrow (14, 43–45).

BMPs belong to the TGF- β super family, which in general inhibits cell growth with exceptions in some systems (40, 46, 47). BMP2/BMP4 signaling is mediated by Bmpr1A or Bmpr1B (46) and through Smad transcriptional factors 1, 5, or 8 together with Smad4 and regulates targeted gene expression (48). BMP activity can be regulated by its antagonists, such as Noggin (49). In a mouse model in which BMPR1a was conditionally inactivated, the stem cell populations were expanded in hair follicle, intestine, and bone marrow, resulting in hair follicle tumors (50), intestinal polyposis (37), and abnormal bone growth and expansion of the HSC

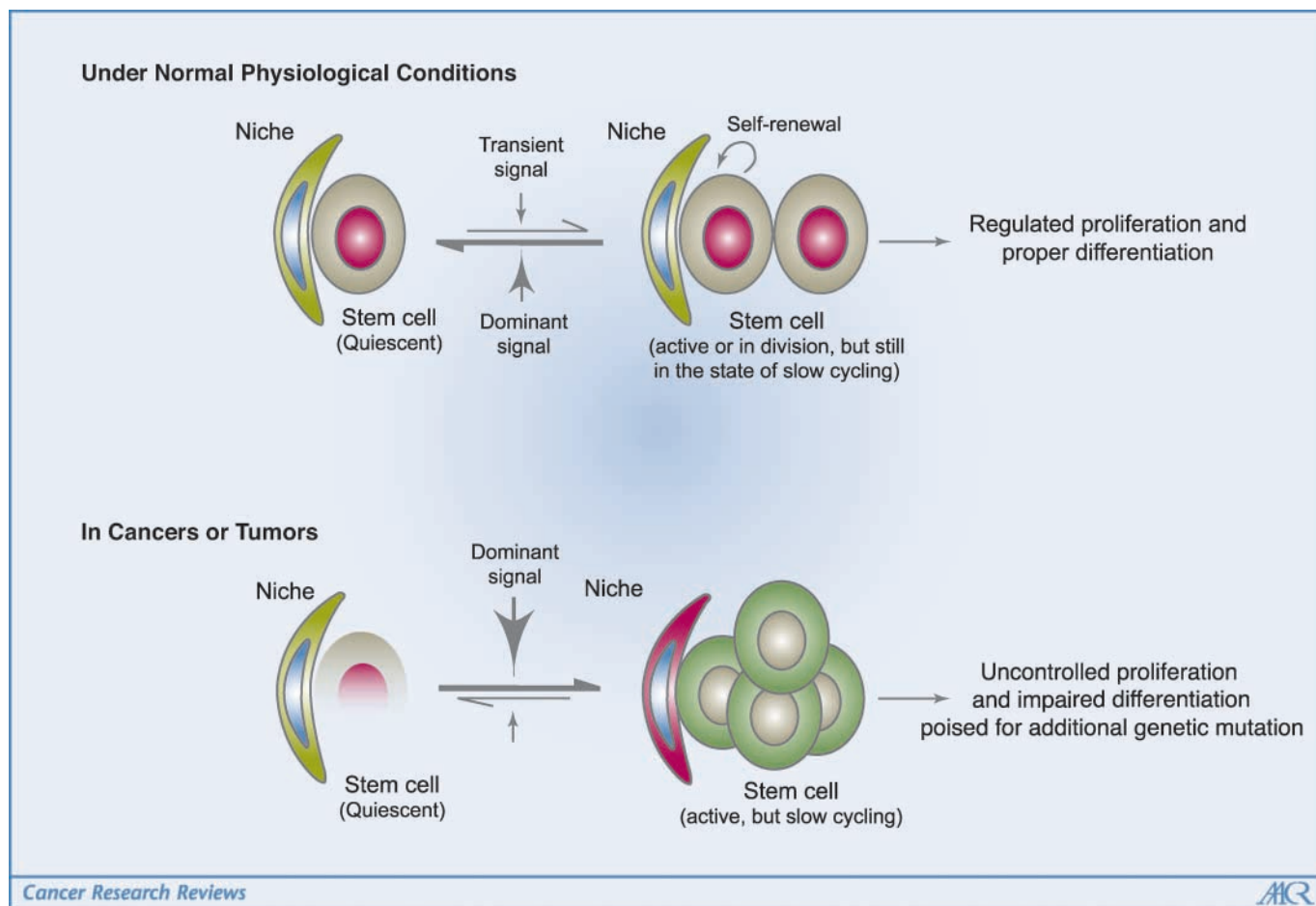


Figure 1. Comparison of the niches under normal and cancerous conditions. The stem cell niche under normal physiological conditions provides an environment that predominantly inhibits both proliferation and differentiation. However, a transient proliferating signal is required to support ongoing tissue regeneration. In cancer or tumors, owing to internal mutations, cancer stem cells become self-sufficient to undergo uncontrolled proliferation or, due to changes in the per se or a change in the niche signals, the niche is converted into an environment with dominant signals favoring cell proliferation and growth. In some cases, a combination of these scenarios may be required. In addition, uncontrolled proliferation of stem/progenitor cells leads to expansion of the progenitor pool, which is poised to accumulate a secondary genetic mutation.

population, respectively (21). These observations have shown that BMP signaling mediated by *Bmpr1a* directly inhibits stem cell proliferation in the niches of intestine and skin and indirectly regulates hematopoietic stem cells through control of its niche. Although BMP4 is constantly expressed in the ISC niche, its antagonist Noggin is transiently expressed in stem cells of the intestines and the hair follicle bulge area (37).⁴ It has been proposed that coordination between Wnt and the transiently expressed Noggin, which overrides BMP inhibition signaling, is required to activate stem cells, at least in skin and intestine (25, 51). The fact that overexpression of Noggin leads to intestinal polyposis supports this model (52).

In summary, the interplay between the BMP antigrowth signal and the Wnt growth-promoting signal regulates the homeostatic balance of stem cell self-renewal and ongoing regeneration. If this balance is disrupted, stem cells may proliferate without restraint, such as when loss of BMP signaling or abnormal activation of Wnt signaling leads to tumorigenesis (14, 37, 45, 52, 53).

Stem Cell Niche: Gatekeeper of Pandora's Box

The role of the niche in maintaining stem cells has been shown in several systems. For example, genetic ablation of the germ line stem cell niche in flies results in loss of stem cells (54). Increasing the niche size in mice leads to an increased number of hematopoietic stem cells (21), and in contrast, depleting the osteoblastic lining cells leads to depletion of hematopoietic tissue (55). However, recent evidence has suggested that the stem cell niche may have another important function that has thus far been underestimated. That function is to prevent tumorigenesis by controlling stem cell proliferation. Here, we hypothesize that deregulation of the niche leading to uncontrolled proliferation of stem cells may result in tumorigenesis (Fig. 1), much like opening "Pandora's box." Recently, R. Dickson's lab reported that deregulation in the mammary gland stem cell niche leads to abnormal expression of TFF α , resulting in the development of breast cancer (56), and this seems to support our hypothesis.

Link between Stem Cell Homing/Mobilization and Cancer Cell Invasion/Metastasis

A basic function of the niche is to anchor stem cells in the appropriate microenvironment. This function is mediated by

⁴ Zhang and Li, unpublished data.

adhesion molecules, including an adherent complex composed of cadherin and β -catenin. It has been reported that different forms of β -catenin interact with different protein complexes. That is, the heterodimeric form of β -catenin/ α -catenin interacts with membrane-bound cadherin, and the monomer form interacts with Tcf in nuclei, and that the phosphorylation of the COOH terminus of β -catenin (by non-Wnt signals) regulates the conversion between the two forms (57). It is, therefore, reasonable to propose that β -catenin is a key molecule bridging two states of stem cells (58): the arrested state when stem cells are attached to the niche through the cadherin- β -catenin adhesion interaction (21, 59) and the activated state in which β -catenin is nuclearly localized (31, 37). Defining the signals that regulate the conformational change of β -catenin through phosphorylation of its COOH terminus to control the conversion of β -catenin from its membrane-bound form to the form favoring Tcf binding will provide insight into understanding stem cell activation, as the β -catenin/Tcf complex will turn on cycle-related genes, including *cyclin D1* and *c-Myc* (60, 61). The signal responsible for regulation of the β -catenin COOH terminus may be required to coordinate with the Wnt signal, which primarily prevents β -catenin from degradation, to fully activate stem cells. Indeed, the fact that a mutation in E-cadherin leads to nuclearly localized β -catenin has been observed in breast cancer seems to support this argument (62).

There is a certain degree of similarity in terms of the molecules and the underlying machinery used by both normal stem cells for homing or mobilization and cancer cells for invasion and metastasis. For example, during HSC activation and mobilization, matrix metalloproteinase-9 (MMP-9) is required for proteolysis of the extracellular matrix components and converting stem cell factor from a membrane-bound form into a free form, which then promotes HSC proliferation and mobilization through c-Kit receptor (63). Intriguingly, the molecules of the MMP family are key molecules involved in the process of cancer cell metastasis (64). Likewise, integrin is required for stem cell migration as evidenced in both hematopoietic and neural systems (65, 66), and integrin has been reported to be associated with tumor cell migration and metastasis (67). Finally, cancer cell metastasis exhibits some

properties shared by stem cells, such as homing and mobilization in which SDF1 and CXCR4 play essential roles (68). It was recently found that SDF1 is also involved in breast cancer cell migration (69). In addition, recent data support the role of the vascular niche in initiating metastasis (70). Thus, molecules involved in stem cell activation and mobilization from the niche and homing to the niche are possible targets for tumorigenesis, cancer development, and metastasis.

Closing Remarks

Normal stem cells in adult somatic tissues and cancer stem cells share the common features of self-renewal and slow cycling. Here, we have proposed another potential niche function in preventing tumorigenesis under normal physiologic conditions. The question arises as to whether or not cancer stem cells are dependent upon the niche, as are normal stem cells. This may vary with different types of tumors or cancers. In general, cancer stem cells resulting from mutations in stem/progenitor cells most likely undergo uncontrolled proliferation. We hypothesize that cancer stem cells may also arise from a microenvironment with dominant growth-promoting signals rather than growth-inhibiting signals. This is supported by the fact that certain types of neuroblastoma require coordination of mutations in both Schwann cells and supportive cells (71) and, in general, rapid tumor growth requires *de novo* angiogenesis, in which the vascular niche provides growth-promoting signals with enriched oxygen and nutrition. In addition, stem cell mobilization from or homing to the niche uses molecular machinery similar to that wrongly used by cancer cells for invasion and metastasis. Exploring this process and the underlying molecular mechanisms will provide important insight into understanding cancer cell metastasis and will benefit developing treatments aimed at destroying cancer stem cells without adversely affecting normal stem cell self-renewal.

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