11

The Stem Cell Niche: The Black Master of Cancer

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1. Introduction

Different populations of cancer cells co-exist within the same tumor; some have properties that closely resemble those of normal stem cells, which gave rise to the concept of cancer stem cells. Interestingly, these particular cancer cells express the same surface markers as normal stem cells, suggesting that cancer can sometimes arise from the malignant transformation of stem cells, such as established for some leukemias. The cancer stem cell model predicts that, even if "conventional" cancer cells can be killed, only the destruction of cancer stem cells allows full recovery. This demonstrates the importance of treatments targeting cancer stem cells for patient outcome. Therapeutic innovations will emerge from a better understanding of the biology and environment of cancer stem cells. Indeed, the tumor environment can create a niche favoring the survival and proliferation of cancer stem cells. It also contributes to resistance against therapy-induced apoptosis by providing both physical and physiological protection. Clinically, it is crucial to get rid of these treatment-resistant quiescent cells and to adapt the therapeutic strategy to reach the cancer stem cells sheltered in niches. In fact, most cancers likely recur because cancer stem cells escape treatment, survive and regenerate the tumor. Current hypotheses under evaluation suggest that this resistance may be due to the preservation of normal stem cell protective mechanisms such as their location in a niche, deregulation of drug efflux/influx transporter expression or alterations in apoptotic, cell cycle and DNA repair mechanisms. In this context, one of the key issues is that cancer stem cell self-renewal is dependent on close interactions with the stem cell niche which regulate the different developmental signaling pathways and are often found deregulated in cancer. However, investigations of the role of the microenvironment in adult stem cell transformation and resistance, especially in solid tissues, have started only recently, likely because of the major technical difficulties involved. Despite this delay, and thanks in part to studies in the hematopoietic system, a gold standard model for stem cell biology, great advances have been made in understanding the importance of the stem cell-microenvironment crosstalk in both normal and cancer tissues. We have now reached the point where conventional anti-cancer strategies can give way to more innovative combined therapy to target these interactions and “re-access” cancer stem cell regulation controls. Targeting these mechanisms by taking advantage of potential differences in the biology of normal and cancer stem cells, such as differences in surface phenotype, self renewal/quiescence and stem cell-niche interactions, might allow successful cancer stem cell targeting and improve cancer treatment outcome. This chapter focuses on

the main issues to be considered for efficient and specific targeting of cancer stem cells within their niche. First we will present the different kinds of adult somatic stem cell niches, their characteristics and functions in normal tissues, which have been particularly well described and studied in the hematopoietic system. We will review recent data on the control by the niche of cell self-renewal, quiescence, differentiation and survival/apoptosis. Then we will discuss the involvement of the cancer stem cell microenvironment in cancer initiation, in the maintenance of residual disease and in treatment escape, a combination of mechanisms that likely drive cancer relapse in both hematopoietic and solid tumors. In conclusion, we will discuss the main therapeutic approaches currently under development and evaluation for targeting interactions of cancer stem cells with their neighboring partners. It is already foreseeable that combinations of conventional therapeutic approaches with specific cancer stem cell-targeting treatments might efficiently cure cancer.

2. Stem cell niches: a critical cell survival architect

More than 30 years ago, the existence of special spatially defined areas that were suspected to supply factors necessary to the survival and development of cells capable to regenerate tissues in adult organisms was postulated (Schofield, 1978). It was suggested that the local environment was critical to maintain cell survival through the delivery of special signals by the so-called "niche" that directs cell proliferation, differentiation and apoptosis. A number of studies have clearly demonstrated that the stem cell niche constitutes a key regulator of stem-cell fate by balancing self-renewal and differentiation (Blanpain et al., 2004; Fuchs et al., 2004; Zhang et al., 2003; Calvi et al., 2003). This concept was later extended to solid tissues and cancers (Moore and Lemischka, 2006; Li and Neaves, 2006). Over the last decades the existence, composition and functions of adult stem cell niches have begun to be elucidated, mainly in the hematopoietic system and, more recently, in solid tissues.

2.1 The hematopoietic model

The concept of stem cell niche was first described in the hematopoietic system. It was proposed that the bone marrow environment, where hematopoietic stem cells reside, is capable to regulate the maturation of hematopoietic stem cells by controlling the balance between two main mechanisms, stem cell quiescence/maintenance, and differentiation and production of mature blood components (Schofield, 1978). However, in order to allow for tissue turnover or injury repair, the stem cell niche must also permit stem cell activation and recruitment for proliferation/differentiation (Schofield, 1978). The normal bone marrow microenvironment (the hematopoietic "niche") regulates the dormancy, survival and non-differentiation of hematopoietic stem cells (Li and Li, 2006) in response to various external signals, therefore constituting a dynamic system. In addition, the niche interacts with stem cells; it does not only behave as an active regulator but also receives feedback from stem cells which actively contribute to the organization of their own niche (Fuchs et al., 2004). Adhesion to both matrix proteins and stromal cells and exposure to their soluble factors (cytokines, morphogens) controls the self-renewal and differentiation of hematopoietic stem cells (Ross and Li, 2006). In this regard, mesenchymal stem cells have been shown to play a central role in the stem cell niche in hematopoietic and other tissues (Docheva et al., 2007; Dazzi et al., 2006). They can differentiate into osteoblasts, the major regulators of hematopoiesis, and secrete many matrix proteins, morphogens, growth factors and cytokines (Calvi et al., 2003; Zhang et al., 2003). Interestingly, it has also been reported that

infusion of *ex vivo*-expanded mesenchymal stem cells enhances hematopoietic stem cell engraftment, thus participating actively in stem cell homing (Dazzi et al., 2006). Immune cells are also an important component of the stem cell niche (Yang, 2007). Mesenchymal stem cells inhibit the immunological functions of antitumor lymphocytes such as natural killer cells (Sotiropoulou et al., 2006) and cytotoxic T lymphocytes (Djouad et al., 2003). Interactions between the different components appear to be important in controlling stem cell function, as illustrated by the impact of mesenchymal stem cells on immune cells (Benvenuto et al., 2007). Finally, inflammatory and oxidative stresses, associated with microenvironmental elements, constitute important regulators of hematopoietic stem cell functions (Ito et al., 2006). Recently, a step forward was made with the identification of different subsets of hematopoietic stem cells such as dormant or homeostatic stem cells. This discovery immediately implied the likely existence, within the bone marrow, of distinct hematopoietic niches supporting and controlling the different hematopoietic stem cell types. Two main types of niches are commonly distinguished according to their location, composition and function on hematopoietic stem cells: the osteoblastic/endosteal niche and the vascular niche. *In situ* experiments have located hematopoietic stem cells within the trabecular-bone area (Zhang et al., 2003). The niche that contains the most dormant stem cells is described as a hypoxic place close to the endosteum which contains osteoblasts, fibroblasts, osteoclasts, perivascular structures and sympathetic neurons (Burness and Sipkins, 2010; Trumpp et al., 2010). The control of the size and composition of the niche has been reported to involve a number of different factors such as Notch or the Bone Morphogenetic Proteins (Kiel and Morrison, 2008; Zhang et al., 2003). Interestingly, this family of proteins has also been known for several years to be a key factor in the control of hematopoietic stem cell fate (Sadlon et al., 2004; Maguer-Satta and Rimokh, 2004). In the bone marrow environment, hypoxia has been initially described to regulate hematopoietic differentiation, in particular toward the erythroid lineage, likely to counteract oxygen deprivation after an injury episode (Perry et al., 2007). Conversely, within the endosteal niche, the hypoxic environment appears to protect the long–lived, deeply dormant stem cells from the toxic effects of oxidative damage caused by reactive oxygen species that otherwise could conduct to the alteration of the stem cell pool. On the other hand, oxygenated perivascular niches represent a network of sinusoids composed of endothelial cells, reticular cells and megakaryocytes (Trumpp et al., 2010). Their function seems to promote hematopoietic stem cell proliferation and differentiation, in particular during blood recovery after an injury. Even if dormant cells could theoretically also locate in vascular niches, these niches remain the principal sites where bone marrow hematopoietic stem cells are mobilized to the peripheral circulation, together with differentiated hematopoietic cells (Burness and Sipkins, 2010). This mechanism is mainly regulated by the SDF-1/CXCR4 chemokine pathway that directs the passage of the cells from or toward the bone marrow. To maintain blood homeostasis, a flux of homeostatic hematopoietic stem cells migrates from endosteal niches through perivascular niches to the circulation. Therefore a continuous traffic of hematopoietic stem cells is observed from one niche to another and to the peripheral circulation, then back to the bone marrow and supposedly to dormancy.

2.2 Insight in solid tissue stem cell niches

As in the hematopoietic system, the niche in solid tissues is defined as the physiological microenvironment which keeps the stem cells quiescent until their self-renewal. The same applies to other stem cell niches present in various tissues and containing various partners

(Blanpain et al., 2004; Moore and Lemischka, 2006). Despite the technical difficulties of investigating the niche composition, location and function in solid mammalian tissues, some examples have been reported in the neural system and in the intestinal and various other epithelia (Burness and Sipkins, 2010). A number of elements common to solid tissue and hematopoietic stem cell niches have then been identified, including cell-cell and cell-extra cellular matrix interactions, as well as diffusible signaling factors mediating signal transduction in order to maintain stem cell survival and self-renewal. For example, in the nervous system the functional interactions of the vascular niche between neural stem cells and endothelial cells through junctional contacts are involved in the increased proliferation of neural stem cells. Similar to neurogenic niches in the hippocampus, neurovascular interaction has been observed in the sub-ventricular zone where numerous polarized stem cells establish connections with the endothelial cells of blood vessels through long basal processes. These stem cells also extend short apical processes to connect to ependymal cells that line the surface of lateral ventricles (Vazin and Schaffer, 2010). Recent data in intestine, brain, hair follicle or skin suggest that, like hematopoietic stem cells in the bone marrow, two main categories of stem cell niches might exist in solid tissues. Evidence in support of this theory comes in part from the observation that in tissues containing low cycling stem cells, participation in homeostasis and repair requires that cells rapidly switch from a quiescent to proliferative state. As in the hematopoietic system, two functional types of niches could be distinguished, one allowing rapid entry into proliferation, as required for tissue regeneration, and one that would maintain long-term growth and self-renewal (Greco and Guo, 2010). Interestingly, another bi-compartmentalization has been proposed for epithelial tissues based on cellular components of the niche. The two compartments would be the epithelial niche where stem cells are in direct contact with the basal lamina and the stromal niche where stem cells interact with another cell type in contact with basal lamina (Morrison and Spradling, 2008). Each type of epithelium has its own mechanism to regenerate from local stem cells. The different stem cell populations cooperatively regenerate all terminally differentiated cell types within the tissue. The microenvironment of epithelial stem cells is generally located near a basement membrane and the stem cells are part of the basal layer. Supportive cells present within the niche protect the stem cells from exogenous factors. Following differentiation, stem cell progenies migrate along the basement membrane and leave the niche (Verstappen et al., 2009). Epithelial niches might be limited by the presence of specific molecules within the extracellular matrix or on neighboring tissues. On the other hand, stromal niches appear to develop independently of the presence of stem cells and to maintain their morphology even after stem cell loss (Morrison and Spradling, 2008). Both types of niches depend on cell-cell junction molecules and stem cells are in contact with their progenies. In all cases and in any proposed classification, the role of niches in solid tissues is the same as in the hematopoietic system, namely to maintain and protect the stem cell pools which are crucial for tissue homeostasis. In all systems, this mechanism appears to be dependent on stem cell interactions with their close environment. A permanent dialogue through recurrent adhesion molecules such as cadherins or integrins is required to maintain stem cell architecture and shape, but this mechanism also constitutes a key regulator of asymmetrical division, and therefore self-renewal, as we will discuss now (Marthiens et al., 2010).

3. The guardian of key features of stem cells

The niche is critical to maintaining stem cell quiescence, the intrinsic self-renewal and undifferentiated character of resident stem cells, but it also regulates exogenous stem cells that tend to home back to that specific microenvironment.

3.1 Asymmetric cell division

Regulating the balance between symmetrical and asymmetrical divisions is critical to maintain the proper number of stem cells within the niche and meeting the demand for differentiated cells in surrounding tissues. Asymmetric cell division is one of the key features of stem cells that allows simultaneous self-renewal and differentiation. Asymmetric division is the process by which a single cell gives rise to two different daughter cells, a major strategy for the generation of cell diversity during the development or renewal of an organism/organ/tissue (Fuchs et al., 2004). However, it is also important to note that asymmetric division is not the only way to maintain stem cell self-renewal since two identical daughter cells are also specified entirely by their position and external signals derived from cells outside the niche (Conti et al., 2005). In particular, this process has been reported to occur in stem cell amplification during regeneration (Morrison and Kimble, 2006). Experiments in *Drosophila* and *Caenorhabditis elegans* have identified three major steps to achieve asymmetrical division: establishment of polarity, localization of fate determinant to one or the other cell pole, and subsequent regulation of the plane of cell cleavage. Upon division, the fate determinants will be asymmetrically distributed between the two daughter cells, one of them retaining stem cell features while the other one is driven toward a more differentiated stage (Marthiens et al., 2010). A number of genetic determinants have been shown to be involved in the intrinsic mechanism that dictates asymmetrical division (Faubert et al., 2004) but the exact pathways involved and their connection with extrinsic elements are still under investigation. However, thanks to studies in animal models like *Caenorhabditis elegans*, great progress has been made in understanding how the stem cell niches give instructive signals to drive asymmetric divisions in order to orchestrate the flow and cell fate of committed progenitors in a spacio-temporally controlled fashion. Asymmetry can be governed by the proximity to the cellular environment, such as the defined niches, that exerts extrinsic physical tension to achieve asymmetrical distribution of the mitotic spindles. Astral microtubules are physical structures that determine centrosome and spindle positioning. The aster traction to one pole of the cell results from a complex network of interactions between cell surface molecules, intra-cellular microtubules and intrinsic elements. Certain adhesion molecules such as APC, cadherins and integrins, have been shown to be involved in this process (Fuchs et al., 2004; Marthiens et al., 2010). For example, the role of cell-to-cell interactions mediated by β1-Integrins is crucial for the maintenance of stemness, especially in the hematopoietic stem cells that home back to the bone marrow (Gottschling et al., 2007). Authors have shown that β1-integrins play a significant role not only in the interaction between hematopoietic stem cells and mesenchymal stem cells but also in the regulation of the long-term fate of hematopoietic stem cells by favoring initial self-renewing divisions and the survival of primitive hematopoietic stem cells. This role of β1 integrin in asymmetrical division has also been demonstrated in solid tissue stem cells such as in the skin or the mammary gland (Marthiens et al., 2010). Therefore close interactions between stem cells and their neighbor cells within the stem cell niche allow adhesion molecules to control the angle of cell division by interacting with astral microtubules that regulate centrosome positioning. In cancer, the loss of this ability of asymmetrical division is thought to lead to the over amplification of a pool of cells that progressively drives to tumorigenesis.

3.2 Stem cell quiescence

The crucial point for the body to achieve homeostasis throughout life is to be able to preserve the stem cell pools from exhaustion and alteration. To that aim, the body employs a

strategy involving specialized stem cell niches, such as the osteoblastic/endosteal niche in the hematopoietic system and the so-called epithelial niche for epithelium tissues that, by their defined composition, are capable to display quiescent signaling to the resident stem cells (Trumpp et al., 2010; Morrison and Spradling, 2008). In order to maintain stem cells through time, it is important that self-renewal divisions of dormant stem cells occur only transiently, for example in response to a physiological need or to injury. Niche components, such as extracellular matrix molecules (laminin, fibronectin, collagen, glycosaminoglycans), provide a physical framework and instructive signals that regulate stem cells, in particular by participating to the maintenance of cell quiescence. It has been described, for instance, that β-integrin regulates the maintenance of neural stem cells and directly induces the expression of other cell surface receptors that relay information to the neural stem cells. Extracellular-matrix molecules also serve to immobilize and locally increase the concentration of a number of soluble signaling molecules such as the Bone Morphogenetic Proteins, Sonic Hedgehog or Wingless proteins, involved in stem cell quiescence (Vazin and Schaffer, 2010). Several receptors have then been demonstrated to be involved in the specific signals that dictate stem cell quiescence, partly by preventing cell division and differentiation. These include the tyrosine kinase receptor Kit (i.e. CD117) that binds Stem Cell Factor (SCF), the receptor for angiopoietin 1 (ANG1) TIE2, the TromboPOietin (TPO) receptor (cytokine receptor MyeloProliferative Leukemia virus receptor, MPL) and the CXC-chemokine receptor 4 (CXCR4) that binds the Stromal Derived Factor 1 (SDF1). Signaling response to their respective ligands inhibits the division of cells, thus preserving their dormancy. In addition, dormant niches seem to be dependent upon low oxygen concentration environment to maintain stem cell dormancy mainly through HIF1α signaling (Guitart et al., 2010; Diabira and Morandi, 2008; Eliasson et al., 2010; Moreno-Manzano et al., 2010). In the hematopoietic system, it is now well known that hypoxia is one of the key factors of the endosteal niche that contribute to maintaining normal stem cells in a dormant stage (Trumpp et al., 2010). All these signals are actively coordinated and presented in a temporally and spatially regulated manner to ensure the balance between stem cell quiescence and activation (Trumpp et al., 2010).

3.3 Stem cell fate

To preserve the stem cell pool from exhaustion, self-renewal divisions of dormant hematopoietic stem cells seem to occur only transiently after injury or mobilization signals. In this particular situation which requires the release of stem cells from their dormant stage, both types of signals have been reported to induce a proteolytic environment that enzymatically cleaves physical hematopoietic-niche bonds. This allows stem cells to migrate from the endosteal niche to the vascular niche where they find proliferation/differentiation signals and eventually leave the bone marrow to be transported to the site of injury by the peripheral system (Trumpp et al., 2010). Therefore, the architectural design of a niche appears to be suited to particular needs of its resident stem cells and, conversely, stem cells may play an important role in organizing and specifying the niche as proposed in the context of breast by the dynamic reciprocity concept (Xu et al., 2009). One of the best described actors in self-renewal maintenance in different systems is the β1-Integrin. This protein belongs to the large family of heterodimeric receptors involved in cell-matrix and cell-cell adhesion. Integrins transduce both “Outside-In” and “Inside-Out” signals involved in cellular processes such as cell morphology, motility, proliferation, differentiation,

inhibition of apoptosis and likely much more (Ho and Wagner, 2007; Docheva et al., 2007; Gottschling et al., 2007; Dylla et al., 2004). In some cases, like in the neural system (Hall et al., 2006) or breast (Shackleton et al., 2006; Stingl et al., 2006), some integrins are even considered as stem cell markers. Their key role in the hematopoietic system has been largely documented, mainly through their binding to fibronectin (main ligand of β1 integrin) or, to a lesser extent, to VCAM-1 (Levesque and Simmons, 1999), in diverse processes of hematopoietic stem cell regulation such as self-renewal, differentiation, mobility and apoptosis (Hurley et al., 1997; Hurley et al., 1995; Jiang et al., 2000a; Prosper and Verfaillie, 2001; Prosper et al., 1998; Priestley et al., 2006; Priestley et al., 2007; Scott et al., 2003). More recently their involvement in stem cell maintenance has been demonstrated in both murine (Taddei et al., 2008) and human (Bachelard-Cascales et al., 2010) breast and studies are currently investigating their role in the biology of stem cells in many other solid tissues. Understanding the fine-tuned regulation that switches stem cells from a deep dormant to a proliferating state is quite complex. As for quiescence maintenance, extracellular matrix-bound molecules such as the Bone Morphogenetic Proteins (Vazin and Schaffer, 2010) could also serve as main regulators to control stem cell self-renewal, proliferation or commitment, as described by us in the hematopoietic system (Jeanpierre et al., 2008; Maguer-Satta et al., 2006; Maguer-Satta and Rimokh, 2004; Maguer-Satta et al., 2003) or by others in the epithelial system (Blanpain and Fuchs, 2006), or for Notch and Sonic Hedgehog in the neural system (for review see (Fuchs et al., 2004; Morrison and Spradling, 2008)). Finally, stem cells respond differently to a two-dimensional substrate and a three-dimensional environment, thus activating different signaling pathways. Integrin signaling, for instance, is involved in extracellular matrix remodeling which controls the niche architecture and therefore impacts

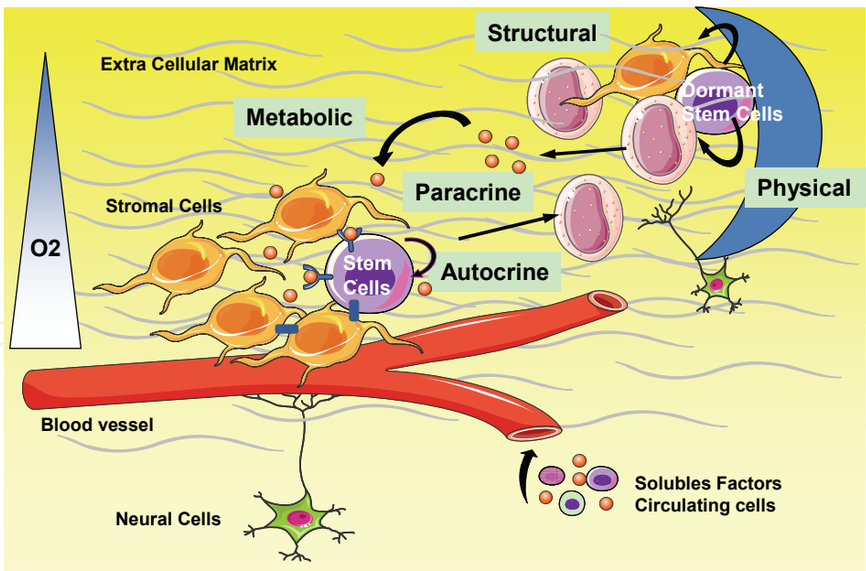

Fig. 1. Parameters of stem cells niches that drive stem cells behavior and/or the reverse, summary of the main parameters involved in stem cell behavior such as dormancy or inversely their commitment, migration. The same elements are involved in the permanent dialogue that exists between stem cells and their niche going from the stem cell toward its environment to modify or regulate its function. Each of these elements can be affected during cell transformation inducing cancer stem cell escape, resistance and persistence.

stem cell behavior and tumorigenesis (Larsen et al., 2006). This has been demonstrated in normal adult stem cells using variations of matrix elasticity to drive stem cell fate (Engler et al., 2006). Moreover, matrix remodeling, notably proteolytic breakdown of fibronectin giving rise to biologically active peptides or to domains of interaction with morphogens or TGFβ regulators, may be involved in the control of hematopoietic stem cell fate either by promoting cell proliferation or commitment toward specific lineages.

The different niche types defined share common features and activate common signal transduction pathways to achieve the slow-cycling, self-renewing, undifferentiated state of their residents (Fig. 1). For that, several different pathways display a number of crosstalks and multigene redundancies. Conversely, each niche is composed of different types of non stem cells and stem cells that constitute this environment and a same signaling pathway can control different cellular functions. Altogether this strongly suggests that the critical genes involved in stem cell fate are likely to vary with the different stem cell types and their location, even if the general mechanisms controlling their behavior remain the same.

4. The under-estimated initiator/actor of cancer

There is growing evidence that, although it has long been largely under-evaluated, the tumor microenvironment plays a very active role in tumor initiation and progression. More than twenty years ago, a few people went against the strong wave of genetic promoters as the only explanation for the etiology of cancer, and claimed that "mutations were not all" in oncogenesis. At that time some scientist argued that the tumor environment was also a major actor in cancer pathogenesis and that it should be taken into account in studies that pretend to understand and treat cancer (Ronnov-Jessen and Bissell, 2009). With the discovery of cancer stem cells, focus turned to their specific microenvironment and studies tried to elucidate the function of their permanent dialogue. It took several decades to actually reach the point where the tumor environment was considered as a key player at all stages of cancer. This led to major observations and gave some insight in its role in cancer initiation, escape and resistance to treatments. The proof of concept came once more from the hematopoietic system where a key clinical observation was made. It is now trivial that the bone marrow microenvironment plays an important role in pathogenesis. A review providing compelling information about the hematopoiesis of donor cell leukemia strongly supports this "seed and soil" hypothesis that has been hanging around for years in the field of solid tumor metastasis research (Paget, 1989; Mueller and Fusenig, 2004; Demicheli, 2001; Greig and Trainer, 1986). The authors clearly underline that, though seemingly rare, leukemia sometimes occurs in normal donor hematopoietic cells transplanted to leukemia patients. The disease is then named Donor Cell Leukemia and must be distinguished from a relapse of the patient's original malignancy as it constitutes a *de novo* leukemia affecting normal transplanted cells (Flynn and Kaufman, 2007). Therefore, it has become quite evident that the hematopoietic niche is involved in the transformation of normal donor cells into leukemia cells; this theory is supported by the fact that no cytogenetic abnormalities have been detected in donor cells. It is even suspected that, as the hematopoietic stem cells present in the graft are responsible for hematopoietic reconstitution in the recipient, Donor Cell Leukemia might arise from abnormal hematopoietic stem cell regulation by the patient's hematopoietic niche (Flynn and Kaufman, 2007). Therefore, the role of the tumor microenvironment in tumor initiation and progression through its different constituting elements (stromal and immune cells as well as extra cellular matrix molecules) is being

increasingly acknowledged. Two main hypotheses could explain features of cancer stem cells: one proposes that transformed stem cell-like populations progressively evade their niche control while the other one considers that the niche itself could be altered during oncogenesis. Actual data document both aspects, indicating that tumors arise from complex combinations of alterations that trigger both the malignant cells and their environment.

4.1 Niche alteration: cause and consequence

A first step to identify and understand the role of niche alteration in cancer development has been the characterization of the cellular content of the niche. In established leukemia, several lines of evidence demonstrate that both cell and matrix components of the bone marrow microenvironment, such as integrins, are clearly modified (Ruoslahti, 1999). Mesenchymal stem cell alterations have then been investigated and several changes have been identified in their transcriptome, phenotype and functions from myeloma patients (Arnulf et al., 2007; Corre et al., 2007). In a number of myeloid or lymphoid leukemias, profound alterations of the bone marrow environment, such as myelofibrosis, are frequently reported. In myeloma, osteolytic lesions and differential expression of integrins and cytokines correlate with early oncogenic events (Hideshima et al., 2004). In Chronic Myelogenous Leukemia, bone marrow macrophages impair the mesenchymal cell support of hematopoiesis (Bhatia et al., 1995a), whereas in Acute Myeloid Leukemia, fibronectin and Wnt ligands are overexpressed (Simon et al., 2005). Alterations of the β1 integrin, not in terms of membrane protein expression but rather as a defect in protein activation, has been shown to be involved in the loss of regulation of leukemic hematopoietic stem cells by the marrow stroma (Bhatia et al., 1995a; Bhatia et al., 1999; Jiang et al., 2000b; Jongen-Lavrencic et al., 2005; Lundell et al., 1997; Lundell et al., 1996). Original signaling pathways downstream of integrin ligation have been involved in normal and leukemic cell survival, proliferation and adhesion (Tabe et al., 2007; Dylla et al., 2004; Melikova et al., 2004). In solid tumors, integrins have also been involved at various levels in breast cancer biology, likely at the level of cancer stem cell (Bissell et al., 2005; Park et al., 2006; Faraldo et al., 2005; Faraldo et al., 2002; Faraldo et al., 2000; Taddei et al., 2003). In addition, a deregulated signal transduction in leukemic cells may allow them to escape microenvironmental control (Astier et al., 2003; Wilson et al., 2004; De Waele et al., 1999). Another example of niche alteration has been reported in solid tumors by pathologists who have described the frequent association of stromatogenesis and neoplasia. This stromatogenesis is an affection of the tumor-associated stroma characterized by many changes such as deregulated expression and organization of fibronectin and collagen, leading to modifications of the stroma-associated tumor that becomes more rigid. Other studies have shown that extracellular matrix stiffness perturbs the original epithelial morphogenesis by clustering integrins and inducing focal adhesion assembly to enhance specific signaling pathways (Paszek et al., 2005). Cells sense elevated extracellular matrix rigidity through their integrins and respond with modified signaling that in turn stimulate integrin expression or change their conformation to induce their activation. This response can be amplified by a signaling cascade involving different molecules (such as Rho, Rock, ERK) that drive surrounding cell proliferation and transformation and extracellular matrix rigidity (Larsen et al., 2006). As a consequence, the tumor microenvironment can send erroneous signals to niche cells, inducing accumulation of proteases and activation of soluble factors, all contributing to alter stem cell control. Altogether, these data indicate that most cancers are likely associated with modifications of the stem cell environment. One of

the consequences possibly contributing to cancer initiation is the deregulation of asymmetric division control by the niche. When the asymmetric division machinery is perturbed tumor growth is observed (Caussinus and Gonzalez, 2005). In support of this hypothesis is also the fact that some gene products that induce asymmetric cell divisions function as tumor suppressor genes, such as reported for APC in colorectal cancer and melanoma. Conversely, gene products that favor symmetric cell divisions act as oncogenes in mammalian cells, such as PKC in lung cancer. Symmetric division then not only favors the expansion of stem cell numbers but might also increase the risk of aneuploidy and accumulation of secondary mutations by impaired mechanisms controlling the mitotic machinery (Morrison and Kimble, 2006). It then becomes important to understand the consequences of this matrix remodeling on normal and cancer stem cell behavior, in particular for drug resistance.

4.2 Cancer stem cells: natural reprogramming in "iPS" by the niche

Of particular interest in the context of cancer, niches have been demonstrated to be capable of reprogramming cells. An experimentally-vacated ovarian germline stem cell niche induced the division of foreign surrounding somatic stem cells which then have given rise to ovarian follicle cells and allowed the dedifferentiation of ectopic follicle progenitor cells at earlier stages of differentiation. These experiments have established the fact that a niche is a stable structure capable to direct cell fate even outside its initial intrinsic differentiation program (Kai and Spradling, 2003). These observations might be in part explained by the reprogramming power of physical constraint. A very elegant study has demonstrated that simple physical constraint can drive stem cells toward one lineage rather than another, indicating that both physical and cellular properties of niches are important in the control of stem cell behavior (Engler et al., 2006). In the past five years, stem cell research has made a major breakthrough by artificially inducing cell reprogramming. Yamanaka et al have developed a strategy that generates from mature differentiated cells a "stem cell-like" entity named iPS for "induced-Pluripotent Stem Cell". Reprogrammed cells display most of the properties of pluripotent stem cells, such as the ability to differentiate into functional mature cells, and present a number of epigenetic modifications (Boheler, 2009). It is intriguing that factors deregulated in the cancer niche, such as hypoxia, have recently been reported to significantly improve the iPS process (Yoshida et al., 2009). The origins of cancer stem cells are still debated and one can hypothesize that the transformation of a true stem cell, such as in Chronic Myelogenous Leukemia, is likely to be an infrequent event. Almost a decade ago, the option that cancer stem cells could arise from the reacquisition of stem cell characteristics emerged (Passegue et al., 2003). It is then tempting to suggest that one of the first steps in tumor initiation is the generation of cancer "iPS" induced by alterations occurring in the niche, such as a change in rigidity, extracellular matrix remodeling or oxygen concentration (Engler et al., 2006; Larsen et al., 2006; Heddleston et al., 2010). In support of this hypothesis is the fact that in cells classified as cancer stem cells the re-expression of embryonic genes or genes involved in self-renewal has often been described and shown to be involved in the cancer stem cell phenotype (Lessard and Sauvageau, 2003; Yin et al., 2010; Godmann et al., 2009). Finally, the niche could induce genetic or epigenetic changes in cancer stem cells (or vice versa) as observed using the iPS technology (Boheler, 2009). These changes provide a growth advantage and induce a differentiation blockade, causing their transformation into cancer stem cells (Issa, 2007; Wang and Dick, 2005).

4.3 Factors that control key surviving pathways

A large number of factors have been reported to favor cancer cell survival. Only a few particularly significant examples of the key role played by the niche in cancer stem cell behavior will be given here. The tumor microenvironment is often hypoxic, due essentially to chaotic vasculature, poor oxygen diffusion across the expanding tumor and irregular blood flow. The oxygenation status of tumor tissues cycles in both spatial and temporal manners. Several studies have shown that hypoxic conditions enhance the metastatic power of cancer cells likely through HIF-dependent pathways (Heddleston et al., 2010). During cancer initiation, a hypoxic environment might favor the transformation of the resident stem cells by potentiating the effect of genes associated with stemness like Notch. At the clinical level, there is a correlation between the presence of a hypoxic zone within the tumor and poor patient outcome, and this could be explained by an increased number of cancer stem cells (Heddleston et al., 2010). This might also explain the disappointing results obtained in some studies of single-agent vascular-targeted treatments aimed at depriving the tumor of oxygen by inhibiting its ability to generate a neo-vasculature in the hope to kill cancer cells. A side effect of this strategy might be a significant increase in the pool of drug-resistant cancer stem cells. However this does not preclude combining anti-angiogenic strategies with other specific anti-cancer stem cell therapies. As stated above, hypoxia has been reported to significantly improve the cell reprogramming by which mature differentiated cells give rise to iPS (Yoshida et al., 2009). The capacity of cancer stem cells to modulate the tumor environment has also been suspected. In solid tumors, several arguments suggest that cancer stem cells, as they are capable to survive in low oxygen concentration, stimulate angiogenesis in response to HIF-dependent signaling. This will help to increase the oxygen level within the growing tumor which otherwise conduct to necrosis of the under oxygenated tumor mass. With growing knowledge, hypoxia has become a critical microenvironment parameter. Indeed, HIF expression in cancer stem cells is now described to be responsible for cell proliferation and tumor survival (Heddleston et al., 2010). Later on during disease progression, continuous or increasing hypoxic conditions can lead to specific activation of local enzymes such as reported for lysyl oxidase, a well-known enzyme that crosslinks collagen. This enzymatic activity does not seem important for cancer initiation but appear essential for metastasis through activation of the protein FAK phosphorylation that stimulates cell migration and contributes to cancer spread (Larsen et al., 2006).

4.4 The perfect hide-out

Alteration of the permanent crosstalk between cancer stem cells and their microenvironment deregulates the balance between dormant and activated stem cells, contributing to tumor resistance (Besancon et al., 2009; White et al., 2006). A consequent literature has documented this aspect of cancer biology in both the hematopoietic context and solid tumors (Hall et al., 2007; Kleeff et al., 2007; Kaplan et al., 2006; Psaila et al., 2006; Tysnes and Bjerkvig, 2007; Lee and Herlyn, 2007b; Lee and Herlyn, 2007a; Mueller and Fusenig, 2004). The bone marrow microenvironment is largely involved in the pathogenesis and maintenance of malignant tumors of hematopoietic origin. In the microenvironment, leukemic stem cells represent a quiescent population of cells that are resistant to standard therapy and different from their normal counterparts. Moreover, mesenchymal stem cells, the second largest population of long-lived stem/progenitor cells in the bone marrow, could favor the growth of tumor cells and their survival by inducing anti-apoptotic signals and further resistance to chemotherapeutic agents, as reported in acute myeloid leukemia (Konopleva et al., 2009).

Integrins are known to be involved not only in regulating the proliferation of extracellular matrix (fibronectin) and stromal cells (osteoblasts, mesenchymal stem cells) but also in the chemoresistance of leukemic stem cells (Fernandez-Vidal et al., 2006; De Toni et al., 2006). Numerous studies indicate that cell-cell and cell-matrix adhesion molecules also protect tumors from treatments. Adhesive interactions between cells or between cells and the extracellular matrix can regulate apoptosis and cell survival in a wide variety of cell types. Several studies have demonstrated that drugs generate a stress-induced anti-apoptotic bcl-2 signaling pathway implicating β1 integrin and fibronectin interaction (Damiano, 2002). Interestingly, anti-β1 antibodies or antisense oligonucleotides enhance the apoptotic process (Hazlehurst et al., 2001). In small cell lung cancer, the emergence of resistance to chemotherapy has also been correlated to high expression of integrins in the extracellular matrix (Hodkinson et al., 2007). The authors have demonstrated that the extracellular matrix, via β1 integrin-mediated PI3-kinase activation, allows small cell lung cancer cells to escape treatment-induced cell cycle arrest, apoptosis and DNA damage. In the mammary system, it has also been demonstrated that β1-integrin plays a key role in treatment resistance (Park et al., 2008). Interestingly, we have demonstrated that β1-integin interaction with its ligand is required to maintain mammary stem cells in their niche at immature stage. Indeed, by using β1 blocking antibodies we have been able to induce further stem cell differentiation (Bachelard-Cascales et al., 2010). Altogether, these observations suggest that resistant breast cancer stem cells use β1-integrin to hide in the niche. In solid tumors, the microenvironment can protect stem cells from the oxygen deprivation due to rapid tumor cell proliferation and abnormal vessel formation (Keith and Simon, 2007). Therefore, the niche provides cancer stem cells with physical and physiological protection from anti-cancer drugs (Elrick et al., 2005).

5. A major target for cancer cure

Accumulated data clearly indicate that stem cell niches are key and active elements in cancer biology: they are involved in tumor initiation, progression and maintenance and therefore constitute an important target in anti-cancer therapy (Adams and Scadden, 2006; White et al., 2006). Observations indicate that the stem cell niche remains one of the key targets for future developments in cancer treatment. Two main strategies are currently developed based on the reciprocal dependence of the cancer stem cells and their niches. One is to attempt to awake quiescent cancer stem cells from dormancy and the other is to make them leave their protective niche. One should however keep in mind that selective anti-cancer stem cell treatments will not immediately eliminate differentiated cancer cells, and might therefore be prematurely dropped if their clinical activity is judged solely by the traditional response criteria of changes in the bulk of the tumor. This implies that re-examining both pre-clinical and clinical drug development paradigms in order to include the cancer stem cell concept might revolutionize the treatment of many cancers. Some drugs are already available that could act, at least in part, by killing cancer stem cells; however, no complete cure has been obtained to date, suggesting that further experimentation with cancer stem cell-targeted therapy is required (Besancon et al., 2009). The major problem for people developing these new drugs is to selectively target cancer stem cells whereas preserving normal stem cells. This question is indeed critical, since many studies have highlighted the extensive phenotypic and functional similarities between normal and cancer stem cells. A possible solution could be based on the fact that interactions between cancer

stem cells and their environment are profoundly altered. The modified cell environment itself can even be considered a relevant treatment target, even if not malignant *per se*. Re-establishing a normal niche might also normalize its dialogue with cancer stem cells and some can imagine that this will help, in cooperation with more conventional therapy, to knock over cancer stem cells.

5.1 How to awake dormant stem cells

In this regard, the crucial role of adhesive interactions between tumor cells and the stroma in response to chemotherapy has been deciphered in various systems (Damiano, 2002; Haslam and Woodward, 2003). In chronic myelogenous leukemia, with the market release of anti-tyrosine kinase inhibitors specific for the fusion onco-protein BCR-ABL (imatinib) (Druker et al., 2001) and because of its toxicity, interferon α has been partially abandoned. But, interestingly, there is a re-emerging interest for interferon α in this indication. CD34+ leukemic samples from patients with BCR-ABL expression have been reported to contain quiescent leukemic stem cells that are particularly resistant to tyrosine kinase inhibitor treatments (Graham et al., 2002). These cells also have a defective integrin-cytoskeletal association that conducts *in vitro* to their restricted mobility (Bhatia et al., 1999). We may hypothesize that this favors chronic myelogenous leukemia stem cell quiescence, but *in vitro* treatment with interferon α restores the integrin-cytoskeletal association (Bhatia et al., 1999). A more recent study has shown that interferon α can also deplete the pool of chronic myelogenous leukemia stem cells and trigger their differentiation, whereas imatinib is only able to inhibit advanced differentiated chronic myelogenous leukemia progenitors (Angstreich et al., 2005). In T-cell leukemia, Kayo and coworkers have demonstrated the existence of side-population cells with stem-like properties, and shown that interferon α is able to trigger their differentiation and enhance their sensitivity to chemotherapy (Kayo et al., 2007). Consistent with these results, an advanced clinical phase 3 trial is currently exploring the efficacy of imatinib and interferon α combination therapy for the treatment of chronic myelogenous leukemia. In addition, several recent studies have reported that agents which can activate quiescent/dormant cells, such as cytokines (G-CSF (Holtz et al., 2007) and interferon α) or other compounds (arsenic trioxide-AS_2O_3), can be efficiently used to induce cancer stem cell cycling (for review see (Essers and Trumpp, 2010)). These examples indicate that it is possible to kill cancer stem cells by combining treatment approaches. It is necessary, first, to awake quiescent stem cells and direct them toward differentiation, likely associated with their release from tumor niches, thus rendering them more accessible to chemotherapy, and, second, to expose these stem cells to more conventional chemotherapeutic drugs (Konopleva et al., 2009). Finally, in glioma, evidence suggests that anti-angiogenic therapy might enhance the efficiency of chemotherapy by disrupting the vascular niche of stem cells (Folkins et al., 2007). The investigators propose that the loss of communication between stem cells and their niche elicits a reduction or loss of certain stem cell properties associated with drug resistance, including dormancy, high proliferation rate and DNA repair. These observations provide a rational explanation for the poor efficiency of anti-angiogenic therapies when used alone and suggest that their use in combination with chemotherapy might open new perspectives in cancer stem cell targeting. Indeed, the hypoxic tumor microenvironment favors cancer stem cell dormancy and survival, as we discussed earlier. Interestingly, HIF1α, in addition to its role on stem cell dormancy, has also been found to regulate stromal cell-derived factor 1 (SDF1/CXCL12) gene expression in endothelial cells that mediate the adhesion, migration and homing of CXCR4-expressing

stem cells. This has been proposed to create a hypoxic microenvironment that facilitates the recruitment, retention and resting of cancer stem cells. This hypothesis is supported by recent data demonstrating the sensitivity of leukemic stem cells to anthracyclines, doxorubicin and daunorubicin, mediated in part by the inhibitory effect of the HIF1α pathway. Direct inhibitors of HIF1α are currently under clinical development and evaluation (for review see (Konopleva et al., 2009)). These data suggest that targeting the hypoxic pathway might then not only help to release cancer stem cells from their niche (as discussed below) but also contribute to shift them from quiescence/dormancy to active cycling, rendering them sensitive to conventional anti-mitotic chemotherapies.

5.2 How to release cancer stem cells from their niche

The niche favors the homing and retention of normal and cancer stem cells which remain in this safe environment, away from circulating cytotoxic drugs, during treatment. This protective role is mediated in part by the chemokine receptor 4 (CXCR4) and its ligand, the stromal cell-derived factor 1 (SDF1/CXCL12) (Larochelle et al., 2006; Papayannopoulou, 2004). Interestingly these molecules have been recently reported to be involved in stem cell dormancy (Trumpp et al., 2010). An antagonist of the CXCR4 receptor, AMD3100, has been investigated in several phase I to III clinical trials exploring hematopoietic stem cell mobilization in leukemic patients with the objective of proposing self-transplantation after cytotoxic chemotherapy (Larochelle et al., 2006). Also, disruption of the SDF1/CXCL12 axis during tumor progression has been shown to induce the migration of cancer stem cells and to make them re-accessible and therefore sensitive to cytotoxic drugs in various leukemia and solid tumors (Gazitt, 2004; Rubin et al., 2003; Yang et al., 2007; Burger and Burkle, 2007). AMD3100 is currently under clinical investigation in combination with a cocktail of mitoxantrone, etoposide and cytarabine (Burger and Burkle, 2007). The CXCR4/CXCL12 axis also constitutes a good anti-cancer stem cell target in at least two solid tumor models, breast and prostate cancers. Inhibition of the CXCR4/CXCL12 axis using another antagonist of the CXCR4 receptor, TN14003, has been explored in a mouse breast cancer metastasis model (Liang et al., 2004). Injection of human breast MDA-MB-231 cancer cells into the tail vein of mice induced several lung metastases. In mice treated with TN14003, metastases were dramatically reduced (Liang et al., 2004). Even if no clear causative link can be established with cancer stem cell depletion by the CXCR4 antagonist these data, combined with results obtained with AMD3100, tend to validate the CXCR4/CXCL12 axis, when expressed in the cancer stem cell subpopulation, as a good candidate for new treatment strategies. As this pathway is shared by both normal and cancer stem cells, concerns have been raised about the potential toxicity of targeting the CXCR4/CXCL12 axis. Normal stem cells would normally be protected from treatments by their microenvironment but, when mobilized, be suddenly exposed to cytotoxic drugs. One solution would be to combine the CXCR4 antagonists with monoclonal antibodies (see below) that would target specifically cancer (stem) cells while sparing their normal counterparts. Another possible approach for releasing cancer stem cells from their microenvironment would be to inhibit their physical attachment to the components of the niche. Obvious targets are the integrins which have been shown to be involved in cancer stem cell maintenance and resistance, as discussed earlier. Interestingly, only few treatments have demonstrated efficacy against this abnormality which is particularly important in the stem cell compartment, likely including leukemic stem cells. Indeed, in the hematopoietic system interferon α seems to be the most efficient, or at least the most documented, drug for restoring full normal functions of β1

integrin in chronic myelogenous leukemia cells (Bhatia et al., 1995a; Bhatia et al., 1995b). In chronic myelogenous leukemia, the role of the specific BCR-ABL fusion protein inhibitor imanitib on integrin correction is still debated as some studies report a partly restored integrin function in immature cells (Bhatia et al., 1998) while other indicate the inefficiency of the drug on integrin defects (Ramaraj et al., 2004; Wertheim et al., 2002). Novel therapeutic strategies must therefore be developed to inhibit integrin-mediated cell survival signals and likely improve response rates. This could be achieved by targeting the downstream signaling of the integrin pathway. It has been proposed that the integrin-linked kinase which interacts with the cytoplasmic domains of β1 and β3 integrins might constitute a good target. This kinase mediates a diversity of functions relating to its role in coupling integrins and growth factor receptors to downstream signaling pathways. Through its downstream targets protein kinase B/Akt and glycogen synthase kinase-3b, the integrin-linked kinase appears to be involved in several oncogenesis-related events, including suppression of apoptosis and promotion of cell survival, as well as cell migration and invasion. Furthermore, increased integrin-linked kinase expression and activity have been correlated with malignancy in several human tumor types, including breast, prostate, brain, and colon carcinomas (Yoganathan et al., 2002). For example, the role of β1-integrin in maintaining mammary stem cells (Bachelard-Cascales et al., 2010) and in the resistance of breast cancer cells (Park et al., 2008) make integrin-linked kinase an interesting target to prevent relapse and/or metastasis in breast or any other type of cancer.

5.3 Emerging strategies

Cell-based therapy has been evaluated for many years in different diseases including cancer. Infusion of *ex vivo*-expanded mesenchymal stem cells has been proposed to enhance hematopoietic stem cell engraftment, especially in the adjuvant setting to treat graft-versus-host disease in cancer therapy (Khakoo et al., 2006), on the basis of anti-tumor properties of mesenchymal stem cells (Elzaouk et al., 2006; Ramasamy et al., 2007). Interestingly and surprisingly, several studies have reported that normal neural stem cells are able to move toward and attach to cancer stem cells in the central nervous system, which makes them eligible tools for the specific delivery of cytotoxic drugs to cancer stem cells (Sakariassen et al., 2007). There is increasing evidence that cancer stem cells in different types of tumors and leukemia share a number of common features, in particular their need of a close interaction with their microenvironment. This suggests that diagnostic and therapeutic monoclonal antibodies and other molecules may be applicable across tumor types. Until recently, most antibody-based strategies targeted antigens expressed by mature differentiated or activated cells. Adhesion molecules, such as CD44 and members of the Integrin family, mainly mediate cell-cell interactions between normal and cancer stem cells and various components of the niche (Chan and Watt, 2001; Ghaffari et al., 1999; Dontu et al., 2005;Ruoslahti, 1999). Also the adhesion molecule CD44 has been demonstrated to be required in acute myeloid leukemia for the homing of leukemic stem cells to their microenvironment where they are maintained in an immature state (Jin et al., 2006). Therefore the use of CD44 as a specific anti-cancer stem cell target has been investigated. Experiments using H90, a specific anti-CD44 antibody, have shown that disturbance of CD44-mediated cell-cell or cell-extracellular matrix adhesion alters the homing and maintenance of acute myeloid leukemia stem cells. This causes their differentiation towards monocytic or granulocytic lineages and depletion of acute myeloid leukemia stem cells in the bone marrow. Moreover, H90-treated mice have shown a reduced homing capacity in secondary recipient organs such as spleen or the bone

marrow of non-injected bones. Interestingly, H90 effects are specific for acute myeloid leukemia stem cells and no homing disturbance is observed when using normal cord blood stem cells. A study performed in serially transplanted mice has shown that H90-treated mice do not developed leukemia, contrary to non-treated mice (Jin et al., 2006). A study using the humanized anti-CD44 antibody ARH460-16-2, which binds to human acute myeloid leukemia $CD34^{+}CD38^{neg}$ cancer stem cells, has evidenced a convincing anti-tumor activity in an AML xenograft model (Abstract Number 3976, AACR2008). Moreover, because CD44 is also present and found effective in other cancer stem cells, such as in breast (Sheridan et al., 2006), prostate (Patrawala et al., 2007), colorectal (Dalerba et al., 2007), pancreatic (Li et al., 2007) and small cell lung (Gutova et al., 2007) cancers, the authors have demonstrated that this antibody also exerts broad effects in solid tumors (Abstract Number 3975, AACR2008). The ARH460-16-2 antibody has already completed Pre-Investigational New Drug evaluation by the FDA, which opens new promising perspectives for cancer treatment. The discovery of new markers of cancer stem cells from different tumor types has led to the development of many monoclonal antibodies in order not only to characterize and isolate the cancer stem cells but also to target them for treatment (for review see (Deonarain, 2008)). As therapeutic antibodies are about to enter large clinical trials, the next decade of translational research and development in this area should see marked improvement in cancer diagnosis, prevention and treatment.

6. Concluding remarks

It has been known that microenvironments that can impose normal tissue architecture can both suppress the malignant phenotype and instruct otherwise malignant multipotent cells to give origin to differentiated cells and engage in normal organ development. Aging, associated with an increase in the number of cell divisions in which the centrosome is not tightly associated with adherent junctions between cells, is suspected to decrease stem cell numbers within the niche. This indicates that the effect of aging on stem cells partly results from impaired niche regulation at different levels. In addition, there is accumulating evidence that continuous input from the microenvironment might also determine the risk and course of tumor development. The more insight we get into the stem cell niche, the more new questions and issues emerge. Among these could be the clarification of whether niches are transiently or permanently occupied, of how they maintain their activity and specialization through time, of how the organism controls the number, size and composition of these niches, and so much more. To complement the advancing knowledge of niche composition and characteristics before and after cancer development, the current challenge is to develop experimental models encompassing the complexity of three-dimensional tissue organization, multiple cell niches and extra-cellular-matrix composition and allowing to grasp the full significance of the microenvironment in normal and in cancer cells. This crucial step will achieve a full understanding of features and functions of the stem cell niches, a real “black master” involved in all phases of cancer development. These findings should translate into a double-barreled therapy targeting both the cancer stem cells and their tumor niche. This would allow elaborating treatments to target cancer stem cells within their niches and ensure access to deeply quiescent cancer stem cells, if such exist, in order to make cancer a curable disease. Complementary approaches, such as the recruitment of useful bystanders like immune cells, should help to kill cancer stem cells or destroy their supporting environment. Undoubtedly, a better understanding of cancer development will evolve into novel strategies of risk assessment, diagnosis, prognosis and therapy.

7. References

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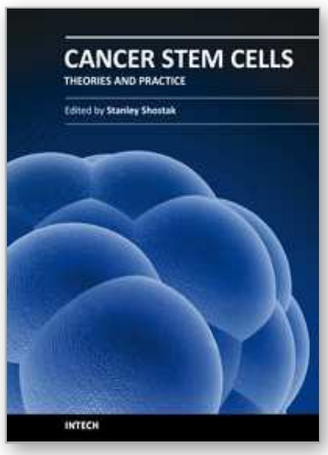

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