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Cancer Stem Cell Niche: The Role of Mesenchymal Stem Cells in Tumor Microenvironment

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1. Introduction

Niche, a specialized physiological microenvironment in which stem cells reside, plays a crucial role in the maintenance of stem cell characteristics such as pluripotency and self-renewal. The stem cell niche is composed of a group of cells providing a physical anchoring site for stem cells with the interaction of adhesion molecules between stem cells and niche cells or extracellular matrices (Li & Xie, 2005). The niche controls stem cell number, proliferation and fate of determination. Thus, a better understanding of the nature of stem cells and their niche will lead to alternative treatment strategies for various diseases, including malignant tumors.

More than a decade ago, the existence of a rare population with both stem cell-like properties and tumor initiating capability was first identified in acute myeloid leukemia and, subsequently, in several solid tumors. These populations with stem cell-like properties were termed 'cancer stem cells (CSCs)', indicating that only a subset of cancer cells were tumorigenic and able to initiate and produce the bulk of tumors, thus also termed 'tumor initiating cells' (Reya, et al., 2001). Although CSCs may not harbor all of the properties of normal stem cells, they are characterized by their ability both to self-renew and to differentiate into certain cell types with limited potential for differentiation and proliferation.

Some functional environments, namely 'cancer stem cell niche', a counterpart of normal stem cell niche, may support CSCs like normal stem cells (Sneddon & Werb, 2007). There are similarities in the maintenance system for the stem cell niches between normal and cancer stem cells such as the presence of molecules involved in adhesion and chemokine-chemokine receptor interaction. On the other hand, it might be possible that the behaviors of CSCs and normal stem cells are regulated by the niche to different degrees (Li & Neaves, 2006). The niche is supposed to control the balance between quiescence and proliferation/differentiation of the stem cells. In cancers, the characteristics of the niche that function to support proliferation and differentiation could be more dominant than is necessary to maintain quiescence. However, the similarities and differences between the normal stem cell niche and the tumor microenvironment are still unclear.

Mesenchymal stem cells (MSCs) are non-hematopoietic stromal cells, mainly existing in the bone marrow and possibly in various tissues, that are capable of differentiating into and contributing to the regeneration of mesenchymal tissues such as bone, cartilage, muscles, tendons and adipose tissue (Chamberlain, et al. 2007).

MSCs secrete several paracrine factors including chemoattractants for endothelial lineage cells, monocytes and macrophages as well as inflammatory factors such as various chemokines and interleukins (Kinnaird, et al. 2004). MSCs could be involved in cell survival, invasion, motility, and interactions with the extracellular matrix through the chemokine signaling that results in the transcription of target genes in cancer cells as well as macrophages and lymphocytes (Roorda, et al. 2010). MSCs are also considered to be the source of tumor-associated fibroblasts (TAFs) that are important components of tumor stroma. Therefore, MSCs play an important role in orchestrating the tumor microenvironment through angiogenesis, modulation of both immune system and tumor stromal architecture.

MSCs may also be involved in the metastatic process (Karnoub, et al. 2007). Tumor metastasis requires numerous cell types and molecules to undertake sequential, multi-step processes such as intravasation and circulation, extravasation and migration, and angiogenesis to form the metastatic foci (Honoki, et al. 2007). The metastatic process is considered to be very complex and inefficient as only ~2% of disseminated cells form micrometastasis and only ~0.02% of cells develop into macrometastasis. One of the possible explanations for this inefficiency is the need for the metastatic cells to find an appropriate environment for themselves. MSCs are thought to play some roles in providing the homing sites for those cells, leading to the establishment of the metastatic foci, either directly or indirectly through the cooperation with extracellular matrices and other cells like macrophages and vascular endothelial cells.

The composition of the niche is very complex and varied in specific tissues even in normal conditions. Thus, the interaction of CSCs with their niche could be even more complex. The current review describes the potential roles of MSCs in tumor progression as the constituents of tumor stroma and niche that affect the cell fate of CSCs. Although the environments constituting a true cancer stem cell niche are still not fully elucidated, the exploration of the precise role of MSCs in cancer could potentially uncover the pathogenesis and mechanisms of progression such as metastasis. This is likely to lead to novel targeted therapies against cancers.

2. Role of mesenchymal stem cells in tumor microenvironment

The tumor stroma consists of a compilation of cells and matrices including fibroblasts/myofibroblasts, immune/inflamatory cells, blood vessels, connective tissues and extracellular matrix (ECM). Tumor-associated stromal cells like fibroblasts/myofibroblasts, immune/inflamatory cells and vascular endothelial cells are considered to be recruited from surrounding normal tissue or from circulation, and contribute to diverse aspects of tumor development and progression. Mesenchymal stem cells (MSCs) have also been demonstrated thier homing ability to the primary tumor site and metastatic sites in several studies (Studeny, et al. 2002, Dwyer, et al. 2007, Hall, et al. 2007), and possibly play a role as a co-conspirator of tumor development. MSCs may interact with tumor cells to promote tumor growth directly or indirectly through autocrine/paracrine manners with soluble

factors as well as anigiogenesis. In addition, MSCs could be the origin of tumor-associated fibroblasts or myofibroblasts contributing to the formation of tumor microenvironment that eventually lead to expansion and progression of tumors (Spaeth, et al. 2009).
It is possible that MSCs have a potencial to provide a specific microenvironment or a niche for cancer stem cells by themselves or as a source of its components. The interaction between stem cells and their specific microenvironment/niche cells will enhance the understanding of cancer development, including metastasis. We will firstly discuss here the general concept of stem cell and niche, then expand it to cancer stem cells and finally focus on the role of mesenchymal stem cells in the tumor microenvironment.

2.1 Stem cell and niche

Stem cells are the subset of cells that have the capacity to self-renew and generate functionally differentiated mature cells. Adult stem cells, including mesenchymal stem cells, are an essential component of tissue homeostasis, which support tissue regeneration, and are considered to reside in a special microenvironment. The fate of stem cells is regulated with a delicate balance between self-renewal and differentiation by both intrinsic programs and extrinsic signals from the environment. There are various intrinsic programs that control stem cell self-renewal and potency, such as Hox genes family for hematopoietic stem cells and Bmi, a polycomb family, for hematopoietic and neural systems (Kyba, et al. 2002, Lessard, et al. 2003, Park, et al, 2003). These intrinsic genetic programs have been shown to be subject to environmental regulation. Therefore, environmental regulatory signals are required to stem cell properties as well as intrinsic genetic programs.
Schofield first proposed the 'niche' hypothesis to define some specific microenvironment that supports stem cells (Schofield, 1978). The niche is a physical anchoring site for stem cells, composed of a group of cells in a special location that functions to maintain stem cells. In recent years, niches have been identified for stem cells in the intestinal, neural, epidermal, and hematopoietic system. The niche maintains stem cells primarily in a quiescent state and the stem cells become activated to divide and proliferate when a stimulating signal reaches to them (He, et al. 2005). The niche generates extrinsic factors that control stem cell fate through regulatory signal molecules, including sonic hedgehog, Wnts, bone morphogenic proteins (BMPs), fibroblast growth factors (FGFs), and Notch (Ivanova, et al. 2002). Stem cells exhibit an asymmetric division, indicating that one daughter cell is maintained in the niche as a stem cell, in terms of self- renew, while other daughter cell leaves the niche to proliferate and differentiate into a matured cell. Above extrinsic factors orchestrate the appropriate regulation of stem cell self-renewal and lineage commitment.
The component of niche or niche cells and involved environmental signals differ in tissue by tissue. For instance, hematopoietic stem cell niche is considered to be composed of osteoblastic and perivascular niche (Fig.1), and Wnt, Notch and BMP signals play a role in self-renewal, differentiation and proliferation (Reya, et al. 2003, Duncan, et al. 2005, Zhang, et al. 2003). While, for intestinal stem cells, they are located at the 4th or 5th position above the Paneth cells, and mesenchymal cells adjunct to the intestinal stem cells function as the niche. There, Wnt signalling plays a positive role in promoting stem cell activation/self-renewal and crypt cell fate, in contrast, BMP signalling restricts stem cell activation/self-renewal and crypt cell fate (van de Wetering, et al. 2002, He, et al. 2004).
When the balance between these controls is disrupted, stem cell may proliferate without restraint that might lead to tumorignesis.

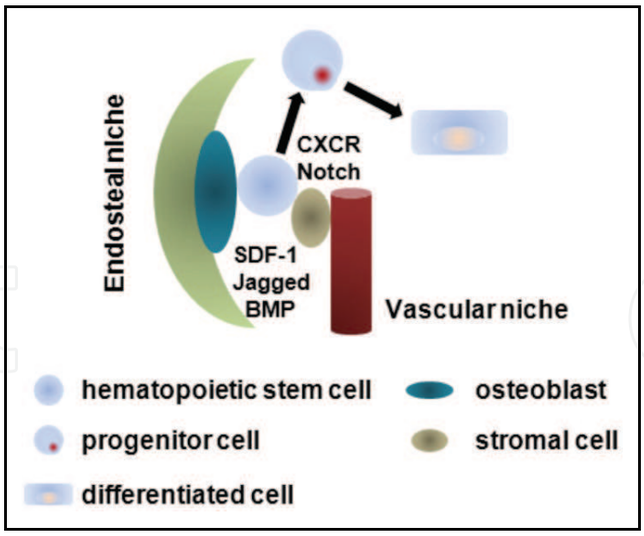

Fig. 1. Model of hemtopoietic stem cell (HSC) niche. The HSC niche is located on the surface of trabecular bone, and spindle-shaped N-cadherin-positive osteoblastic cell plays an important role to regulate HSC behavior, with an interaction of different types of stromal cells by secreting different microenvironmental signals

2.2 Normal stem cell and cancer stem cell, and their niches

Recent numerous researches have generated a new concept of tumor progression modeling for the cancer growth based on the cancer stem cell hypothesis (Fig. 2, Dick, 2008). The properties of cancer tissues have been defined the following characteristics; (i) limitless capacity to replicate, (ii) self-sufficiency for growth signals, (iii) insensitivity to antigrowth signals, (iv) evasion of apoptosis, (v) sustained angiogenesis, (vi) tissue invasion and metastasis (Hanahan et al., 2000). Since majority of those characteristic are considerably sharing with normal stem cell properties, the hypothesis has emerged indicating that tumor tissue, like normal tissue, is continuously repopulated from pools of self-renewing stem–like cells, termed as 'cancer stem cells' (Table 1). Cancer stem cells exist as a side population on the top of hierarchy within tumors, possessing stem-like properties like self-renewing and expression of stem cell-related genes/markers, and they are truly involved in tumor initiation.

Somatic Stem Cell	Cancer Stem Cell
Origin of cellular pedigree	Origin of cellular pedigree
Organ generation Tissue regeneration	Cancer initiation Relapse and Metastasis
Self - renew Pluripotency	Self - renew (Pluripotency)
Tissue reconstruction	Tumor formation

Table 1. Comparison between normal somatic and cancer stem cell

As described above, in normal adult tissues, stem cells depend on the integration of both cell-intrinsic and cell-extrinsic factors for proper, homeostatic tissue maintenance. It is likely that there is a functional microenvironment to support cancer stem cells, a counterpart of normal stem cells and their niche.

Involvements of several factors have been indicated in the interaction between cancer stem cells and their microenvironment. Dick and colleague and Van Etten and colleague respectively showed that CD44 is essential for the homing and engraftment of the cancer stem cells to the niche for acute myeloid leukemia and chronic myeloid leukemia (Jin, et al. 2006, Krause, et al. 2006). Interestingly, the molecular mechanisms of leukemia cell homing to the niche resemble those of the interaction between normal hematopoietic stem cells and the vascular niche.

Another example is that CD133-positive brain tumor cells, that contain cancer stem cells, selectively adhere to the endothelial cells that possibly form a vascular niche (Calabrese, et al. 2007). CD133-positive cells have been extensively studied in colon, prostate and pancreatic cancers, and further study will reveal the molecular mechanism underlying the relationship between CD133-positve cancer stem cells and the niche.

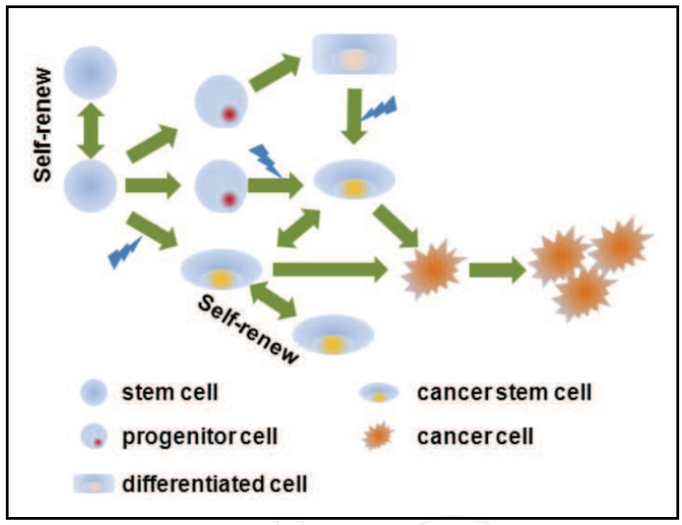

Fig. 2. Hypothesis for the development of cancer stem cells. Stem cell and/or progenitor cells with accumulated genetic alteration show sustained or reacquired self-renewal capacity, and at certain point, these cells, so called 'cancer stem cells' give rise to more differentiated, but not fully matured cancer cells with aggressive proliferation

Several cellular components have also been indicated as the cancer stem cell niche with specific signal transduction pathways. For instance, endothelial cells in the vasculature of the brain maintain neural stem cell properties, in part through Notch signalling (Shen, et al. 2004), and this is the same as the brain cancer stem cells and their vascular niche (Hovinga, et al. 2010). Another extensively studied example is the mesenchymal stromal cells in cancer stem cell niche in the intestine. In normal intestine, stem cells reside in a stem cell niche composed of epithelial cells and mesenchymal cells of the myofibroblast lineage lining the crypt. Currently, the Wnt signalling cascade is considered to be a prominent force controlling cell proliferation, differentiation, and apoptosis to maintain stem cell fate at this region (Clevers, 2006). As the counterpart of the normal intestinal stem cell niche, tumor -

associated myofibroblasts and mesenchymal stem cells are shown to be major components of the colon cancer stroma (Mishra, et al. 2008). Colon cancer stem cells have been shown high Wnt activity and orchestrated by myofibroblasts residing in the tumor stroma through the hepatocellular growth factor pathways (Vermeulen, et al. 2010).
These data suggest that there is a strong link between cancer stem cells and the microenvironment as well as that between normal stem cells and their niche, courageously indicating the presence of cancer stem cell niche.
However, unlike normal stem cell niche, the behaviours of cancer stem cells might be regulated by the niche to different degrees (Li & Neaves, 2006). The stem cell niche under normal conditions predominantly inhibits stem cells from both proliferation and differentiation, and a transient proliferating signal is required to activate tissue regeneration. Contrary, in tumors, cancer stem cells could be self-sufficient to undergo uncontrolled proliferation due to their internal mutations and/or changes in the niche signals. This leads the hypothesis of cancer stem cell niche as an environment with dominant signals to tumor cell proliferation and growth more favourably compared to the normal stem cell niche.

2.3 Homing of mesenchymal stem cells in tumor stroma

The concept of adult mesenchymal stem cells (MSCs) was first proposed almost four decades ago (Friedenstein, et al. 1970), then have been extensively investigated on molecular and functional characterization of these cells. Although the definition of MSCs is commonly accepted as bone marrow-derived, adherent to plastic surface, with the ability of self-renew and differentiation into bone, cartilage and adipose tissues, the specific marker or phenotype to definitively identify or describe these cells are still lacking. This is because MSCs reside not only in bone marrow but also in many other tissues through the entire body, and presumably MSC-like cells or MSC subsets exist with retaining MSC features.
It has been shown that MSCs can be recruited to the site of wound healing to repair damaged tissues, and so as to tumors like breast cancer, colon cancer, ovarian cancer, glioma, melanoma and osteosarcoma (Karnoub, et al. 2007, Studeny, et al. 2004, Nakamizo, et al. 2005, Komorava, et al. 2006, Djouad, et al. 2003, Brune, et al. 2010). These MSCs exhibit specialized features tailored for each particular tissue. As described above, tumor-associated fibroblast (TAFs), including myofibroblast, are part of tumor stroma that functionally and structurally supports tumor progression and development in conjunction with other components like vasculature, inflammatory cells and extracellular matrix (Sullivan, et al. 2008). There are also several evidences indicating that MSCs invade tumors and function as TAFs (Direkze, et al. 2004). TAFs have been shown to promote tumor progression through the production of growth factors like TGF-β, chemotactic factors like SDF-1 and monocyte chemotactic protein-1, angiogenic factors like VEGF and matrix metalloproteinases (MMPs) leading invasion and spread of tumor cells. Although the origin of tumor stromal fibroblasts is not fully elucidated, it is possible to consider some of these stromal cells including TAFs as a 'specialized' subset of MSCs. (Haniffa, et al. 2007, Stagg, 2008). Therefore, either MSCs themselves or specialized MSCs like TAFs in the stroma are key players directly or indirectly involved in tumor progression (Fig. 3).
As cancers are sometimes referred to as 'wounds that never heal' (Dvorac, 1986), the microenviroment of a solid tumor is very similar to the environment of an injured tissue. Thus, tumor growth is often associated with a variety of cells and factors in a similar manner with the wound healing and tissue repair sites. Several studies have shown the involvment of MSCs for injured tissue repair. In that process, chemokines and chemokine

receptors such as CXCR4, CXCR12 and CCL5 have been indicated in the tissue-homing ability of MSCs (Dwyer, et al. 2007), and TGF-β family and Wnt signals play important roles in MSCs-mediated tissue repair (Mishra, et al. 2005). Like these factors, many players involved in MSCs for tumor progression are very similar to the wound repair response (Dvorac, 1986).

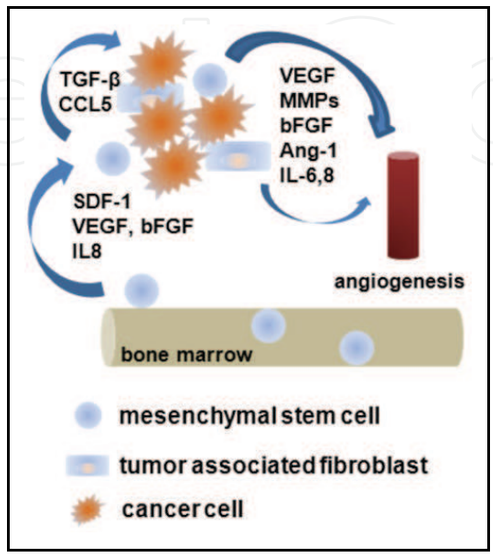

Fig. 3. Hypothesis for the involvement of mesnechymal stem cells in tumor progression. Mesnechymal stem cells migrate in tumor tissue and incorporate into TAFs. TAFs stimulate cancer cell proliferation through the growth factor signals like TGF-β. MSC itself or TAFs could participate in angiogenesis by secreting factors like VEGF and MMPS

Another contribution of MSCs in tumor development would be pro-invasive potential homing to the metastatic site for cancer cells, possibly the cancer stem cells, to create a so called 'premetastatic niche' (Kanoub, et al. 2007). The ability of a tumor to metastasize may depend on the ability to establish distant niches suitable for them as well as the characteristics of tumor cells themselves. MSCs colonize the premetastatic niche before metastatic tumor cells have arrived in response to signals from the tumor cells. Factors like CCL5, SDF-1, VEGF and MMPs are also involved in this phenomenon (Kaplan, et al. 2007). Although numerous studies indicated the homing ability of MSCs to primary and metastatic site, one might argue that the homing of MSCs might not be completely tissue specific and could distribute to a wide range of organs. So far, no data are available where MSCs detected in tumor stroma originate from whether the local mesenchyme or bone marrow. Therefore, detailed mechanisms of participating molecules involved in homing of MSCs to tumor site should be further investigated for the development of therapies targeting MSC-tumor cell interaction.

2.4 Role of mesenchymal stem cells in tumor progression

Intrinsic capabilities of tumor cell itself have been focused on the research of tumor progression including invasion and metastasis. On the other hand, recent advances of the research on tumor microenvironment indicate that components of heterogeneous population of stromal cells such as fibroblasts, immune cells can enhance tumor progression

with their dynamic interactions. MSCs are considered to be involved in many aspects as the origin of tumor stromal fibroblasts, source of soluble factors to attract immune cells and angiogenesis.
In fact, the relationship between MSCs and tumor cells could be dual. Thus, both primary and metastatic tumor cells actively attract MSCs from either bone marrow or surrounding tissues where they contribute to the tumor microenvironment as described above; vice versa, MSCs stimulate tumor cells to produce a variety of cytokines and other growth factors.

2.4.1 An immunomodulator in the process of tumor development

Immunosuppressive properties of MSCs contribute in part to the tumor developments. MSCs have been shown to suppress the lymphocyte proliferative response in a broad way regarding the types of stimulation and of lymphocyte population (Di Nicola, et al. 2002, Djouad, et al. 2003). A number of mechanisms have been reported for these effects, such as secretion of anti-inflammatory factors (Rasmusson, 2006), modulation of the function of the major immune cell population (Glennie, et al. 2005), cell cycle arrest in the G0/G1 phase on B lymphocyte (Corcione, et al. 2006), modulation of development and function of cytotoxic T cells and dendritic cells (Rasmusson, et al. 2003, Jiang, et al. 2005), inhibition of interferon-γ production by activated natural killer cells (Aggarwal & Pittenger, 2005).
These mechanisms could be clue to explain how tumor cells evade the immune system. One might hypothesize that tumor cells can harness MSCs that manipulate the immune system through several ways described above, and eventually evade the immune attack (Yen & Yen, 2008).
Beside immunosuppressive effects, recruitment of tumor infiltrating macrophages or tumor associated macrophages (TAMs) could be another role of MSCs. The role of TAMs is multifaceted, as not only providing supportive microenvironment for malignant cells but also inducing oncogenic mutations in surrounding cells in earliest carcinogenesis (Pelham, et al. 2006). TAMs could be a heterogeneous population and whose possible common origin would be monocytes actively recruited into tumor site. Monocytes can migrate in response to chemokines such as CCL2, CCL5, CXCL8/IL-8 and SDF-1, and also to growth factors like vascular endothelial growth factor (VEGF) produced by MSCs as well as tumor cell itself (Murdoch, et al. 2004, Barleon, et al. 1996). Migrated monocytes differentiate into TAMs (Mantovani, et al. 2002), and eventually contribute to tumor progression *via* production of growth factors and regulation of pro-angiogenic switch (Lin, et al. 2006).

2.4.2 A source of soluble factors involved in angiogenesis

The formation of tumor vessels requires the proliferation and directional migration of vascular endothelial cells through basement membrane and stroma toward pro-angiogenic stimuli, such as soluble chemoattractants like VEGF, basic fibroblast growth factor (bFGF) and angiopoietins (Ang-1).
Specialized MSCs in tumor stroma, like TAFs as described above, play an important role for the formation of tumor vessels. MSCs and/or TAFs produce several pro-angiogenic factors including VEGF, FGFs, Ang-1, platelet derived growth factor (PDGF) as well as cytokines such as IL-6, 8 and TNF-α (Kinnaird, et al. 2004). These molecules are involved in the recruitment and activation of endothelial cells through paracrine manner as well as direct cell – cell contacts (Zacharek, et al. 2007).

Tumor angiogenesis requires active remodeling and integration of new cells into existing structures and is the result of a complex tumor – stroma crosstalk, involving multiple ligands and cellular signaling pathways. SDF-1/CXCL12 axis and MMPs are critical players to recruit and engraftment of marrow derived endothelial progenitors for growth of new vessels from pre-existing vasculature (Genis, et al. 2006).

MMPs secreted from stromal cells including MSCs and TAFs play the diverse roles in not only degradation of the extracellular matrices, but also cleavage of proteinases, chemokines and chemotactic factors, growth factors and cell surface receptors, and cell matrix adhesion molecules (Coussens, et al. 2002) to participate in restructuring tumor microenvironments including angiogenesis. Proteolytic cleavage of angiogenic factor, secreted protein acidic rich in cysteine (SPARC)/osteonectin is also indirect effect of MMPs to regulate the tumor angiogenesis (Sangaletti, et al. 2003).

Then, VEGF from MSCs and TAFs in tumor stroma stimulate budding of existing vessels and proliferation of new vascular channels. Although VEGF is a potent vascular growth factor and the main stimulus for the formation of tumor vessels, it is implicated in many aspects of cancer growth such as extracellular matrix remodeling and generation of inflammatory cytokines and other molecules involved in the pro-angiogenic and pre-metastatic niche (Kaplan, et al. 2005). The main stimulus for secretion of VEGF is hypoxia, which results in the recruitment of endothelial progenitor and mesenchymal stem cells to sites of ischemia, that in turn additional VEGF production leading to tumor angiogenesis and generation of tumor stroma (Okuyama, et al. 2006).

2.4.3 A source of niche cells for cancer cells / cancer stem cells

For normal stem cells, the microenvironment or niche where they reside is important to maintain the stemness, and to regulate proliferation and differentiation. The similarities between normal stem cells and cancer stem cells as shown in Table I could extend the attractive concept of stem cell niche to the presence of cancer stem cell niche. There have been several studies indicating the specialized cancer stem cell niches may participate in the tumor development (Calabrese, et al. 2007, Gilbertson & Rich, 2007), and is considered to play an important role in virtually every aspect of the tumorigenic cascade including the metastatic process as well as drug resistance.

Usually, metastasis occurs in an organ-selective manner described as the 'seed and soil' hypothesis which indicate that local microenvironment of specific organs seems to be more receptive to particular tumor cells than other organs. Thus, disseminated tumor cells need to meet a suitable microenvironment in order to survive and initiate a secondary tumor. The metastatic process is very complicated and inefficient with multi-steps such as intravasation, circulation, arrest, extravasation migration and angiogenesis (Honoki, et al. 2007). Tumor stromal cells including MSCs might be involved in several phases of the metastatic process with the interaction of cancer stem cells (Fig. 4).

Mesenchyaml stem cells have the ability to enhance growth and metastasis of certain cancers like colon cancer (Shinagawa, et al. 2010), and have been proposed to give rise to tumor-associated fibroblasts that further promote tumor progression. The metastatic potential of breast cancer cells and osteosarcoma cells has also been shown to be strongly enhanced when coinjected with MSCs through the paracrine signaling events (Karnoub, et al. 2007, Xu, et al. 2009). In this context, MSC-derived CCL5 appears to be an essential factor to enhance the growth and invasiveness of tumor cells. IL-6 from MSCs is also involved in

growth promotion effect for osteosarcoma cells (Bian, et al. 2010). MSCs also produce chemoattractant proteins like SDF-1 and MCP-1 that attract circulating tumor cells like B leukemia cells, breast cancer cells (Burger & Kipps, 2002, Molloy, et al. 2009).
Transition to TAFs from MSCs has been shown to contribute to the tumor growth through fibrovascular network expansion and production of tumor-stimulating paracrine factors (Spaeth, E.L. 2009). Activated fibroblasts or TAFs have been found also at liver metastasis, where they promote tumor outgrowth (Olaso, et al. 1997). Fibroblast activation is probably involved in priming the premetastatic niche with fibronectin deposits (Kaplan, et al 2005) to attract tumor cells to their preferable sites for metastasis. Moreover, the infiltration of activated fibroblasts or myofibroblasts precedes the recruitment of vascular endothelial cells in the hypoxic avascular metastatic environment, and they produce VEGF to promote angiogenesis and transition to a vascular stage (Olaso, et al. 2003). In addition to paracrine signaling, MSCs protect tumor cells against apoptosis and promote initial tumor cell proliferation mainly by direct cell – cell contact interactions (Roorda, B.D. 2010). All of these data suggest that MSCs are directly or indirectly involved in the metastatic process as the source of niche for metastatic tumor cells.

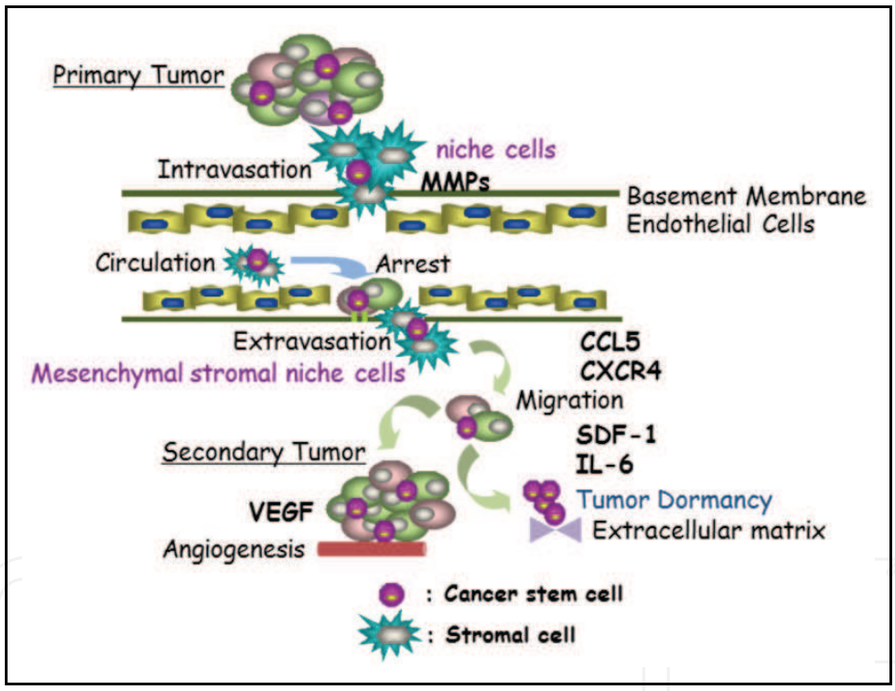

Fig. 4. Possible involvement of tumor stromal cells including MSCs/TAFs in clustering metastatic model. Metastatic tumor cells, possibly including cancer stem cells, complete a very complicated metastatic process cooperating with tumor stromal cells. Soluble factors such as MMPs, CCL5, CXCR4, SDF-1, IL-6 and VEGF secreted from MSCs/TAFs participate in the metastatic process

Besides of the effect on tumor progression, tumor stromal cells may contribute to the drug resistance through complex mechanisms such as the direct cell contact, the interaction of extracellular matrices (ECM) and soluble factors (Nefedova, et al. 2003). Soluble factors that mediate drug resistance are produced by a dynamic interaction between tumor cells and

stromal cells. IL-6 and SDF-1 are known to mediate resistance to various chemotoxics in hematological and epithelial cancers. IL-6 activates c-FLIP and STAT3 signaling that result in protecting tumor cells from TNF-related apoptosis-inducing ligand (TRAIL) and FAS-mediated apoptosis (Duan, Z, et al. 2006, Perez, et al. 2008). SDF-1 increases β1 integrin-mediated adhesion of myeloma and small lung cell carcinoma, leading to drug resistance in ECM-adhered tumor cells (Sanz-Rodriguez, et al. 2001, Hartmann, et al. 2005). Integrin-mediated adhesion increases the activation of cytokine signaling pathways and also leads to a state of tumor dormancy. For instance, β1 integrin amplifies IL-6-induced STAT3 signaling (Shain, et al. 2009) as well as leading tumor cells to cell cycle arrest (White, et al. 2006) that result in drug resistance eventually. β1 integrin-mediated adhesion to ECM components also leads to cell cycle arrest through p21 and p27 up-regulation (Fischer, et al. 2005), which contribute to drug resistance (St. Croix, et al. 1996).

Taken together, although there are no direct evidences indicating MSCs or TAFs provide the niche for cancer stem cells nor they are not the only player for cancer stem cell niche, these tumor stromal cells could have bystander effects to participate in tumor progression as the niche cells, providing dominant signals to tumor cell proliferation and growth, and recessive signals to lead cancer cells into the dormant state with the interaction of ECM. Both signals eventually contribute to tumor progression such as metastasis and drug resistance.

2.5 Therapeutic implications of mesenchymal stem cells in cancer

There are several possible different ways to imply targeting MSCs into therapeutic purpose. Firstly, targeting paracrine loop of soluble factors could disrupt the interaction between tumor cells and MSCs, which contributed many aspects of tumor progression and drug resistance. Inhibition of VEGF receptor tyrosine kinase activity and receptor tyrosine kinase for FGF blocks a paracrine IL-6 production by stromal cells, and leads to apoptosis of tumor cells (Lin, et al. 2002, Bisping, et al. 2009). Small molecule inhibitor of SDF-1 receptor CXCR4 increases the chemo-sensitivity of leukemic cells and prolongs survival of leukemic patients (Zeng, et al. 2008). Since both IL-6 and SDF-1 also play an important role in the microenvironment of solid tumors as described above, the therapeutic approaches that disrupt communication between tumor cells and stromal cells such as MSCs/TAFs could be feasible against solid malignancies.

Secondly, MSCs that migrate to tumor site would be useful as carriers of oncolytic or immune-modulatory adenoviruses or as direct target of 'activated' or genetically altered stromal cells. MSCs have been engineered in a number of different ways as the vehicles delivering cytotoxic drugs, stimulating the immune response or blocking angiogenesis. MSCs modified to express IFN-β and γ were able to inhibit tumor growth (Studeny, et al. 2004, Li, et al. 2006). MSCs infected with adeno- or retrovirus encoding IL-12 showed inhibitory effects on tumor growth through the activation of NK cells and CD8+ T cells (Elzaouk, et al. 2006). Bone marrow-derived progenitors with suicide gene integration used as delivery vehicles have also been shown to reduce tumor size and vascularity (Komarova, et al. 2006). Tumor-associated angiogenesis was inhibited by MSCs infected with adenovirus to express NK4 *via* antagonizing HGF-c-met signalling pathway (Kanehira, et al. 2007).

Several studies suggested the direct inhibitory effects of MSC itself against tumor growth of, for instance, mouse Lewis lung carcinoma, B16 melanoma (Maestroni, et al. 1999), and rat colon cancer model (Ohlsson, et al. 2003). Involvements of non-inflammatory cytokines and Akt activity have been suggested on these effects, however, the exact factors mediating the anti-tumor activities of MSCs have not been clearly identified.

Although MSCs have a potential in cell-based anti-cancer therapy, the safety of using MSCs is still questionable, because homing of MSCs is not selective and genetically engineered MSCs could undergo malignant transformation. Thus, the precise action of MSCs will need to be studied to develop the safe and specific treatments.
Another possible target would be the homing mechanisms by which cancer stem cells migrate to metastatic sites or the factors that govern the cellular dynamics within their 'pathological niche' or 'cancer stem cell niche', where MSCs possibly play a role in several aspects of tumor progression.
Further study will be required to understand the details of components, regulation and interaction between cancer stem cell and their niche to develop a novel treatment strategy.

3. Conclusions

Pro-tumorigenic contribution of MSCs is still not fully uncovered. This is in part explained by the presence of heterogeneous population due to the lack of exact definition of MSC population, and the complexity of their interaction with tumor cells and the large range of cytokines and growth factors. However, a number of evidences suggest that MSCs are actively recruited into tumor site, and contribute to tumor microenvironment as either themselves or as the tumor-associated fibroblasts. They directly or indirectly regulate tumor cell proliferation, differentiation, immune tolerance, angiogenesis, metastasis and drug resistance through the interaction with numerous cytokines and growth factors as well as providing niche to the cancer cells or cancer stem cells in cooperated with ECM. Although MSCs can be friends or foes of tumor cells, depending on their constituents of population including the origin and stage of differentiation and also the type of tumor cells to be interact with, further investigation will define the role of MSCs in tumor progression that leads to novel strategy for cancer therapy.

4. Acknowledgment

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Cancer Stem Cells - The Cutting Edge

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Over the last thirty years, the foremost inspiration for research on metastasis, cancer recurrence, and increased resistance to chemo- and radiotherapy has been the notion of cancer stem cells.The twenty-eight chapters assembled in Cancer Stem Cells - The Cutting Edge summarize the work of cancer researchers and oncologists at leading universities and hospitals around the world on every aspect of cancer stem cells, from theory and models to specific applications (glioma), from laboratory research on signal pathways to clinical trials of bio-therapies using a host of devices, from solutions to laboratory problems to speculation on cancersâ€™ stem cellsâ€™ evolution. Cancer stem cells may or may not be a subset of slowly dividing cancer cells that both disseminate cancers and defy oncotoxic drugs and radiation directed at rapidly dividing bulk cancer cells, but research on cancer stem cells has paid dividends for cancer prevention, detection, targeted treatment, and improved prognosis.

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