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REVIEW

Perspectives on Mesenchymal Stem Cells: Tissue Repair, Immune Modulation, and Tumor Homing

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Mesenchymal stem cells (MSCs) or MSC-like cells have been identified in a variety of different tissues that share molecular expression profiles and biological functions but also retain a unique differentiation preference depending on their tissue origins. MSCs play beneficial roles in the healing of damaged tissue by directly differentiating to many different resident cell types and/or by secreting several trophic factors that aid tissue repair. Aside from MSCs' reparative stem cell function, they drive immune responses toward immunosuppression and anti-inflammation. This novel function of MSCs opens up new avenues for clinical development of MSC immune-therapeutics to treat uncontrollable, life threatening, severe, chronic inflammation and autoimmune disease. Unexpectedly high rates of MSCs' tumor homing capacity and their tumor supporting capability have also been noted in tumor-bearing animal models. In this review, we will discuss MSCs' basic cell biology and perspectives on MSCs in terms of tissue repair, immune modulation, and tumor homing.

Key words: MSC, Tissue repair, Immune modulation, Tumor homing, Adipose stem cell, Inflammation

INTRODUCTION

MSCs, also called as bone marrow stromal cell (BMSC), were first identified as fibroblast-like stromal cells residing in trabecular bone anastomoses of long bone, which secrete many kinds of cytokines and growth factors that support the proliferation and the differentiation of hematopoietic stem cells (HSCs) (Friedenstein et al., 1970). At early stages of HSC culture, MSCs or BMSCs were used as feeder cells to maintain HSCs *in vitro*. In 1999, Pittenger et al. revealed that MSCs can differentiate into a variety of mesenchymal derived cells such as osteoblasts, chondrocytes, and adipocytes *in vitro* (Pittenger et al., 1999) and this opened up an opportunity for clinical application of MSCs. Since then, MSCs have been used as cellular sources for cell therapy or tissue engineering products to regenerate bone, cartilage, and adipose tissues. More recently, it was reported that transfused MSCs can be differentiated into cells other than mesodermal cells including epithelial cells, neurons, and glial cells, and also have new functions such as suppressing immune responses in a variety of inflammation or autoimmune related diseases animal models (Nauta and Fibbe, 2007; Salem and Thiemermann, 2010). Due to immune-privileged characteristics of MSC, widespread clinical use of *ex vivo* cultured allogeneic or autologous MSCs are in trials for steroid refractory acute graft versus host disease (GvHD) (Le Blanc et al., 2004), Crohn's disease (Ciccocioppo, 2011; Mannon, 2011), type I diabetes mellitus (DM) (Zanone et al., 2010), acute myocardial infarction (AMI) (Kocher et al., 2001; Chen, 2010), chronic obstructive pulmonary disease (COPD) (D'Agostino et al., 2010), acute radiation syndrome (Lange et al., 2011), and so on. Even though clinical benefits of transplanted MSCs on tissue repair and/or immune modulation are anticipated, the high cost for *ex vivo* cell culture and the

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possibility of tumor formation after extensive cell expansion still remains an unsolved problem. Instead of expensive *ex vivo* cell cultures, small molecules or growth factors recruiting endogenous stem cells to the site of tissue injury are also being explored as a new paradigm in stem cell therapy (Hong et al., 2009, 2011). Recent findings of circulating and homing of BMSCs in tissue injury (Hong et al., 2009) or in pathophysiological conditions (Rochefort et al., 2006; Rosová et al., 2008) are other possible applications of stem cell therapeutics. In this review, multiple facets of MSCs as therapeutic cells will be discussed.

MSCs OR MSC-LIKE CELLS FROM DIFFERENT TISSUE ORIGINS

MSCs or MSC-like cells were identified in bone marrow, adipose tissue (Gronthos et al., 2001; Zuk et al., 2002), dental pulp (Gronthos et al., 2011), and gingiva (Zhang et al., 2010) and can be classified into BMSCs, adipose-derived mesenchymal stem cells (AdMSC), dental pulp mesenchymal stem cell (DPMSC), and gingiva MSC (GMSC), respectively, and cord blood MSC. Their incidences are quite variable depending on tissue origins and donor age. Among them, AdMSCs are the most abundant.

Autologous BMSCs can be obtained from bone marrow aspirates but their frequency among mononuclear cells (MNC) is very low. This low retrieval of BMSC is probably due to strong adherence of BMSCs to the stroma, which requires a novel strategy to dislodge adherent cells or mobilize them to migrate to a more accessible location such as peripheral blood. An extremely low incidence of BMSC in bone marrow aspirates may be circumvented by using G-CSF (granulocyte-colony stimulating factor) or GM-CSF (Granulocyte-macrophage colony-stimulating factor) to mobilize BMSC to the blood (Orlic et al., 2001). However, several previous studies suggested that G-CSF can mobilize only EPC (Endothelial progenitor cell) but not BMSC to the peripheral blood, some of which could be then redirected to the injured tissue of AMI (Orlic et al., 2001; Yoon et al., 2005) for a limited time window after an injury. Furthermore, a strong inflammatory response of G-CSF to the injury, one of unwanted side effects of G-CSF, limits its clinical use for AMI tissue repair and other ischemia-induced tissue damages. Recent findings of a novel function of substance-P (SP) as an injury-inducible messenger to mobilize bone marrow stem cells to the blood and then to engage in the tissue repair clearly elucidates the presence of an endogenous healing mechanism that recruits BMSCs to the site of tissue repair (Hong et al., 2009) (Fig. 1). This small molecule, an 11 amino acid peptide drug, enables one to harvest substantial numbers of BMSCs in the withdrawn blood sample and may substitute endogenous BMSC mobilization for elaborate *ex vivo* cell culture of BMSCs.

In contrast to the low incidence of BMSC, AdMSCs are more abundant and seem to have several advantages if their differentiation capacity and immune modulator function are comparable to those of BMSCs.

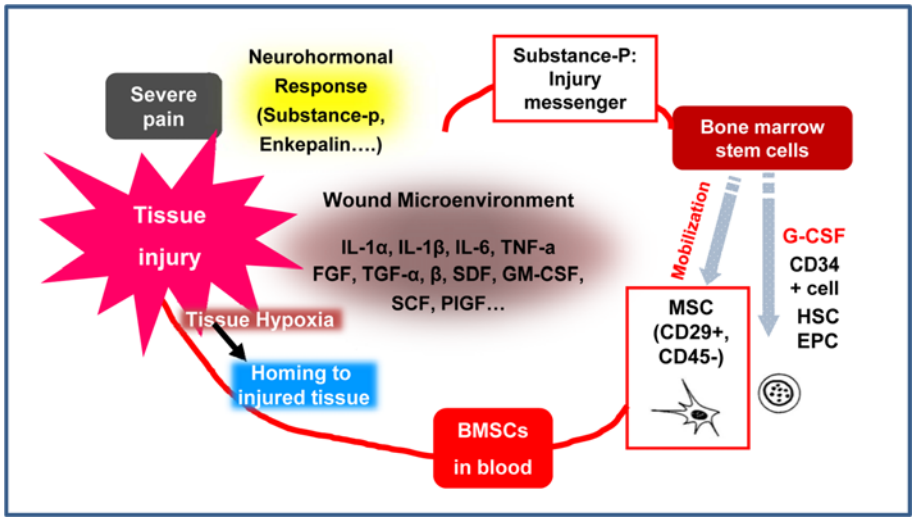

Fig. 1. Schematic view of BMSC mobilization driven by SP. SP-peptide is released from the injured site immediately after the tissue injury and diffuses into the peripheral blood. This is the first step for SP's engagement in the endogenous healing mechanism, inducing BMSC participation as an injury-inducible messenger. The SP level in the blood is an important parameter for BMSCs to sense tissue injury. SP can mobilize reparative stem cells (BMSCs) to the peripheral blood. SP-mobilized reparative stem cells then home to the injured tissue and become engaged in tissue repair.

The frequency of AdMSCs represents approximately 2% of total lipoaspirate cells, compared to a BMSC frequency of 1 in 25,000 and an MNC frequency of 1 in 100,000 in bone marrow (Kingam et al., 2004). In addition, the broad distribution of fat tissue in our body and greater accessibility of fat stores (such as subcutaneous fat and abdominal fat) could provide another source of stem cell donor tissue. In this regard, the AdMSC is an attractive, readily available type of adult stem cells that have become increasingly popular for use in mesenchymal tissue repair and in other therapeutic applications.

A variety of other tissues harbor MSC-like cells. Dental pulp is considered to be a little bone marrow-like structure where DPMSC are identified. DPMSCs also share common characteristics with BMSCs, but preferentially differentiate to odontoblasts (Seo et al., 2004; Gronthos et al., 2011). These features of DPMSC support the regeneration of bio-tooth from DPMSCs that are obtained from autologous teeth and cryopreserved in a tooth bank. Gingiva also harbors gingiva-derived MSCs, which possess multipotent differentiation capabilities and display immunosuppressive and anti-inflammatory functions. They inhibit the proliferation of T lymphocytes and promote the generation of regulatory T cells (Treg) (Zhang et al., 2009, 2010). Cord blood MSCs are similar to BMSC and have a prominent capacity for differentiation and proliferation. Many types of clinical studies that use Cord blood MSCs are in clinical trials for GvHD, Crohn's disease, IBD, AMI, osteoarthritis, and so on.

MSCs or MSC-like cells, even though their tissue origins are different, possess similar cellular and molecular characteristics (Dominici et al., 2006), including adherence to plastic, multipotent differentiation potential to osteoblasts, adipocytes, and chondroblasts, and expression of cell surface antigens such as $CD73^+$, $CD90^+$, $CD105^+$, $CD34^-$, and $CD45^-$. Recently, Crisan et al. (2008) suggested that some MSC-like cells from fat tissue are perivascular cells that are associated with blood vessel walls and express $CD140b^+$ (PDGFR-β), $CD146^+$, and $NG2^+$. These cells also retain a multipotent differentiation potential similar to traditional BMSCs. This finding may be a reason why stem cells are more abundant in fat tissue than in bone marrow, considering ample vascular structures in the adipose tissue. Furthermore, AdMSCs have the capacity to differentiate not only into cells of mesodermal lineages, but also, into neuronal and glial cells *in vitro* and *in vivo* (Zuk et al., 2002; Kokai et al., 2005; Kingham et al., 2007; Chi et al., 2010). Thus, MSCs or MSC-like cells may have similar clinical potential in several defined systems.

MSCs or MSC-like cells are identified based on several criteria: surface markers analysis by fluorescence activated cell sorting (FACS), fibroblastic colony forming units (CFU-F), and multipotent differentiation capacities *in vitro* and *in vivo*. Surface expression profiles of $CD29^+$, $CD90^+$, $CD105^+$, $CD106^+$, Stro-1^+, $CD34^-$, $CD11b^-$, and $CD45^-$ and their combinations are currently used for sorting MSCs at an early stage after their isolation. The CFU-F assay is a useful method for analyzing a stem cell pool from primary isolates, which is important for expectation of the degree of cell expansion during the cell culture. MSCs, even though derived from different tissue origins, show multi-

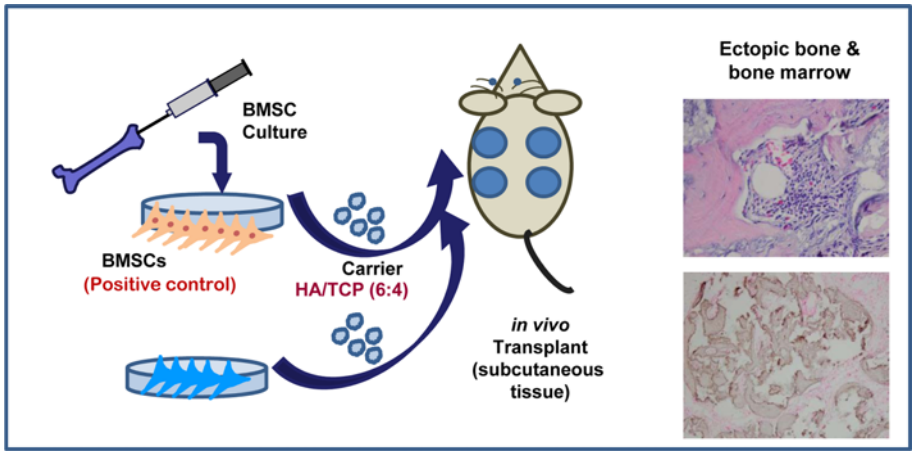

Fig. 2. Ectopic bone and bone marrow formation of BMSC. BMSCs have multipotent differentiation capacity *in vitro* if proper conditions are met. The capacity of ectopic bone and bone marrow formation becomes a hallmark for BMSC. SP-mobilized BMSCs were transplanted with hydroxyapatite and tri-calcium phosphates (HA/TCP) to the subcutaneous tissue of nude mice to form collagen-rich bone matrix and bone marrow filled with hematopoietic cells and adipocytes. The comparison group was BMSC without SP as a positive control.

potent differentiation capacity *in vitro* if proper conditions are met. However, this criterion does not always correspond to their *in vivo* differentiation capacity. However, MSC-like cells derived from sources other than bone marrow usually do not retain the capacity to regenerate ectopic bone and bone marrow formation when transplanted with hydroxyapatite and tri-calcium phosphates (HA/TCP) to the subcutaneous tissue of nude mice (Fig. 2). Therefore, this capacity of ectopic bone and bone marrow formation remains a hallmark for BMSC so far.

MSCs OR MSC-LIKE CELLS AS REPARATIVE STEM CELLS FOR TISSUE REPAIR

BMSCs play a role as reparative stem cells in a variety of tissue injuries by directly differentiating to mesenchyme cells (Orlic et al., 2001; Toma et al., 2002; Yoon et al., 2005) or cells other than mesenchyme cells such as neural epithelial cell types as shown in bleomycin-induced lung injuries (Ortiz et al., 2003; Rojas et al., 2005), liver injury (Sato et al., 2005), and skin injuries (Sasaki et al., 2008). Several lines of evidence support the idea that non-mesenchyme differentiation of BMSCs accumulate in epithelial damage (Ortiz et al., 2003; Rojas et al., 2005) but the molecular mechanism of the mesenchymal to epithelial transition (MET) of BMSC in the injured tissue has not been elucidated yet, and it is not clear whether this MET process is transient or irreversible. Furthermore, it needs to be clarified whether BMSC-regenerated epithelia are functionally tight epithelia or are more like pathologic ones such as transitional epithelia.

The reparative function of BMSCs was best studied in AMI at an early stage of BMSC therapeutics (Orlic et al., 2001; Toma et al., 2002; Yoon et al., 2005). Due to limited regenerative capacity of the heart, myocardial infarction (MI) results in irreversible myocardial cell loss and functional impairment, eventually leading to heart failure and death (Lewis et al., 2003). In previous reports, potential therapeutic benefits of BMSC transplantation have been demonstrated (Strauer et al., 2002; Menasche et al., 2003; Perin et al., 2003; Pittenger and Martin, 2004). Their therapeutic effects have been attributed to their potential to differentiate into many different cell types such as cardiomyocytes, endothelial cells, and vascular smooth cells (Zimmet and Hare, 2005; Minguell and Erices, 2006) and/or to trans-differentiate ventricular myocytes to cardiomyocytes, which was demonstrated in animal models and in human MSCs (Xu et al., 2004).

Several stem cell mobilizing agents such as G-CSF (Shi et al., 2002), SDF-1 (Pitchford et al., 2009), VEGF, angiopoietin-1 (Hattori et al., 2001), and so on have been found to accelerate tissue repair. The mechanism for mobilization and homing has been rather extensively investigated in AMI. Ip et al. (2007) showed that MSCs utilize integrin $\alpha 1$ for myocardial migration and engraftment, instead of the CXC receptor 4 being involved in EPC homing to the ischemic myocardium. Currently, BMSCs and/or EPC transplantation still show low engraftment and low functional improvement in AMI.

MSCs or MSC-like cells are more expected for CNS tissue repair as alternative cell source, instead of neural or neural derived cells. Neural stem/progenitor cells are localized in the subventricular zone of the lateral ventricle and the subgranular zone within the dentate gyrus of the hippocampus in adults (Kuhn et al., 1996; Doetsch et al., 1999), which are not readily accessible for autogenic cell therapeutics. Thus, alternatively accessible donor cells to substitute for autologous neural stem cells are required.

For the last decade, researchers tried to get MSCs to differentiate to neuronal and glial cells. Numerous papers have suggested that BMSCs or AdMSCs could be used to treat neurological disorders, but direct evidence is still lacking as to whether these cells can functionally behave like neuronal or glial cells *in vivo*. Recently, it was suggested that trophic effects of MSCs; i.e., secre tions of neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), angiogenic factors such as angiopoietin-1, and vascular endothelial growth factor (Zhang et al., 2002; Neuhuber et al., 2005; Crigler et al., 2006; Yilmaz et al., 2010) and immuno-modulating factors (Gordon et al., 2008; Kassis et al., 2008) may enhance neural survival and differentiation and stimulate angiogenesis and migration of endogenous neural stem cells to the injury site, which eventually might improve neural function in CNS injury or disease.

Direct conversion of BMSC or AdMSC to a neural lineage has not yet made significant progress, but approaches to their differentiation to Schwann cell (SCs), axon-myelinating cells in the peripheral nervous system (PNS), became recent topics (Dezawa et al., 2001; Tohill et al., 2004; Caddick et al., 2006; Keilhoff et al., 2006; Kingham et al., 2007; Jiang et al., 2008; Chi et al., 2010). By using retinoic acid, forskolin, bFGF (basic fibroblast growth factor), and heregulin-beta-1 (or GGF-2) (Zavan et al., 2010) and/or by adopting spheroid induction culture, BMSCs or AdMSCs were able to acquire typical SC phenotypes, expressing SC markers such as Sox10, p75, S100, Krox-20, L1, PLP/DM20, PMP22, ErbB2, PDGFr-aa, O4, A2B5, P0, and

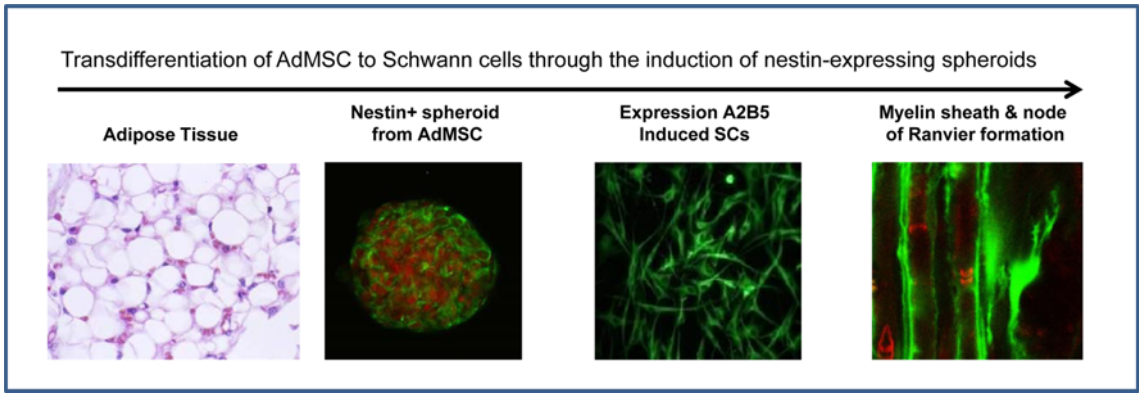

Fig. 3. Differentiation of AdMSC to myelinating SCs. By adopting a spheroid induction culture method, AdMSCs were induced to form a nestin-expressing spheroid (nestin: green, nucleus: red) and then a typical SC phenotype expressing SC markers such as A2B5, similar to naïve SCs *in vitro*. Transplantation of induced EGFP-expressing SCs to a spinal cord injury revealed that induced SCs engage in myelin sheath formation and in the node of Ranvier, which is seen by the formation of Caspr (red), at the lesion site (This figure contains published data (Chi GF et al., 2010) and its reuse was permitted by the publisher).

MBP and secreting several neurotrophic factors such as NGF, BDNF, CNTF, GDNF, as did naïve SCs (Chi et al., 2010). Furthermore, the induced SCs were successfully engrafted to the lesion site of contusion-spinal cord injury, where a PNS type myelin sheath was regenerated on CNS axons (Fig. 3). Thus, such cells show therapeutic promise in the repair of CNS as well as PNS damage even though only a small portion of transplanted cells participated in myelin sheath formation at the lesion site.

BMSCs and AdMSCs are also proposed for the repair of retinal tissues in degenerative retinal diseases such as age-related macular degeneration (AMD) and retinopathy. AMD is characterized by damage to the retinal pigment epithelium (RPE), which could be managed if the RPE could be regenerated earlier. BMSCs and AdMSCs have been used to regenerate RPE and neural retinal tissue. (Otani et al., 2004; Harris et al., 2006; Harris et al., 2009; Vossmerbaeumer et al., 2009; Singh et al., 2011). However, it was not clearly demonstrated that BMSCs can be directly converted to RPE, or whether its immune-modulating function plays a major role in the amelioration of severe chronic inflammation of AMD, and thus in the delay of AMD progression.

MSCs FOR IMMUNOMODULATION

MSCs modulate the inflammatory response by down-regulating pro-inflammatory cytokines and/or up-regulating anti-inflammatory factors and also possess remarkable immunosuppressive properties. MSCs suppress T-cell and natural killer (NK) cell functions and induce regulatory T-cells (Aggarwal and Pittenger, 2005; Nauta and Fibbe, 2007; Ryan et al., 2007; Selmani et al., 2008; Uccelli et al., 2008; Zhang et al., 2009, 2010), and modulate dendritic cell activities (Jiang et al., 2005; Kim and Hematti, 2009; Spaggiari et al., 2009). Those novel functions of MSCs promoted both autologous and allogeneic BMSCs to an immunotherapeutic agent in a variety of autoimmune and severe inflammation-related diseases such as GvHD (Le Blanc et al., 2004), type I DM (Abdi et al., 2008), Crohn's disease (Ciccocioppo, 2011; Mannon, 2011), COPD (D'Agostino et al., 2010), sepsis (Németh et al., 2009), and wound healing (Zhang et al., 2010). Recently, it was revealed that MSCs, regardless of their tissue of origin, display immunosuppressive and anti-inflammatory functions *in vitro* and *in vivo*.

Several reports support the idea that BMSCs modulate a variety of T cell responses by producing cytokines and/or by direct cellular contact. BMSCs, after mitogen stimulation, produce numerous cytokines; especially interleukin-6 (IL-6) and transforming growth factor-β (TGF-β) (Liu et al., 2009; Oh et al., 2009), both of which regulate pro-inflammatory T helper 17 (Th17) cells and anti-inflammatory Foxp3+ regulatory T cells (Treg) (Bettelli et al., 2006; Weaver et al., 2007; Casiraghi et al., 2008). In addition, BMSCs or AdMSCs prevent T cell responses to cellular and nonspecific mitogenic stimuli, targeting both naive and memory CD4 and CD8 T cells (Di Nicola et al., 2002; Krampera et al., 2003). Thus, MSCs regulate differentiation and development of different T-cell subsets, all of which could constitute a novel immune-regulatory function.

MSCs also regulate NK cells, a major effector cell of the innate immunity system (Trinchieri, 1989; Biron, 1997). Natural cytotoxicity receptors, NKp46, NKp30, and NKp44, are crucial for the cytotoxic activity and

cytokine production of NK cells. In particular, in NK cells cultured with MSCs, NKp44 activating receptor, which is absent in resting NK cells but expressed upon their activation, is not expressed (Spaggiari et al., 2008). Again, cytokine-induced proliferation of freshly isolated resting NK cells is highly susceptible to MSC-mediated inhibition (Spaggiari et al., 2006). MSCs inhibit the IL-2-induced proliferation of resting NK cells, expression of the activating receptors of NK cells, and secretion of interferon-γ of resting NK cells by approximately 80%. Therefore, MSCs are expected to regulate innate immunity by abrogating activation of resting NK cells.

As previously shown, MSCs educate macrophages to be polarized to a novel type of alternatively activated macrophages (Kim and Hematti, 2009) and stimulate macrophages to secrete IL-10 in an experimental sepsis model (Németh et al., 2009). Alternatively activated macrophages, commonly called M2 type macrophages, are characterized by increased expression of CD206, a high level of IL-10 and IL-6, and a low level of TNF-α. Several studies have shown that M2 macrophages can produce mediators essential in the resolution of inflammation, the promotion of tissue modeling, and the elimination of tissue debris, thus facilitating survival/proliferation of both resident and replacing cells, and consequently promoting wound repair (Savage et al., 2008; Martinez et al., 2009; Daley et al., 2010; Menzies et al., 2010). Thus, therapeutic MSCs may play dual roles in tissue repair by terminating devastating inflammation and creating a more receptive microenvironment for the survival of reparative MSCs in injured tissue (Fig. 4).

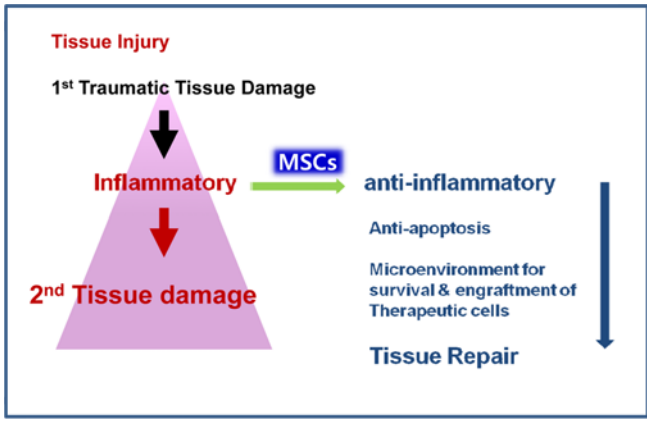

Fig. 4. Anti-inflammatory effect of MSCs in tissue repair. Traumatic tissue injury turns on a primary inflammatory response at the injury site, which in turn elicits much bigger inflammation-induced secondary tissue damage. If the inflammation period is sustained, wound healing is delayed and chronic inflammation may occur. If MSCs are delivered to the injured site at an early phase of inflammation, an anti-inflammatory environment may be created and further secondary tissue damage may be prevented. Under those anti-inflammatory conditions, apoptosis of host cells in the injured site may be prevented and cell debris and dead cells can be cleared by alternatively activated macrophages, which may be transformed by MSCs. Thus, therapeutic MSCs may play dual roles in tissue repair by terminating devastating inflammation and creating a more receptive microenvironment for the survival of reparative stem cells in injured tissue.

MSCs' HOMING TO TUMOR: PROS OR CONS

A tumor consists of malignant cells associated with a large variety of surrounding cells constituting the tumor stroma. Recently, it has become clear that tumor stroma plays an important role in cancer initiation, development, local invasion, and metastases (Li et al., 2007; Ahmed et al., 2008). During tumor development, tumor-associated stroma cells are recruited from locally derived host fibroblasts or from circulating MSCs (Roorda et al., 2009). As shown in the case of multiple myeloma, many MSCs derived from myeloma patients are significantly different from those from healthy donors, whose abnormalities range from differences in gene and protein expression to allelic abnormalities (Reagan and Ghobrial, 2011). Alterations in MSC function can be initiated by co-culture through a combination of cell-to-cell interactions and the secretion of chemo-attractant cytokines (Reagan and Ghobrial, 2011), which then contribute to tumor progression. In a variety of experimental tumor models, co-transplantation of MSCs supports tumor growth, survival, bone marrow colonization, metastasis, and evasion from the immune system (Djouad et al., 2003; Reagan and Ghobrial, 2011). Numerous studies showed that transfused MSCs preferentially home to the site of the tumor. In addition, MSCs, as expected from MSCs' inherent anti-inflammatory and immunosuppressive functions, may help tumor cells to escape host immune surveillance and nullify adoptive cancer immune-therapeutics. This circumstance in the tumor setting is definitively an unwanted effect of MSCs, which is outbalanced by MSCs' beneficial effects in tissue repair and control of abnormal immune response.

On the other hand, this could provide a rationale for MSCs to be strategically developed as a tumor targeting delivery vehicle. Several reports have proven the efficiency of MSCs as a carrier for *in vivo* delivery of various clinically relevant anticancer factors, including cytokines, interferon, pro-drugs or replicative adenoviruses, and monoclonal antibodies, which were shown by inhibition of tumor growth after engraft-

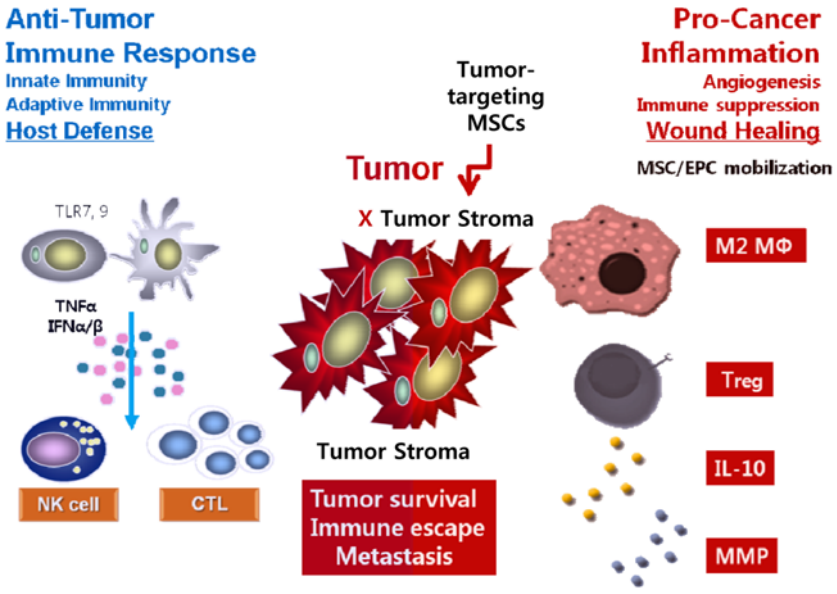

Fig. 5. Tumor-homing capacity of MSCs and development of a tumor-targeting vehicle. Transfused MSCs preferentially home to the tumor stroma, which creates supporting stroma for tumor growth and an immunosuppressive environment to escape host immune surveillance, which is one of the unwanted effects of MSCs. This could be strategically developed as a tumor-targeting delivery vehicle for anticancer therapeutics and suicide genes.

ment of tumor-targeting MSCs within or in the vicinity of tumors (Dwyer, 2010; Niess et al., 2011). This seems to work best in specific tumor types such as sarcoma and pancreatic and breast carcinoma. MSCs designed to carry tumor-specific killing activities, called "the Mesenkillers" may be proper to eradicate the specific tumor (Grisendi, 2011) (Fig. 5). However, it is too early to generalize this principle to all types of cancer therapy. But the remarkable tumor-homing capacity of MSCs may be taken advantage of in the future if other safety tools could be designed.

CONCLUSION

MSCs or MSC-like cells, even though their tissue origins are different, are quite similar in expression of molecular markers and biological functions. MSCs are expected as reparative stem cells for a variety of tissue injuries or disease by differentiating to many different types of resident tissue cells. More frequently, in clinical scenarios such as chronic inflammation, life threatening steroid refractory immune rejection, and autoimmune syndrome, MSCs' other novel function, an immune modulating effect, is adopted for the therapeutic rationale. However, in certain tumor settings, MSCs' immune modulatory function, in combination with their tumor homing preference, may provide a reason for their causing unwanted tumor progression. This tumor homing capacity of MSCs can be strategically utilized as a novel tumor-targeting anticancer therapeutic. In conclusion, recent progress in MSC therapeutics promises benefits for numerous uncontrolled diseases that cannot be met by conventional medication. Also their possible risk for the progression of tumors was uncovered. Therefore, MSC therapeutics can be advantageously developed as a specific tumor-targeting delivery vehicle.

ACKNOWLEDGEMENTS

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