Review Article

Mesenchymal Stem Cells and Cancer — for Better or for Worse?

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The importance of the microenvironment and stroma in the evolution and progression of solid tumors has re-emerged in the past few years. Recently, mesenchymal stem cells (MSCs), which are the progenitors of stromal cells and fibroblasts, have also been found to interact with cancer cells. Most commonly isolated from the bone marrow, MSCs are multipotent adult stem cells with immunomodulatory effects and the ability to home to sites of injury. These properties, clearly useful for therapeutic purposes, have recently been found to be abused by cancer cells for their own end. However, reports also show that MSCs can inhibit tumor growth under certain circumstances. This review briefly describes what is currently known about this emerging field of cancer-MSC biology, which is bringing new knowledge to an old disease and may hopefully reveal new ideas and targets for treatment.

Journal of Cancer Molecules 4(1): 5-9, 2008.

Keywords:

mesenchymal stem cells

cancer microenvironment

immunosuppression

cell therapy

Cancer continues to be a global problem of epidemic proportion [1]. Over the decades, tremendous efforts spent on studying the disease have revealed much in terms of the molecular and genetic alterations that the cancerous cell undergoes over time to allow for growth, invasion, and finally metastasis. Recently, the microenvironment surrounding the cancer cells has been receiving renewed interest, revisiting the "seed and soil" hypothesis of cancer first put forth by Paget in 1889 [2-5]. Solid tumors depend on a three-dimensional structure for their existence and growth, which is comprised of a complex mix of cell types and tissues, including endothelial cells, immune cells, stromal cells, and extracellular matrix (ECM[2])[2]. Importantly, these cancer-associated cells may not only be involved in the disease process itself, but also can be potential targets for therapy. The role of endothelial cells in tumor growth and metastasis is now well established, and research in angiogenic processes has yielded effective drug targets for treatment [6]. More recently, it has been shown that the surrounding stromal and inflammatory cells also play a critical role in angiogenesis and may on the contrary, protect the tumor from normal processes of eradication [2]. Thus, stromal cells and their associated matrix, as well as cells of the immune system, are now seen to be integral in carcinogenesis and metastasis.

While the initiating event often occurs in the cancer cell itself, the stroma has been called a "co-conspirator" in the subsequent evolution and progression of the disease. Injury to the stroma, such as exposure to tumor-promotor chemicals and irradiation, results in acquisition of a tumor-promoting phenotype [7,8]. There is also genetic evidence for a role of fibroblasts in cancer: in transgenic mouse studies, the deletion of fibroblast secreted protein-1 (FSP-1) leads to a phenotype that is less likely to form tumors or metastasis [9]. However, when the FSP-1$^{-/-}$ mice are injected with tumor cells which are admixed with wild-type fibroblasts, tumor development and metastasis are re-established. Moreover, enzymes known to participate in carcinogenesis and previously thought to be secreted by the cancer cells only, now have been shown to be produced by stromal elements as well. These proteins include matrix metalloproteinases (MMPs) which are involved in carcinogenesis, tumor progression/invasion, and possibly in recruitment of new vessels [10]. Furthermore, growth factors and cytokines such as vascular endothelial growth factor, transforming growth factor-β, and stromal cell derived factor-1 (SDF-1) also have prominent roles in stromal cell-related carcinogenesis and epithelial tumor progression, and exactly how these factors interact with each other is being actively studied [11-17].

In addition to mature stromal elements affecting carcinogenesis, attention has now turned to the progenitor cells of the stroma, the mesenchymal stem cells (MSCs). MSCs are adult stem cells which have received much press of late, since demonstration of clonal multipotency [18]. These cells are most commonly found in the mononuclear cell fraction of the bone marrow and isolated by their adherence to plastic tissue culture plates [19]. Increasingly, similar cells have been isolated from a number of other sources including lipoaspirate and many fetal tissues [20-26]. MSCs are able to form colonies of fibroblastic cells and express a varied repetoire of cell surface markers such as CD73/SH-3/SH-4 and endoglin/CD105/SH-2, but no hematopoietic markers of CD34, CD14, CD45, or CD117/c-kit [27]. Previously thought to act only as support for hematopoiesis within the bone marrow, MSCs are now known to possess potent differentiation capabilities, differentiating easily into mesodermal phenotypes of adipocytes, osteoblasts, chondrocytes, and

Received 4/6/08; Revised 4/9/08; Accepted 4/9/08.

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[2]**Abbreviations:** ECM, extracellular matrix; FSP-1, fibroblast secreted protein-1; MMPs, matrix metalloproteinases; SDF-1, stromal cell derived factor-1; MSCs, mesenchymal stem cells.

muscle cells, as well as some extra-mesodermal cell types including neural, pancreatic, and hepatocytic phenotypes (for review, see [28]). These properties of MSCs have generated much excitement, making them potentially useful for therapeutic applications. Moreover, recent findings of immunosuppressive effects in MSCs make these cells especially attractive in terms of allogeneic use, tremendously increasing prevalent use of MSCs beyond just the autologous setting [28,29]. Indeed, it has been proposed that MSCs may actually be "universal donor cells", not requiring immune matching, and perhaps even becoming "off the shelf" products [29]. In addition, MSCs have been shown to home to sites of inflammation and injury, making these cells ideal for cell therapy in a number of disease processes [30]. As a result of these findings, MSCs are currently being investigated in clinical trials for a wide spectrum of indications, ranging from cell replacement to immunotherapy [31,32].

It is known that under normal circumstances, transplanted MSCs will home to the bone marrow [33,34]. If there is injury, however, MSCs can preferentially mobilize to the sites of inflammation [35,36], as well as migrate across the endothelium, hypothesized in a manner similar to that of leukocyte trafficking [37]. Indeed, many of the adhesion and chemokine receptors on leukocytes involved in such processes can also be found on MSCs. MSCs have been reported to express a number of adhesion molecules, including integrins (CD29, α1 to α5, β1, β3, β4), CD44, CD54/ICAM-1, CD106/VCAM-1, and CD166/ALCAM [27]. It has recently been demonstrated that the integrin VLA-4/CD49d/α4 is involved in MSC adhesion to endothelial cells and transmigration [38]. Tissue inhibitor of metalloproteinase-1 (TIMP-1), on the other hand, appears to inhibit MSC migration [39]. In terms of chemokine receptor expression on MSCs, several have been found, with the most consistent finding being expression of CXCR4, the receptor for SDF-1 [34,40-44]. The picture of how various adhesion molecules and chemokines are involved in MSC migration is still very tentative, and awaits much more research for clarity.

The homing of MSCs to tumors was among the earliest phenomenon of MSC-cancer interactions to be reported. In an *in vivo* mouse model, injected human MSCs bearing GFP could be found preferentially migrating to implanted human melanoma tumors [45]. Subsequently, there have been more studies showing MSCs homing to tumors and even to sites of metastasis [46]. This property was rapidly exploited for therapeutic use as well as for tracking of the stem cells [47-51]. However, the interactions between MSCs and tumor cells are not limited to homing, but seem to include more adverse effects. Djouad *et al.* in 2003 found that co-transplantation of MSCs with melanoma cells in mice enhances tumor engraftment and growth, results which persisted even when the MSCs were transplanted at a site distant to the tumor cells [52]. Further research by the same team showed that the presence of MSCs allowed for earlier growth of tumor but had no effect on metastasis [53], whereas Karnoub *et al.* found that MSCs when admixed with tumor cells increased the metastatic potential of several breast cancer cell lines [54]. The most intriguing report so far comes from Houghton *et al.*, who showed that, under conditions of chronic inflammation, transplanted bone marrow cells – which the authors determined most likely to be MSCs – contributed to *Helicobacter pylori*-associated gastric cancer [55]. This study is in line with MSCs' ability to migrate to inflammatory cues, evoking the hypothesis of cancer as a non-healing wound [5,56].

The emerging picture on MSCs and cancer cell interaction appears to involve two inherent properties of these stem cells: their immunosuppressive effects and their ability to migrate. The immunosuppressive properties of MSCs are now well documented, with many studies focusing on the utility of these effects in terms of transplantation [28,30,32]. Bone marrow MSCs from humans, baboons, and mice have been shown to decrease the immune response of lymphocytes *in vitro* and *in vivo* [52,57-60]. The immunosuppressive properties are broad, effective whether the stimulation is specific or non-specific [57-60], across species [52,57,61], and across different populations of lymphocytes [52,57,61-64]. A number of mechanisms have been found to be responsible for these effects, such as secretion of anti-inflammatory molecules including cytokines (for summary, see [65]), prostaglandin E_2 [66], and indoleamine 2,3-dioxygenase [67,68]; modulation of dendritic cell development and function [63,66,69]; suppression of lymphocyte cytotoxic effector functions [70,71], and increasing the number of regulatory T cells [64,72], a population of immunosuppressive lymphocytes. MSC immunomodulation share many similarities to maternal-fetal tolerance [46]. Sadly, these mechanisms are eerily reminiscent of strategies employed by tumor cells to evade the immune system [73]. Thus, cancer cells are able to manipulate the body's own efficient tolerogenic mechanisms for their own end. The unanswered key question remains why MSCs are able to evade immune attack. One hypothesis is that MSCs are attracted to sites of injury to mediate "immunological homeostasis" – along with regulatory T cells and secretion of anti-inflammatory molecules – limiting excessive tissue damage [29]. It may be that cancer cells are able to harness MSCs' "good intentions" for their own end, in much the same way that they manipulate various aspects of the immune system. Much work is still needed to close the gaps in our knowledge on this aspect of MSC biology [65].

Unlike MSC immunomodulation, the underlying mechanisms in homing of MSCs to tumors and subsequent interactions are just beginning to be revealed. In one recent report, it was shown that secretion of SDF-1, a potent chemoattractant secreted by marrow stromal cells for hematopoietic stem cells, was increased when MSCs were exposed to the conditioned medium of cancer cells [74]. Using both *in vivo* and clinical data on breast cancer, two recent studies have found that MSCs migrate to tumor sites. Dwyer *et al.* showed that monocyte chemotactic protein-1 (MCP-1) secretion by breast cancer cells was responsible for the homing of MSCs to tumors, both locally and systemically [46]. On the other hand, Karnoub *et al.* found that although MSCs would home to tumors, it did not disseminate along with tumor cells to metastatic sites. Instead, it was the secretion of CCL5/RANTES by MSCs after physical contacted with cancer cells that was responsible for enhancing the metastatic potential of several breast cancer cell lines [54]. Irradiation of tumors, which releases inflammatory mediators, has also been shown to increase the engraftment of MSCs to the tumors [75]. As have been found with mature stromal elements, MSCs also appear to secrete a number of MMPs and ECM-degrading enzymes – specifically MMP-2, TIMP-2, and membrane type 1-MMP – which may explain the ability of these cells to pass through the basement membrane [39].

While most reports to date implicate MSCs with having tumor-promoting effects, there have been a few studies showing the opposite result. Khakoo *et al.* found that injection of MSC in a model of Kaposi's sarcoma actually inhibited tumor growth in a dose-dependent manner [76]. In fact, although Djouad *et al.* found that injected MSCs (10^3 ~ 10^5 cells with 10^4 tumor cells) allowed for earlier growth of tumors, low MSC numbers (10^2 MSCs with 10^4 tumor cells) unexpectedly induced rejection of the tumors [53]. The results in these two studies highlight the importance in the details of the experimental design. Cell numbers have been known to affect MSC immunomodulatory properties, which are lost when low doses of MSCs are used, resulting con-

Print ISSN 1816-0735; Online ISSN 1817-4256

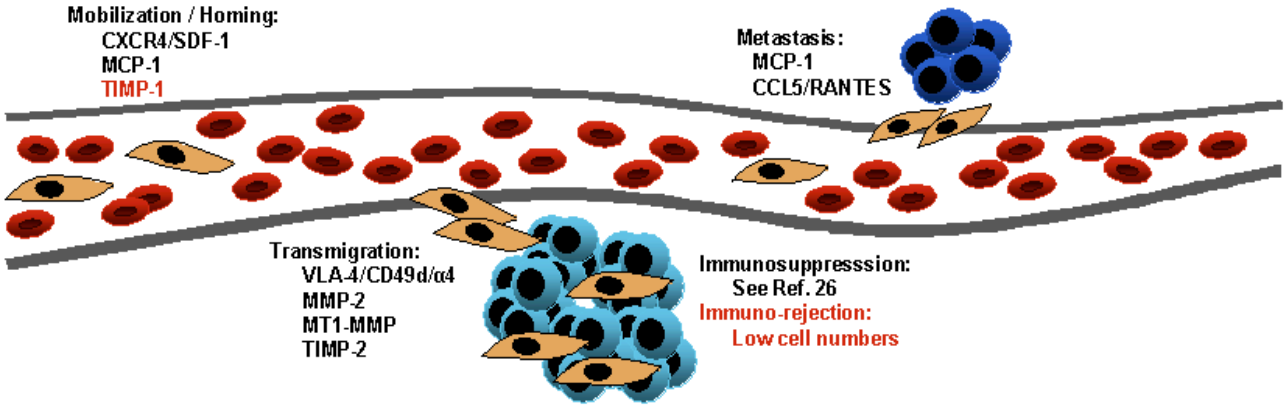

Figure 1: Mechanisms of MSC and cancer interactions (black, pro-tumorigenic; red, anti-tumorigenic). MSCs (brown cells) are able to migrate and home to tumors (light blue cells for primary site; dark blue cells for metastasis) where transmigration through endothelium and basement membrane may occur (gray lines). Immunomodulation and secretion of chemokines by MSCs may affect tumor engraftment and metastasis.

versely in increasing rather than decreasing lymphocyte proliferation [77]. Different results between reports may also be reflective of the lack of standardization in MSC cell culture techniques, including isolation methods and length of time in *in vitro* culture, all of which are known to introduce phenotypic variation [78].

The evidence for MSCs as active participants in cancer is just emerging (Figure 1), with more questions raised than answered. A critical issue is whether the current models used in the studies accurately reflect what is actually happening in the natural setting, since most *in vivo* experiments use high numbers of exogenously introduced MSCs, an unlikely scenario in the endogenous state. Moreover, since the reports have been limited to a few types of cancers, it is still unknown how MSCs interact with other cancers, if at all. Although extrapolations are often made to tumors in other organ systems, there is much evidence that cell-cell interactions and mechanisms are highly specific not only for a particular organ system, but even for a particular histological cancer type [10]. Nevertheless, new findings in this area have been significant and may yet result in paradigmatic shifts in our thinking of cancer formation and evolution. Much remains to be answered regarding the microenvironment of the tumor, and research into this area will not only add new scientific knowledge but should also bring forth new therapeutic ideas and targets in the continued fight against a devastating and lethal disease.

Acknowledgments

This work was funded in part by the NSC (Taiwan) grant 96-3111-B-400-001 (to B. L. Yen and M.-L. Yen) and the DOH (Taiwan) grant 97LCP008-3 (to B. L. Yen).

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