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Mesenchymal Stem Cells: How Can we Realize their Therapeutic Potential in Cancer Therapy?

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Abstract

Mesenchymal stem cells home to the tumour stroma from the bone marrow, influencing early tumour development and metastasis. Mesenchymal stem cells have been shown to be promising vehicles for cancer therapy due to this tropism for tumour sites, their immunoprivileged status, easy extraction from bone marrow and facile transfection. Mesenchymal stem cells have been used to deliver gene therapy in the form of cytokines or adenovirus and as part of prodrug strategies. However, in order for these agents to be tested in clinical trials, the biology of mesenchymal stem cells must be further investigated. At present there is variation between research groups surrounding mesenchymal stem cell isolation and characterisation methods, as well as in how the cells are delivered to *in vivo* models, making studies hard to compare. Research examining the attraction of mesenchymal stem cells to tumours has found that the cells home towards a wide range of growth factors, cytokines and proteases. Once part of the tumour stroma, mesenchymal stem cells may have both pro- and anti-tumorigenic effects, increasing tumour growth, angiogenesis and metastasis and decreasing immune activation in some systems, and in others, reducing tumour cell proliferation and development of metastases. Understanding more precisely which subsets of mesenchymal stem cells support or undermine the development of the tumour at various timepoints will enable an effective clinical trial strategy for mesenchymal stem cell-based cancer therapies to be developed and replicated with different cancers and treatment sites.

Keywords: Mesenchymal stem cell; Tumour associated fibroblast; Stroma; Proliferation; Metastasis; Targeted therapy; Cytokine; Protease; Growth factor

Abbreviations

MSC: Mesenchymal Stem Cell; PDGF: Platelet Derived Growth Factor; TIMP: Tissue Inhibitor of Matrix Metalloproteinases; MMP: Matrix Metalloproteinase

Introduction

The tumour stromal compartment is widely acknowledged as having an influential role both in the early development and late metastasis of a tumour [1]. Mesenchymal Stem Cells (MSCs) form part of the tumour stroma, homing to the tumour from the bone marrow [2]. In a GFP-positive bone marrow transplanted mouse model with syngeneic ID8 ovarian tumours, it was found that half the tumour stromal cells were derived from the bone marrow [3].

Studies of bone marrow-derived MSCs in the tumour have shown that these cells can influence tumour development [4] and hence manipulation of MSCs or use of MSCs as delivery vehicles are promising therapeutic strategies in cancer treatment. However, a number of issues, particularly concerning basic MSC biology and identification, remain to be addressed before MSC-based strategies can be expected to reach clinical trials.

Mesenchymal stem cell identification and isolation

MSCs are multi-potent, bone marrow-derived, non-haematopoietic cells which resemble fibroblasts in culture. The primary means of MSC identification in older studies was often simply the adherence of cells to plastic following several days in culture [5]. However, following guidance given by the International Society for Cellular Therapy proposal of 2006 [6], this definition was tightened, and MSCs are now commonly characterized in terms of their cell surface markers and the cell types to which they differentiate.

Classification of MSCs in these two ways forms an important part of their isolation procedure, whether they are extracted from bone marrow, blood, tumour or another source. The cell surface markers recommended by the International Society for Cellular Therapy include CD105, CD73 and CD90, as well as the lack of hematopoietic markers CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR [6]. However, confusion is still prevalent, since some research groups use only a selection of these markers, whereas other authors prefer to measure larger groups of proteins, or define subsets of mesenchymal stem cells using additional markers, such as Nestin, expressed in MSC-like cells which co-localise with and maintain haematopoietic stem cells in the bone marrow [7]. These variations in methodologies can make studies difficult to compare meaningfully.

In terms of differentiation, MSCs classically mature to become osteoblasts, chondrocytes and adipocytes, and the testing for differentiation to each of these is common during isolation of new batches of cells. MSCs have also been shown to differentiate to myocytes, pericytes or tumour associated fibroblasts *in vivo*,

depending upon the requirements of the site to which they are recruited [8,9].

MSC fate once absorbed into a tumour appears be quite varied, including formation of fibroblasts, pericytes, adipocytes and osteoblasts, as well as tumour associated fibroblasts, although no study as yet has defined the conditions under which each cell type might be found. Mouse model studies have concluded that anywhere between 20% and 90% of tumour associated fibroblasts are derived from MSCs [2,3,10-12], which may highlight tumour model-specific differences as well as varying definitions of the MSC. In a rare human-based study, activated fibroblasts with Y chromosomes were found in female allogenic bone marrow transplant patients with rectal and gastric neoplasia, who had earlier received bone marrow from male donors [13].

The role of MSCs in cancer development and progression

Overall, the presence of MSCs in the tumour stroma might be expected to promote or inhibit tumorigenic characteristics including growth, angiogenesis, metastasis and immune system evasion, resulting in enhanced or inhibited tumour progression. Techniques used to explore this issue range from co-culture or other *in vitro* strategies, to *in vivo* studies in animal models. Many *in vivo* studies use fluorescent imaging approaches, such as the mouse bone marrow transplant model, in which wild type mice are given a transplant of fluorescent bone marrow cells from, for example, a green fluorescent protein-expressing mouse. The movement of the fluorescent cells can be followed and cells can even be isolated from the tumour for further *in vitro* study [3].

A number of studies have concluded that MSCs contribute to pro-tumorigenic stromal function. MSCs were shown to increase initiation and growth rates of a variety of tumour types including gastric cancer [13], esophageal cancer [14] and MCF7/Ras breast cancer [4], generally through the secretion of anti-apoptotic and pro-proliferative cytokines, for example via production of CCL5 (RANTES) and interleukin-6 in breast cancer models ([4,15] and see Zimmerlin et al. [16] for a more complete list of cytokines). It is also possible that cytokines found to be produced by MSCs in non-cancerous situations, for example, in wound healing, hematopoiesis and arteriogenesis, might also be secreted in cancer [17-19].

MSCs have also been shown to promote late stage cancer progression, including enhancement of invasion, motility and metastasis of cancer cells *in vitro* and *in vivo*. An increase in metastatic characteristics was seen in MDA-MB-231 breast cancer cells in an orthotopic mouse model [20], esophageal cell lines TE-1 and Eca109 *in vitro* and *in vivo* [14] and A549 lung cancer cells [21].

Other pro-tumorigenic effects of MSCs in tumour stroma include promotion of angiogenesis via differentiation to mural cells or pericytes, or the secretion of vascular endothelial growth factor [22-24]. MSCs in the tumour stroma were also found to regulate immune system function, with an overall immunosuppressive effect. For example, MSCs inhibited the proliferation of leukocytes in solid tumours [25] and decreased proliferation of B cells and the activation of helper T cells [26,27].

A number of conflicting conclusions, in which MSCs in tumour stroma are shown to be anti-tumorigenic, have also been presented. For example, Kaposi sarcoma tumours in mice were growth inhibited by around two thirds via inactivation of Akt-mediated pathways in the presence of MSCs [28] and murine hepatoma and lymphoma cell line growth was reduced by up to 90% *in vitro* and *in vivo* [29]. Similar results were found using lung cancer cell line A549 and metastasis was also inhibited [30,31]. MSCs have also been shown to decrease breast cancer cell migration and invasion via production of the tissue inhibitors of matrix metalloproteinases TIMP-1 [32] and TIMP-2 [33].

From these results it is difficult to determine what the overall effect of the presence of MSCs in patient tumour stroma would be. It seems likely that the effect would be context dependent, varying depending on tumour types, other aspects of the microenvironment and the extent of tumour progression. The variation in experimental results seen may depend upon different isolation methods for the MSCs used, providing an example of the importance of standardization of these techniques. Assumptions made by most researchers regarding the older definition of MSCs as the plastic adherent cells, which also provides a very convenient means of cell collection, should also be questioned. A related set of experiments showed that isolation by plastic adherence results in a varied population including myeloid-like cells. Separation of the myeloid MSCs from the rest of the population, followed by co-implantation of each population into mice along with lung cancer cells demonstrated that only the population containing the myeloid-like cells promoted tumour growth and metastasis [3], calling into question the conclusions of some of the studies mentioned above which relied upon this method of MSC collection.

Other variations in experimental technique may also be important, for example, the effect of MSCs *in vivo* may be altered by the method of administration: in some cases, MSCs were co-injected with tumour cells and in other studies they were added at different timepoints via intraperitoneal or tail vein injection. Studies comprehensively comparing different isolation methods and other changes in protocol, including tumour type and the particular mixture of stromal cells may be required to pull this information together.

Another important issue that requires clarification is raised by a study that examines the role of MSCs in a non-solid tumour type. MSCs were shown to increase the adhesion of multiple myeloma cells to the bone marrow, promoting their proliferation and providing protection from chemotherapy [34]. The work highlighted the differences between MSCs from healthy donors and those from patients, a difference which could also be generated by co-culture of MSCs with cancerous cells [35]. Since most studies using freshly isolated mouse or human MSCs do extract them from healthy donors, serious consideration to this point should be given before attempting draw conclusions relating to cancer patients. Further research in this area, comparing MSCs from healthy donors and those with cancer, should be undertaken.

In summary, the cells that make up the tumour stroma provide the tumour with a complex balance of pro- and anti-tumorigenic signals. MSCs also appear to contribute to both tumour progression and inhibition, although the majority of current evidence is on the pro-tumorigenic side.

How are MSCs attracted to the tumour site?

It is hypothesised that MSCs would migrate towards a tumour since inflammatory signaling from the tumour resembles that of an unhealed wound [36]. Signaling resulting in MSC homing to tumours has been shown to be provided by growth factors, cytokines and proteases.

Growth factors such as insulin-like growth factor-1, epidermal growth factor, vascular endothelial growth factor and Platelet-Derived

Growth Factor (PDGF) have been described as having a role in MSC migration. These growth factors attract MSCs across a Boyden chamber membrane without further stimulus being required, can act synergistically with cytokines and have their pro-migratory effect blocked by antibodies or specific inhibitors [24,37-40]. In an intracranial mouse model of glioma, low PDGF-BB-expressing U87 cells attracted fewer MSCs and grew to a smaller size than high expressing clones [39].

Cytokines involved in MSC attraction towards tumours include interleukin-6 and -8, neurotrophin-3, transforming growth factor-β and stromal-cell derived factor-1 α, which were shown to be important in various cancer cell types including glioma, colorectal and breast cancers [13,38,41-44]. *In vivo*, inhibitors of stromal-cell derived factor-1α blocked MSC recruitment and tumour development in a mouse model of gastric cancer [13].

Proteases also play a role in allowing MSCs access to the tumour site, and can increase cell migration *in vitro*, acting as attractants in their own right, sometimes even without their protease activity. Most studies have focussed on the matrix metalloprotease enzymes, the MMPs. MMP-2 and membrane type 1 MMP have been shown to be important for the migration and invasion of MSCs alone [44-46], as well as MSC tropism towards medulloblastoma, breast and prostate tumours [47,48], whereas MMP-1 has a defining role in migration towards glioma [49] and inflammatory cytokines such as tumour growth factor-β, interleukin1-β, tumour necrosis factor-α or stromal cell derived factor-1α may have an indirect effect by up-regulating these enzymes [44].

The most likely scenario in a human patient is that a mixture of growth factors, cytokines and proteases is important in MSC homing to the tumour site. What exactly this mixture is and whether it varies between tumour types and even individuals remains to be discovered.

The promise of MSCs in cancer therapy

Testing of MSC-based approaches for cancer therapy has so far been concentrated on exploiting MSC tropism for tumour sites to deliver gene therapy, drugs or viruses to the tumour in a targeted way. No strategy has as yet progressed to clinical trial; instead studies report results obtained *in vitro* or in animal models.

For example, intravenous injection of interleukin-12 expressing MSCs completely eradicated tumour growth in B16 melanoma, 4T1 breast and Hca hepatoma tumours in mice. No toxicities were observed and an increased apoptotic index and reduction in lymphatic sprouting were also found [50]. In C26 colon and B16F10 melanoma mouse models, chemokine (C-X3-C-motif) ligand 1-expressing-MSCs reduced metastatic nodules and resulted in longer survival [51]. MSCs engineered to secrete interferon-β suppressed growth of breast, prostate, pancreatic and melanoma cancers in animal models [52-55], as did interleukin-12-expressing MSCs in renal cell cancer [56]. MSCs have also been transduced with interferon-γ [54], Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) [53,57-60] and soluble decoy receptors such as type-I insulin-like growth factor receptor [61].

There are a number of instances of MSCs used in prodrug strategies. For example, the expression of cytosine deaminase by MSCs converted 5-fluorocytosine to 5-fluorouracil in colon and melanoma cancers [62,63]. In another study, MSCs expressing rabbit carboxylesterase converted a camptothecin derivative to the active drug SN-38 in glioma [64]. MSCs have also been used as a vehicle for tumour-specific delivery of viruses, including a conditionally replicating adenovirus in an orthotopic renal cell carcinoma model. Tumour burden was reduced by 45% and large necrotic areas of tumour were present, which were lacking when the virus was not packaged in MSCs for delivery [40].

Other possible therapeutic approaches using MSCs, such as depletion of MSCs in the tumour and the blocking of MSC homing to tumours, are less well explored. Studies in pancreatic cancer have found that the proportion of MSCs in a tumour increases as time goes on [65,66], suggesting blocking the MSC homing process towards a tumour might alter the normal tumour progression. *In vivo* studies examining cytokine effect in MSC recruitment have shown that even a partial block of MSC recruitment can lead to a reduction in tumour size and metastasis [13,39]. In another study, using conditional knockout in a background of transgenic C57Bl/6 mice, Nestin-positive cells were depleted in bone marrow and the effect on the hematopoietic stem cell niche studied. This significantly changed the behaviour and location of the hematopoietic stem cells [7], an idea which may be able to be extended to solid tumours.

Advantages and possible problems with the use of MSCs in cancer therapy

MSC-based therapies hold many important advantages as potential cancer therapeutics. The cells are accessible and straightforwardly expandable *in vitro*, if we accept current isolation techniques. MSCs have been found to be easily genetically modified with little impact on their phenotype and there is a lack of immune rejection in the patient. A comprehensive body of animal model work has demonstrated that exogenously cultured and injected MSCs specifically home to and survive in tumour sites without being incorporated into normal tissue (see Droujinine et al. [67], for more examples). There have been as yet no clinical trials in cancer patients, but from the hundreds of human trials conducted in other diseases including ischemia, chronic obstructive pulmonary disease, Crohn's disease and graft-versus-host disease, no incidences of acute toxicity or malignant transformation have been reported [68,69]. However, safety databases summarising this data contain small numbers of patients and lack long-term follow-up [70] and so the problem cannot be considered to be resolved completely. It has been reported, for example, that patients who have received bone marrow transplants do have a higher incidence of solid tumours, however it is not known whether this caused by hematopoietic or mesenchymal stem cells or another aspect of the treatment [71]. MSCs intravenously injected into uninjured mice are cleared and undetectable in the mouse body after 7 days [72], lowering the risk of long-term effects. It is possible that this fast clearance would lower the therapeutic efficacy of MSCs, although this has not yet been tested.

Another potential pitfall is the development of clotting events following MSC infusion. MSCs are reported to express pro-coagulant molecules such as Tissue Factor and Collagen I in vesicles close to the cell surface, and this expression increases with passage number [73]. However, so far, thrombotic events following MSC therapy have not been reported in humans. Potential lethal micro-vascular plugging has been found to occur in animal experiments, which may need to be further investigated [74,75].

The heterogeneity of MSCs from patient to patient and from collection method to method may lead to contamination with cells of another lineage which may have different effects on a tumour from the

MSCs themselves, suggesting that a definitive set of markers for MSCs and refined purification procedure are urgently required. Studies characterising which populations of MSCs do actually home to tumours and comparing MSCs derived from tumours and from healthy patients would aid greatly in the possibilities of bringing MSC-based cancer therapies into the clinic. In other words, research which steps back and examines the basic biology of MSCs and their interaction with tumour sites is what is most required to be able to link the MSC-based therapeutic strategies which have been proposed with human trials.

Also to be considered are the potential regenerative effects on the tumour of a large influx of MSCs appearing at the cancer site, as would occur in cell-based cancer therapy. And since the role of MSCs in the bone marrow is immunosuppression, the effect on the immune system at the tumour site of an influx of MSCs should also be examined.

Maximising the potential of MSCs in cancer therapy: Summary

Manipulating the tumour stromal compartment or using its properties to deliver drugs in a targeted manner is a very promising strategy in cancer therapy. Stromal cells make up a greater volume of the tumour than the mutated cancer cells and do not themselves mutate to develop chemoresistance. Since MSCs originate outside the tumour, altering their behaviour, especially their homing patterns, may disrupt the protumorigenic stromal microenvironment and could be a powerful avenue for controlling tumour development and reducing tumour advancement, including metastasis. This would, however, require an increased understanding of MSC biology, right from the basic level of cell type definition, to overall homing mechanisms *in vivo* and influence on tumour behaviour in the complex microenvironment of the tumour, so that conclusions which could be generalised across tumour types could be drawn.

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