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Title: Advances in Mesenchymal Stem Cell (MSC) Mediated Gene Therapy for Cancer

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Abstract

Mesenchymal Stem Cells (MSCs) have a natural tropism for tumors and their metastases, and are also considered immunoprivileged. This remarkable combination of properties has formed the basis for many studies investigating their potential as tumour-specific delivery vehicles for suicide genes, oncolytic viruses and secreted therapeutic proteins. The aim of this review is to discuss the range of approaches that have been used to exploit the tumour-homing capacity of MSCs for gene delivery, and highlight advances required to realize the full potential of this promising approach.

Introduction

Despite significant advances in the field of gene therapy for cancer, two major obstacles remain which continue to limit the clinical potential of this approach: lack of tumour tropism of vectors, and stimulation of an immune response. These barriers preclude systemic administration of current vectors to efficiently target metastatic disease. The combination of cellular therapy and gene delivery is an attractive option as it will potentially protect the vector from immune surveillance, and support targeted delivery of a gene or therapeutic protein to the tumour site.

Mesenchymal Stem cells (MSCs)

Mesenchymal Stem Cells (MSCs) are non-haematopoietic stem cells that have generated a significant amount of interest in this context, as a result of their apparent ability to home to the tumour site following systemic delivery. MSCs have an inherent ability both to self-renew and differentiate into multiple lineages including osteoblasts, chondrocytes and adipocytes [1]. They are readily isolated from the stromal compartment of bone marrow, along with a number of other sources including adipose tissue, trabecular bone, and skeletal muscle [2]. Although a single marker for MSCs has not been isolated, a panel of specific antigens has been identified, including expression of CD105, CD73 and CD90 in greater than 95% of the culture, and absence of CD14, CD34, CD19, HLA-DR and CD45 [3]. When introduced systemically to healthy animals, MSCs have been shown to home preferentially to lung, liver and bone, and were found to a lesser extent in other tissues. However, upon injury, the migratory pathway changes to preferentially target sites of injury [4]. Although MSCs have potential uses in regenerative medicine and a number of different disease models, this review will specifically focus on their potential for

targeted gene delivery in the context of cancer. This is an exciting area of research that has gained considerable momentum in recent years, with studies reporting engineered MSCs specifically targeting multiple tumor types followed by local secretion of therapeutic proteins (IFN- β [5-7], IL-2 [8-9], IL-12 [10-12], PEDF [13], NK4 [14], TRAIL [15-18]), expression of prodrug activating suicide genes (HSV-tk [19-21], CD [22]), and delivery of replicating oncolytic viruses [16, 19, 23-25]. A major advantage of MSCs in this setting is that they are considered immunoprivileged, possibly due to low expression of Ag (HLA) MHC class 1, and no expression of CD40, CD80 & CD86 [4]. They are also known to secrete prostaglandin, TGF β and hepatocyte growth factor, which regulate the T cell immune response, thereby decreasing probability of a cytotoxic T cell response to transduced cells [17]. Resident MSCs suppress both transient and continuous immune surveillance, which aims at facilitating the healing process [26]. However, this immune privilege in the context of cancer has the potential to support tumour progression. Djouad et al [27] reported growth of B16 melanoma cells in allogenic animals only in the presence of MSCs, suggesting that protection from the host immune response supported tumour establishment [27]. Further studies by the same group revealed that MSCs administered in low numbers with Renca adenocarcinoma cells actually induced tumour rejection [28]. MSCs were also shown to inhibit outgrowth of colon carcinoma in rats, with complete inhibition seen when the number of MSCs were at least equal to the number of tumor cells. Tumour establishment using the mixed cell population was found to induce more infiltration of monocytes and granulocytes than the individual populations alone [29]. This may be explained by the fact that high numbers of MSCs have been shown to suppress alloreactive T cells, with very low numbers found to stimulate lymphocyte proliferation [30]. Indeed additional evidence suggests that the context with which MSCs are introduced in vivo may influence their immune phenotype [26].

Tumour Tropism

Tumour specific migration of MSCs is not completely understood, but appears to be dependant upon the biological properties of the tumour microenvironment, as well as the native tropism of selected cells. Integration of MSCs into the tumour stroma is thought to be mediated by high local concentrations of inflammatory chemokines and growth factors. The tumour microenvironment is considered a site of chronic

inflammation [31]. This environment may mediate MSC migration through secretion of soluble factors such as epidermal growth factor (EGF), vascular endothelial growth factor-A (VEGF-A), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), stromal-derived growth factor-1 α (SDF-1 α /CXCL12), IL-8, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), Ang1, monocyte chemoattractant protein-1 (MCP-1/CCL2), haematopoietic growth factor (HGF), transforming growth factor- β 1 (TGF- β 1) and urokinase-type plasminogen activator (uPA) [32-37].

The process of MSC mobilization to the tumour is thought to be regulated similarly to leukocyte migration through integrins and adhesion molecules [38]. Molecules involved in leukocyte trafficking, such as tethering, rolling, adhesion and transmigration from the bloodstream to the tissue are expressed on MSCs. These include integrins, selectins and chemokine receptors. Both P-selectin and VCAM-1 have been found to influence the adhesion of MSCs in endothelium [39].

MSCs express a wide range of molecules including growth factors, chemokines, adhesion molecules and toll-like receptors (TLRs) on their surface [38-44]. MSCs are known to functionally express chemokine receptors CCR1, CCR4, CCR7, CCR9, CCR10, CXCR4, CXCR5, CXCR6, CX3CR1, and c-met, which has been increasingly linked to tumour tropism [40-43]. The mechanism of MSC migration is however still not fully elucidated.

The most documented chemokine receptor implicated in targeted homing of MSCs is CXCR4, which has potential in cell mobilization and homing [45]. A study by Wynn et al, reported that CXCR4 is highly expressed on MSCs, however mainly intracellularly (83-98 %) rather than on the surface [46]. Another study reported no detectable CXCR4 expression on MSCs [42]. It has been suggested that variable expression of CXCR4 on MSCs in different studies may be related to sensitivity of the trypsin digestion procedure used [44], differences in culture conditions, and heterogeneity of MSC populations. In vitro 3D culture of MSCs as spheroids was shown to increase SDF-1 α signaling, which restored functional expression of its receptor CXCR4 and homing potential that is crucial for therapeutic applications [47]. Although the tumour tropism of MSCs is generally accepted, it is certainly dependent on the tumour model. Variation in levels of MSC engraftment reported in different studies may be explained by differences in MSC isolation, culture conditions, and

experimental protocols used. However, within individual studies, variable levels of MSC engraftment have been reported in different tumour types, most likely due to differences in the microenvironment created by the tumour in question [48]. The proportion of MSCs engrafted was not found to be related to tumour size [48].

A recent study further highlighted the role that the degree of inflammation in a tumour microenvironment plays in the level of MSC recruitment [7]. In a study of MSC-IFN- β mediated therapy of pancreatic cancer, treatment with an anti-inflammatory agent resulted in reduction of MSC engraftment in the tumour, and reversed the tumour inhibitory effects observed [7].

Enhancing Tumour Tropism of MSCs

- **Modification of Tumour microenvironment**

The apparent role of inflammation in MSC-tumour tropism has also been harnessed to increase engraftment through tumour irradiation, which is associated with release of several cytokines from exposed tissue [48-49]. Klopp et al [49] found that low dose irradiation of the tumour microenvironment enhanced MSC tropism and engraftment at the tumour site. Irradiation resulted in apoptosis and increased release of inflammatory signals at the site of radiation, including tumour necrosis factor- α (TNF- α), platelet-derived growth factor (PDGF), as well as chemokines CCL2 and CCR8 [49]. The effect of tumour radiotherapy on localisation of lentivirus-transduced MSCs in a variety of tumour types has also been reported [48]. Irradiation increased MSC localisation in LoVo, HT-29 (colon), MDA-231 (breast), but not UMSSC1 (head and neck) xenografts. This study also reported a modest elevation in CCL2 expression in irradiated tumours, although it was not found to correlate with MSC infiltration [48]. Inflammation plays a critical role in tumour progression [50] and so stimulation to support MSC homing to tumours would not be a viable option. However, radiotherapy is frequently a component of cancer therapy and so could work in combination with MSC based gene delivery to support improved targeting of MSCs to tumours.

- **Modification of MSC surface**

While variations in MSC engraftment have been observed in different tumour models, attempts are being made to improve tumour tropism and infiltration through

modification of the MSC surface. Cell rolling is a critical step of the adhesion cascade supporting rapid deceleration of cells from the blood stream, and is mediated by selectins expressed on the endothelium of the target organ. Immobilized Sialyl Lewis X (SLeX) on MSCs was shown to induce cell rolling on P selectin surface under dynamic shear flow conditions *in vitro*, and may have potential applications in improving MSC engraftment *in vivo* [51]. In one study, where native MSC tropism for the tumour of interest was not detected, MSCs were engineered to overexpress the Epidermal Growth Factor Receptor (EGFR) which binds TGF- α and EGF. Transduced MSCs had enhanced migratory properties towards GL261 gliomas or B16 melanoma *in vivo* [52]. Following establishment of improved engraftment, the cells were further engineered to secrete IFN- γ , resulting in increased animal survival [52].

MSC-mediated Virus Delivery

A significant advantage of MSCs as cellular vehicles is their accessibility for genetic manipulation *in vitro*. Recent studies have incorporated the use of lentivirus [13, 16, 48, 53] retrovirus [10, 19-20, 22], or plasmid [21] mediated transduction, however the majority remain Adenovirus based [5-8, 11, 14-15, 17-18, 23-25, 54-55]. MSCs have a low coxsackie and adenovirus receptor (CAR), high integrin phenotype, which results in low transfection efficiency using wild-type adenoviruses. Modification of the adenovirus fiber or knob domain has been used to improve adenovirus mediated transgene expression. Incorporation of an arginine-glycine-aspartate (RGD) motif into the adenovirus fiber, or 5/3 knob domain of human adenovirus serotype 3 supports CAR independent transfer and improves MSC transduction efficiency [14, 23-25, 55]. This has evolved to include the use of conditionally replicating adenoviruses, which support delivery of an increased viral load specifically to the tumour site [23-25]. Clearly the timing is important here to avoid toxicity to MSCs prior to engraftment at the target site. The cycle of MSC adenovirus replication has been reported to have relatively slow kinetics which may allow time for MSCs to reach the target site before replication causes cell death [56]. The delivery of oncolytic viruses does not rely on long term survival and proliferation of cellular vehicles, as they are destroyed by viral replication. Capsid modified oncolytic adenoviruses have been coupled with the use of transcription specific promoters to limit ectopic viral amplification in non-target cells [55]. MSCs have also been engineered to express the Herpes Simplex Virus-

thymidine kinase (HSV-tk) followed by administration of the prodrug ganciclovir (GCV) for targeted cancer suicide gene therapy [19-21]. Based on similar principles, retrovirus transduction of adipose derived MSCs to express cytosine deaminase (CD), followed by systemic administration of the prodrug 5-fluorocysteine (5-FC), mediated a strong antitumour effect in vivo [22].

Localized Delivery of Therapeutic Proteins

Along with their tumour tropism, MSCs have been shown to integrate into and persist in the tumour stroma [5]. This has supported their use as delivery vehicles for various biological agents, whose systemic administration is precluded due to their short half-life and toxicity at the doses required for therapy. MSCs can efficiently produce biological products at tumour sites and so have the potential to improve pharmacokinetics of secreted agents [5].

In a number of tumour models, MSCs expressing IFN- β have been shown to result in decreased tumour burden and increased animal survival [5-7]. Increased systemic levels of IFN- β , or secretion at sites distant from the tumour were not effective, indicating that regional secretion was required [5-7]. MSCs engineered to secrete IL-12 and embedded in a matrix adjacent to tumours were also reported to have a significant therapeutic effect [10]. Similar to findings in the case of IFN- β , regional secretion was required, with no reduction in growth observed when the implant was placed in the opposite flank to the tumour [10].

MSCs expressing the HGF antagonist, NK4 in vivo, were also found to prolong animal survival by inhibiting tumour associated angiogenesis, lymphoangiogenesis and induction of cancer cell apoptosis [14]. Local secretion of pigment epithelium-derived factor (PEDF) in a model of hepatocellular carcinoma (HCC) through lentivirus transduction of MSCs similarly resulted in lower tumour volume, reduced lung metastases and improved survival through inhibition of tumour angiogenesis [13].

Further, MSCs secreting IL-2 [8-9] or IL-12 [10-11] were shown to elicit an immunological reaction, and stimulate inflammatory cell infiltration of the tumour tissue. The observed anticancer effect was shown to be immune mediated and absent in immunodeficient animals [10]. Delivery of MSC-IL-12 did not cause systemic toxicity and resulted in increased serum and tumour levels of IL-12. In contrast, administration of Ad-IL-12 only increased serum IL-12 levels and induced systemic

toxicity [11]. Therefore it appears that MSC mediated local delivery of a therapeutic agent may be better tolerated by the host without inducing an unacceptable immune response [11].

Tumour necrosis factor related apoptosis inducing ligand (TRAIL) induces caspase mediated apoptosis in tumour cells that overexpress the receptor. MSCs, like most healthy tissues, are resistant to TRAIL induced apoptosis due to very low levels of active receptors [17]. As a result of this, MSCs secreting TRAIL have been used in models of lung, breast, cervical and brain cancer in vivo, resulting in significant anti-tumour effects [15-18, 53]. In one study using a lentiviral vector, TRAIL expression was placed under the control of a *tet* promoter, supporting conditional activation using doxycycline [16]. In an animal model of lung metastases of breast cancer, this controlled, local delivery of TRAIL completely cleared metastatic disease in a selection of animals [16]. Interestingly, when MSC-TRAIL cells were coinjected with tumour cells for subcutaneous tumour formation, only doxycycline mediated activation on the day of tumour cell inoculation (D0) caused a significant decrease in tumour weight. Activation following tumour establishment (D25) did not result in a change in tumour burden [16].

Potential role in Tumourigenesis

Although beyond the scope of the current review, the potential role of MSCs in tumour initiation or promotion is a significant concern that must be addressed fully to allow MSC mediated therapy for cancer to realize its full potential. This remains a topic of continued debate. Expansion of MSCs in vitro will be required for therapeutic application and so their stability in culture is paramount. Spontaneous transformation of human MSCs has been reported following long term passage in vitro [57] [58], while Bernardo et al [59] found no evidence of hMSC transformation. Indeed the majority of studies have shown that human MSCs are stable, while murine MSCs are more prone to genetic transformation during in vitro culture, and may be capable of forming sarcomas in vivo [59-63]. Although transformation of human MSCs appears unlikely, and very rare, these studies certainly emphasise the importance of stringent monitoring of MSCs, including karyotyping, before application in the clinical setting. MSCs have also been implicated as tumor supportive when co-injected in the presence of a variety of tumour cell types, including breast [64-67], ovarian [68], melanoma [27], glioma [69-70] and colon [71-72]. However, the majority of these

studies used an equal or even excess number of MSCs over tumour cells. The data generated provides important information on interactions between MSCs and tumour cells, although the models are unlikely to reflect the *in vivo* situation. MSCs were shown to integrate into the tumour stroma and demonstrated to exert their effects at least partly through secretion of paracrine factors including CCL5, IL-6 and SDF-1 α [64-65, 68]. There is also evidence that MSCs may serve as precursors for carcinoma associated fibroblasts and/or pericytes, playing a potentially important role in tumour angiogenesis through differentiation and the release of proangiogenic factors [67-69, 71-76]. Additionally, as previously mentioned, the immunosuppressive qualities of MSCs may support tumour development and progression through protection of cancer cells from immune surveillance [27].

Conversely, co-injection of MSCs has also been shown to result in tumour suppression in a model of colon cancer [29], hepatoma [77], and melanoma [78].

In terms of MSC-mediated gene delivery, understanding the role of MSCs following engraftment at the site of a pre-established tumour is required. The majority of studies outlined here, using MSCs engineered to deliver therapeutic agents, have resulted in significant anti-tumour effects *in vivo*. Unmodified MSCs were also shown to result in tumour suppression in some cases [7-8, 79], with the majority showing no effect on tumour progression following engraftment at the site of an established tumour [13, 18, 23, 53, 55, 69, 75]. However, repeat IV administration of MSCs over three weeks was shown to stimulate increased tumour growth in a model of pancreatic cancer [21]. Similar to the level of MSC engraftment in tumors, it seems that the effect of MSCs following engraftment will be tumour specific, probably dependant on a range of factors including the method of MSC isolation and culture, the experimental model, the number of cells engrafted in the tumour, and the milieu of growth factors and inflammatory cytokines present within the tumour microenvironment.

Conclusion

The studies outlined highlight very promising potential for MSC-mediated delivery of therapeutic agents directly to tumour tissue, with remarkable progress made in the past decade. Clearly MSCs have a number of advantages as cellular vehicles- they are relatively easy to isolate and expand, specifically target tumours and their metastases following systemic delivery, can be transduced efficiently with a range of vectors,

have immunosuppressive properties, the ability to express therapeutic proteins in secretory form, and can support amplification of oncolytic viruses. However, the potential for MSC-mediated tumour promotion must be addressed. Further understanding the biology of MSCs, and the specific combination of factors controlling their tumour-specific migration and persistence will support translation to the clinical setting.

Abbreviations

MSC = Mesenchymal Stem Cells; EGF = epidermal growth factor; VEGF = vascular endothelial growth factor ; FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; SDF-1 α /CXCL12 = stromal-derived growth factor-1 α ; IL = interleukin; GM-CSF = granulocyte-macrophage colony-stimulating factor; MCP-1/CCL2 = monocyte chemoattractant protein-1; HGF = hepatocyte growth factor; TGF = transforming growth factor; uPA = urokinase-type plasminogen activator VCAM = vascular cell adhesion molecule-1; SleX = Sialyl Lewis X; CAR = coxsackie and adenovirus receptor; HSV-tk = Herpes Simplex Virus-thymidine kinase; GCV = ganciclovir; CD = cytosine deaminase; 5-FC = 5-fluorocysteine; PEDF = pigment epithelium-derived factor; TRAIL = Tumour necrosis factor related apoptosis inducing ligand; IFN = interferon; MHC = major histocompatibility complex;

Competing interests

The authors declare that they have no competing interests.

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