Mesenchymal stem cells as delivery vectors for anti-tumor therapy

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Abstract: Recent studies have demonstrated mesenchymal stem cells (MSCs) are able to migrate specifically to tumors and their metastatic sites when administered intravenously. This characteristic tumor tropism has opened up an emerging field to utilize MSCs as vectors to deliver anti-cancer agents for targeted therapies. Genetically engineered MSCs can specifically migrate to various tumors and locally secrete therapeutic proteins, such as interferon β (IFN-β) and IFN-γ, interleukin 12 and 24, tumor necrosis factor-related apoptosis inducing ligand (TRAIL) or suicide gene/enzyme prodrug. In addition, MSCs have also been engineered to deliver oncolytic viruses and drug-loaded nanoparticles. Here, we present the characteristics of MSCs, the current progress on MSC mediated anti-cancer agents delivery systems and the interaction between MSCs and tumors.

Keywords: Mesenchymal stem cell (MSC); delivery vector; cancer therapy

Introduction

Cancer remains a major public health problem worldwide and it is one of the leading causes of mortality and morbidity (1). The principal approaches of cancer therapy include surgical treatment, chemotherapy and radiotherapy. However, despite improvements in therapeutic methods, many tumors remain to have poor prognosis after traditional therapy, due to relapse and metastasis. Biological therapy has been noted as a novel strategy to various tumor diseases, especially for the relapsed patients. One of the major challenges of cancer biological therapy lies in the inefficient delivery of therapeutic agents to the tumor sites due the relapsed or metastatic tumors are often smaller and directly inaccessible. It has recently been shown that mesenchymal stem cells (MSCs) are able to migrate specifically to and integrate into tumor stroma and track microscopic metastasis when administered by intravenous in vivo (2,3), and this property can be used to deliver anti-cancer agents for tumor treatment. However, the interaction between tumors and MSCs remains controversial. This review focuses on the application of MSCs for targeted delivery of anti-cancer agents to tumors, and on the interaction between tumors and MSCs.

Sources and characteristics of MSCs

Human MSCs are a rare stromal cell population that resides primarily in adult bone marrow (BM), and considered as non-hematopoietic multipotent stem-like cells that have self-renewing potential, capable of differentiating into lineages of mesenchymal or non-mesenchymal tissues, including osteoblasts, chondrocytes, adipocytes, myocytes, tendon and neuronal cells, etc. (4,5). Since Pittenger et al. demonstrated the successful isolation of multipotent MSCs from human BM, it has become the principal source to obtain MSCs (4). However, only a small percentage of the total number of BM populating cells is MSCs (0.01-0.001% of mononuclear cells isolated by ficoll density gradient); moreover, the invasive isolation procedure and the decline in MSC characteristics with donor’s age also restrict its clinical application (6). In addition, adipose tissue has...
recently proven to serve as an alternative source of MSCs. Although it’s abundant in nature, an invasion isolation procedure is still required to collect the tissue (7). MSCs obtained from the Wharton’s Jelly (WJ) of umbilical cords (UC), UC blood or placenta have gained much attention over the last years since they can be easily isolated, without any ethical concerns, from tissues which are discarded after birth (8). Moreover, those extra-embryonic tissue-derived MSCs have little or low immunogenicity due to the lack of expression of co-stimulatory molecules, possess a broader multipotent plasticity and proliferate faster than adult MSCs (9). Accumulating evidences demonstrate that extra-embryonic tissue-derived MSCs are an attractive stem cell source for clinical applications (10-12).

There are no specific cell markers that can be used to categorically define human MSCs, and current characterization based on combination criteria of adherence to plastic, expression of CD73, CD90 and CD105 but lack of haematopoietic cell markers such as CD34, CD45, CD19, CD11b, HLA-DR on the cell surface and multi-differentiation potential into osteoblasts, adipocytes and chondroblasts in vitro (13). Moreover, MSCs can be easily engineered with viral vectors and provide long-term gene expression without affecting their MSC phenotype (14,15). Interestingly, MSCs have the ability to accumulate at the site of damaged tissue, inflammatory and cancer sites when administered intravenously in vivo (15-17). Hence, these characteristics make MSCs to be used for regenerative therapy and as cellular vehicles for the delivery of anti-cancer agents specifically to tumors. This targeted therapy can facilitate the anti-cancer agents to accumulate at local tumor sites and reach effective concentrations, especially in favor of the deep-seated solid tumors and the micro-metastatic tumors that are not often accessible directly.

**MSCs as delivery vectors for cancer therapy**

More and more investigators have explored MSCs in delivering anti-cancer agents due to its ability of tumor tropism. The anti-cancer agents carried by MSCs mainly include retroviral or adenoviral vectors expressing tumor-suppressed gene, oncolytic viruses and drug-loaded polymeric nanoparticles (Table 1).

**Viral vectors engineered MSCs**

Human MSCs have been engineered to provide targeted delivery of anti-cancer agents by adenovirus or retrovirus transduction. The earliest application of MSCs to targeted cancer therapy was direct delivery of interferon β (IFN-β) gene (18). MSCs were transduced with an adenoviral vector carrying the IFN-β gene, followed by i.v. injection into melanoma xenografts mice. The results showed that treatment with IFN-β-MSCs significantly reduced tumor growth and prolonged survival of tumor-bearing mice (18). Based on this discovery, more researchers have since studied the therapeutic efficacy of genetically modified MSCs from various tissues and their ability to act as cellular vehicles. In addition to IFN-β gene (19,20), other tumor-suppressed genes including IFN-γ (21,22), IL-12 (23,24), IL-24 (25) (Table 1).

### Table 1  Anticancer agents utilized to genetically modified mesenchymal stem cells (MSCs)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Agents</th>
<th>Models</th>
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<tbody>
<tr>
<td>Viral vectors</td>
<td>IFN-β</td>
<td>Metastasis (melanoma)</td>
<td>(18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orthotopic (glioma, ovarian)</td>
<td>(19,20)</td>
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<td></td>
<td>IFN-γ</td>
<td>Subcutaneous (lung)</td>
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<td>In vitro (leukemia)</td>
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<td></td>
<td>IL12</td>
<td>Orthotopic (ovarian)</td>
<td>(23)</td>
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<tr>
<td></td>
<td></td>
<td>Subcutaneous (melanoma, breast, hepatoma)</td>
<td>(24)</td>
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<td></td>
<td>IL24</td>
<td>Subcutaneous (lung)</td>
<td>(25)</td>
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<td></td>
<td>TRAIL</td>
<td>Orthotopic (hepatocarcinoma, glioma)</td>
<td>(26,27)</td>
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<td></td>
<td></td>
<td>Subcutaneous (lymphoma)</td>
<td>(28)</td>
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<td></td>
<td>HSV/TK</td>
<td>Orthotopic (glioma)</td>
<td>(30)</td>
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<td></td>
<td>CD</td>
<td>Subcutaneous (melanoma, colon)</td>
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<tr>
<td>Oncolytic virus</td>
<td>CRAd</td>
<td>Orthotopic (glioma, breast)</td>
<td>(33,34)</td>
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<td></td>
<td></td>
<td>Metastasis (breast)</td>
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<td></td>
<td>Paclitaxel</td>
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<td>(38)</td>
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and tumor necrosis factor-related apoptosis inducing ligand (TRAIL) (26-29) have been utilized to engineer MSCs, and could be produced locally in the tumor microenvironment to treat a wide range of cancers by inhibiting tumor cells growth or inducing apoptosis, as described in Table 1.

MSCs have also been used to serve as vehicles for suicide gene/enzyme prodrug systems, which can convert non-toxic prodrug into toxic anti-metabolites and kill tumor cells selectively. Uchibori et al. discovered that injection of MSCs producing herpes simplex virus thymidine kinase (HSV-TK) retroviral vectors in the proximity of tumors with administration of prodrug GCV suppressed tumor growth through bystander-mediated tumor cell killing in vitro and in vivo (30). In other two different studies, MSCs expressed cytosine deaminase (CD) treatment resulted in therapeutic cell homing into tumor sites and mediated melanoma (31) and colon cancer (32) growth inhibition. Nevertheless, these approaches are limited by the toxicity to the MSCs.

**Oncolytic viruses loaded MSCs**

In addition to the delivery of tumor-suppressed genes, MSCs have been employed as carriers and amplifiers to deliver oncolytic viruses to tumor sites, leading to destroy of tumor cells by viral replication and spread surrounding tumor tissues. At present, the therapeutic efficacy of MSCs engineered by conditionally replicative adenovirus (CRAd) and oncolytic measles virus (MV) has been evaluated in experimental and clinical trials. This targeted therapy has been shown to improve survival and suppress metastasis in a human glioma model (33), melanoma and breast cancer model (34), and a lung metastasis model (3) using oncolytic CRAd. Besides, attenuated MV-infected MSCs cell delivery system could also inhibit liver cancer growth (35), and prolong survival of animals bearing ovarian cancer (36), eluding the presence of immunity against MV in vivo.

**Drug-loaded nanoparticles engineered MSCs**

Recently, Li et al. have demonstrated that silica nanorattle-doxorubicin anchored MSCs could be capable of accumulating in tumors and slowly releasing the drug with high cell viability. The increased and prolonged doxorubicin intratumoral distribution further contributed to significantly enhanced tumor cell apoptosis in human glioma xenografts (37). Similarly, MSCs loaded with paclitaxel containing nanoparticles have showed active tumor-tropism and released paclitaxel at tumor site locally in a mouse orthotopic lung tumor model (38). This strategy has the potential to be developed as a targeted tumor therapy with high efficiency and low systematic toxicity. The therapeutic benefit of this strategy should be further examined in orthotopic and metastatic tumor models.

**Interaction between cancer and MSCs**

The ability of MSCs to accumulate at tumor sites makes them extremely attractive for directed cancer therapy. However, MSCs are not simple inert vectors, the possible direct effect of MSCs on tumor growth should not be neglected. At present, no consensus exists on the effects of MSCs may have on the host. For example, Qiao’s study proved that MSCs inhibit growth of breast cancer cells via depression of Wnt signaling (39), while Karnoub suggested the MSCs promote tumor development in a subcutaneous breast tumor model (40). Additionally, no positive or negative effect of MSCs was revealed in a glioblastoma model (26) and in a Non-Hodgkin’s lymphoma (28). The diverse effects of MSCs on tumor growth among these studies might be due to the different source of MSCs, the different animal models, and the route of MSCs administration.

Furthermore, it is known that MSCs have profound immunosuppressive effects. Ling et al. demonstrated that MSCs could create an immunosuppressive microenvironment and thus promote tumor growth using humanize murine MSCs by incorporating the human IDO gene into MSCs derived from mice lacking the Nos2 gene (iNOS−/−) (41). This strategy has got rid of species variation and represents the immune state in human closely. However, immunologic deficiency mice were employed in the general studies about MSCs used in cancer therapy, which cannot reflect immunosuppressive effect of MSCs on the tumor. Besides, MSCs could enhance tumor growth by some other mechanisms, such as the VEGF pathway (42), and chemokine CCL5 secretion (40).

As clinical applications of MSCs develop further, the assessment of the long-term fate of therapeutic MSCs is critical, and we should seek to develop a system allowing control over the growth and survival of MSCs post tumor treatment. In the oncolytic viruses-loaded MSCs delivery strategy, oncolytic viruses replicated in MSCs and destroyed them eventually and eliminate the tumor promotion effects (3,33-36). Martinez-Quintanilla et al. have developed an efficient stem cell based therapeutic strategy that MSCs engineered to co-express HSV-TK and s-TRAIL,
simultaneously allowed killing of glioblastoma multiforme cells and assessment and eradication of MSCs post treatment (43). Moreover, Ramos et al. have also described a suicide system based on an inducible caspase-9 (iCasp9) protein to eliminate MSCs used in therapy (44).

Conclusions

MSCs are emerging as effective vectors for targeted anticancer treatment. As this promising therapy is to be translated into clinical application, there are many basic questions to be resolved, such as the optimal timing of delivery, the number of cells injected, and the effect of MSCs on tumors. So, more studies about MSCs as vectors for anti-cancer therapy are urgently needed to push this strategy to the clinic.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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