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SHORT COMMUNICATION

Mesenchymal stem cell: a new horizon in cancer gene therapy

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Cancer is one of the main problems in public health worldwide. Despite rapid advances in the diagnosis and treatment of cancer, the efficacy of current treatment strategies is still limited. There are promising new results in animal models whereby mesenchymal stem cells (MSCs) can be used as vehicles for targeted therapies. The use of MSCs as therapeutic biological vehicles in cell therapy has several advantages, including immune-silence, tumor tropism, easy and rapid isolation, *ex vivo* expansion, multilineage differentiation and the capacity to deliver a number of therapeutic agents. Some studies have shown that the microenvironment of the tumor provides a preferential niche for homing and survival of MSCs. Here, we have highlighted various applications of MSCs in cancer gene therapy.

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MESENCHYMAL STEM CELLS AND CANCER

Mesenchymal stem cells (MSCs) are a class of bone marrow-derived stem cells that can differentiate into osteoblasts, chondrocytes and adipocytes *in vitro*.[1,2] Contrary to bone marrow-derived stem cells, MSCs might be used in cell therapy without the morbidity and death associated with bone marrow transplantation.[1] The International Society for Cellular Therapies has proposed a standardized phenotype for MSCs. Typical human MSCs (hMSCs) express CD105, CD90 and CD73 but not CD79a, CD45, CD34, CD19, CD14, CD11b and HLA-DR on its surface.[1] Most hMSCs or hMSC-like adult progenitors differentiate to mesoderm derivatives like fat, bone and cartilage.[1,3] Immune cells migrate into inflammatory sites, hematopoietic stem cells and metastatic tumor cells.[1,3] The mechanisms responsible for MSC migration have been extensively explored, and the key role of adhesion molecules and receptors as well as that of activated endothelial cells in facilitating such a targeted movement has been highlighted. It has been observed that MSCs can migrate specifically to primary and metastatic tumor sites everywhere in the body.[1] The tumor-migrating capacity of MSCs has prompted efforts to manipulate these cells in order to overexpress antitumor molecules to be used as a potential tumor-targeted treatment strategy.[1,4] MSCs are recognized to extravasate like leukocytes, after interaction with adhesion molecules and integrins.[2] They express very late antigen 4, which binds to its counterpart adhesion molecule vascular cell adhesion molecule-1 on the endothelium.[2,4] MSCs express many types of chemokine and cytokine receptors on their cell surface and respond to different ligands *in vitro*.[5] The most probable mechanism for migration is the response to chemotactic mediators secreted from cancerous sites.[1,5] It is well documented that tumors produce a large variety of chemokines and cytokines that could serve as ligands for the MSC receptors, thereby mediating the migration of MSCs toward cancerous sites.[1,5] The homing ability of MSCs could be employed for the delivery of pro-apoptotic factors to the tumor microenvironment. On the other hand, there are some studies revealing the immunosuppressive properties of MSCs, their potential to induce cancerous transformation and their capability to enhance tumor growth and metastasis in some experimental models. This necessitates the evaluation of potential adverse side effects through clinical trials before therapeutic use in humans.[4,5] MSCs are dynamic vehicles and could exert both pro-apoptotic and pro-survival effects on tumors. Their pro-apoptotic properties encompass blocking of Akt and NF-κB signaling.[5] MSCs stimulate apoptosis in several malignancies. They also exert pro-survival effects by inducing vascular endothelial growth factor and STAT3 activation.[5] By suppressing immune cells, MSCs reduce tumor immunosurveillance. MSCs also induce autophagy and discharge of pro-survival paracrine agents, as well as blockade of cyclin D2 (Figure 1).[2,5]

MESENCHYMAL STEM CELLS AND CANCER GENE THERAPY

MSCs are recognized as promising tools for gene therapy in a number of diseases such as cancers.[6] MSCs could be isolated from many tissues such as bone marrow, fetal liver, umbilical cord blood and adipose tissue.[4,6] They have a high proliferative capacity and the ability to differentiate into many cell types.[2,6] Importantly, the innate tendency of MSCs for migration to malignant sites makes these cells particularly promising for the effective cellular delivery of antitumor agents including cytokines, interferons or pro-drugs.[1,4,7] Furthermore, the utilization of genetically engineered MSCs may highlight an effective alternative therapeutic approach capable of overcoming clinical restrictions related to the systemic administration of cytokines and medications with short half-life and high toxicity.[2,4] New progresses in gene therapy have shown promise and opened new horizons to improve the standard care of patients with advanced cancers like melanoma and glioblastoma.[1,2,7] Recently, engineering toxin-resistant therapeutic stem cells has been proposed as an efficient strategy for brain tumor therapy. Integration of stem

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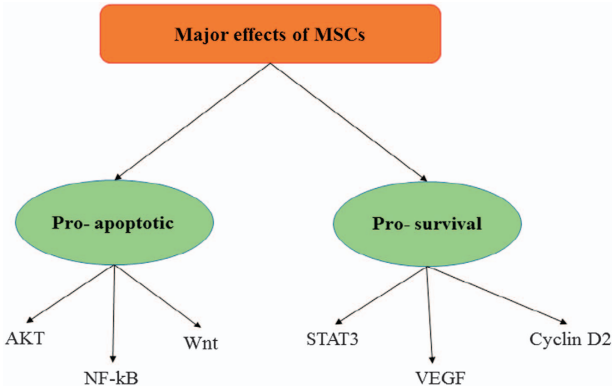

Figure 1. Major effects of mesenchymal stem cells (MSCs).

Table 1. Various genes delivered by mesenchymal stem cells (MSCs)

Gene	*Cancer*	*Reference*
IL-2	Glioma	9
IL-12	Ewing sarcoma Renal cell carcinoma	10
IL-18	Glioma	1
TSP-1	Glioma	7
IFN-β	Prostate cancer lung	1
IFNγ	Leukemia	1
CX3CL1	Multiple lung tumors	1
PE cytotoxins	Glioblastoma	8
HSV-tk	Glioma	1
TRAIL	Glioma	1

cell-based engineering and delivery of PE cytotoxins have shown promise for the management of one of the most malignant cancers known as glioblastomas.[8] These strategies may have a significant role in the therapy of other malignancies, but their role in the management of patients requires confirmation by the findings of clinical trials. Table 1 shows various genes targeted by MSCs in different malignancies.

CONCLUSION

Identification of new drug delivery systems is an important part of cancer therapy. Although a large number of new therapeutic strategies have emerged, none has yet demonstrated the ability to cure this cancer. In this regard MSCs appear to be promising new tools. The natural tropism of MSCs for tumor cells makes them excellent vehicles for tumor-targeted therapies. Also, the use of genetically modified MSCs may overcome limitations associated with systemic administration of some cytokines and anti-neoplastic agents with a short half-life and high toxicity. Finally, three important issues regarding the utilization of MSCs as vectors remain to be addressed: (i) MSCs are not simple delivery vehicles but cells with active physiological process and hence they produce and secrete a wide array of growth factors, cytokines and chemokines; in this regard, they might provide pro-survival signals for tumor cells resulting in enhanced tumor burden and metastases. (ii) How many MSCs need to be given and when and where should they be administrated? (iii) MSCs might themselves undergo malignant transformation due to cancerous microenvironments. Thus, a comprehensive knowledge of MSC physiology within the tumor microenvironment and more robust studies characterizing their homing mechanisms might improve the proposed therapies. For the reasons and evidence outlined above, we believe that MSCs could have a significant role in future treatments of melanoma and other cancers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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