REVIEW ARTICLE

Unveiling the Potential of Therapeutic Mesenchymal Stem Cells in Cancer Treatment

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Abstract

Recent studies have suggested that mesenchymal stem cells (MSC) can migrate to tumor-specific regions and stem cell-based therapies have potential in treating several cancers. Such cells are genetically modified to express certain pro-apoptotic factors, pro-drugs, anti-proliferative agents, therapeutic proteins, and anti-angiogenic agents at the tumor sites. It is also evident that new modalities of cancer therapies are needed immediately which would push this research to the clinic and render MSCs as potential vectors for targeted therapy. The current review focuses on different sources of MSC used against tumors, the interactions and behavior of MSCs in the tumor microenvironment, and the usage of MSC as delivery vectors.

Key words: Anti-proliferative agents, mesenchymal stem cells, pro-apoptotic factors, targetted therapy, tumor micro environment

INTRODUCTION

Cancer remains a significant medical issue around the world, and it is one of the main causes of mortality. The chief methodologies of disease treatments include surgery, chemotherapy, and radiotherapy.[1] However, despite the enhancements in therapeutic strategies, numerous tumors remain unresponsive and tend to have a poor prognosis after conventional treatment, because of metastasis. Biological therapies have been noted as a novel technique for different tumor-related diseases, particularly for relapsed patients.[2] One of the major difficulties of cancer biological treatment lies in the inefficient delivery of therapeutic agents to the tumor sites, as metastatic tumors are directly inaccessible.[3] Recent studies indicated that mesenchymal stem cells (MSCs) not only move specifically to tumor microenvironment, but also integrate into tumor stroma. In any case, the interaction between tumors and MSCs remains questionable.[4] This review focuses on the utilization of MSCs for targeted therapy against tumors as it is one of the main challenges of cancer treatment relating to the delivery of anti-tumor agents and pro-apoptotic components to the tumor site.

SOURCES FOR MSC

Stem cells have unlimited self-renewal properties and are able to produce more differentiated progenitors. They include both embryonic and adult stem cells, of which, BMSCs are the best characterized and widely accessible.[5] They have been studied extensively and are a potential source for the treatments of various diseases including Parkinson's disease and juvenile disease. MSC are multipotent stem cells, widely identified by their self-renewal ability and plastic adherence,

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and these cells can be successfully isolated from a number of organs including, bone marrow, brain, liver, kidney, lung, muscle, pancreas, skin, adipose tissue, cord blood, and human placenta, while they were first isolated from mononuclear cells derived from bone marrow.[6] MSCs derived from bone marrow have the potential to give rise to all cell types following implantation into early blastocysts.[7] Bone marrow-derived MSCs require an invasive and painful procedure that provides a small number of cells and the life span of these cells decline with patient age.[8] Adipose tissue obtained from subcutaneous tissue represents the most abundant potential source for harvesting MSCs efficiently using simple techniques.[9] Umbilical cord blood, obtained after removal of the placenta, is a rich source of MSCs.[10] Mononuclear cells can be isolated and cultured from the cord blood, and cells in heterogenous adherent layers have been shown to have a fibroblastiod morphology, and express same markers as MSC derived from bone marrow, namely, Cytosine Deaminase (CD) 13, CD29, CD49e, CD54, and CD90. All three cell types differentiate into Osteocytes and chondrocytes that are associated with the properties of MSCs.[11]

MSC MIGRATION

Although the mechanisms by which MSC migrates and reaches the home target that is not fully understood. Extensive studies have shown that MSC depends on different cytokine/receptor pairs SDF-1/CXC chemokine receptor-4 (CXCR4), SCF-c-Kit, HGF/c-Met, VEGF/VEGFR, PDGF/PDGFr, MCP-1/CCR2, and HMGB1/RAGE to migrate to target tissues. Among these, Stromal cell-derived factor SDF-1 and its receptor CXCR4 are important mediators that play a significant role in the migration of MSC toward tumor cells.[12] In addition, a recent study has reported that macrophage migration inhibitory factor, a potent pro-inflammatory cytokine is involved in MSC migration.[13] Most recent studies reported that MSC are attracted to sites of irradiation and it might promote specificity of MSC migration and engraftment. It has been shown that MSC and other stem cell types monitor tumor metastases and treat them effectively by either stem cell release factors or by expression of the tumor transgenes with which they have been engineered.[14] These studies provide a reasonable rationale for the development of anti-tumor therapies that build on MSC by designing them into carriers [Figure 1].

MSC AS DELIVERY VECTORS FOR ANTI-TUMOR THERAPY

Delivery of interleukins (IL) and interferon's

ILs are cytokines that help in the regulation of inflammatory and immune responses. They also show tumorocidal effects in the tumor microenvironment. The anti-cancer surveillance can be improved by activating cytotoxic lymphocytes and NK cells which can be done by delivering ILs using MSCs.[15] In a recent study, it was demonstrated that MSCs which were engineered to express and release (IL)-12, prevented the tumor cell metastasis into lymph nodes and other internal organs.[16] Studies on combinatorial immunity development in TME by engineering MSCs to express Interferon-gamma and (IL)-7 resulted in higher density levels of intra-tumoral T-cells.[17] Interferons exhibit proapoptotic effects, but its usage is limited due to the toxicity associated with it. In breast cancer models on delivering (IFN)-β *in vivo* efficacy against tumor was observed.[18]

Delivery of pro-apoptotic proteins and anti-angiogenic agents

Pro-apoptotic proteins like Tumor necrosis factor-related apoptosis-induced ligand (TRAIL) are delivered using MSCs.[19] TRAIL is a member of TNF family that helps in inducing apoptosis by activating caspases in the tumor microenvironment. Induction of apoptosis was observed in cell lines or mouse models of gliomas, lung, and breast cancers. A secretable version of TRAIL protein has to be designed because it belongs to membrane protein and its cleavage from the membrane becomes difficult.[20] Recent investigations showed that MSCs were resistant to TRAIL-governed apoptosis, when engineered to express S-TRAIL they induced apoptosis in glioblastoma stem cells *in vitro*.[21] Self-sustained growth is observed in TME due to angiogenesis and several molecules of ECM act as signaling agents in this process. In a few findings reduction of tumor-associated vasogenic brain, edema was observed in patients when anti-angiogenic drugs are delivered using MSCs.[22]

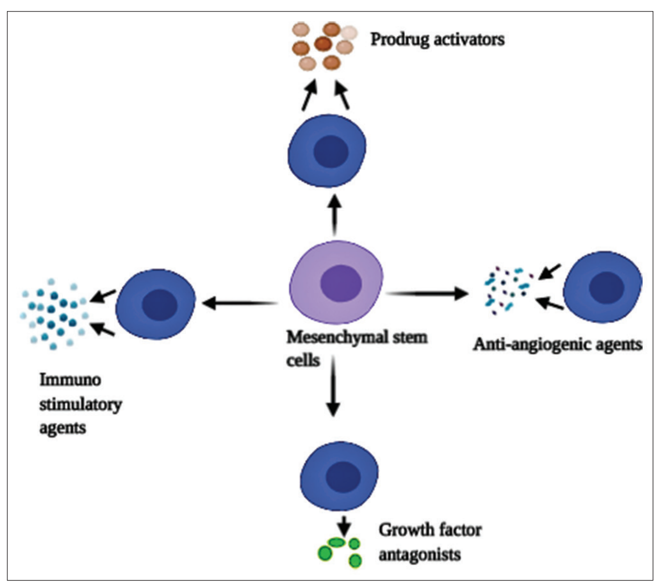

Figure 1: Strategies of using MSCs in cancer therapy and stem cells designed to express several antitumor effects

Delivery of pro-drugs

Selective destruction of tumor cells in TME is done by converting non-toxic pro-drugs into toxic anti-metabolites.[23] Thymidine kinase, CD, and Ganciclovir were evaluated in clinical trials. Such stem cells can act as pharmacogenic pumps as they have cancer killing feature. For the 1st time, such investigations were carried out using CD which is capable of converting non-toxic fluoro cytosine to 5-fluoro uracil, a chemotherapeutic drug that can selectively inhibit rapid proliferation of cancer cells.[24]

ADVANTAGES AND DISADVANTAGES OF USING MSCs FOR ANTITUMOR THERAPY

The ability of MSCs to directly migrate to tumors makes them attractive for directed cancer therapy. MSCs are active cells with effects on both physiological and pathological processes and have a profound immunosuppressive effect.[25] When T cells were cultivated with MSCs, they did not proliferate with antigenic or mitogenic stimuli. Similar effects observed with B cells and dendritic cells, leading to a reduction in plasma cell maturation and production of antibodies and antigen presentation.[26] MSCs affect immune cells by various mechanisms including direct cell contact and release of many soluble factors. Due to cell-cell contact-induced inhibition, intravenously administered MSCs were able to inhibit the growth of KS in a mouse model. It has also been shown that the release of soluble factors by MSCs reduces tumor growth and development in glioma, melanoma, and lung cancer.[27] Phase 2 clinical trials are currently being performed to investigate whether the anti-inflammatory and reparative function of MSCs can support patients with moderate-to-severe chronic obstructive lung disease.[28] Further, MSCs tend to have intrinsic antitumor properties as well. When hepatoma cells were injected intraperitoneally, proliferation rate reduced and was accompanied by an increase in cancer cell apoptosis and a reduction in malignant ascites.[29] In an attempt, intratumoural injection of MSCs was given to increase the survival rate of rats with glioma and inhibit tumor growth. However, it is important to consider the role of MSCs in specific types of cancer in the context of their immunosuppressive, reparative, and angiogenic properties in particular. It is observed that subcutaneously-delivered allogeneic melanoma cells only produced tumors in mice with the co-administration of MSCs, and immunosuppression was thought to be a crucial factor for this observation.[30] A study demonstrated an earlier development of tumors when syngeneic Renca kidney cancer cells were implanted with MSCs. In addition, MSCs development of trophic factors has also been implicated in improving tumor growth and spread. MSCs have also been shown to promotemetastasis of breast cancer cells in a mouse subcutaneous xenograft model.[31] The production of IL6 by MSCs was also involved in the increased growth of breast cancer cells. The potential of these cells for malignant change is another concern about the use of MSCs as an anticancer delivery agent, especially in view of their unlimited capacity for proliferation.[32] However, a recent study carried out to determine the potential susceptibility of human bone marrow-derived MSCs to malignant transformation concluded that MSCs remained suitable for cell therapies.[33]

CONCLUSION

Recent clinical investigations have shown that stem cell-based therapies hold tremendous promise for the treatment of several cancers. MSCs are well placed to be used as vectors for anticancer treatment as they specifically migrate toward tumor regions, interact with different tissue environments in addition to their easy availability, non-immunogenic nature, and relative ease of manipulation in vitro. Few studies represented the anti-oncogenic potential of MSCs when loaded with chemotherapeutic drugs and/or modified with therapeutic genes. MSCs are engineered to successfully deliver ILs and interferons, pro-apoptotic proteins, anti-angiogenic agents, and pro-drugs to reduce tumor growth, elimination of metastases, and improvement in survival. Although MSCs are emerging as promising anti-cancer agents, there are still few challenges as some reports implicated MSCs in promoting the growth of certain cancers and metastases. In addition, the mechanisms by which MSC migrates and reach the home target is not fully known. Hence, a thorough understanding of MSCs and a further clinical investigation is critical when developing MSC based therapies for cancer treatment.

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