

Potential of Mesenchymal Stem Cell based application in Cancer

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ABSTRACT

Stem cell based treatments are being increasingly explored for their possible potential to treat various cancers. Mesenchymal stem cells believed to possess anti-tumor potential and are preferred for their properties like immune privileged nature, ability to migrate to the site of tumor and capability for multilineage differentiation. This tumor tropism property of MSCs could be utilized to deliver anti-tumor biological agents to the site of tumor. In a tumor micro-environment, MSCs are believed to play both, a pro-tumorigenic and an anti-tumorigenic role. However, this is dependent on a host of factors like, types of MSCs, its source, type of cancer cell line under investigation, in vivo or in vitro conditions, factors secreted by MSCs and interactions between MSCs, host's immune cells and cancer cells. Among several cytokines secreted by MSCs, TRAIL (Tumor necrosis factor related apoptosis inducing ligand) is reported to be pro-apoptotic for tumor cells. The MSCs from bone marrow and adipose tissue have been studied quite extensively. Deriving MSCs from sources such as umbilical cord blood and umbilical cord tissue is relatively easier. Umbilical cord tissue preferred for MSC derivation due to their abundant availability. These MSCs believed to up regulate TRAIL expression in MSC-cancer cell co-culture system resulting in induction of apoptosis in cancer cells. However, umbilical cord tissue derived MSCs needs to be studied for expression pattern of TRAIL in a co-culture system. We present a review article on different studies reporting both, pro-tumorigenic and anti-tumorigenic properties of MSCs.

KEYWORDS: Mesenchymal Stem Cells, Cancer, Anti-cancer, Tumor, Tropism

INTRODUCTION

Cancer, known medically as a malignant neoplasm (new tissue), is a broad group of various diseases, involving unregulated cell growth. Cancer is generally treated with combination of therapies that include chemotherapy, radiotherapy, surgical resection, immunotherapy and monoclonal antibody therapy.

The discovery of anti-cancer therapy in the mid-twentieth century was aimed at development of chemotherapeutic agents to target cancer cells.¹ However; conventional cancer therapies (surgery, chemotherapy or radiotherapy) have their own

limitations since these treatments do not deal with the challenge of tumor recurrence & metastasis following initial remission. Also, these conventional therapies lack precise specificity to target only cancer cells. This failure of cancer treatment is usually not contributed by lack of primary response or initial induction of remission, but by relapse or tumor recurrence after therapy, in which tumor-initiating cells might play a crucial role. There are several reports which demonstrate presence of tumor-initiating cells, popularly known as cancer stem cells, which support tumor growth and these cells can be targeted to eradicate cancer from its

source.^{2,3,4} Tumor-initiating cells can be optimally defined as those tumor cells that have ability to regrow the tumor from which they were isolated and identified. The term 'cancer stem cell' does not mean that the cell derived from normal stem cell.⁵ Rather, cancer stem cells produce tumors. The self-renewal and differentiation of cancer stem cells is maintained and regulated by its own niche. The traditional anti-cancer therapy targets only the differentiated tumor cells and not tumor initiating cells; by this consideration these treatments, to a significant extent, are limited to symptomatic treatments only. Recent advances in finding treatment options for cancer are exploring anti-cancer properties of human stem cells. It is the need of the hour to find out type of stem cells which are anti-cancer in nature by their interaction with tumor cells and its effect on tumor growth. We bring you a synopsis of such developments in the scientific community contributing to the possible cancer treatment using stem cells.

STEM CELLS

The discovery of stem cells in 1963 by E.A. McCulloch & J.E. Till opened infinite possibilities of use of these progenitor cells to treat various human illnesses.^{6,7} Their findings resulted into discovery of undifferentiated, self-renewing, progenitor cell population which are referred as stem cells. Stem cells, on the basis of their origin, can be divided into four broad categories; embryonic stem cells which are capable of a self-renewal and differentiation into cells of all tissue lineages;⁸ foetal stem cells which are located in foetal tissues and are multipotent in nature; adult stem cells are partially committed stem cells located in specific stromal niche and can be obtained from the mesodermal tissues such as BM,⁹ muscle,¹⁰ adipose tissue,¹¹ synovium¹² and periosteum¹³ and umbilical cord blood stem cells are divided into two sub-categories hematopoietic and mesenchymal stem cells.

Of all these, the type of stem cells which are widely studied for their anti-cancer properties are mesenchymal stem cells (MSCs).¹⁴ MSCs are adult stem cells which were first identified in the stromal compartment of bone marrow by Friedenstein et al in 1960s.^{15,16}

MSCs are preferred as these cells have the potential of multi lineage differentiation into bone, cartilage & fat cells,¹⁷ immune privilege nature,¹⁸ affinity for site of injury or tumor, ease of availability and maintenance in the culture and storage. The multi lineage differentiation potential of MSCs confer them crucial role in tissue regeneration and have been used experimentally to repair tissue damage in various disease conditions.^{19,20}

1990s is marked by the investigation of safety and efficacy of MSCs in clinical applications. The first study reported that MSCs are safe with complete remission in hematological malignancies.²¹ In this study 15 human subjects with hematological malignancies were infused with autologous cultured MSCs resulting into safe and complete remission. Another encouraging evidence about safety of MSCs came up when MSCs were successfully utilized to treat children affected by osteogenesis imperfecta.²² MSCs reported to be safe for application in heart degenerative diseases, inflammatory diseases and spinal cord injuries.^{23,24,25} MSCs from autologous origin were safe in treating liver disease,²⁶ brain injury²⁷ and myocardial infarction.²⁸

MSCs express major histocompatibility (MHC) class I surface markers and are negative for MHC class II expression. Also, they lack the co-stimulatory molecules CD40, CD80 and CD86. Despite expression of low levels of MHC class I antigens that results the activation of T cells, the absence of co-stimulatory molecules cannot initiate secondary signals, thus leaving the T cells anergic.²⁹ Low levels of expression of MHC class I is important in protecting MSCs from natural killer cell-mediated cytotoxicity and cells that do not express MHC class I are targeted and destroyed.³⁰ In fact, MSCs are immunosuppressive in nature¹⁸ which is the prerequisite in allogeneic cell therapy based transplant.

TROPISM OF MSCs TOWARDS INJURY OR TUMOR

The discovery that mesenchymal stem cells (MSCs) are recruited into tumors has led to a great deal of interest over the past decade in the role of MSCs in tumors. This MSC tropism towards site of tumor has been put forth by Maestroni et al. in 1999,³¹ wherein they proved homing of MSCs to the

tumors. The tumors are characterized as 'wounds that do not heal' and the MSC tropism to wounds is very well documented in many reports.^{32,33} MSCs interact with tumor cells in number of ways, which have the potential to support or suppress tumor growth. Report by Maestroni et al. (1999)³¹ has shown that bone marrow derived MSCs release some soluble factors that inhibit lung carcinoma and B16 melanoma growth in mice. Tropism of MSCs for glioma was first evidenced by implantation of rat MSCs into rats having syngeneic gliomas.³⁴ It is also demonstrated that MSCs possess selective tropism for gliomas which is comparable with tropism by human neural stem cells (hNSC).³⁵ The potential of hNSCs is limited by difficulties in harvesting and ex-vivo expansion of the same.³⁶ In contrast, MSCs can be readily harvested and expanded from numerous sources without any practical difficulty as described above. As stated earlier tumor mimics a wound which serves as a continuous source of cytokines & chemokines³⁷ thereby recruiting respondent cell types including MSCs. This homing potential of MSCs is evidenced in almost all tested human cancer cell lines³² such as melanoma,³⁸ pancreatic cancer,³⁹ ovarian cancer,⁴⁰ colon cancer,⁴¹ breast cancer,⁴⁰ lung cancer,⁴² Kaposi's sarcoma⁴³ and malignant glioma.⁴⁴

The probable mechanism of tumor-specific migration of MSCs is not fully understood, but seems to be dependent upon biological properties of tumor micro-environment.⁴⁵ High concentrations of inflammatory chemokines & growth factors believed to be responsible for integration of MSCs into tumor stroma. Since tumor is considered a "wound", its micro-environment is considered as a site of chronic inflammation.³⁷ It is reported that it may be this micro-environment which mediates MSC migration through secretion of soluble factors such as epidermal growth factor, vascular endothelial growth factor-A, fibroblast growth factor, platelet-derived growth factor, stromal-derived growth factor-1 α (SDF-1 α /CXCL12), Interleukin-8 (IL-8), Interleukin-6 (IL-6), granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, Ang1, monocyte chemoattractant protein-1 (CCL2), hematopoietic growth factor, transforming growth

factor beta-1 and urokinase-type plasminogen activator.^{34,45,46,47,48,49}

MSCs could be ideal delivery vehicles for anti-tumor biological agents owing to their properties like tumor tropism, integration into tumor stroma³⁸ and immune privileged nature.⁵⁰ Number of anti-tumor genes have been engineered into MSCs and successfully demonstrated anti-tumor effects on various cancer models, to list a few, IFN- β on pancreatic cancer,³⁹ IL-12 on melanoma and hepatoma,⁵¹ IFN- α on melanoma,⁵² IFN-r on leukemia,⁵³ IL-2 on glioma,³⁴ NK4 on lung cancer⁵⁴ and TRAIL on breast cancer,⁴² glioma⁴⁴ and lung cancer.⁵⁵ MSC tropism is also reported to be utilized to deliver oncolytic viruses to tumor sites. Genetically modified oncolytic viruses such as Adenoviruses are tested as anti-tumor weapons. Study also confirmed that there is decrease in tumor burden in animals treated with oncolytic virus delivered by MSC carriers compared with the direct injection of the adenovirus.⁵⁶

MSCs – PRO-TUMORIGENIC OR ANTI-TUMORIGENIC?

There are other observations suggesting that, in the tumor micro-environment, MSCs have several tumor growth promoting functions, including expression of growth factors, promotion of tumor vessel formation and creation of tumor stem cell niches.^{57,58} It is believed that MSCs may contribute to tumor growth in several ways: (1) by promoting angiogenesis; (2) by creating a niche to support cancer stem cells survival; (3) by modulating the organism's immune response against cancer cells; and (4) by promoting formation of metastasis.⁵⁹

Through extensive literature survey, we observed that pro-tumorigenicity and anti-tumorigenicity of MSC on cancer probably depends on many factors which are explained in detail below.

It appears that the source of MSCs is determinant of response to tumor; in one study researchers reported umbilical cord blood-derived MSCs causes brain tumor regression but adipose tissue-derived MSCs promotes the same.⁶⁰ Tumor growth promotion is also reported in gastric cancer models,⁶¹ breast subcutaneous tumor models⁶² & ovarian cancer.⁶³ Another study reports that

melanoma cells lead to tumor formation only in the presence of MSCs when injected subcutaneously into an allogeneic recipient.⁶⁴

Furthermore, tumor progression or regression is also dependant on in vitro or in vivo conditions.¹⁴ Tumor progression by MSCs were reported in melanoma A375 cells but was absent in glioblastoma 8MGGBA cell line,⁶⁵ which is indicative of tumor cell specific behavior of MSCs. To investigate and understand whether advantages outweigh disadvantages of MSCs as therapeutic agent, it is imperative to review some more studies.

Yet again, there are reports indicating MSCs as possibly the most promising delivery vehicle for a cell-based targeted cancer gene therapy⁶⁶ & they serve as cytotoxic for certain type of cancer cells.⁶⁷ In another study MSC conditioned media resulted in the downregulation of NFkB in hepatoma and breast cancer cells which decreased cancer cell in vitro proliferation.⁶⁸ It has been reported that MSCs results into suppression of tumor growth in models of Kaposi's sarcoma,⁴³ Lewis lung carcinoma,³¹ glioma,³⁴ colon carcinoma,⁶⁹ malignant melanoma,^{31,70} breast cancer,⁷¹ pancreatic cancer⁷² and prostate carcinoma.⁷³ Table 1 shows some of the in vivo experiments and possible mechanisms of action of MSCs to restrict tumor progression.

It has been observed that bone marrow MSCs release soluble factors which shown significant reduction in tumor growth and progression in melanoma, lung carcinoma³¹ and in glioma models.³⁴ The group of researchers reported umbilical cord blood-derived MSCs inhibits proliferation of Glioblastoma Multiforme by up-regulating secretion of TRAIL.⁶⁰ The downregulation of Wnt signaling pathway in breast cancer reported to be related to secretion of dickkopf proteins (DKK-1).⁶⁸

In another study, a completely novel approach was implemented by isolating two phenotypes of MSCs, called MSC1 and MSC2 from mixed population of MSC.⁸⁰ Researchers in this study concluded that MSC1 is pro-inflammatory while MSC2 is immunosuppressive in nature. In continuation with this study, same group reported that MSC1 is anti-tumorigenic while MSC2 is pro-tumorigenic in nature.⁸¹

Wnt pathway plays a crucial role in stem cell self-

renewal and differentiation. It has been reported that human tumor progression is a result of an aberrant Wnt pathway.⁷⁴ The evidence that MSCs inhibit Wnt pathway reported by study wherein researchers co-cultured MSCs with human hepatoma cells (H7420) that resulted in decreased cell proliferation, increased apoptosis and downregulation of all target genes of Wnt signaling (Bcl-2, c-Myc, PCNA and Survivin). The results were obtained when MSC conditioned medium was used, which is indicative of involvement of paracrine effect.

As can be seen, mechanisms of anti-tumor properties of MSCs are not fully elucidated and more insights are awaited, it is presumed that it has a strong relation to downregulation of Akt, NFkB & Wnt signaling pathways.⁷⁵ Stem cells and tumor cells have similar signaling pathways regulating self-renewal and differentiation, including Wnt, Notch, Shh and BMP pathways.^{76,77,78} Stem cells possess strong regulatory control over these pathways, while tumor cells do not possess the same. Loss of regulation of pathways involved in multiplication leaves tumor cells immortal and they multiply without any control.

Multiple mechanisms have been postulated to be contributing to anti-tumor potential of MSCs. Few of the probable mechanisms include apoptosis caused due to upregulation of TRAIL, cell cycle arrest, direct cytokine mechanism, blocking of PI3K/AKT pathway, expression of tumor suppressor genes, downregulation of Wnt pathway and expression of DKK1.

CONCLUSION

Discovery of stem cells paved its way in making new cell therapy options available to patients suffering from various diseases. The therapeutic potential of stem cells is being extensively studied for the possible treatment of degenerative diseases and lifestyle disorders ranging from autoimmune diseases, multiple sclerosis, diabetes mellitus, ischemic diseases like stroke, heart failure, cartilage repair, liver cirrhosis, neurological disorders like Parkinson's disease, Huntington's disease and spinal cord lesions. Recently, yet another application of stem cells is being explored in an attempt to find out possible cell therapy for various malignancies

Table 1: Probable anti-cancer mechanism of MSCs on different animal models of cancer- Summary of few *in vivo* experiments using different animal models of cancer indicating MSC source, type of animal model, mode of MSC infusion, observations and probable mechanism of action involved in tumor regression

Reference	Otsu 2009 ⁷⁰	Doi 2010 ⁷²	Cousin2009 ⁷⁹	Chanda 2009 ⁷³	Ren 2008 ⁵²
Observations					
Cancer	Melanoma	Pancreatic cancer	Pancreatic cancer	Prostate cancer	Prostate cancer
Cancer cell type	B16F10	PAN02	Capan-1	Osteolytic human prostate cancer cells PC3 expressing firefly luciferase	Mouse metastatic prostate cancer cell line TRAMP-C2
MSC source	Bone marrow	Umbilical Cord Tissue	Adipose tissue	Bone marrow	Bone marrow: Undifferentiated BMMSCs transduced with 1000 MOI of rAAV6-IFN- β or rAAV6-GFP
Animal model	Subcutaneous graft in C57/BL mice	Orthotopic xenograft in C57/BL mice	Subcutaneous xenograft in athymic nude mice	Male SCID mice with intratibial injection	Prostate cancer cells lung metastasis in male C57BL/6 mice
Mode of MSC infusion	IT injection	IP injection	IT injection	Intratibial injection	IV injection
Observations	Regression in tumor size	Regression of tumor size with enhancement in survival time	Regression in tumor size	Inhibition of tumor growth	Regression in tumor growth
Possible mode of action	Apoptosis induction and angiogenesis inhibition	Interference with proliferation and G0/G1 arrest	Interference with proliferation and G1 arrest	New bone formation around tumor cells in tibia restricted growth of prostate cancer cells	Tumor apoptosis, anti-angiogenesis and induction of NK cell activity

like renal cell cancer, breast cancer, lung cancer, ovarian cancer, leukemia, melanoma, pancreatic cancer, malignant glioma and so on.

MSCs could be the next candidate of choice being considered for the treatment regime of cancer; especially in allogeneic mode they could possess tropism for solid tumors, immune privileged nature, ease of availability and maintenance etc. Application of MSCs for the possible treatment of tumors has divided the scientific society into two schools of thoughts. One school of thought states MSCs plays crucial role in tumorigenesis by promoting angiogenesis, creating a niche to support cancer stem cells survival, modulating the organism's immune response against cancer cells and promoting formation of metastasis. The other school demonstrated anti-tumor effect of MSCs in few specific cancers.

The exact mechanisms of anti-tumor property of MSCs are yet to be understood. However, predominant studies relate it with downregulation of Akt, NFkB & Wnt signaling pathways.

The source of MSC seems to contribute to anti-tumor properties against particular malignancy. Anti-tumor effect of umbilical cord blood derived MSCs was evident against brain tumor but the same effect was missing with MSCs derived from adipose tissue. The reasons for this can be a subject of new research.

Majority of MSCs studied for anti-tumor properties are derived from sources like bone marrow and adipose tissue. However, there are very few reports of usage of umbilical cord tissue as a source of MSCs. Umbilical cord tissue is a rich source of MSCs, the extraction procedure is relatively non-invasive, there are not ethical concerns and are available in abundance. The MSCs

derived from umbilical cord tissue needs to be studied further for their anti-tumor properties in detail.

This is a very interesting area that is worth following closely. Physicians, research community and others involved in cancer treatment will look forward to this new dimension with great deal of interest and the space is worth watching for new developments in near future.

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CONFLICT OF INTEREST

There is no conflict of interest.

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