Mesenchymal Stem Cells for Anti-Cancer Drug Delivery

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Abstract: Self renewal, extensive proliferation and multilineage differentiation ability *in vitro* and *in vivo* make mesenchymal stem cells (MSCs) powerful tools for tissue engineering. Beyond their potential uses in regenerative medicine, an emerging field of research aims to utilize MSCs for anti-cancer treatment. These strategies are based on the remarkable ability of MSCs to localize and integrate into tumor stroma and deliver anti-cancer agents (US20100055167, US20120207725, US20120010499). Genetically engineered MSCs can specifically target different tumor types and locally secrete therapeutic proteins such as interferons α and β, interleukins 2 and 12 or chemokine CX_3CL1 (US20110027239, US20120087901, WO2012071527). In addition, MSCs have also been engineered to deliver oncolytic viruses, for targeted chemotherapy using enzyme prodrug conversion or for inducing tumor cell apoptosis by delivering tumor necrosis factor-related apoptosis inducing ligand (TRAIL) (WO2012106281). The patent databases FPO and Delphion were used to locate patents that were published between 2005 and 2013. Here, we present the current progress and the most recent patents on MSC anti-cancer drug delivery systems and discuss future directions in the field.

Keywords: Cancer therapy, drug delivery, mesenchymal stem cells.

INTRODUCTION

One of the many challenges of cancer treatment concerns the delivery of anticancer drugs to the site of the tumor. Bone marrow-derived stem cells (BMSCs) have the ability to migrate specifically to, and incorporate within tumors, which makes them a potentially exciting drug delivery tool [1].

The BMSCs include two groups of cells: haematopoietic progenitor stem cells (HSCs) and mesenchymal stem cells (MSCs) [2]. The International Society for Cellular Therapy has recommended minimum criteria based on cell adherent properties, surface markers and differentiation potential for defining multi-potent human MSCs (Table **1**) [3, 4].

The MSC characteristics of extensive proliferation, self-renewal and multilineage differentiation make them a promising tool for tissue engineering and regenerative medicine [5-9]. During both proliferation and differentiation, MSCs interact with other cells through both cell-cell interactions and paracrine signaling, involving the secretion of growth factors, cytokines, antifibrotic or angiogenic mediators [10, 11].

Primary MSC targets are regions of new stroma formation including sites of hematopoiesis, inflammation, and injury. Interestingly, MSC localization and persistence in solid tumor stromal tissue have also been reported [12-16]. Furthermore, exogenously delivered MSCs' are also preferentially locallized to tumors. These tumor tropism abilities make MSCs a suitable tool for tumor therapy as delivery vehicles for various biological agents [17, 18]. Numerous *in vivo* studies using animal tumor models have shown that these cells preferentially migrate to tumors. Regardless of delivery methods (intravenously [19-24], intraperitoneal [25] or intracerebral [20]) MSCs predictably migrate, incorporate, and survive in cancer tissue. One explanation is that MSCs have a variety of surface chemokine and cytokine receptors that respond functionally to a large array of molecules that are secreted by tumors [16, 26, 27].

In several studies, immunoregulatory and proliferative effects of MSCs on tumor growth were investigated leading to two main mechanisms that are likely involved in the enhancement of tumor growth by MSCs. First, cell-to-cell cross talk between MSCs and tumor cells contribute to tumor progression [28, 29], and second, the suppressive effects of MSCs on the immune system facilitate tumor genesis, as shown for the inhibition of melanoma rejection, possibly mediated by regulatory $CD8^+$ T cells [15, 30].

The ability of MSCs to migrate specifically to tumors has led several groups to engage them for delivering anticancer agents (Table **2**). There are numerous studies reporting engineered MSCs specifically targeting different tumor types followed by local secretion of therapeutic proteins, such as interferon α (IFNα) [31, 32] and β (IFNβ) [17, 20, 23, 31, 32], immunostimulatory interleukin (IL)12 [33], immunomodulatory cytokine IL2 [34] or chemokine CX_3CL1 (fractalkine) [22]. MSCs have also been engineered to deliver conditional replicative oncolytic viruses to reduce tumor

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Table 1. **Criteria for Defining Multi-Potent Human MSCs.**

Criteria	Description	
Criterion I	**Cells being adherent to plastic under standard culture conditions**	
Criterion II	**Positive for the expression of:**	**Negative for the expression of:**
	CD105 CD73 and CD90	CD34, CD45, CD11a, CD19, CD79a, CD14, CD11b and histocompatibility locus antigen (HLA)-DR
Criterion III	Under a specific stimulus, MSCs differentiate into osteocytes, adipocytes and chondrocytes both *in vitro* and *in vivo*.	

Table 2. **MSCs as Anticancer Drug Delivery Systems.**

Anticancer Agent	Effect	References	Experimental Model
Interferon β (IFNβ)	Therapeutic protein, apoptosis, decreased tumor mass and increased animal survival	[17, 20, 23, 31, 32]	Gliomas, mouse prostate cancer, lung metastasis model, pancreatic tumors
Interferon α (IFNα)	Therapeutic protein, immunostimulatory	[31]	Mouse melanoma lung metastasis model
Interleukin (IL)12	Immunostimulatory	[33, 48, 49]	Lung and breast cancer
Cytokine IL2	Immunomodulatory	[34, 50]	Rat glioma model
Chemokine CX₃CL1	Activates T cells and NK cells	[22]	Metastatic cancer
Replicative oncolytic viruses	Reduce tumor growth and spread *in vivo*	[25, 36, 37]	Lung and breast tumor models, metastatic cancer
Cytoreagents for gene therapy and targeted chemotherapy	Enzyme prodrug conversion	[38, 39, 40, 41, 42, 43]	Mice melanoma, human glioblastoma cells, pancreatic carcinoma, colon tumors
Tumor necrosis factor-related apoptosis inducing ligand (TRAIL)	Apoptosis	[19, 45, 46, 47]	Metastatic cancer, brain tumors, lung cancer model, intracranial glioma

growth and metastasis *in vivo* [25, 35-37]. Furthermore, MSCs serve as therapeutic cytoreagents for gene therapy as well as vehicles for targeted chemotherapy with an enzyme prodrug conversion [38-43]. Strong antitumor effects have been reported following administration of gene modified MSCs expressing tumor necrosis factor-related apoptosis inducing ligand (TRAIL) [19, 44-47]. In experimental cancer models, TRAIL was found to cause apoptosis selectively in glioma and lung cancer, while sparing non-cancer cells. Also, MSCs secreting IL-12 [33, 48, 49] or IL-2 [34, 50] were shown to initiate an immunoreaction and stimulate inflammatory cell infiltration in the tumor tissue but did not cause systemic toxicity [49].

MSCs can be isolated from adult tissues, including bone, fat, skeletal muscle, synovium, dental pulp, and fetal tissues, including umbilical cord blood, placenta, amniotic membranes and fluid, and Wharton's jelly [8, 29]. Although, MSCs derived from different sources share many traits, they differ in several aspects of gene expression and physiology

[29], leading some to view the proposed use of MSCs in cancer therapies as dangerous. New facts about MSC promotion of tumor vascularization and growth have been reported and are discussed later in this text.

RECENT PATENTS RELATING TO MSCs AND THEIR USE AS ANTICANCER DRUG DELIVERY SYSTEMS

It is especially important to consider the role of MSCs in the context of their immunosuppressive, reparative and angiogenic properties in specific cancer types. A further concern of the use of these cells as an anticancer delivery agent is the potential for malignant change, particularly in view of their capacity for proliferation.

In a patent published in 2006 by Furcht *et al.*, methods for isolation of multipotent adult stem cells and its use for treating cancer are described. MSCs were genetically altered to express a tumoricidal protein, an anti-angiogenic protein,

or a protein expressed on the surface of a tumor cell in conjunction with a protein associated with stimulation of an immune response to an antigen. In this invention, MSCs were promoted as a novel vehicle for cancer therapies that can be induced to differentiate to form endothelial cells or precursors which will home to endothelial tissues when delivered either locally or systemically. The cells participate in angiogenesis by integrating into the blood vessels in the newly-formed tumors. Upon stimulation, genetically engineered cells undergo apoptosis and the newly-formed blood vessels can be disrupted and thus blood flow to the tumor can be eliminated [51]. An example of an externally-delivered element would be the transfection/transduction of a gene that promotes apoptosis under control of a tetracycline response promoter [52]. In this system, the target gene can be activated by administration of doxycyline [52-54]. In 2010, the same group published another invention that described genetically modified MSCs that secrete products into the extracellular environment which are toxic to tumor cells or disrupt angiogenesis, such as pigment epithelium-derived factor (PEDF) [55]. Another approach is to utilize MSCs as a vector for delivering cancer vaccines. MSCs can be isolated from the patient, cultured *ex vivo*, genetically modified to express the appropriate antigens, and reintroduced into the subject to produce an immune response specific to the receptors expressed on the tumor cells.

The use of MSCs and a demonstration of their various applications are given by Pittenger and Aggarwal in a patent published in 2011 [56]. The explained methods are for treating autoimmune disease, promoting wound healing, and inducing angiogenesis in tissues and organs (Table **3**). The authors have examined the interactions of MSCs with isolated immune cells, including dendritic cells (DC1 and DC2), effector T-cells (Th1 and Th2), and NK cells. They discovered that MSCs may regulate the production of various factors that could regulate several steps in the immune response. These findings may be employed in the treatment of disease conditions and disorders, including autoimmune diseases, allergies, arthritis, inflamed wounds, alopecia areata, and periodontal diseases. In addition, it is believed that MSCs stimulate peripheral blood mononuclear cells (PBMCs) to produce vascular endothelial growth factor, which stimulate the formation of new blood vessels. Furthermore, it is believed that MSCs stimulate DCs to produce IFNβ, which promotes tumor suppression.

In another example, methods for stem cell therapy using direct inhibitors of lysophosphatidic acid (LPA) were provided [57]. Application of MSCs in two therapeutic areas (oncology and immune and inflammatory diseases) were also of interest in the recently published patent [58]. The authors aim to avoid a central problem in adult stem therapy, namely the inability to predict the behavior of transplanted cells in a patient's body. One of the concerns is the purity of cells and the potential to transplant cell populations that already have been differentiated which may not act in the intended manner. Here, methods for stimulating and isolating MSCs have been described. Stimulated MSCs (MSC1) compared to non-stimulated MSCs (MSC2) demonstrated elevated secretion of IL4, IL6, IL8 and IL10, CXCL5, reduced secretion of transforming growth factor (TGF)β1 and TGFβ3 and increased indoleamine 2,3-dioxygenase activity. In one em-

bodiment, a method for treating ovarian cancer is provided by delivering isolated MSC incubated with at least one selected Toll-like receptor ligand (TLR) for up to 2 h, where *in vitro* studies show divergent effect of MSC1 and MSC2 on co-cultures of different human cancer cell lines with MSC1 and MSC2 [58].

TGFβ is also of interest in another invention that describes effective treatment of autoimmune diseases by TGFβ-incorporated MSCs [59]. According to a present disclosure, the authors provide a composition for treatment of autoimmune diseases including TGFβ-encoding MSCs introduced with TGFβ-encoding nucleotide sequence and a pharmaceutically suitable carrier. The composition may be administered to the organism by any known method, for example, orally or non-orally.

A new approach for targeting brain tumor cells has been developed using stem cells to deliver therapeutic agents to tumor areas. For targeted delivery, neural stem cells (NSCs) have been well studied and applied first. For example, a group of authors have demonstrated that neural stem cells (NSCs) possess significant migratory behavior with extensive tropism to gliomas when administered intracranial [60-63]. NSCs distribute throughout the primary tumor and migrate together with widely outgrowing tumor microsatellites. Moreover, when NSCs are implanted intracranial at sites distant from the tumor, they migrate through the normal parenchyma and localize in the tumor. This behavior of NSCs has been exploited as a tumor-targeting strategy for glioma gene therapy [42, 60-63].

The new invention, presented by Zhang *et al*. published in 2010 [64], provided technology for treatments of central nervous system (CNS) tumors with stem cells (Table **3**). Briefly, the disclosure provides a modified stem cell controlled-release vehicle with anti-neoplastic agent. A controlled-release vehicle is selected from a group consisting of nanoparticles, biocompatible polymers, polymeric matrices, liposomes and lipospheres. The modified stem cells exhibit tropism to glioma cells, leading to a locally-concentrated dose of the anti-neoplastic agent which may kill or damage the target cells or tissues, resulting in destruction of the tumor seen by reduction of the tumor size or volume. The modified stem cells may be administered after surgery, or to patients that for one or more reasons has not and/or cannot undergo surgery or conventional radiotherapy or chemotherapy. In addition, for more effective therapy the modified stem cells may be loaded with more than one chemotherapeutic agent for targeting neoplastic cells.

The use of magnetic nanoparticles for labeling MSCs in cancer treatment is given in a recently published invention by Janes *et al*. [65]. The authors developed a new technique that utilized MRI to track MSCs labeled with biocompatible iron oxide nanoparticles. They suggested that labeled-MSCs can be used for the delivery of anti-tumor factors directly to the site of tumors. Furthermore, the iron oxide nanoparticles incorporated into the MSCs can also be used to damage the tumor by thermotherapy.

An interesting approach given in the invention of Deng *et al*., is a combined use of MSCs and protein vaccine for treating cancer (Table **3**) [66, 67]. The authors present a

Table 3.   Patents Subjected to MSCs and their Use.

Patent/Year	Inventor(s)	Reference	Description of the Invention
US7015037 (2006)	Furcht, L.T, Verfaillie, C.M., Reyes, M.	[51]	MASCs isolation methods and MASCs as a novel vehicle for cancer therapies.
US7659118 (2010)	Furcht, L.T., Verfaillie, C.M., Reyes, M.	[55]	Genetically altered MASCs toxic to tumor cells.
US20110142807 (2011)	Pittenger, M.E., Aggarwal, S.	[56]	MSC for treating autoimmune disease, promoting wound healing, and promoting angiogenesis.
US20100055167 (2010)	Zhang, A., Guan, Y., Chen, L.	[64]	Modified stem cells may be loaded with one or more chemotherapeutic agents for targeting neoplastic cell.
US 20110027311 (2011)	Deng, W-P., Chang, H-K., Wei, H-C., Wu, T-H.A.	[66]	Combination of protein vaccine and MSC (encoding at least one oncogenic protein) for treating cancer.
WO2012051210 (2012)	Betancourt, A.M.	[58]	MSCs and related therapies
US20120207725 (2012)	Cho, S.G., Park, M.J., Park, H.S, Cho, M.L.	[59]	Uses of MSCs incorporated with TGFβ nucleotide sequence
US20120010499 (2012)	Janes, S.M., Lythgoe, M.F., Pankhurst, Q.	[65]	Uses of MSCs incorporated with nanoparticles for cancer treatment
US20130052272 (2013)	Cohen, S.	[68]	Uses of cell extracts for treatment and prevention of cancer.
WO2013023040 (2013)	Sabbadini, R.A.	[57]	Stem cell therapy using inhibitors of LPA

method based on administration of a mammal-effective amount of stem cells encoding an oncogenic protein and a vaccine composition of immunogenic protein capable of eliciting an antibody specific effect against the oncogenic protein. Cancer vaccine therapy appears to be an attractive approach for cancer treatment because it has potential to target systemic tumors at multiple sites and specificity to distinguish healthy cells from neoplastic one.

Cancer can be initiated from epigenetic and genetic alterations of the genome presented as activation of oncogenes and inactivation of tumor-suppressor genes. The epigenetic alterations manifest as cell proliferation, inhibition of apoptosis and induction of angiogenesis. Whether a cell will obtain a malignant phenotype or not depends on differentiation state and epigenetic conformation. A recently published invention explains pharmaceutical compositions and methods for treatment of proliferative diseases such as cancer. The present invention is based on the fact that intra- and extracellular components of cells, particular stem cells, can serve as a rich source of biomolecules. These biomolecules can be growth factors, cytokines, structural elements and transcription factors, which can be involved in epigenetic reprogramming, or act to alter or reverse the malignant nature of the cancer cell and tissues [68].

MSCs GENETICALLY MODIFIED TO EXPRESS A SUICIDE GENE FOR TREATING A CANCER

MSCs expressing a suicide gene show excellent and highly selective anticancer effects. The method is based on selective conversion of a prodrug to an anticancer agent at the site of the cancer. Suicide genes are capable of converting a non-toxic prodrug to corresponding anticancer drug. For example, cytosine deaminase (CD) can convert 5-fluorocytosine (5-FC) to cytotoxic 5-fluorouracil (5-FU) which kills neighboring cells (bystander effect). The direct administration of 5-FU cause's cytotoxicity and leads to adverse side effects, but combination of a suicidal gene and 5-FC makes it possible to generate 5-FU selectively around tumor cells [69, 70]. Another example of a suicide gene is encoding herpes simplex type 1 thymidine kinase (HSV-TK), which converts non-toxic gancyclovir into a toxic phosphorylated metabolite [38]. Patents published in 2010 and 2012 by Nelson [71], provide a method for treating patients with pancreatic cancer through introducing a therapeutically effective number of genetically modified MSCs by IV. Engineered MSCs can selectively express cytotoxic protein when they come into proximity of the tumor's stromal tissue. Briefly, the patents provide a method for treating pancreatic tumor in human subjects by CD34⁻ modified cells with herpes simplex viral thymidine kinase encoding region operable linked to a RANTES promoter. The method first introduces about 1×10^5 to 1×10^9 cells/kg body weight of genetically modified CD34⁻ stem cells into the patient's blood followed by gancyclovir in a manner permitting the herpes simplex viral thymidine kinase to render the gancyclovir cytotoxic.

The patent published in 2005 by Snyder *et al.* [72] relates to treatments of CNS tumors with modified and unmodified stem cells (Table **4**). Particularly, the method explains systemic treatment of CNS and other tumors using NSCs which,

Table 4.   Patents Subjected to MSCs Genetically Modified to Express a Suicide Gene.

Patent/Year	Inventor(s)	Reference	Description of the invention
US20050019313 (2005)	Snyder, E.Y., Aboody, K.S., Brown, A.B., Breakefield, X.O.	[72]	Method of systemic treatment of CNS and other tumors.
US20080241115 (2008)	Suh, H-Y., Chang, D-Y., Kim, S-S., Yoo, S-W., Lee, Y-D.	[74]	Provides a kit for treating a cancer comprising an expression vector, with suicide gene, MSC and a prodrug of an anticancer agent.
US20090117050 (2009)	Cady, C., McAsey, M.	[75]	Methods for detecting and treating ovarian cancer with stem cells.
WO2010119039 (2010)	Nelson, P.	[71]	Genetically engineered MSCs and method of their use to treat tumors.
US20120087901 (2012)	Nelson, P.	[71]	Engineered MSCs and methods of using them to treat tumors.

like MSCs, fulfilled the requirement for cells with high migratory potential to the tumor and metastases site [73]. After a certain time, the stem cells migrate to the tumor site and systematically administered 5-FC would be converted by stem cells to toxic 5-FU [72].

Another study exploited safe and effective anticancer agents through expression of a suicide gene in MSCs which migrate into brain cancer in an animal model (Table **4**) [74]. The authors patented a kit for cancer treatment which consists of an expression vector with a suicide gene, MSCs and a prodrug of an anticancer agent. They suggest bone marrow, peripheral blood or cord blood as a source for MSC isolation.

For the first time, stem cells have been used for detection and treatment of ovarian cancer in an invention published in 2009 by Cady and McAsey (Table **4**) [75]. Their method includes administering labeled stem cells to patients having, or suspected of having, a cancer and detecting the distribution of the stem cells. In some configurations, the label can be nanoparticles like mono-crystalline iron oxide which can be detected by magnetic resonance imaging. Treatment methods include administration of stem cells hosting a therapeutic agent such as an enzyme which converts the prodrug (5-FC) into a cytotoxic metabolite.

MSCs MEDIATED VIRUS DELIVERY AND DELIVERY OF THERAPEUTIC PROTEINS

A significant advantage of MSCs as cellular vehicles is that they are relatively easy to genetically manipulate *in vitro*. In a majority of trials, adenovirus was used as a delivery vector. Low transfection efficiency using wild type adenoviruses results from the fact that MSCs have low levels of adenovirus receptor and a high-integrin phenotype. Modification of the adenovirus with incorporation of an arginine-glycine-aspartate section improves MSC transduction efficiency [36, 37]. Newly generated conditionally replicating adenoviruses provides increased delivery of viral load specifically to the tumor site [25, 35, 37]. It is critically important to avoid premature toxicity to MSCs prior to engraftment at the target site. By using an adenovirus with relatively slow kinetics, one can avoid early cell death [76].

One of the difficulties in the treatment of conditions such as cancer is the need to deliver large quantities of the therapeutic agent for extended periods of time. One approach is to use MSCs as micro carriers for protein delivery [77]. The invention of Paek from 2011 is based on this theory, and describes an adipose-derived stromal cell (ASC)-based delivery system for therapeutic delivery of biologically active anti-cancer agents. Some of the suggested deliverables to the tumor mass are anti-cancer protein molecules, apoptosis-inducing molecules, or an agent that inhibits the expression of an oncogene. The authors showed that ASC populations migrate and home into the cancer tissue making it possible to deliver a high dose of an anti-cancer agent locally and directly to the tumor site. In addition, ASCs have a short half-life in the circulation, so systemic non-specific responses will be minimal. This method allows the use of higher concentrations of the anti-cancer agents for more effective cancer treatment [78]. Integration of MSCs in the tumor stroma allows delivery of required dose of biological agents with short half-life or prominent toxicity. MSCs also can produce biological products at tumor sites and improve agents' pharmacokinetics [17]. One of the pioneering studies in this field is the work of Studeny *et al.* [79] where MSCs or stromal cell precursors were genetically modified to produce a therapeutic agent. The production of the therapeutic agent was localized in a specific area because gene modified cells preferentially localize in the target microenvironment. Exemplary microenvironments include a tumor or a wound in a tissue and/or organ. An anticancer agent includes, but is not limited to cytokines, a hormone, an enzyme, a signaling molecule, or an anti-angiogenic polypeptide. The therapeutic agent may be IFNα, IFNβ or similar. For example, with animal tumor models it has been shown that application of MSCs expressing IFNβ resulted in decreased tumor mass and increased animal survival. This fact brings new potential to the use of MSCs for regional secretion of IFNβ, because increased systemic levels of IFNβ and secretion at distant sites are not effective [20, 80]. Regional secretion is also required for a therapeutic effect of IL-12, and there are reports of significant therapeutic effect of MSCs engineered to secrete IL-12 [48]. Furthermore, MSCs secreting IL-12 [33, 48, 49] or IL-2 [34, 50] were shown to initiate an immunore-

action and stimulate inflammatory cell infiltration in the tumor tissue. Delivery of MSC-IL-12 increased tumor levels of IL-12 and did not cause systemic toxicity [49].

MSCs secreting TRAIL have been used in different models of cancers *in vivo*, resulting in significant anti-tumor effects [19, 46, 47, 65, 81, 82]. On the other side, MSCs (like most healthy tissues) are resistant to TRAIL-induced apoptosis due to their low levels and/or inactive receptors [46]. In addition, in the TRAIL transfected adult mesenchymal stem cells, fetal-MSCs and umbilical cord matrix stem cells, there is almost undetectable levels of apoptotic pathway components such as caspase-8 and -9 [83]. Delivery of this agent has advantages over some of the other anticancer MSC delivery systems described above since there appears to be very limited effects on non-cancerous tissues. Current clinical trials for TRAIL therapy in the form of recombinant protein and monoclonal antibodies show promising early results [84, 85]. However, targeted delivery of TRAIL with MSCs overcomes some of the problems which occurred in recombinant TRAIL therapy. MSC-TRAIL is more physiological than the monoclonal antibodies with much better half-life and delivery across the blood-brain barrier [1]. In an animal model study of lung cancer, local delivery of TRAIL by MSCs led to a reduction in tumor growth and significantly decreases lung metastases [19]. Also, therapeutic combination of the inhibitor of lipoxygenase MK886 and TRAIL-secreting human MSCs provided targeted and prolonged delivery of TRAIL in mouse models of glioma and *in vitro* [86]. The ability of TRAIL to selectively target tumor cells makes it an attractive candidate for therapy of malignant brain tumors [87]. In the invention of Shah, the methods of implantation of therapeutically engineered MSC with anti-tumor agents into tumor sites after surgery was presented. The results showed that MSC-TRAIL cytotoxic therapy is highly effective in inducing apoptosis and that TRAIL is a potent inhibitor of brain tumor growth. It was suggested that the present approach would significantly improve treatment outcomes [87].

NEW CONCERNS ABOUT USE OF MSCs FOR TUMOR TREATMENT

Great progress has been made in the research of MSCs, which generated a significant amount of interest as a result of their ability to home to the tumor site after systemic delivery. The proposed use of MSCs in cancer therapies is controversial, however, due to MSC promotion of tumor vascularization, promotion of cancer progression and the invasive tendency of tumors have been previously reported [29, 88, 89]. In some peritoneal cancers, like ovarian, bone delivered MSCs have been described as located around the tumor cells and in the ascitic fluid and no longer defined as multipotent as they are unable to differentiate in different cell lineages. They are defined as being carcinoma-associated (CA-MSCs) and present some characteristic markers of Carcinoma-Associated Fibroblasts (CAFs) [90]. A few authors and their research groups recently published that MSCs also can be involved in the development of chemoresistance to different chemotherapies through the release of factors in the neighborhood of tumors [91-95]. A number of targeted therapeutics are currently under development targeting not only cancer cells but also cells from the microenvironment such as

endothelial cells or mesenchymal stem cells. Although, these therapeutic approaches seem promising, they carry many side effects associated with the elimination of cells not involved in cancer progression or in chemoresistance. This is only a brief overlook on this topic because there is still no evidence which supports this hypothesis, and hope still remains as many authors have described cells from the microenvironment which display several differences with their parent cells. Akimoto *et al.* [29] in their work isolated primary glioblastoma multiforme (GBM) cells and used MSC co-culture and co-transplantation assays to analyze characteristics. They demonstrate that Umbilical cord blood-derived MSCs (UCB-MSCs) inhibit GBM proliferative activity, whereas Adipose tissue-derived MSCs (AT-MSCs) support GBM proliferation and presents their findings that the source of MSCs is very important for their clinical application. Differences also lie between cells of the same origin but which have evolved differently depending on the organ and associated pathologies. Parental cells (such as macrophages, neutrophils or MSCs) can mostly be found with antitumoral properties. In their study, Teng *et al.* [96] show that DNA hypermethylation within a specific tumor suppressor gene is sufficient to fully transform a somatic mesenchymal stem cell and proposed that under the influence of different environmental niches, these transformed stem cells could give rise to tissue-specific cancers. In agreement with previous reports suggesting contradictory effects of MSCs on tumor cell proliferation [34, 38, 97], some types of MSC show tumor cell cytotoxicity, while others do not. The proliferation of some cancer cells was enhanced by adding MSCs to the culture [88, 89] while on the other hand, some groups have reported the anticancer activity of MSCs [17, 20, 23, 42, 47, 97-99]. Conventional anticancer drug screening is typically performed in the absence of accessory cells of the tumor microenvironment, which can alter antitumor activity. Preclinical drug testing in the absence of relevant tumor microenvironment interactions may explain, at least in part, the gap between preclinical and clinical efficacy in cancers [100]. The inhibitory effect of MSCs on different types of tumor proliferation should be investigated before MSCs are used as a tool for drug delivery. However, very little is known about what actually causes the switch of a cell surrounding a tumor from inhibiting tumor growth to tumor-promoting. Therefore, given the evidence this hypothesis will be challenging.

CURRENT & FUTURE DEVELOPMENTS

A central issue in cancer chemotherapy is the severe toxic side effects of anticancer agents on healthy tissues, which invariably imposes dose reduction, treatment delay or even discontinuance of therapy. Toxicity for healthy organs can be significantly diminished by employing a drug delivery systems which targets only cancer cells. The ultimate goal of this area of research is the development of an anticancer therapy for humans and use of specific targeting to produce significantly less host toxicity than traditional agents and much higher local concentrations of antitumor agents.

Traditional chemotherapeutic agents are administered systemically. This may have undesirable side effects if the anti-cancer drug acts non-specifically on non-cancer cells, and may also result in only a small amount of the anti-cancer

drug actually reaching the site of the tumor. Additionally, the natural process of angiogenesis which provides vascularization and nutrients to the tumor may causes a concomitant increase in the size of the tumor. In some instances an antitumor drug or chemotherapeutic agent have been directed to the site of the tumor and specifically targets cancer cells using cell-surface targeting moieties, also called tumor associated antigens. However, even these methods suffer from a lack of effectiveness as the tumor associated antigens are not necessarily ubiquitous.

Accordingly, there is a need for more targeted tumor therapies.

This review highlights the potential for MSC-mediated delivery of therapeutic agents directly to tumor tissue based on the MSCs ability to localize and integrate into the tumor stroma. There are studies reporting engineered MSCs specifically targeting different tumor types followed by local secretion of therapeutic proteins such as, IFNα and IFNβ, IL12, IL2 or CX3CL1. MSCs have also been engineered to deliver conditional replicative oncolytic viruses. Furthermore, MSCs serve as therapeutic cytoreagents for gene therapy and vehicles for targeted chemotherapy with an enzyme prodrug conversion. Strong antitumor effects have been reported following administration of gene modified MSCs expressing TRAIL. Further understanding of the biology of MSCs, and the specific combination of factors controlling their tumour-specific migration and persistence will help these technologies translate to the clinical setting. To ensure the safety of anticancer therapy using MSCs and in agreement with previous reports suggesting contradictory effects of MSCs on tumor cell proliferation, the characteristics of MSCs themselves are quite important and should be investigated before using an MSC-based therapy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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