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Mesenchymal Stem Cells: vector for targeted cancer therapy

Binh Thanh Vu, Ngoc Kim Phan, Phuc Van Pham*

Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh city, Vietnam

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ABSTRACT

Mesenchymal stem cells (MSCs) have been studied extensively due to their potential to differentiate to cell types of varying lineages.Adipose tissue and umbilical cord blood are two tissues frequently used to obtain MSCs. Due to tumor tropism of MSCs and their ability to protect encoded cytotoxic genes, MSCs have garnered interest as a potential vector for targeted therapy, with limited damage to normal tissues. The tumor microenvironment plays a critical role in ensuring the survival of cancer cells through promotion of MSCs to differentiate into cancer-associated fibroblasts (CAFs), which promote tumor growth and metastasis. Through specific interactions between ligands and receptors expressed on MSCs and cancer cells, respectively,MSCs can home to necrotic tissues or inflamed sites in the body, including the tumor microenvironment. In fact, an inflammatory tumor environment is similar to a wound healing environment. This review discusses the preeminent characteristics of MSCs and their influence ontumor cell growth and metastasis. MSCs may represent an encouraging platform for cancer treatment. The combination of MSC and gene therapy represents a potentially outstanding strategy to specifically target and effectively destroy tumor.

Keywords: Cancer stem cells, cancer-associated fibroblasts, mesenchymal stem cells, stem cell/gene combined therapy, tumor microenvironment

Introduction

Cancer continues to be a huge disease burden across the globe, even despite more improvements in prevention, diagnosis and treatment of cancer. One of the main obstacles in cancer treatment remains the fact that the cancer cells cannot be completely destroyed and that specific target of cancer cells is still incomplete. Conventional cancer therapies remain limited. Surgery is invasive and only effective with large tumors; but most cancers are known to become metastatic and surgery is futile for those metastatic cancer cells in the bloodstream).

* *Corresponding author: Phuc Van Pham, Email: pvphuc@hcmuns.edu.vn*

Both chemotherapy and radiation therapy produce unwanted damage to normal cells, and often serious side effects for the patient. Despite robust treatment with conventional therapies, residual cancer cells linger in the body because of weak tumor-specific attack. In addition, another important consideration is that anti-cancer drugs used in cancer treatments have a very rapid half-life *in vivo*. This raises the requirement to establish a therapeutic strategy with a vehicle that can transport cytotoxic gene products directly to malignant cells. Mesenchymal stem cells (MSCs) have been becoming a major interest as a vehicle for this approach; combining gene therapy and stem cell therapy is a promising direction to overcome existing limitations in the fight against cancer.

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) have been studied extensively because of the following reasons: (i) MSCs bear the characteristics of stem cells, including the ability to self-renewal and the potential to differentiate. Although MSCs are derived from the mesodermal layer during embryonic development, they possess the potential to differentiate to cell types of other lineages, either within or across germ lines (Anderson et al., 2001; Jiang et al., 2002); (ii) MSCs exist in different types of tissue throughout the body, which allows a diversification of sources from which collect to MSCs; this helps overcome concerns in acquisition of stem cells. Although isolating MSCs from bone marrow (BM) is challenging, MSCs can now be easily isolated from adipose tissue or umbilical cord blood; (iii) the application for use of MSCs in clinical treatment is overall easier and incurs fewer moral obstacles than the application of embryonic stem cells (ES) or induced pluripotent stem cells (iPS).

In the BM, hematopoietic stem cells and MSCs are both multipotent stem cells present at low frequency ($1/10^4$-10^5 mononuclear cells). Related studies showed that MSCs have a strong ability to proliferate without loss of their phenotype or multilineage potential (In 't Anker et al., 2004). Based on the most common features of MSCs, such as expression markers, physiological characteristics as well as ability to differentiate into osteogenic, chondrogenic and adipogenic cells, researchers have been able to identify MSCs easily throughout the body (da Silva Meirelles et al., 2006; Fukuchi et al., 2004; Momin et al., 2010; Romanov et al., 2003). This suggests MSCs may have a particularly important role in tissue regeneration. MSCs were first obtained from BM; indeed, BM-derived MSCs, to date, are still considered the standard cell source in research applications. However, the process of BM-derived MSC acquisition is highly complicated, which adversely affects the ability to receive MSC donors (Bentzon et al., 2005; Kern et al., 2006; Mueller and Glowacki, 2001). Therefore, there is a need for alternative sources of MSCs, without greatly affecting MSC number, differentiation potential and lifespan. Adipose tissue and umbilical cord blood are the two most promising tissues. Adipose tissue has the following advantages: (i) it is usually obtained from subcutaneous tissue and represents reduced invasion; (ii) it maintains MSCs called adipose-derived stem cells (ADSC), which is considered to be an autologous stem cell source in personalized cell-based therapies. Mononuclear cell populations obtained from umbilical cord blood have been shown to also be a rich source of MSCs. Umbilical cord blood derived MSC have two main advantages: (i) the number of stem cells in cord blood are higher than other adult tissues; and (ii) the majority of stem cells in cord blood are naive, which may be due in part to higher telomerase activity (Chang et al., 2006), thus they have higher proliferation (Goodwin et al., 2001). MSCs derived from adipose tissue or umbilical cord blood are mostly identical with those from BM (Bieback et al., 2004; Erices et al., 2000).

Particularly, MSCs have characteristics that are superior to other types of stem cells, making MSCs rise as a superior candidate for stem cell therapy. These characteristics include: (i) MSCs are adult stem cells and therefore their application in autologous therapy is easily

implemented and with reduced possibility of causing graft versus host disease (GvHD). Even in the case when autologous MSCs are not available, umbilical cord blood can serve as a qualified source for acquiring MSCs to adequate quantity. In addition, since MSCs have immunosuppressive properties, one can use allogenic MSCs with appropriate HLA compatibility; (ii) *in vivo* MSCs are involved in the recovery of damaged tissues because of the ability to secrete and recruit tissue regenerative stimulants. Due to their trophic nature to direct factors to damaged tissues, MSCs have been increasingly evaluated as a potential vector for targeted therapies, with minimal effects on normal tissues; (iii) MSCs are one of the few kinds of stem cells which can be obtained from the body's tissues, cultured and manipulated *in vitro,* and then transplanted back into the body without causing serious complications, and under appropriate control. In addition, manipulation of MSCs is easy, without being extensively time-, labor-, and cost-consuming.

Prochymal is a MSC-containing product approved in Canada, which is also the first product in the world applying stem cell therapy in the disease treatment. Although these MSCs are derived from allogenic individuals their efficiency remains high, as expected, due to the fact that MSCs have the ability to suppress immune responses. MSC grafts modulate the immune system via cell-cell interaction and through soluble factors. MSCs secrete immunosuppressive molecules, including hepatocyte growth factor, prostaglandin E2, TGF-β1, indoleamine 2,3-dioxygenase, nitric oxide and IL-10. Contact-dependent mechanism, via B7H1 (also known as PD-L1 or CD274) interactions, can also explain MSC-mediated immune suppression. As a result, the function of a broad range of immune cells, including T cells, B cells, NK cells and antigen-presenting cells, are downregulated(Stagg, 2007).

MSCs have the ability to home to the tumor location through a specific interactions between ligands and their respective receptors expressed on MSCs and on tumor cells in their microenvironment (Massague et al., 2000; Mishra et al., 2005). Many researchers have been focusing on the use of MSCs as vehicles to deliver targeted cytotoxic agents to cancer cells. This innovative approach has several advantages: (i) compared to naked or polymer-enclosed anti-cancer drugs, MSCs can deliver drugs to the desired location without damaging normal tissues; (ii) MSCs can secrete drugs through exosomes, which enable drug delivery to take place over a longer period, avoiding acute severe side effects associated when a high dose of drugs is injected in the body. This allows the lifetime of the drug flow to be extended, thereby restricting repeated drug delivery into the body in order to achieve clinical efficacy.

MSCs have been collected from various tissues. There are many reports on the expression of molecular markers on their cell surface which makes it easier to acquire and evaluate the MSC population. MSCs highly express CD105 (endoglin), CD73 (ecto-5′-nucleotidase) and CD44 (hyaluronate receptor), but are negative for CD45 and CD31, which are markers for hematopoietic and endothelial cells, respectively. MSCs are also characterized by low level of major histocompatibility complex (MHC) class I molecule expression, which contributes to the limited ability of the immune system to be activated and to reject the allogenic MSC graft.

There are also many reports on the mechanism of MSC homing to damaged tissue or sites of inflammation, including the tumor microenvironment which mimics a wound healing environment. The homing process of MSC is a dynamic navigation via gradient chemotaxis among a range of ligand-receptor bonds, notably the binding between CXCL12 (SDF-1) and CXCR4. In addition, MSCs express other chemokines and chemokine receptors which have a role in ensuring their migration to neoplastic tissues; these include CCR1, CCR7, CCR9, CX3CL1, CXCR4, CXCR5 and CXCR6 (Honczarenko et al., 2006). Moreover, MSCs express various growth factors (GF) and GF receptors which help them easily move to the tumor microenvironment where the GFs, e.g. HGF-cMet, are being continuously secreted.

One very important question that warrants consideration is whether the MSCs, particularly allogenic MSCs, are really safe in clinical use. MSCs are adult stem cells which, as they age, lose telomere length after repeated cell divisions. During the process of isolating and culturing MSCs according to clinical standards, they are obtained without any malignant changes. There are many agencies in developed countries that have allowed the use of MSCs isolated from umbilical cord blood, as a potential source of MSCs which replaces the BM, in the treatment of many serious diseases. The results demonstrate that disease can go into remission without any serious side effects.

Tumor microenvironment

Cancer has been and will continue to be a big burden of disease across the world, with continued mortality and impact on quality of life for patients. Although the traditional methods for cancer treatment have increasingly improved, clinical results clearly show that surgical therapy, chemotherapy and radiation therapy cannot eliminate all cancer cells. In addition, the side effects of those therapies cause serious harm to the patients. One characteristic of malignant cells is the ability to acquire resistance to the chemotherapy or radiation therapy. Tumor cells then become more difficult to be killed, leading to increased proliferation, invasion and metastasis, and ultimately increasing the risk of death for cancer patients.

Importantly, a major reason why anti-cancer therapy resistance develops is the presence of stem-like cancer cells, known as cancer stem cells. In addition, the tumor microenvironment plays a critical role in ensuring the survival of cancer cells. There are several hypotheses to explain the establishment of a tumor microenvironment. It can mimic an inflamed tissue state, due to similarities of in cellular and non-cellular components of a damaged tissue microenvironment and of a tumor microenvironment. This explains the reason why tumors are sometimes referred to as "wounds that never heal". The role of MSCs in supporting the proliferation of cancer cells is, thus, very important.

Beside cancer cells, cancer-associated fibroblasts (CAFs), which are differentiated from MSCs, play a key role in the tumor microenvironment. CAFs secrete factor stromal cell-derived 1α (SDF-1α; also known as CXCL12) which interacts with CXCR4 expressed on cancer cells, promoting tumor proliferation. CAFs also generate an extracellular matrix (ECM), through secretion of molecules, including collagen, laminin, heparansulfate, proteoglycan. The ECM becomes a scaffold for cancer cells to anchor, spread and proliferate. Moreover, the ECM is sometimes compared to an energy warehouse because it contains growth factor (GFs) secreted by both cancer cells and stromal cells. During cancer cell invasion and metastasis, GFs and cytokines are released from the ECM, promoting survival of cancer cells and prolonged metastasis. Moreover, the tumor microenvironment also contains cells of the immune system and blood vessels that supply nutrients and oxygen to the tumor. Initially, immune cells infiltrate the tumor with the aim of destroying abnormal cells, including cancer cells, via induction of chemokines which are secreted by tumor initiating cells. However, the tumor microenvironment is immunosuppressive, causing immune cells to fail in their cytotoxic function and promoting tolerance. Tolerized immune cells secrete GF and other cytokines which promote tumor growth.

The tumor microenvironment not only supports tumor formation and growth but it also promotes metastasis of cancer cells. The larger the tumor mass is, the less nutrients and oxygen the cancer cells receive, leading to hypoxia. Hypoxia activates transcription factor HIF-1/2 expression which in turn promotes cancer cells to secrete proangiogenic molecules, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), CCL2, CXCL-1, -5, -8, -12, and -13. The CXCL12 and CXCR4 interaction is responsible for angiogenesis and metastasis. However, it is clear that vascular endothelial cells proliferate more slowly than

cancer cells, leading to abnormal blood vessel formation in the tumor microenvironment. Unlike normal blood vessels, the tumor vasculature has several distinct features: unstable perfusion, abnormal vascular density, primitive vessels due to lack of basement membrane, an endothelial lining, pericytes, and smooth muscle. Aberrant or leaky neovasculature is responsible for reduced distribution and removal of molecules in blood. This would explain why anti-cancer drugs often do not reach tumor tissues but instead damage normal cells, causing serious side effects.

In order to metastasize, cancer cells must invade tumor stroma to penetrate into the bloodstream. This leads to degradation of a small part of the ECM. A variety of proteins are involved in ECM degradation, including matrix metalloproteinase (MMP), adamalysin-related membrane protease, bone morphogenic protein (BMP) metalloproteinase, endoglycosidase and tissue serine protease. Moreover, tissue plasminogen activator, urokinase, thrombin and plasmin promote extensive remodeling and stimulate alternative signaling from the cell surface.

One of the most studied molecules responsible for ECM degradation is MMP, which is mostly secreted by inflammatory cells, including mast cells, macrophages and neutrophils. Inflammatory cells are attracted to the tumor location by induction of chemokines that are secreted in the tumor microenvironment, such as CCL-2 (MCP-1), -3 (MIP-1a), -4 (MIP-1b), -5 (RANTES) and CXCL12 (SDF-1). Upon arrival, inflammatory cells secrete GF, cytokines and chemokines, all which facilitate tumor growth and progression.

As mentioned before, the metastatic process begins when cancer cells invade the tumor stroma to intravasate into the circulatory system, and ends when cancer cells extravasate into targeted tissues. It is then that cancer cells establish new tumors, i.e. regenerate a new tumor microenvironment. This requires the recruitment of stromal cells, in which TAFs has the important role. TAFs include matrix-synthesizing/matrix-degrading cells, myofibroblasts, fibrocytes, or pericytesdifferentiated from MSCs (Silzle et al., 2004)). In tumor development, there is a balance between ECM degradation and synthesis; cellular survival requires ECM stability.

Therapeutic application of MSCs in cancer treatment

Initially, hematopoietic stem cell therapy was used in cancer treatment. The results were limited because blood cell recovery was slow in patients. With the ability to secrete hematopoietic cytokines, MSCs have a positive impact on hematopoiesis(Koc et al., 2000).

In the study of Ruan, et al., the authors applied MSCs as "a tool to detect mines". MSCs were fluorescently labeled then injected into tumor-bearing mice to determine the location of cancer cells. The results showed that MSCs "home" directly to cancer cells and were able to locate them through CCL19/CCR7 and CXCL12/CXCR4 axis loops (Ruan et al., 2012).

MSCs facilitate tumor cell dissemination

Malignant cancer cells favorably metastasize to bone, even though bone is one of the main locations where tumor-initiating cells are already present. The existence of MSCs in compact bone helps to facilitate interactions with cancer cells; for instance, MSCs facilitatemetastasis of cancer cells into BM. For bone resorption, tumor cells stimulate BM-resident MSCs: (i) to markedly increase levels of interleukin-6, an osteoclast-activating factor (Sohara et al., 2005); (ii) to express chemokine CCL5 (also called RANTES), which acts in a paracrine loop on cancer cells to enhance their motility, invasion and metastasis (Karnoub et al., 2007); (iii) to facilitate disseminated breast cancer-initiating cells (BCIC) to enter BM of patients with primary breast cancer, partly through Tac1-mediated regulation of SDF-1alpha and CXCR4 (Corcoran et al., 2008), and through GD2 and CD2, expressed on bone marrow mesenchymal stem cells (BM-MSCs) (De Giorgi et al., 2011).

MSCs are attracted to tumors because the tumors have a similar environment as wound healing. MSCs increase the motility of cancer cells by activating ADAM10 (also known asCDw156 or CD156c) (Dittmer, 2010). TNF-alpha is the most potent inflammatory cytokine present in the tumor microenvironment. Exposure to BM-MSCs to TNF-alpha promotes locomotion of cancer cells through CXCR3 ligand (Shin et al., 2010). IL-1alpha, secreted by inflammatory cells, also induces MSCs to promote the growth of cancer cells (Cheng et al., 2012).

TGF-beta1-dependent immunosuppression is one of mechanism by which MSCs support tumor growth. MSCs increase the frequency of regulatory T cells (Tregs), and as a result, NK cell and CTL functions are inhibited and granzyme B production is decreased (Patel et al., 2010). MSCs migrate and differentiate into tumorstroma cells, including CAFs and even vascular endothelial cells, which then enhance angiogenesis in the tumor microenvironment (Albarenque et al., 2011; Shinagawa et al., 2010; Zhang et al., 2010).

Cancer stem cells, which are also known as tumor-initiating cells (TICs) are responsible for tumor initiation, maintenance and metastasis. Tumor-derived MSCs significantly increase tumor initiation caused by TICs, even transplanted TICs (Lanza et al., 2012). Through expression of matrix metalloproteinases 1 and 3, BM-MSCs support metastasis of invasive cancer cells. They also efficiently chemoattract endothelial cells (Zhao et al., 2012).

MSC/gene therapy combination: "Trojan Horse" to target specific tumor locations

MSCs represent an outstanding vehicle for gene delivery. Cytosine deaminase (CD), which converts prodrug 5-FC (5-fluorocytosine) to toxic 5-FU (5-fluorouracil), is one cytotoxic gene that has been extensively investigated in gene therapy applications. Interestingly, MSCs engineered to deliver CD (CD-MSC) were not sensitized to 5-FC, thus showing they can overcome the often deleterious effect of a suicide gene expression by a cellular vehicle. CD-MSC can deliver the transgene to the site of tumor formation and mediate strong antitumor responses (Kucerova et al., 2007). Lentiviral (LV)-transduced MSCs do not show altered features in cell growth, differentiation capacity or migration preferences (Kallifatidis et al., 2008). MSCs delivering recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) showed profound anti-tumor effects without affecting their "stem-like" properties or survival (Sasportas et al., 2009). In addition to virus-based gene delivery system, it is feasible to use non-viral vectors to transfer therapeutic genes to MSCs (Hu et al., 2012).

MSCs act as a shield to protect the tumoricidal gene therapy vector in the bloodstream. Compared to viral-based gene transfer methods, transduction of an adenoviral vector expressing TRAIL into MSCs showed stability in circulation, as well as induction of high levels of virus-neutralizing antibodies (Mohr et al., 2008). Importantly, TRAIL-engineered MSCs can produce anti-cancer agents locally and continuously (Moniri et al., 2012), resulting in decreased bone and lung metastases (Reagan et al., 2012).

Adipose-derived mesenchymal stem cells (ADSC) are available for personalized medicine. ADSC have also been engineered to express TRAIL, and were capable of mediating malignant cell apoptosis without any significant or apparent toxicity to normal tissues (Grisendi et al., 2010). MSCs armed with TRAIL migrate to tumor and reduce tumor growth. Interestingly, MSC/gene combined therapy has a synergistic effect when combined with traditional treatments (Loebinger et al., 2010).

Adeno-associated virus (rAAV) have also been evaluated for gene modification of MSCs, including to constitutively express interferon (IFN)-beta. The most notable results of IFN-beta-expressing MSC therapy was the ability to trigger anti-cancer immune activity (Ren et al., 2008). Particularly, high levels of IFN-beta were detectable only in the tumor microenvironment, and normal levels of dendritic cells (DC), $CD8^+$ T cells and $CD4^+/Foxp3^+$ regulatory T-cells (Tregs) were detected.

Cancer cell-replication-related signaling pathways, including those of Stat3, Src, Akt, cMyc and MMP2, are down-regulated. As a result, primary tumor growth and metastasis are inhibited (Ling et al., 2010).

The amniotic fluid plays a very important role in the development of the fetus. Human amniotic fluid-derived mesenchymal stem cells (AF-MSCs) were successfully expanded and manipulated by lentivirus to express interferon beta (IFN-beta). The gene modified AF-MSCs had the ability to reduce tumor growth (Wang et al., 2012), as well as prolong survival of tumor-bearing mice (Bitsika et al., 2012).

Immunotherapy has many advantages in cancer treatment; perhaps the most important one is the ability to harness and activate the immune system to destroy cancer cells. Immunotherapy remains still a relatively new therapy compared to conventional therapies. The strategy relies on effector cells to generate immune reactions strong enough to eliminate the tumor, but without causing hypersensitivity or autoimmune reactions. Immunotherapy includes the cellular components, such as effector cells, and non-cellular components, such as cytokines and antigens, which stimulate immune responses. Many kinds of cytokines have been used in immune therapy but their anti-tumor therapeutic efficacy is still low. This is due to the fact that most cytokines are injected into the bloodstream, causing systemic toxicity. Umbilical blood mononuclear cell (UBMC)-derived mesenchymal stem cells (UBMC-MSCs) expressing IL-21 showed delayed tumor growth and prolonged survival in ovarian-cancer-bearing mice (Hu et al., 2011). Lentivirus-mediated TNF-alpha-expressing MSCs induced apoptosis in cancer cells via antiangiogenic effects (Zhang et al., 2011). Moreover, MSCs and protein vaccination, in combination, demonstrated a significant inhibition of tumor growth and lung metastasis (Wei et al., 2011).

Suicide gene therapy have been attracting great attention from the scientific community. Its principle is based on therapeutic (usually cytotoxic) gene transfer to specific tumor locations in the body. A harmless prodrug is administered into the body; when the pro-drug reaches the tumor site, enzymatic activity encoded from the suicide gene converts the prodrug into a toxic drug, which then destroy cancer cells at the site. MSCs can be engineered to selectively express herpes simplex virus-thymidine kinase (HSV-tk) gene; these engineered MSCs accumulate at the tumor site. Following ganciclovir infusion, MSCs expressing HSV-tk are activated and can suppress tumor growth (Uchibori et al., 2009) and significantly prolong survival of tumor-inoculated animals (Bak et al., 2010), by creating a toxic tumor-specific environment without transduction of suicide gene to normal organs (Conrad et al., 2011).

Angiogenic prevention is a way to limit tumor growth and control cancer cell metastasis. Endostatin and angiostatin are potent inhibitors of tumor angiogenesis. Endostatin-engineered MSCs can overcome the limitation of short half-time and toxicity related to virus-mediated endostatin gene therapy (Jiang et al., 2010). Zheng et al. demonstrated that adenoviral transduction of human placenta-derived mesenchymal stem cells (hpMSCs) to deliver endostatin has many promising results; for instance, the toxic effects were specific to the tumor site with significantly decreased blood sprouts and dramatically increased tumor apoptosis index (Zheng et al., 2012).

Tumor vasculature plays an extremely important role in tumor cell maintenance and metastasis. Anti-angiogenesis mediators contribute to new era of hope for cancer patients. Expression of pigment epithelial-derived factor (PEDF), a potent anti-angiogenesis mediator, did not adversely affect MSC biology. MSC-MDA7 reduced tumor growth. Moreover, MSC-PEDF reduced growth in even more aggressive cancer models, and were able to completely prevent prostate tumor establishment *in vivo*(Zolochevska et al., 2012).

The interaction between tumor cell and MSCs: The interaction between two opposite charges

Stimulated by molecules secreted in tumor microenvironment, human adipose tissue-derived

mesenchymal stem cells (hADSCs) differentiate into cancer-associated myofibroblasts or fibroblasts, which play a pivotal role in tumorigenesis. Cancer-derived lysophosphatidic acid (LPA) induces the differentiation process through multiple signaling pathways involving TGF-beta1-Smad (Jeon et al., 2008), Rho kinase, ERK, PLC and phosphoinositide-3-kinase (Jeon et al., 2010).

Once MSCs differentiate into osteoblasts, CCL2 level is significantly elevated. The bone-derived CCL2 induces migration of breast cancer cells. After co-culture with MSCs, breast cancer cells also overexpress genes involved in CCL2-mediated signaling pathways (Molloy et al., 2009).

Prevention of adipocyte differentiation is one of approach that cancer cells use to control MSC differentiation into cell types which support tumor cell homing and progression. High presence of matrix metalloprotease-9 (MMP-9) and urokinase plasminogen activator (uPA) in cancer cell-conditioned media confirmed this effect (Xu et al., 2009). MSCs also upregulate MMP-2 and MMP-9 in prostate cancer cells, which in turn promote cancer cell proliferation, migration and invasion (Ye et al., 2012).

Cancer cells interact with each other and with the surrounding environment through direct interaction; additionally, communication among cells in the tumor microenvironment is mediated through soluble molecules. These molecules can be directly secreted and have autocrine or paracrine influence once they interact with compatible receptors expressed on target cells. When surface receptors are not available, to ensure that the signal to stimulate cancer cell proliferation is maintained, cancer cells secrete these molecules through exosomes. Exosomes supply a diverse source of cytokines, chemokines, and growth factors, and enter target cells more easily through membrane fusion. Ovarian cancer-, breast cancer-, gastric cancer-derived exosomes contribute to the development of tumor-associated myofibroblasts, derived from MSCs. The exosomes also increase expression of tumor-promoting factors, SDF-1, VEGF, CCL5 and TGF-beta, by activating both SMAD-dependent and SMAD-independent intracellular signaling pathway (Cho et al., 2011; Cho et al., 2012; Gu et al., 2012).

The impact of isolation and culture of MSCs on cancer cells is unclear. Studies have focused on identifying how conditioned media-derived from MSCs alters the characteristics of the cancer cells. Halpern et al. analyzed MSC-conditioned media and revealed the presence of numerous cytokines, most notably CXCL1 and CXCL5, which significantly enhanced the migration of mammary cancer cell lines (Halpern et al., 2011).

Tumor associated MSC (TAMC) secrete pro-tumoral cytokines; of these, CXCL12 is considered to display strong protective effects through CXCL12/CXCR4 interaction in ovarian cancer cells (Lis et al., 2011). TGF-beta-mediated salivary gland cancer cells recruit MSCs and, in turn, MSCs disperse cancer cell connections and reduce the expression of E-cadherin in cancer cells. Moreover, the invasion of salivary cancer is enhanced under a chemokine CXCL12 gradient produced by MSCs (Ma et al., 2012a).

The existence of cancer stem cells (CSCs) has been demonstrated. Like all tissues that contain stem cells, the tumor consists of heterogeneous stem cell populations. The CSCs are organized based mainly on the state of cell differentiation, e.g. on expression of pluripotency markers, such as aldehyde dehydrogenase. MSCs can accelerate tumor growth by increasing the breast CSC population, through cytokine loops involving IL6 and CXCL7. Primary human breast cancers and tumorxenografts represent MSC-CSC niches, enhancing drug resistance and pluripotency through activation of the IL-6/JAK2/STAT3 pathway (Hsu et al., 2012; Liu et al., 2011a). Carcinoma-associated MSCs (CA-MSCs) have been identified in a majority of human ovarian tumor samples. CA-MSCs increase expression of BMP2, BMP4 and BMP6, which promote tumor growth by increasing the number of CSCs (McLean et al., 2011). Cancer cells and MSCs can interact in a reciprocal fashion. For example,

cancer cells secrete interleukin-1 (IL-1), which stimulates prostaglandin E(2) (PGE(2)) secretion from MSCs. IL-1 and PGE-2 induce MSCs to produce a variety of cytokines. MSC-secreted PGE-2 and cytokines , in turn, can act on cancer cells to induce activation of beta-catenin signaling and formation of cancer stem cells (Li et al., 2012). Co-culture of cancer cells with MSCs increased the population of CD133+ gastric carcinoma cells (known as CSCs) through the wingless-type MMTV integration site (WNT) family member 5A (WNT5A) and transforming growth factor-beta (TGF-beta)-induced (TGFBI) genes (Nishimura et al., 2012). The epithelial-mesenchymal transition (EMT) was detected very early during embryonic development; the EMT process helps facilitate cell rearrangement and organ formation. The process of carcinoma development through metastatic initiation is thought to mimic the EMT process. Cell-cell connections, via firm bonds, are what limits movement of epithelial cells. In a microenvironment where nutrients and oxygen are deficient, as in the tumor microenvironment, the epithelial-like cancer cells undergo EMT to establish mesenchymal-like cancer cells, liberating the cell-cell and cell-ECM interactions, and initiating metastasis. Cancer cells which undergo EMT are considered to be tumor-initiating cells. MCF7 cells underwent EMT after co-culture with human adipose-derived MSCs (hAD-MSCs). The mechanism which MSCs induce cancer cell EMT is primarily mediated by transforming growth factor-beta1 (TGF-b1) (Xu et al., 2012).

It is obvious that the tumor microenvironment (which is nutrient-deprived and hypoxic) and the inflammatory factors present in the microenvironment play a pivotal role in enhancing the hypoxia-inducible factor 1alpha (HIF-1alpha)-dependent pathway.IFN-gamma and TNF-alpha, known as two of most potent inflammatory molecules, further accelerate tumor angiogenesis through VEGFproduced by MSCs (Liu et al., 2011b). Breast cancer-associated MSCs secrete EGF and provide a favorable microenvironment for tumor cell growth via the EGF/EGFR/Akt pathway (Yan et al., 2012).

Anti-tumor cell property of MSCs

Although many studies have showed that MSCs support tumor formation, survival and malignancy, other reports have indicated that MSCs have the ability to kill cancer cells. The latter observation came from studies of MSCs (isolated from cancerous tissues) which had the ability to promote tumor growth. By chemoattractant mechanisms and employment of molecules generated from MSCs, cancer cells sustain growth and escape from attack by the immune system. MSCs isolated from healthy tissues have become a powerful tool for gene therapeutic transfer to cancer tissues based the ability of MSC to show tumor tropism. MSCs have an inhibitory effect on MCF-7 cells as well as K562 cells, via expression of dickkopf-1 (Dkk-1, a well-known negative regulator of WNT signaling pathway) (Qiao et al., 2008; Zhu et al., 2009).

Donor MSCs can inhibit tumor progression and prevented osteoclastogenesis(Chanda et al., 2009; Secchiero et al., 2010). Human MSC-conditioned medium downregulate expression of VEGF in tumor cells, thereby suppressing tumorigenesis and tumor angiogenesis (Li et al., 2011). During co-culture, human umbilical cord mesenchymal stem cells (HUMSCs) induced apoptosis of breast cancer cells through both cell-cell contact and formation of a novel cell-in-cell phenomenon. In the animal models, HUMSC injection also efficiently inhibited metastatic breast cancer (Chao et al., 2012).

After co-culture with hUCMSCs, breast CSCs show an increased number of apoptotic cells. In xenograft models, tumor tissues from the mice treated with hUCMSCs showed significantly reduced levels of PI3K and AKT proteins, exhibiting clearly reduced tumor volume and tumor weight (Ma et al., 2012b). Wharton's jelly MSCs (hWJSCs) were grown in the presence of breast and ovarian cancer cell conditioned medium (MDA-TCM, TOV-TCM) without impacting changes in their characteristics or transforming them to a TAF phenotype, and showed no stimulatory growth effect on both cancer cells (Subramanian et al., 2012).

Conclusion

Stem cell therapy has been widely used in the treatment of diseases, including cancer. The selection of stem cells in cancer treatment can lead to therapeutic success or failure. MSCs are a type of adult stem cells with great potential for applications of tissue regeneration and cancer therapy. For cancer application, MSCs have increasingly become a vehicle for effective gene transfer due to their tumor tropism without affecting healthy tissues. Furthermore, MSCs protect gene therapy products before releasing the products to destroy specific malignant cells. The combination of MSCs and gene therapy has shown encouraging results and is a promising anti-cancer strategy. Standards for the isolation, culture and gene manipulation of MSCs will need to be further established and understood in order to avoid their malignant transformation.

Abbreviations

MSCs Mesenchymal stem cells; CAFs cancer-associated fibroblast; ES embryonic stem cells; iPS induced pluripotent stem cells; BM bone marrow; ADSC adipose-derived mesenchymal stem cell; GvHD graft versus host disease; MHC major histocompatibility complex; GF growth factor;SDF-1α stromal cell-derived 1α; ECM extracellular matrix; MMP matrix metalloproteinase; BMP bone morphogenic protein; Tregs regulatory T cells; TIC tumor-initiating cells; CD cytosine deaminase; 5-FC 5-fluorocytosine; 5-FU 5-fluorouracil; LV Lentiviral; TRAIL tumor necrosis factor-related apoptosis-inducing ligand; IFN interferon; DC dendritic cell; UBMC Umbilical blood mononuclear cell; HSV-TK herpes simplex virus-thymidine kinase; IL interleukin; TGF-b transforming growth factor-beta; EMT epithelial-mesenchymal transition; VEGF vascular endothelial growth factor; bFGF basic fibroblast growth factor; TICs tumor-initiating cells; BM-MSCs bone marrow mesenchymal stem cells; hpMSCs human placenta-derived mesenchymal stem cells; hADSCs human adipose tissue-derived mesenchymal stem cells; CSCs cancer stem cells; CA-MSCs carcinoma-associated mesenchymal stem cells; HUMSCs human umbilical cord mesenchymal stem cells

Competing interests

The authors declare that they have no competing interests.

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