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The Pros and Cons of Mesenchymal Stem Cell-Based Therapies

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Abstract

The need to search for new, alternative treatments for various diseases has prompted scientists and physicians to focus their attention on regenerative medicine and broadly understood cell therapies. Currently, stem cells are being investigated for their potentially widespread use in therapies for many untreatable diseases. Nowadays modern treatment strategies willingly use mesenchymal stem cells (MSCs) derived from different sources. Researchers are increasingly aware of the nature of MSCs and new possibilities for their use. Due to their properties, especially their ability to self-regenerate, differentiate into several cell lineages and participate in immunomodulation, MSCs have become a promising tool in developing modern and efficient future treatment strategies. The great potential and availability of MSCs allow for their various clinical applications in the treatment of many incurable diseases. In addition to their many advantages and benefits, there are still questions about the use of MSCs. What are the mechanisms of action of MSCs? How do they reach their destination? Is the clinical use of MSCs safe? These are the main questions that arise regarding MSCs when they are considered as therapeutic tools. The diversity of MSCs, their different clinical applications, and their many traits that have not yet been thoroughly investigated are sources of discussions and controversial opinions about these cells. Here, we reviewed the current knowledge about MSCs in terms of their therapeutic potential, clinical effects and safety in clinical applications.

Keywords

mesenchymal stem cells, somatic cell therapy, transplantation, engraftment, immunomodulatory properties

Introduction

In the 1960s, Friedenstein et al. identified a population of fibroblast-like cells that formed clonal colonies *in vitro* (CFU-F, Colony Forming Unit-Fibroblast)[1]. Friedenstein's observations allowed for the discovery of a specific type of cell, currently referred to as mesenchymal stem cells (MSCs). MSCs are primary, non-specialized, nonhematopoietic, plastic adherent cells with great proliferation potential and the capacity for self-renewal and differentation[2].

In 2006, the International Society of Cellular Therapy (ISCT) proposed basic criteria for defining human multipotent mesenchymal stromal cells whose name then evolved to MSCs. In addition to their plastic adherent properties under standard culture conditions and trilineage differentiation capacity into osteoblasts, chondrocytes and adipocytes, > 95% of the MSCs population is positive for the three specific surface markers—CD73 (SH3/4), CD90 (Thy-1), and CD105 (SH2)—and do not express CD45, CD34, CD14, CD11b, CD79a, CD19, or major histocompatibility complex (MHC) class II[3,4]. MSCs also express others markers, including CD9, CD10, CD13, CD29, CD44, CD49, CD51, CD54 (ICAM-1), CD117 (c-kit), CD146 (MCAM), CD166 (ALCAM), and Stro-1, but the expression of specific combinations of the markers appear to be host tissue dependent[5]. Although a wide range of positive markers describing MSCs has been identified, no single marker has been indicated as specific for MSCs.

It should be also noted that the potential of MSCs for differentiation and proliferation may vary considerably between different MSC sources[6,7]. It has been suggested that these differences are a result of the direct influence of the specific microenvironments in which they primarily reside[8,9].

Despite increasing numbers of reports describing MSCs, numerous controversies have arisen regarding the proper

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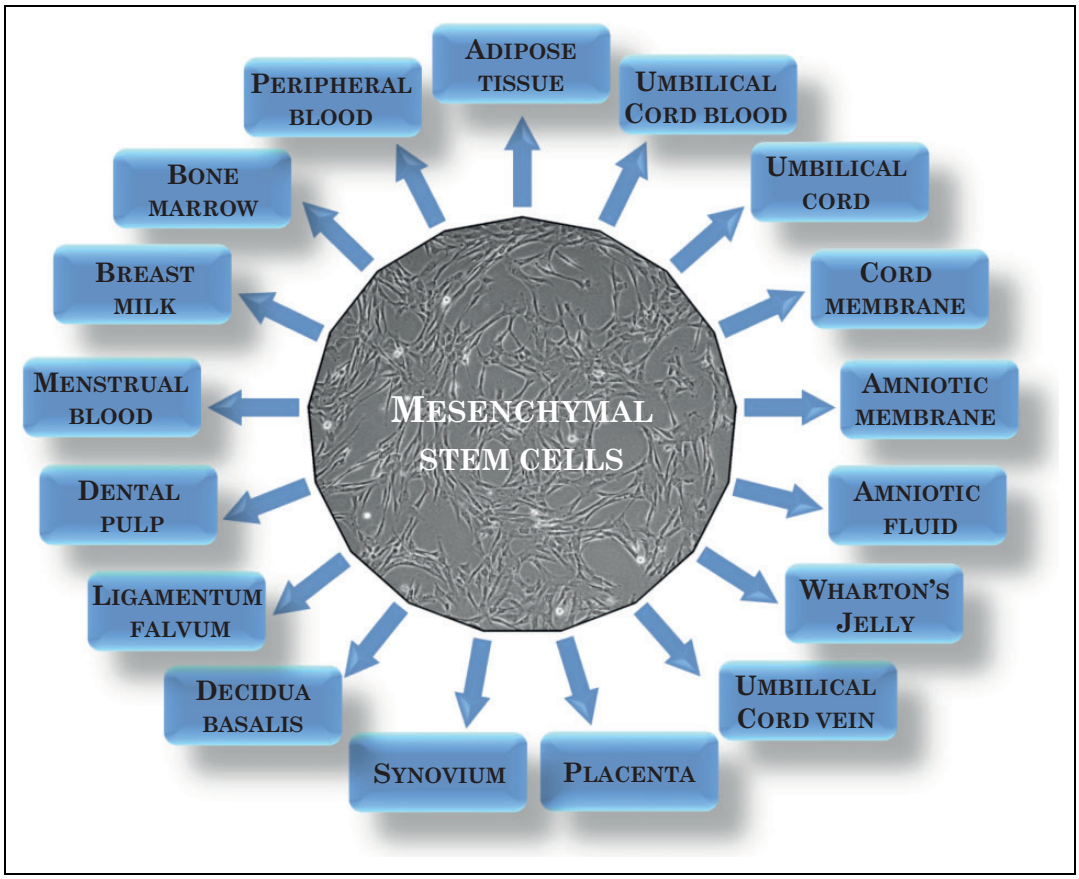

Fig. 1. Mesenchymal stem cells sources.

identification of MSCs. It appears that the criteria proposed by the ISCT are not sufficient because MSCs isolated from different tissues represent a relatively heterogeneous group of cells in terms of differentiation, proliferation abilities, and cell surface expression[6,10–13].

Mesenchymal Stem Cells—the Main Players in Cell Therapy

The fact that MSCs can be isolated from numerous sources[1,2,6–8,10] (Fig. 1), their relative ease to culture *in vitro*, their ability to differentiate into several different cell types, and their special immunological properties make MSCs a promising tool for cell therapy and tissue regeneration. The best known and the most commonly used source of MSCs is bone marrow (BM)[14]. BM is the tissue in which MSCs were first identified. Another easily accessible source of MSCs is adipose tissue[15]. Obtaining MSCs from these sources requires invasive procedures. Interestingly, rich sources of MSCs include birth-associated tissues that are treated as medical waste, such as placenta, umbilical cord, amniotic fluid, and amniotic membrane. Among those tissues, umbilical cord blood[16] is believe to contain MSCs; however, the use of this source is questioned by some researchers because of low efficiency of their isolation[17]. MSCs derived from Wharton's jelly of the umbilical cord (WJ-MSCs) appear to have great future clinical utility due to their limited heterogeneity and some unique properties, such as ease of their isolation and culture, availability in several tissues, their immunomodulatory properties, ability to self-regenerate, differentiate into several cell lineages, and the lack of ethical problems resulting from their use[18]. Moreover, in contrast to BM or adipose tissue, the acquisition and isolation of birth-associated tissues, including WJ-MSCs, do not require invasive surgical procedures; therefore, the isolation process does not pose any risk of complications for the donor, giving them an advantage over other MSC sources. Currently, new sources of MSCs have been proposed. MSCs are found in dental pulp, periodontal ligament, tendon, skin, muscle, and other tissues[19] (Fig. 1). However, there are differences in isolation efficiency that are related to the availability, condition, and age of the donor tissue. A very important issue is the age of the donor's cells[20]. Cells obtained from younger donors are less susceptible to oxidative damages and changes, they age considerably more slowly in culture, and they have a higher proliferation rate[21,22].

Currently, many studies focus on the use of MSCs in cell therapy. MSCs are used as a tool to treat degenerative changes in joints and to reconstruct bones and cartilage, and are used in plastic surgeries, aesthetic medicine,

cardiovascular diseases, endocrine and nervous system diseases, cell transplantation, and in the repair of damaged musculoskeletal tissues[23]. Due to the special properties of these cells, such as their rapid proliferation, high differentiation capacity, and the ability to migrate into the site of damage, new clinical applications are being tested.

BM-MSCs are the most frequently used in clinical settings[24]. BM-MSCs were also first to be registed by the Food and Drug Administration as a drug against Graft versus Host Disease called "Prochymal"[25]. Recently, "Alofisel" has been registered by the European Medicines Agency to treat complex perianal fistulas. The drug is based on expanded adipose-derived stem cells[26]. In both cases the drugs are allogeneic, which provides strong advantage other autologous products due to possibility of detailed testing regarding both safety and potency before release. Nowadays other sources of MSCs are also used for clinical therapies. Our research group used MSCs isolated from Wharton Jelly to treat patients with acute myocardial infarction, showing the safety and feasibility of such therapy[27]. Currently, we are conducting phase II/III randomized, double-blinded clinical trials with the use of the product "CardioCell" that is based on WJ-MSCs in three indications: acute myocardial infarction (AMI-Study, EudraCT Number: 2016-004662-25), chronic ischemic heart failure (CIHF-Study, EudraCT Number: 2016-004683-19), and non-option critical limb ischemia (N-O CLI-Study, EudraCT Number: 2016-004684-40).

However, it should be noted that although we possess great knowledge about their *in vitro* characteristics, we still know much less about the *in vivo* behaviors of MSCs. They can act both directly—due to their ability to differentiate[28]—and indirectly, by producing and secreting many factors that enhance the endogenous regeneration potential of injured tissue[19].

The new approach in stem cell therapy is the use of extracellular vesicles (EVs), which can be used as a substitute for MSCs[29]. EVs as a therapeutic vector have the paracrine effect without the direct involvement of the cells. They are released from stem cells and they supply many components such as mRNA, DNA, and proteins to the target site[30]. This approach is described in many recent studies[31,32] but a thorough understanding of the mechanism of action of EVs is still required.

Migration and Homing of Mesenchymal Stem Cells

The therapeutic effect of MSCs depends on their ability to reach the injured site, which is possible due to their ability to migrate, adhere, and engraft into a target tissue. Several factors affect the therapeutic efficacy of MSCs' homing. Among them, culture conditions, the number of passages, donor age, delivery method, and host receptibility play important roles[33–36]. It has been shown that freshly isolated cells compared with *in vitro*-cultured cells have a higher engraftment efficiency[37], which can be a result of the aging/differentiation process that cells undergo in *in vitro* culture conditions[38,39]. Culture conditions also have a significant impact on homing capacity, as they can modify the expression of the surface markers involved in this process. As an example, CXCR4, a chemokine receptor, is involved in the migration of MSCs. It has been shown that CXCR4 expression is lost on BM-MSCs during culture[37,40,41], whereas the presence of cytokines (e.g., HGF, IL-6), hypoxic conditions, or direct introduction using viral vectors allow for restoration of its expression[42–44].

In addition, MSCs isolated from older donors show altered compositions and functions of membrane glycerophospholipids[45]. All of these aspects affect MSCs' ability to migrate, home, and engraft into a site of injury.

The efficacy of cell therapy largely depends on the delivery method. The most common method of administration of MSCs is intravenous infusion[46–48]. However, before the cells reach their target, the majority are trapped within capillaries of various organs, especially in the lungs[46,49–52]. This attrition can be explained by the fact that MSCs are relatively large cells and express various adhesion molecules. Despite the fact that MSCs can become trapped in the lungs, numerous pieces of evidence suggest that they are able to home to injured tissue[50,53]. Interestingly, recent data also suggest that despite the problems associated with intravenous infusions, this route results in similar efficacy as other modes of delivery of MSCs[54]. In some instances, intra-arterial injection seems to be a more effective route. It has been shown that delivery of MSCs through the internal carotid artery more effectively facilitates their migration and homing into injured brain compared with administration via the femoral vein. The risk associated with this route of delivery includes occlusions, which can arise in microvessels[53]. When the MSCs were delivered directly to the heart, near the damaged area, the number of cells that reached the peri-infarct region was much higher[55].

As has already been mentioned, the necessary condition for effective MSC-based therapy is for the cells to reach the site of injury and home to the affected tissue. There is no doubt that specific receptors and adhesion molecules and interactions with endothelial cells play crucial roles in this migration and homing. Cell adhesion proteins are expressed in the plasma membrane, such as integrins, which are involved in cell adhesion to extracellular matrix proteins (EMC), such as collagen, fibronectin, and laminin[38,56–60]. *In vivo* studies have shown that MSCs exhibit chemotactic properties and, after intravenous injections, are able to attach to endothelium and migrate between endothelial cells toward injured tissue in response to factors that are upregulated under the inflammatory conditions[61–64]. However, the detailed mechanisms of their transendothelial migration (TEM), diapedesis, and homing to sites of injury and inflammation have not yet been explained in detail. It is presumed that this mechanism may be similar to that of leukocytes (Fig. 2)[65–67] but is performed with the participation of different adhesion molecules. To date, many chemokines and

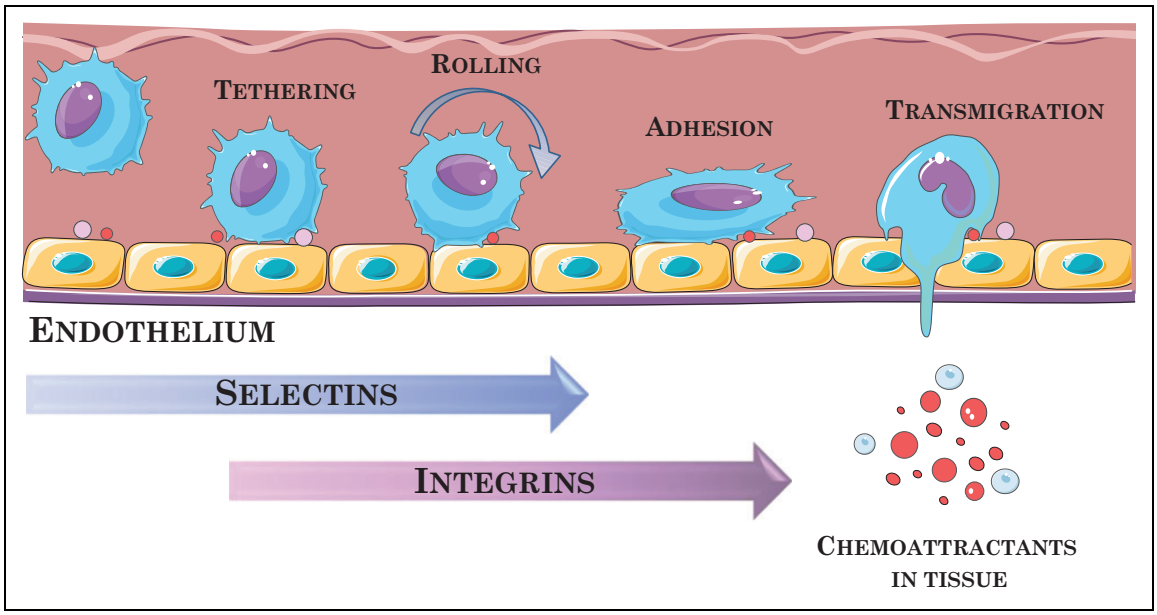

Fig. 2. Schematic of leukocyte transmigration through the endothelium. It is supposed that MSCs migration occurs in a similar manner. The graphic was prepared using modified art elements from Servier Medical Art, found at https://smart.servier.com.

growth factors have been identified (e.g., EGF, VEGF-A, FGF, PDGF-AB, HGF, TGF-b1, TNF-α, SDF-1α, IL-6, IL-8, IGF-1), including their receptors, adhesion molecules, and metalloproteinases, that are involved in the MSCs migration process (e.g., CXCL-12, CCL-2, CCL-3, CCR4, CXCR4, VCAM, ICAM)[55,59,65,68–71]. Many reports suggest that damaged tissue expresses specific factors that act as chemoattractants to facilitate the migration, adhesion, and infiltration of MSCs to sites of injury, as in the case of leukocytes trafficking to sites of inflammation. However, although the leukocyte recruitment process (i.e., binding to endothelial cells, rolling, adhesion, and TEM) is well understood, the mechanism of the interaction between MSCs and endothelial cells will require more detailed investigations. Studies by Rüster et al. showed that the ability of MSCs to bind and roll on endothelial cells was derived from human umbilical cord vein cells. Once the MSCs adhere to endothelium, they become shaped like protrusions and roll. The molecules involved in this process have been identified and include P-selectin and VLA-4 expressed on MSCs and VCAM-1 on endothelial cells (VLA-4/VCAM-1 interaction)[65]. It has also been confirmed that a vital role in the homing and migration of MSCs is played by the proteolytic enzymes matrix metalloproteinases (MMPs)[37,41].

Immunological Properties of Mesenchymal Stem Cells

It is generally accepted that MSCs do not display immunogenic properties, so they can be transplanted to an allogenic host without need for immunosuppression. The mechanism of their action is based on their immunomodulatory properties as well as immunosuppressive activity. They are able to suppress proliferation and activation of different cells of the immune system. These interactions may occure directly (i.e., cell–cell interaction) and indirectly (via soluble factors), and this pathway of suppression is independent of MHC matching between MSCs and T cells [39,72,73]. The immunomodulating effect of MSCs is reflected in many T-cell properties, such as activation and proliferation, and in this way they efficiently suppress an immune response[73]. The MSCs suppress the proliferation of activated T cells by secreting substances, such as indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2)[74–76]. They also suppress the development of pro-inflammatory Th17 cells and stimulate regulatory T cells by secreting immunosuppressive cytokines including IL-6, IL-8, IL-10, TGF-β, and HGF. In addition, the nonclassical HLA class I molecules (HLA-G) expressed by MSCs exert immunosuppressive effects on various immune cells; that is, they inhibit T-cell proliferation and cytotoxic T lymphocyte-mediated cytolysis, and they also induce the development of tolerogenic dendritic cells and inhibit natural killer cell cytolytic functions[77–80]. It has been shown that HLA-G contributes to decrease graft rejection[81]. MSCs also participate in regulation of Th1/Th2 balance (T helper cells) by affecting the level of interleukin-4 (IL-4) and interferon (IFN)-γ in effector T cells. MSCs disturb maturation, differentiation, and functions (i.e. cytokine secretion) of dendritic cells (DCs), which play a crucial role in antigen presentation. There is much evidence that MSCs inhibit the proliferation, differentiation, and chemotaxis of B cells[75,82,83]. They also prevent monocyte differentiation into DCs. Because of their immunoregulatory properties, they are

protected against cell lysis and the cytotoxic effects of the host's immune system.

The immunophenotype of MSCs is generally described as: MHC I^+, MHC II^-. They also do not express the costimulatory molecules (CD40, CD80, CD86) and hematopoietic markers CD45, CD34, CD14, CD11, CD19, and CD18 (LFA-1; leukocyte function-associated antigen-1), which makes them non-immunogenic. MHC class I may activate T cells, but with the absence of costimulatory molecules, the T cells are non-reactive[84–88].

Safety of Mesenchymal Stem Cell Therapies

Many studies have been conducted thus far to investigate the safety of MSC-based therapies. Clinical trials show that *in vitro*-cultured human MSCs are less susceptible to adverse changes.

A Canadian group analyzed clinical trials in which BM-MSCs were used. After a thorough analysis of 36 studies, they found that there was no relationship between the use of MSCs and tumorigenic potential, and no serious side effects of the therapy were reported[89]. The safety and impact of MSCs therapy were also investigated by Karussis et al. in patients with multiple sclerosis and amyotrophic lateral sclerosis[90]. In 34 examined patients, during a study lasting 25 months, no serious adverse effects resulting from the therapy were observed. In addition, 20 patients were examined 1 year after transplantation, and the MRI results did not show any disturbing changes[90]. However, more long-term studies and observations regarding the safety of using MSCs therapies will be required.

However, one study reported that the use of autologous adipose tissue-derived MSCs (AT-MSCs) in a patient with chronic kidney disease resulted not only in the improvement of renal function but also in fibrosis of the interstitial tissue and atrophy of the tubules, which could suggest nephrotoxicity of the applied MSCs[91]. Another group investigated the efficacy of the allogeneic treatment of MSCs administered to the aortas of patients with acute kidney injury after cardiac surgery. No differences were observed between the treated group and the control group in terms of improvement of renal function or in the occurrence of adverse events[92].

Tatsumi et al. demonstrated in an *in vivo* model that the administration of AT-MSCs may result in thrombus formation around the cells through a coagulation mechanism, which can also cause pulmonary embolism due to the accumulation of cells in the lung region[93]. This finding was confirmed by other studies performed using umbilical cord MSCs, which showed the procoagulant properties of these cells after peripheral vein injection[94]. Many researchers currently focus on thromboinflammation, also known as the instant blood-mediated inflammatory reaction, which can occur after transplantation of MSCs[95,96]. Taking into account all of these issues, it is clear that more long-term studies and observations regarding the safety of using MSCs are required.

Despite the many cons for using MSCs in clinical settings, there are still a few issues that need to be resolved for the successful application of MSCs. One of them involves obtaining sufficient numbers of the cells. Unfortunately, during *in vitro* culture, cells at higher passages age due to decreased telomerase activity[97]. In addition, during long-term culture, MSCs lose their potential to differentiate and begin to exhibit morphological changes[98]. Even more importantly, long-term culture might lead to the increased probability of malignant transformation[99,100]. Certain components of the culture medium and growth factors may predispose the cells to such processes. There is also a risk of viral and prion transmission after administration of the cells[101].

The Dark Side of Mesenchymal Stem Cell Biology

When using stem cell-based therapies, all possible undesirable effects should be considered. The risk associated with tumorigenesis after stem cell transplantation is widely discussed in the literature. In a certain sense, stem cells can be compared to tumor cells because of their ability to proliferation for a long period of time, high viability, and resistance to apoptosis[102]. Many components may affect the potential tumorigenesis after MSCs transplantation, including the donor's age, host tissue, growth regulators expressed by recipient tissue, and mechanisms that control the behavior of the MSCs at the target site[103–105]. Also, manipulations and long-term *in vitro* cultures of MSCs can cause genetic instability and chromosomal abberations[105]. Many cumulative factors can give a response in the form of a spontaneous tumor transformation. Patients who are transplanted with stem cells often undergo long-term chemotherapy or radiotherapy, so their immune system does not work properly, which may also be associated with the risk of tumorigenesis[106].

Protumorigenic Effect of Mesenchymal Stem Cells

The direct role of MSCs in promoting tumorigenesis has been investigated by several research groups in animal models. Results obtained for BM-MSCs show that the cells can engraft and home to many different types of solid tumors[107–111]. MSCs have been injected simultaneously with tumor cells *in vivo*. BM-MSCs promoted tumor growth in a colon cancer model[109] and in breast cancer[108], colorectal cancer[112], ovarian[113], prostate[114], lung[107], and gastric carcinoma[115].

A highly complex tumorigenesis process involves many factors that promote tumor growth, one of which is hypoxia[116]. The published data indicate that BM-MSCs can be associated with tumor progression by the secretion of proangiogenic factors[107].

MSCs have also been examined in the tumorigenic context due to the identification of carcinoma-associated fibroblast (CAF) cells, tumor-associated fibroblast (TAF) cells, and other tumor-associated cells, such as endothelial and pericyte-like cells, since MSCs can differentiate into these cell types under appropriate conditions[117]. *In vitro* and *in vivo* studies have shown that BM-MSCs cultured together with tumor cells may adopt the CAF-like phenotype, and the tumor microenvironment predisposes the transformation of these cells into α-smooth muscle actin (α-SMA)-expressing myofibroblasts[118]. Depending on the research model used, the percentage of MSCs taking part in this phenomenon varies. In an ovarian cancer model, it was found that the percentage of MSC-derived CAF cells ranged from 60 to 70%, whereas in the pancreatic cancer model, the percentage was only approximately 20%.

In studies by Karnoub et al., mice were used to graft non-metastatic breast cancer cells together with MSCs (BM-MSCs)[108]. The results of this study showed that, compared with mice injected only with cancer cells, the mix of MSCs and cancer cells increased the metastasis potential. The special engraftment properties and specific tropism of injected GFP $^{+}$ BM-MSCs into a mouse tumor model were also shown by Ren et al.[119]. Interestingly, it has been shown that the actions of stem cells (including nonhematopoietic and hematopoietic stem cells) in combination with different tumor cells can vary *in vitro* and *in vivo*. *In vitro*, MSCs cells showed antiproliferative activity, stopping in the G1 phase, in contrast to *in vivo* studies, where MSCs caused faster tumor growth[120].

The Bright Side of Mesenchymal Stem Cell Biology

MSCs display a dualistic nature in relation to their tumorigenicity. Some studies have also shown their antitumorigenic effects. Factors secreted by MSCs may have antitumor properties. Clarke et al. showed that breast cancer cells cultured in MSC-conditioned medium exhibit significant migratory inhibition compared with cells cultured in a standard medium. The tumorigenesis effect of MSCs may be exerted by the secretion of the proteins TIMP-1 and TIMP-2, which inhibit the activity of the MMPs that are involved in migration processes[121].

The inhibition of tumor cell growth was also shown by Bruno et al.[122]. A human hepatocellular carcinoma cell line (HepG2), a human ovarian cancer cell line (Skov-3), and Kaposi's sarcoma cell lines co-cultured in the presence of BM-MSCs exhibited reduced *in vitro* growth. In addition, microvesicles (MVs) isolated from MSCs caused significant decreases in tumor cell proliferation through inhibiting cell cycle progression and inducing apoptosis and necrosis of the tumor cells. These observations were confirmed by *in vivo* studies in which tumor growth was slowed down by the administration of BM-MSC-derived MVs[122].

Similar data were obtained with MVs derived from human WJ-MSCs. Wu et al. observed that WJ-MSC-derived MVs down-regulated the phosphorylation of Akt protein kinase and activated p53/p21 in bladder tumor cell lines[123]. Oxidative stress, which occurs in damaged tissues, is a natural process after the occurrence of damage. Therapies that use stem cells mainly focus on the regeneration of damaged tissues. Thus, the enhanced apoptotic resistance of MSCs, which is the result of regulation of the apoptosis process through complex cellular pathways, is highly desirable in the regeneration process that is the result of MSC therapy[102,124].

There is no unambiguous answer regarding the potential of MSCs in tumorigenesis. In fact, the effect of MSCs depends not only on the tumor model used but also on the method of culture, cell heterogeneity, dose, secreted molecules, and many other factors that have not yet been fully understood.

Other Restrictions Related to the Application of Mesenchymal Stem Cells

Many studies (both preclinical and clinical trials) show increasing evidence of the therapeutic effectiveness of MSCs. However, many studies also provide evidence of low engraftment of MSCs due to their short-lived viability after injection[125,126]. It has also been demonstrated that after MSCs are transplanted, many of them are trapped in the lungs, resulting in a reduction in the population of cells that occupy the target site[127]. However, portions of MSCs populations reach damaged tissue, such as infarcted myocardium, traumatically injured brain, fibrotic liver, and various types of tumors[125]. The method by which the cells are administered may be an important factor in their reaching their intended destination. The advantage of the targeted application of these cells versus systemic administration is reductions in cell losses during delivery and cell migration[128].

The low immunogenicity of the MSCs makes cell transplantation well tolerated by the recipient organism, reducing the likelihood of rejection of the transplantation. However, differentiated MSCs may exhibit low or no therapeutic effects. Huang et al. demonstrated that differentiated MSCs have increased immunogenicity due to MHC-I and MHC-II expression[129].

Most of the studies conducted show that a single transplantation of MSCs is safe and does not induce an immune response. However, repeated administration of MSCs may result in the production of allo-antibodies[130]. Moreover, the fetal bovine serum (FBS) used in the MSC culture medium may cause an immune response in patients who have received such cells. Von Bonin et al. showed that the transplantation of MSCs that had been in contact with FBS induced the production of antibodies against FBS in the recipient's blood[131].

Concluding Remarks

Stem cells are undoubtedly a great hope for the treatment of many diseases. Since they occur in many adult tissues and do

not raise ethical issues, they have great advantages over embryonic stem cells. Due to their unique features, such as their ease of isolation and culture, availability in many tissues, their immunomodulatory properties, and the lack of ethical problems resulting from their use, we believe that they can be used in both autologous and allogeneic transplantations. Despite numerous *in vitro* and *in vivo* studies, the mechanisms underlying MSCs transmigration and homing require further detailed examination. Nevertheless, there is no doubt that the cells can migrate and home to injured tissues. More research is emerging regarding the potential long-term risks associated with MSCs therapy. Long-term studies and observations will be necessary to investigate the long-term effects of MSCs therapies, including the negative effects. Based on our data, allogeneic clinical use of the MSCs seems to be promising tool in regenerative medicine.

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