Open Access Review Article

The Utilization of Mesenchymal Stem Cell Therapy in the Treatment of Human Diseases

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MSC is the most important type of adult stem cells. These are multipotent and can be obtained from various sources, including adipose tissue, bone marrow, liver, and cord blood. MSCs are capable of self-renewal and could differentiate into various cell types. MSCs can be grown in-vitro, and these are known to execute anti-inflammatory, anti-fibrotic, anti-tumor, anti-apoptotic, and immunomodulatory effects. Many studies have reported that autologous or allogenic administration of MSCs to treat various diseases is relatively safe. Following transfusion, MSCs show low immunogenicity. MSCs could travel to inflammatory or damaged tissue sites. These could also reach the tumor site and home there and contribute to suppression of tumor growth. In this review, we have summarized the important properties of MSCs, their role in the treatment of cancer, immune diseases, and regeneration of damaged tissues. The information about the application of MSCs in different therapeutic strategies may help better understand the pros and cons of MSCs therapy in human diseases.

Key words: Cancer, Drug delivery, Immune system, MSC, Regenerative medicine.

Introduction

Embryonic stem cells and adult stem cells are the main types of stem cells. The pluripotent nature of embryonic stem cells enables these cells to form embryonic structures while adult stem cells could undergo self-renewal and transform into various cell types. Mesenchymal stem cell (MSC) is one of the main types of adult stem cells. [1, 2] These were first discovered in 1970 by Friedenstein. MSCs can be obtained from multiple sources, including bone marrow, fat, umbilical cord tissue and blood, muscle tissue, amniotic fluid, etc. Figure 1. [3, 4]

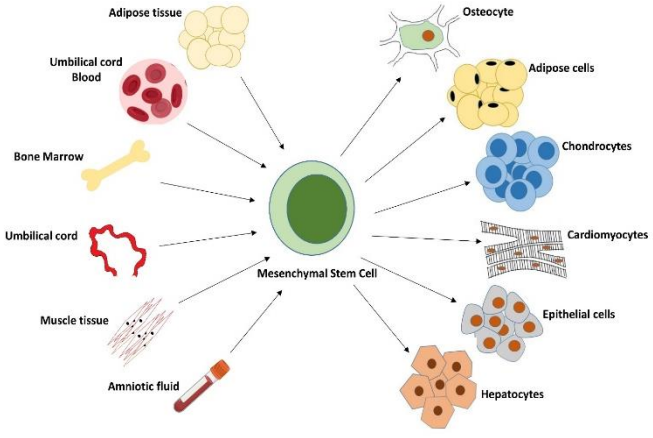

Figure 1. Different sources of MSCs and common MSCs differentiated cell types.

The biological properties of MSCs could be different as per their tissue source, but there are some important characteristics that MSCs, from any source must exhibit. The International Society for Cellular Therapy (ISCT) described these characteristics as follows: When MSCs are grown in-vitro, these must adhere to plastic surfaces. There must be the expression of CD73, CD90, CD105 surface antigens and absence of expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, HLA-DR surface antigens on the surfaces of MSCs.[5] Under directed cell culture conditions, these must show differentiation into mesodermal cells like adipocytes, chondrocytes, osteoblasts, and ectodermal or endodermal cells like neuronal cells, cardiomyocytes, hepatocytes, or epithelial cells. [6, 7]

Currently, MSCs are the most common cells being used in cell-based therapeutic approaches. Important advantages like MSCs can be acquired easily from multiple sources; these can be grown in-vitro at large scales, these exhibit low immunogenicity, and excellent differentiation capability make them favorite candidates to be used in cell-based treatment approaches.[8,9] Allogenic and autologous MSCs transfusions have been successfully administered in many studies. MSCs have been utilized in several clinical studies to treat various human pathological conditions like renal, cardiovascular, neurological, hepatic, and lung disorders.[10-13] These have also been employed in regenerative medicine and oncology to repair damaged tissues and treat cancer.

MSCs have also shown potent immunomodulatory effects. These could secrete a variety of immune mediators, which could interfere with cellular signaling mechanisms and contribute to achieving therapeutic effects in immune diseases.[14, 15] Given the abilities mentioned above, it can be summarized that MSCs are strong tools for cell-based therapies to treat various human diseases.

Salient biological features of MSCs

Besides owning auto-renewal and multidirectional differentiation potential as other stem cells, MSCs are associated with other unique properties. MSCs could interact with immune cells to modulate immune responses; these could also participate in paracrine signaling. Additionally, MSCs possess the characteristic of poor immunogenicity. Therefore, immunological rejection is less likely to occur during cellular therapy with MSCs.

Moreover, MSCs can move towards locations of inflammation and tumors in the body and could settle there. Therefore, based on the characteristics mentioned above, MSCs have significant potential in treating age-related or pathological damage to tissues. These could act as an excellent means of replacement cells for repairing age or disease-related damage to tissues and organs. MSCs could offer broad-spectrum therapeutic benefits in the treatment of Inflammatory, autoimmune disorders, and cancer.

The ability of MSCs to regulate the immune system

MSCs could suppress the growth of natural killer cells and attenuate their cytotoxicity by releasing the prostaglandin E2 (PGE2), soluble human leukocyte antigen G5 (sHLA-G5), and indoleamine 2,3-dioxygenase (IDO).[16] MSCs could also interfere with the differentiation of monocytes into dendritic cells and suppress the growth of dendritic cells.[17] MSCs, through the release of PGE2, could attenuate TNF gene expression and enhance IL-10 expression by dendritic cells.[18, 19] MSCs-mediated modulatory effects not only affect the differentiation and maturation of DCs. MSCs also interfere with their antigen-presenting ability to T lymphocytes, resulting in immunosuppression.[20]

Additionally, MSCs secrete significant quantities of interleukin 6 (IL-6), which helps minimize respiratory outbursts and provide protection to neutrophils. [16]

MSCs also play their modulatory role in the acquired immune system. MSCs secrete high quantities of PGE2, IDO, TGF-b1, HGF, iNOS, and HO-1, which interfere with the proliferation and maturation of CD4 T lymphocytes. Consequently, the maturation of B lymphocytes and the generation of antibodies are affected. [21, 22]

MSCs could induce immune tolerance. HLA-G5, secreted by MSCs, suppresses the cytotoxic activity of CD8 T lymphocytes and enhances the propagation and maturation of regulatory T cells. Which then act to maintain homeostasis and immune tolerance.[23, 24] Additionally, several research investigations have shown that during the state of inflammation, MSCs can transform the pro-inflammatory activity of macrophages to anti-inflammatory activity. MSCs could drive such transition by secreting TNF-a-stimulating gene 6 (TSG-6), PGE2, and IDO. These immune mediators act on macrophages to alter their immune-regulatory role from immune activators to immune-suppressors Figure 2A .[25]

MSCs induce minimum immune responses

Literature review indicates that exogenous MSC transfusion suppressed the activation of lymphocytes and prolonged the skin transplantation survival time.[26] Another study reported that allogeneic, semi-compatible, and mismatched bone marrow-derived MSC transplants may successfully treat GVHD, suggesting that stringent compatibility was unnecessary for treating GVHD. These findings indicate that low Immunogenicity of MSCs is important for the success of allogeneic MSC transplantation in preclinical and clinical usage.[27, 28]

Studies have demonstrated that MSCs constitutively express the MHC class I (MHC I). [29] The expression of MHC 1 is important because it shields MSCs from the harmful actions of NK cells.[30] MSCs also express HLA-G, which is an MHC-like protein. HLA-G proved to lower the chances of NK-mediated rejection following allogeneic MSC transplantation. [31, 32]

Furthermore, activated or resting MSCs do not promote the propagation of peripheral blood mononuclear cells (PBMCs) in the resting state and do not trigger PBMC propagation, which is responsible for inducing an inflammatory response. This finding further suggests that activated or resting MSCs exert minimum immunogenicity. [33]

Immune mediators secreted by MSCs like IL-10, TGF-b1, and PGE2 could effectively suppress the propagation of PBMCs and cytotoxic activities of T cells.

The abovementioned findings indicate that allogeneic MSC transplantation can be carried out with no or minimum host immunosuppression Figure 2B.[34, 35]

The migratory and homing abilities of MSCs

MSCs can move towards the site of lesions in various health conditions like tissue damage, inflammation, and tumors. The migration and settling down of MSCs at the lesion site are called homing.[36] Secretion of various cell adhesion molecules by MSCs and expression of chemokine receptors at their surfaces enable MSCs to carry out homing.[37] Like leukocytes, MSCs follow activation, adhesion, and migration steps to complete homing.[38] Inflammation or tissue damage causes the release of specific cytokines, which activate the vascular cell adhesion molecule-1 (VCAM-1) and α4β1 integrin (VLA-4) on the surfaces of endothelial cells and MSCs, respectively.[38, 39]

Besides cytokines, inflammatory and damaged tissues sites also trigger the secretion of growth factors like Hepatocyte growth factor (HGF), stromal cell-derived factor-1 (SDF-1), macrophage inflammatory protein-1 (MIP-1), and hyaluronic acid (HA). These growth factors bind to related receptors on MSCs and facilitate the MSCs-endothelial cells adhesion.[40, 41] Further, the secretion of matrix metalloproteinase 2 (MMP-2) and membrane type-1-MMP (MT-1-MMP) by MSCs cause degradation of extracellular material and let MSCs cross basement membrane and reach the injured site.[42]

MSCs could adhere to vascular endothelium through active capture or passive capture process.

Through the active capture method, the movement of MSCs towards vascular endothelial occurs through capillaries. In this method, the movement of MSCs is smooth and is in the direction of blood flow.[43] Once MSCs reach the vascular endothelium close to damaged sites, these are activated and migrate through the vascular endothelium to the inflammatory or damaged site Figure 2C. [44, 45]

While in the passive capture method, the movement of MSCs is through is not smooth. Due to their large size, their movement is hindered in capillaries. As a result, these are squeezed by the capillary wall and passively lodged inside endothelial cells. This course of action might affect the direction of blood flow and further contribute to capillaries' blockage.[46] Furthermore, in the passive capture process, MSCs could end up at a damaged site, or their route could also deviate to normal organs like lungs.[33, 35] This fact urges the importance of the careful selection of cell concentration and intravenous transfusion method during cell therapy with MSCs.

The use of MSCs in the treatment of human diseases

The possession of multipotent differentiation capacity by MSCs makes them a suitable candidate for their use in cell-based therapies. Further, the immunomodulatory

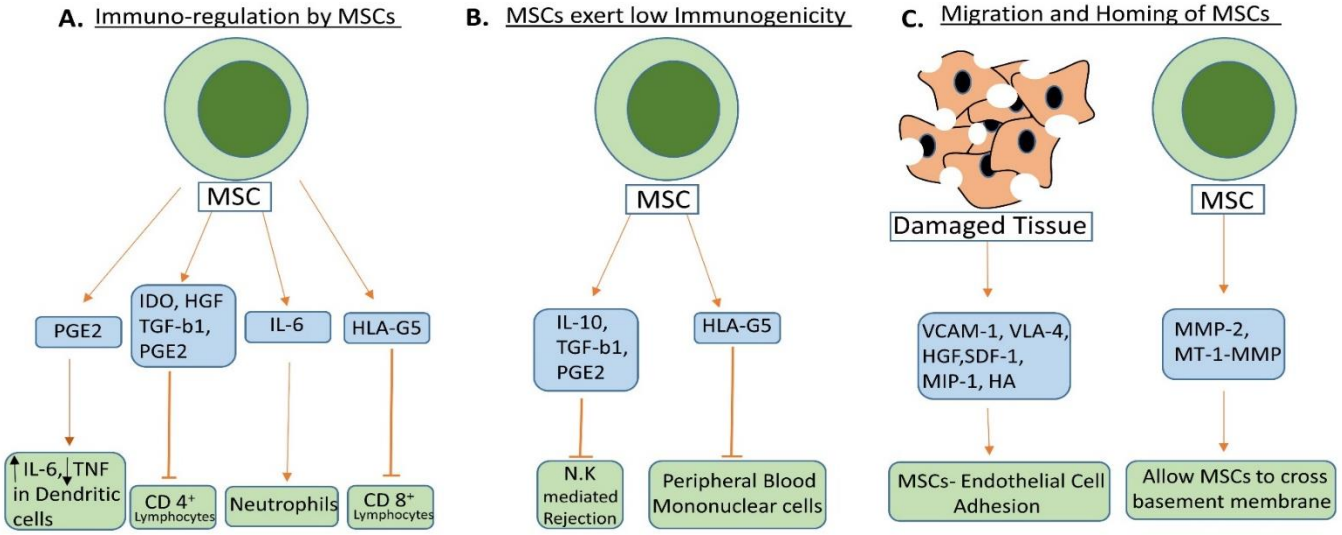

Figure 2. Important Biological functions of MSCs

effects, low immunogenic effects, and the ability to home at damaged tissue site support their utilization in multiple therapeutic strategies. [34]

The therapeutic effects of MSCs in regenerative medicine

One of the essential components of Regenerative medicine is stem cell therapy. In regenerative medicine, the therapeutic effects of stem cells are achieved by delivering stem cells to the damaged tissue site. Following transfer to the damaged site, the differentiation, regenerative abilities of stem cells, and the activation of paracrine signaling by stem cells contribute to healing tissue damage and restoring altered tissue functions. [47, 48]

MSCs therapy is considered a practical approach to treat disease in regenerative medicine. MSCs can be isolated from multiple sources; these are well capable of proliferation and differentiation. Most importantly, these exert low immunogenic effects and secrete a variety of cytokines and growth factors. These merits make MSCs favorite candidates to be used in regenerative medicine.[49] In situ transplantation of MSCs to patients, systemic delivery of MSCs, or transplantation of specific cell types obtained after controlled in-vitro differentiation of MSCs is common means of using MSCs therapy to treat diseases in regenerative medicine. [50]

Several studies used MSCs as therapeutic agents to treat cardiovascular diseases, hepatic diseases, lung tissues, renal tissues, and damages to cartilage tissue. A study was conducted to evaluate the effects of MSCs therapy in the myocardial infarction mice model. This study showed that following the systemic delivery of MSCs, these moved towards the myocardial infarction site and homed there. At the damaged site, MSCs differentiated into vascular smooth muscle cells, vascular endothelial cells, and cardio-myocyte, thus repairing the damage and improving the cardiac tissue's function. [51]

Another study reported the therapeutic effects of MSCs therapy in damaged lung tissue. The findings showed that MSCs moved towards damaged lung tissue, differentiated there, and repaired the damage. Furthermore, MSCs secreted the inflammation inhibitory and growth-promoting substances to repair the damaged tissue. [52]

Recently a study investigated the therapeutic effects of insulin-like growth factor-1 containing MSCs in the myocardial infarction mice models. The findings showed that the transformed MSCs reduced the infarction and prevented the cardiac tissue from apoptosis and fibrosis.[53]

In clinical studies, MSCs therapy also proved to be an effective regenerative medicine treatment approach. In 2003, a clinical study was conducted in which six patients with myocardial infarction were given autologous bone marrow-derived MSCs. It improved the functions of left ventricles in four patients and reduced the infarction size in five patients. [54]

Another study reported that the systemic delivery of allogenic MSCs into a patient suffering from severe aplastic anemia promoted the hemopoietic function of bone marrow by releasing hemopoietic growth factors. It resulted in the improved functioning of the bone marrow matrix. [55] Similarly, MSCs therapy-based clinical studies in liver cirrhosis also showed that the transplantation of MSCs or cells obtained from controlled in-vitro differentiation of MSCs resulted in enhanced liver functioning. [56]

Recent studies revealed a variety of MSCs' biological properties and future clinical applications. These findings suggest that MSCs based therapies could be effective regenerative medicine therapy approaches. MSCs will need to be better understood in future research from a multidisciplinary approach to meet the objective of routinely utilizing MSCs in regenerative medicine.

The immunoregulatory function of MSCs in human diseases

Besides the role of MSCs in regenerative medicine, these are also known to modulate immune responses. MSCs can regulate immune effects triggered by autoimmune diseases, tissue damage, and cell transplantation. [57]

MSCs are known to suppress the activation and propagation of B and T cells, growth and differentiation of dendritic cells. These could promote immune tolerance by stimulating the growth of regulatory T cells and suppressing the function of NK cells and macrophages. [58]

MSCs could exert inflammation inhibitory effects; repair damaged tissue and home at inflammatory or damaged tissue sites. Given these merits, MSCs have been utilized in many clinical studies to treat autoimmune

disorders, inflammatory diseases, and graft-versus-host disease (GVHD). In 2008, a preclinical study was conducted to evaluate the effects of MSCs therapy in arthritis. MSCs were given to the collagen-induced arthritis mice model. This treatment increased the population of FoxP3 expressing CD4þCD25þ regulatory T cells, reduced the volume of inguinal lymph nodes, and decreased the swelling of the ankles. Findings showed that MSCs treatment efficiently treated arthritis in mice models. [59]

Acute lung injury is considered a fatal health condition that damages alveolar epithelial and capillary endothelial cells. Studies have reported that MSCs treatment could be beneficial for acute lung injury as it diminishes the alveolar-capillary permeability and extravascular pulmonary edema of lung tissue.[60] Similarly, a treatment approach using umbilical cord-derived MSC was conducted. The findings showed that MSCs treatment prevented lung injury in Escherichia coli mediated sepsis in mice model. [61]

Another study reported the therapeutic success of MSCs therapy in a sepsis mouse model. Following transplantation, MSCs released PGE2, which reprogrammed the functions of macrophages so that macrophages started releasing high levels of IL-10. Thus, anti-inflammatory effects were produced, and mice models were relieved of sepsis.[62] One study evaluated the effects of MSCs treatment in GVDH in the liver and intestine. The results showed that five days following MSCs administration, bilirubin levels decreased in the patient's body. After two weeks, the patient resumed eating activities. [63]

MSCs could regulate the function of T cells. By releasing chemokines like monocyte chemoattractant protein-1 (MCP-1), CXCL9, CXCL10, and CXCL11.[64] MSCs can attract T cells. By releasing cytokines like TGF-b, HGF, IL-10, and PGE2, MSCs can suppress the growth and activation of T cells. By the actions of cytokines, MSCs could also decrease inflammation by increasing the population of regulatory T cells, TH2 and TH17 cells.[65] A phase I clinical study showed that adipose-derived MSCs treatment could be beneficial for inflammatory bowel disease. It reported that fistula healed inpatient after eight weeks of MSCs administration and did not recur within one year.[66]

MSCs also proved to be suitable candidates for treating systemic sclerosis. In a clinical study, a patient was given allogenic MSCs, and the patient's condition started to improve within seven months of treatment. [67] Sun L conducted a clinical study to treat systemic lupus erythematosus (SLE) using MSCs. The treatment strategy showed significant effectiveness against SLE and improved kidney function inpatient after MSCs delivery. [68] Jiang R conducted a clinical study in which 10 patients suffering from type II diabetes were recruited. Patients were administered with placenta-derived MSCs thrice every month for three months. This treatment decreased insulin dependency and increased the levels of the serum-c peptide in treated patients. Further, MSCs therapy also alleviated diabetic-associated renal and CVD complications. [69]

The findings of the studies, as mentioned earlier, revealed that MSCs could provide potent therapeutic effects in the treatment of autoimmune disorders, inflammatory disorders, and GVHD. However, certain inconsistencies are still associated with MSCs therapies, like lack of data about standard transplantation dose, standard delivery method, and standard treatment time. Further research needs to be conducted to solve such issues to get more accurate and potent effects of MSCs therapy.

Treatment of tumors through MSCs therapy

As the tumor grows, the tumor cells release significant quantities of immune mediators, which create an inflammatory state in the tumor microenvironment.[70] The immune mediators secreted by tumor cells could attract MSCs to the tumor site. Many studies investigated the ability of MSCs to migrate towards the tumor site. These studies showed that MSCs could travel to tumor sites in different types of cancers like lung cancer, brain cancer, prostate cancer, colon cancer, pancreatic cancer, skin cancer, and ovarian cancer. MSC also exhibited “homing” at tumor site. [37, 71]

Given the advantages of MSCs like low immunogenicity, tumor homing makes them suitable candidates for developing strategies for cancer therapy. [72]

Tumor therapy with MSCs: the mechanism of action

The employment of MSCs in cancer therapy is gaining popularity among the scientific community. Several studies reported that MSCs could affect tumor cell functioning by decreasing tumor cell viability, inducing cell cycle arrest and apoptosis. MSCs are reported to

have low or minimum effects on normal cells. A study conducted by Lu Y showed that MSCs suppressed the tumor cell growth and spared the normal cells. [73]

Dasari reported that cord blood-derived MSCs attenuated the levels of apoptotic inhibitory protein and suppressed the glioma cell growth. Sasportas also reported that MSCs traveled to the glioma tumor site and induced apoptosis of glioma cells. Another study reported that TNF-a-activated MSCs enhanced the expression of TRAIL (TNF-related apoptosis-inducing ligand) and caused tumor cell death. [74-76]

Moreover, Atsuta reported that MSCs could trigger the binding of Fas ligand (Fas-L) with Fas receptors on tumor cells and could cause cell death in multiple myeloma mice models. MSCs suppressed the tumor growth and inhibited the migration of tumor cells towards the lungs and kidneys. By doing so, MSCs therapy prolonged the mice model survival rate. [77]

Recently, a study reported that umbilical cord-derived MSCs (UC-MSCs) could stop the progression of the cell cycle at G0/G1 phase in leukemia cells by suppressing the expression of oncogenes. Yuan Che reported that exosomal miR-143 isolated from bone marrow-derived MSC could negatively affect the activity of trefoil factor 3 (TFF3) in prostate cancer cells to suppress their migration and invasion. [78, 79]

The above data showed that MSCs could suppress the growth of tumor cells and could inhibit their migration and invasion. Similarly, these can cause apoptosis and cell cycle arrest in different cancer cell types.

MSCs could deliver genes of interest at the tumor site

Almost three decades ago, the idea of utilizing MSCs for gene therapy was proposed by professor Armand Keating. Because of important characteristics of MSCs like tumor homing and evasion of host immune responses, genetically engineered MSCs could exhibit promising anti-tumor effects. MSCs expressing tumor suppressor genes or carrying tumor inhibitory agents to the tumor site have proven effective against cancer. [80, 81]

For the first time, James produced transgenic changes in MSCs and transfected MSCs with the IL-3 gene to make them IL-3 expressing cells. This modification enabled MSCs to express IL-3 without any changes in their innate characteristics. Further, Studeny constructed interferon b (IFN-b) expressing MSCs to treat melanoma and achieved successful tumor inhibitory results. [82] These findings encouraged other researchers to work in this field of research. Xin engineered CX3CL1- overexpressing MSCs and performed systemic delivery of these MSC to lung tumor mice models. Modified MSCs inhibited tumor growth and increased the survival rate of mice models. [83] Seong also conducted systemic delivery of green fluorescent protein (EGFP) labeled TNF-related apoptosis-inducing ligand (TRAIL) expressing MSCs to glioma mice models. Seven days after the delivery, green fluorescence was detected in mice brains, and further monitoring showed that tumor growth reduced significantly after 14 and 21 days. The results indicated that MSCs migrated to the brain and inhibited tumor growth.[84] Qiao manufactured MSCs containing osteoprotegerin gene expressing adenoviruses and injected them in osteoma mice models. The findings showed that the treatment remained successful, and osteoma growth was inhibited. [85]

Our research group engineered E1s modified MSCs to carry replication-deficient adenoviral vector p53/p21 expressing MSCs to the tumor site. In mice models, the novel MSCs based delivery was employed to carry therapeutic adenoviral vectors to prostate and lung tumor sites. Results showed that MSCs containing adenoviral vectors reached the tumor site, home there, and inhibited the growth of tumors. [86, 87]

The above data showed that MSCs could be employed to deliver the gene of interest to tumor site in an efficient manner.

MSCs could carry drugs at the tumor site

Besides gene delivery, MSCs also showed promising potential to deliver drugs to the tumor site. MSCs could carry drugs, move towards the tumor site and deliver the drug to the tumor site. Nanoparticles are the most prominent drug coating materials that can be packaged into MSCs and delivered to tumor sites. Drug coated polymer and lipid nanoparticles can be packaged into MSCs by endocytosis and lipid fusion, respectively. [88, 89]

Data showed that within seven days of packaging of nanoparticles into MSCs, the innate characteristics of MSCs like the survival, differentiation, and tumor-homing remained unaffected. [90] A study investigated the percent survival of nanoparticles in MSCs. The result showed that three days after the packaging of MSCs

with polymer nanoparticles and lipid nanoparticles, 95% of cells showed the presence of polymer nanoparticles, and 45% of cells showed the presence of lipid nanoparticles. The reason for a decrease in the percentage of the nanoparticles containing cells is thought to be cell division.[91]

MSCs deliver the drug-coated nanoparticles to the tumor site possibly through the following mechanism: Nanoparticles enter the MSCs in the form of endosomes. After entry, these are engulfed by lysosomes. The nanoparticles remained unaffected by the actions of hydrolytic enzymes in lysosomes. The nanoparticles disrupt the lysosomal membrane and release into the cytoplasm. Further, these nanoparticles enter into tumor cells, thus, deliver the drug to tumor cells. [92, 93] Several studies have demonstrated the therapeutic effects of MSCs containing drug-coated nanoparticles. MSCs have been utilized to deliver coumarin-6 and silica nanodoxorubicin drugs to the tumor site to treat glioma. [94] Moreover, MSCs have also been used to deliver porphyrins-coated fluorescence core-shell nanoparticles and paclitaxel-coated nanoparticles to treat osteoma and lung cancer, respectively. [95, 96] The above findings show that MSCs could be promising carriers of drug-coated nanoparticles.

Some studies have highlighted the controversial role of MSCs in tumor treatment. Although MSCs proved to be promising anticancer agents that could act directly as antitumor agents or carry antitumor agents to the tumor site. It has been reported that MSCs could promote tumor growth and angiogenesis. [97] So, employing MSCs in clinical settings requires more data on safety, effectiveness, and a better understanding of mechanisms responsible for MSCs and tumor cell interaction.

The applications of MSCs in clinical studies

For the last two decades, MSCs have been extensively utilized in clinical settings to evaluate the efficiency of MSCs based cell therapy in various health conditions. Many clinical trials are being conducted to investigate the effectiveness of MSCs therapy in several human disorders. [98, 99]

MSCs possess particular abilities, including the ability to home at the site of inflammation or tumor, low immunogenicity, viral vectors or drug load carrying capacity, immune regulatory capacity, the release of various chemical substances, multipotent differentiation. These merits make MSCs the suitable candidates to be used in clinical studies.[100]

Literature review showed that the first MSC-based clinical study was conducted in 1995 in blood cancer patients. [101] In this study, MSCs were isolated from patients, isolated MSCs were grown in-vitro, and then patients received autologous MSCs transfusion. Further, another clinical study employed allogenic MSCs transfusion to patients with GVHD and obtained promising therapeutic results. [102] Optimistic Results of many MSCs therapy-based clinical studies encouraged researchers to investigate MSC therapy's efficacy in various health conditions. Public Clinical Trial Database shows that 3,779 MSCs based clinical studies are being conducted to check the therapeutic effects of MSCs therapy in a wide range of pathological conditions.

The data shows that most clinical trials are in phase 1 or II, and fewer clinical studies have entered in phase II or IV. Besides ongoing studies, participant recruitment for new clinical studies is also going on (http://clinicaltrials.gov) as of 20th October, 2021.

Several clinical studies conducted to treat various human diseases like acute myocardial ischemia, stroke, cirrhosis, amyotrophic lateral sclerosis, and GVHD have been completed. The findings of these studies showed that MSCs based therapies produced safe and potent therapeutic effects in patients.

The limitations of MSCs therapy in clinical studies

Although MSCs-based therapies proved to be potent and safe in many clinical trials. Some recent studies showed that MSCs could pose potential risks during therapy. MSCs could undergo misdifferentiation, these could promote tumor growth and could induce unwanted immunosuppression. [103]

A study reported misdifferentiation of MSCs following transfusion in glomerulonephritis mice models. After reaching renal tubules, MSCs differentiated into adipocytes, interfered with normal kidney functions, and promoted chronic kidney diseases. [104] It is also observed that MSCs could form microemboli in the capillaries of mice models and contribute to forming osteosarcoma-like lung lesions. [105] Additionally, it is also found that MSCs could induce unwanted immune

suppression. In a clinical study, MSCs were given to GVDH patients. Following treatment, 1/3 of patients showed viral infection. The immunosuppressive effects of MSCs were thought to be the reason for viral infection in the patients.[106] MSCs are also found out to be associated with the promotion of tumor growth. Unmodified MSCs could differentiate into tumor cells. These could minimize the effects of drugs by metabolizing the chemotherapy drugs and also could attenuate the host anti-tumor immune response.[107]

Several studies have reported that under certain conditions, MSCs could transform in tumor cells. [108] Similarly, it is found that MSCs metabolized asparaginase drug in acute lymphoblastic leukemia cells. By doing so, these greatly minimized the effects of chemotherapy in acute lymphoblastic leukemia.[109]

The above data showed that great care should be taken in the selection of patients for MSCs therapy. Patients with poor immune conditions and patients with chances of developing tumors must be carefully given MSCs therapy. Furthermore, there is a need to gather more data on the safety and effectiveness of MSCs based therapy, especially in clinical settings.

Conclusions

MSCs considered the most important stem cells among adult stem cells. MSCs can be obtained from a wide range of sources. MSCs could undergo self-renewal and differentiate into multiple cell types. MSCs have the ability to move towards injured, inflammatory, and tumor sites. These could reach the sites of regeneration and could home there with minimal host immune activation. MSCs could also act as carriers of viral vectors and drugs. These can selectively carry the therapeutic agents to a target site in the body. Given these merits, MSCs have been extensively investigated in preclinical and clinical studies for their therapeutic effects. MSs have shown potent therapeutic effects in cancer, autoimmune diseases and also successfully repaired various damaged tissues. Several MSCs therapy-based clinical studies at different levels are being conducted to treat a variety of human diseases. Some studies also reported few demerits associated with MSCs therapy in preclinical and clinical settings, which urges the careful selection of MSCs therapy for different patients. Because of all these findings reported in the literature, we have summarized the use of MSCs therapy in important health conditions, including cancer, autoimmune diseases, and tissue regeneration. The information about the application of MSCs in therapeutic strategies may be beneficial in the better understanding of pros and cons of MSCS therapy in different human diseases.

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