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REVIEW ARTICLE

Mesenchymal stem cell: Challenges, opportunities and controversies in Cancer therapy

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ABSTRACT
MSCs are a common cell type in regenerative medicine. Numerous studies indicate that MSC-based therapies can be used to treat neurological disorders, cardiac ischemia, diabetes, and bone and cartilage disorders. Cancer-fighting capacity of MSCs is controversial. Emerging evidence indicates that MSCs shrink cancer cells, contrary to previous findings. Before planning a cancer treatment based on MSCs, it is essential to determine if MSCs promote or inhibit tumour growth. Here, we examine the therapeutic applications of MSCs for regenerative medicine and tissue repair, with an emphasis on cancer, particularly CNS tumours. The double-edged sword of MSCs in oncological treatment and MSC-based anti-cancer chemical delivery systems will also be investigated. Stem cell treatment is the subject of significant research. The MSC treatment holds tremendous hopes for translational medicine. Numerous aspects of MSC therapy require explanation. Due to diverse techniques, the consequences of stem cell therapy remain unknown. The majority of in vivo MSC studies have revealed safety and potential. The therapeutic benefits of MSC-based treatment are not spectacular, and long-term observations and follow-up results should reflect a potential danger associated with the use of MSCs in specific cell niches. Additionally, the article explored the therapeutic applications of stem cells in the realm of cancer. In addition to discussing the existing varied functions of MSCs in cancer therapy, this essay examined the future potential of this topic.
Keywords: Cardiac Ischemia, Diabetes, Double-Edged Sword, Oncological Treatment

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INTRODUCTION

MSCs possess the capacity to regenerate themselves and differentiate into multiple lineages. They were discovered in bone marrow first, and thereafter in adipose tissue, muscle, peripheral blood, hair follicles, teeth, placenta, and umbilical cord [18]. MSC progenitors are in the perivascular zone, which promotes a quiescent-resting state and homeostasis. MSCs enter the bloodstream when a tissue is damaged and proinflammatory cytokines attract them to injury sites. MSCs are nicknamed "inflammation guardians [40].

The clinical application of MSCs for autologous transplantation is intriguing. Numerous clinical trials employing MSCs have been performed, and more are now ongoing. More than 2,000 patients have been treated using allogeneic or autologous MSCs grown in culture [51]. In general, MSC therapy was beneficial. Incorporating long-term data into the evaluation of MSC transplantation risk is essential. In vitro and in vivo studies provided proof of MSC differentiation [35]. Recent research suggests focusing on MSC paracrine properties, such as the release of extracellular vesicles containing mRNAs, regulatory

microRNAs, bioactive proteins and compounds, and the production and secretion of a large number of regulatory substances, as opposed to MSC direct differentiation and cell replacement [8]. MSCs boost endogenous repair processes in injured tissues in vivo by secreting chemicals and influencing immune response, hence enhancing the efficacy of MSC-based therapies [38].

MSCs may have diverse features based on their tissue of origin, but they must meet three ISCT requirements. First, in vitro-grown MSCs must be plastic-adherent. MSCs must express CD73, CD90, and CD105 but not CD45, CD34, CD14 or CD11b, CD79 or CD19, and HLA-DR. Third, cultivated MSCs must differentiate into mesodermal cell types (adipocytes, chondrocytes, and osteoblasts). MSCs can also differentiate into ectodermal and endodermal cells, such as neuronal, cardiomyocyte, hepatocyte, and epithelial cells.

MSCs have an innate tropism toward damaged locations, which is modulated by chemoattractant signals. CXCL12 is a common injury trigger. A subpopulation of MSCs expresses CXCR4, which binds to CXCL12 to mediate cell migration [32].

Mesenchymal stem cells are the most popular variety for clinical usage. MSCs can move to wounded locations in response to environmental signals and stimulate tissue regeneration by releasing pleiotropic paracrine substances. MSCs can inhibit the immune system, enhance cell survival, and induce angiogenesis via interacting with the host niche. MSCs' immunosuppressive effect is particularly attractive for clinical usage since it reduces transplant rejection. MSCs can be acquired from minimally invasive sources (e.g., peripheral blood, adipose tissue) and rapidly grown for clinical use.

This enables the creation of an autologous (patient-specific) medication within a therapeutic window. MSCs derived from adult tissue circumvent ethical issues associated with embryonic origins. All of the features of MSCs make them a formidable tool for regenerative medicine.

MSCs can differentiate into mesodermal, ectodermal, and endodermal cells, according to research. MSCs' adaptability and self-renewal make them therapeutic targets for cancer treatment and tissue regeneration. MSCs have enormous potential in therapy, but they also pose a threat due to their tendency to develop into cancer-associated fibroblasts, which encourage tumour growth through their secretome and apoptosis resistance. MSCs have proven ineffectual in anticancer therapy due to their conflicting involvement in cancer progression and regression. To maximise MSCs' therapeutic potential, it's necessary to understand their molecular pathways [15]. This article will address the complexity of MSCs, their prospective applications in cancer therapy, and the existing obstacles facing MSC.

THERAPEUTIC POTENTIAL OF MSC IN DIFFERENT OTHER DISEASES

Review of literature with studies describing MSC based therapy

MSC-based therapies have been used to treat neurological diseases, cardiac ischemia, diabetes, and bone and cartilage disorders in preclinical trials. The therapeutic potential of MSCs is determined by their mobility to wounded tissues. Immunosuppressive, anti-apoptotic, anti-fibrotic, angiogenic, and anti-inflammatory growth factors, cytokines, and extracellular vesicles are secreted by engrafted cells.

These advantages are partially explained by the increased cell proliferation in the ischemic hemisphere of transplanted rats. By releasing neurotrophic factors important in neuronal survival, bone marrow MSCs restored motor function and slowed neurodegeneration in a mouse model of Friedreich's ataxia [53, 42].

Research findings have shown that, MSC-treated pigs have more angiogenesis, less apoptosis, and less fibrosis in the ischemic heart. Bone marrow-derived MSCs improve insulin sensitivity in type 2 diabetic rats through increasing GLUT4 expression [47]. In more recent research, it was discovered that administering human adipose-derived MSCs by intranasal administration could protect mice from neurocognitive deficits caused by cranial radiation [50].

MECHANISM OF THERAPEUTIC POTENTIAL

Ability to migrate

The success of advanced therapeutic pharmaceuticals hinges on their ability to reach target tissues. Chemoattractant signals alter the intrinsic tropism of MSCs toward injured tissue sites. CXCL12 is a common cause of damage. CXCR4 is expressed by a subpopulation of MSCs and binds to CXCL12 to facilitate cell motility [32].

Tissue Repair Ability

MSCs aid in tissue repair and regeneration through different mechanisms. The pleiotropic features of MSCs augment their therapeutic potential. When wounded, MSCs release anti-apoptotic, anti-inflammatory, immunomodulatory, anti-fibrotic, and angiogenesis-promoting chemicals. [33] The therapeutic effects of MSCs are due to their anti-inflammatory and immunomodulatory properties. As

sensors of inflammation, MSCs emit soluble molecules like TGF, IDO, TNF, Interleukin 10 and INF, which interfere with the immune system and influence the inflammatory landscape [40].
MSCs restrict T and B cell growth, reduce natural killer cell activation, and impede monocyte-derived dendritic cell production and maturation. MSCs induce the production of immunosuppressive regulatory T lymphocytes. MSCs are immunosuppressive due to soluble substances and cell-to-cell interaction. Direct interaction between MSCs and proinflammatory macrophages induces immunological tolerance by inducing TSG-6. MSC-mediated immune response modulations drive healing, scarring, and fibrosis, promoting tissue repair and regeneration [21].
MSCs' multilineage differentiation capability is another therapeutic characteristic. MSCs can differentiate into brain cells, cardiomyocytes, hepatocytes, or epithelial cells [15]. Researchers propose that differentiated MSCs can dedifferentiate and transdifferentiate into cells of another developmental lineage [49].
MSCs can replace injured or dead cells from diverse tissues due to their versatility. Several investigations show that MSCs engraft at the injury site briefly after administration and then vanish. These show MSCs must activate tissue-repair pathways in the host niche (16). Cross-talk between MSCs and injured tissue microenvironment results in proliferation and differentiation of local precursor cells. Systemic treatment of MSCs reduces radiation-induced intestinal epithelium injury in mice via activating the Wnt/-catenin signaling pathway, which drives intestinal stem cell proliferation and maintenance [36].

USE OF MSC IN CANCER THERAPY

MSCs have led the development of cell-based oncology therapeutics in the last decade. MSCs are important for individualised cell-based therapeutics because they may be collected with minimally invasive techniques and rapidly increased [12]. ClinicalTrials.gov lists 25 MSC-related clinical studies. Few trials using MSCs to treat cancer directly are described in Table 1.

- Clinical application (Studies and ongoing clinical trial for the use in various cancers):
- Mechanism of therapy (Pro-tumor activity and anti-tumor activity)

Table1: Few trials using MSCs to treat cancer

Objective of the study	Type of cancer	Therapeutic agent used	Phase of trial/Outcome of study	Hyperlink of clinical trial/ cite in-text reference
To investigate the toxicity of allogeneic bone marrow-derived MSCs loaded with oncolytic adenovirus DNX-2401.	Glioma	BM-MSCs-DNX2401	I	https://clinicaltrials.gov/ct2/show/NCT03896568
To investigate the toxicity of MSC-derived KrasG12D siRNA exosomes.	Pancreatic cancer	iExosomes	I	https://clinicaltrials.gov/ct2/show/NCT03608631
To test the safety and anti-tumor activity of TRAIL-modified MSCs.	Lung Cancer	MSC-TRAIL	I,II	https://clinicaltrials.gov/ct2/show/NCT03298763
To determine where bone marrow-derived MSCs (BM-MSCs) go after systemic administration	Prostate Cancer	BM-MSCs	I	https://clinicaltrials.gov/ct2/show/NCT01983709
To determine the maximum tolerated dose of bone marrow-derived MSCs expressing INFb (BM-MSC-INF) that can be administered to ovarian cancer patients, and to	Ovarian cancer	BM-MSC-INFβ	I,II	https://clinicaltrials.gov/ct2/show/NCT02530047

evaluate their safety.				
To test the feasibility and safety of combining UC-HSC and MSC.	Hematologic malignancies	MSCs UC-HSC	I	https://clinicaltrials.gov/ct2/show/NCT02181478
Determine maximum dose, safety, and efficacy of intratumoral GX-051	Head and neck cancer	GX-051	I	https://clinicaltrials.gov/ct2/show/NCT02079324
To assess the safety of bone marrow-derived, ICOVIR5-infected MSCs in children and adults with metastatic and resistant solid malignancies.	Solid tumors	CELYVIR	I,II	https://clinicaltrials.gov/ct2/show/NCT01844661

Pro-tumor activity

MSCs' pleiotropic activities may also confer pro-tumor functions. Metastatic human breast cancer cells promote CCL5 production from MSCs, which enhances tumour invasion. Seminal data show that MSCs can prevent tumour cell death by secreting VEGF and bFGF [23, 39, 26].

MSCs can induce tumour angiogenesis, which nourishes and oxygenates tumours. MSCs recruited in breast and prostate tumours increase angiogenic factors such as TGF, VEGF, and Interleukin 6, which promote tumour growth and vascularization. TGF1 expression linked with microvessel density in hepatocellular carcinomas from mice implanted with human MSCs. According to this study, MSCs promote tumour angiogenesis via TGF [55].

MSCs can also respond to soluble cues released by cancer cells and transform into CAFs that promote tumour growth. Cancer-secreted TGF promotes the transformation of MSCs into CAFs. Due to their active secretome, which includes immune-modulating agents (CXCL12, Granulocyte Macrophage Colony-Stimulating Factor), pro-angiogenic factors (VEGF, TGF, PDGF), pro-survival factors (Hepatocyte Growth Factor, Insulin like Growth Factor 1, Interleukin 6), and extracellular matrix modulators (MMP, Tissue Inhibit), the transformation of MSCs into CAFs contributes to tumour progression (22). Recent research indicates that the engulfment of MSCs by breast cancer cells alters the tumour's transcriptome profile, particularly in oncogenic pathways. This MSC engulfment enhances the stemness, invasion, and metastasis of breast cancer [6].

Anti-tumour activity

MSCs have been used as cancer therapies despite evidence of their pro-tumorigenic activity. MSCs secrete cytotoxic chemicals such as TRAIL, which preferentially triggers apoptosis in cancer cells [52, 1]. Bone marrow MSCs enhance apoptosis and limit glioma U251 cell proliferation by downregulating PI3K/AKT signaling [30].

MSCs injected intravenously inhibited the growth of Kaposi sarcoma tumours by blocking AKT activation. In breast carcinomas, umbilical cord MSCs suppressed ERK1/2 and AKT activation, lowering cell proliferation and inducing cell death. Wnt signalling enables MSCs to inhibit the development of tumour cells. A mechanistic investigation into the inhibitory effect of MSCs on breast cancer cells revealed that MSC-secreted Dickkopf-1 (Dkk-1) inhibits Wnt signalling (41) (14). Bone marrow MSCs inhibit vascular development in ΔGli36 glioma xenograft by downregulating PDGF/PDGFR. When tumour lysates were treated with MSCs, PDGF-BB protein expression was reduced, which linked with lower levels of activated PDGFR- and its downstream target AKT. MSCs suppressed angiogenesis in a melanoma mouse model, reducing tumour development. *In vitro* studies revealed MSC-induced capillary degeneration caused anti-angiogenic effects [27, 19]. MSCs stimulate anti-tumor immune responses by the release of inflammatory mediators, such as TGF. As with other signalling molecules, TGF plays a dual role in cancer genesis. TGF signalling is both pro-tumor and anti-cancer. Restoring TRIII expression reduces tumorigenicity during the course of breast cancer [4, 10].

MSC mediated targeted therapy in cancer (Delivering anti-cancer payload)

Over the past decade, researchers have studied stem cells as Trojan horses to deliver anti-cancer payloads to tumour cells. Due to their ability to travel to tumour locations, MSCs are a promising therapeutic carrier. Genetic engineering is a frequent way to make MSCs that kill cancer cells. MSCs are

genetically engineered with viral particles to express cytokines like INF. It has been demonstrated that human umbilical cord mesenchymal stem cells that have been transduced with adenoviral vectors expressing IFN can effectively suppress the growth of breast cancer cells by inducing apoptosis in those cells [46, 29].

Human umbilical cord MSCs expressing interleukin-18 inhibit the proliferation and spread of breast cancer in mice. MSCs engineered to express TRAIL have extraordinary antitumor activity [17, 13]. X. Jiang and colleagues used nanoparticles to create human MSCs modified to express TRAIL for targeting and eliminating cerebral gliomas in mice. TRAIL-expressing MSCs decreased tumour development, caused apoptosis, reduced microsatellites, and prolonged animal survival in a mouse model of orthotopic glioblastoma xenografts [20]. In MSC engineering for cancer therapy, proteins other than cytokines have been utilised. BMP4-expressing MSCs inhibit tumour growth and prolong the longevity of mice with glioma. MSCs modified to express PTEN enhanced the cytotoxicity of glioma cells [17].

In cancer therapy, microRNAs (miRs) are employed to modulate post-transcriptional gene expression. MSCs express miRs that can be packaged into vesicles and delivered to neighbouring cells for therapeutic purposes. MSCs have been engineered to carry microRNAs against cancer. Using lentiviral vectors, MSCs were engineered to produce extracellular vesicles with high levels of miR-124a, which demonstrated an anti-tumor effect in many patient-derived glioma stem cell lines [44, 24].

MSCs containing oncolytic viruses are an effective anti-tumor treatment. Infected MSCs decreased the formation of lung cancer tumours in mice and attracted T lymphocytes to these lesions. MSCs expressing the oncolytic adenovirus CRAd5/F11 inhibited tumour formation in a subcutaneous mice xenograft model of colorectal cancer. Different forms of oncolytic herpes simplex virus have been used to arm MSCs that track metastatic tumour lesions and lengthen the lives of mice with brain-metastasized melanoma [43, 11].

MSCs armed with anti-cancer medicines are another cancer Trojan horse. In vitro research found that gingival-derived MSCs primed with Paclitaxel, Doxorubicin, or Gemcitabine prevent squamous carcinoma growth [7, 37]. Paclitaxel-loaded MSCs fought glioma in rats. Recent research focuses on improving MSC payload and delivery capacity. Nanoparticles are a promising way to boost the anti-tumor efficacy of anti-cancer-drug-loaded MSCs. Encapsulated drugs accumulate preferentially at the target site, avoid burst release, and reduce side effects [34, 54, 25].

CHALLENGES, CONTROVERSIES AND LIMITATION OF MSC BASED CANCER THERAPY

Engineered MSCs are an innovative cancer treatment. Transplantation and survival of MSCs limit their therapeutic application. Biomaterials increase cell retention in cell therapy to treat diverse ailments. This biomaterials and stem cell combination can repair and replace whole organs [9, 55]**.** The administration of therapeutic MSCs on biomaterials to treat postoperative brain cancer was revealed in a recent study. This technique employs biodegradable fibrin scaffolds seeded with mesenchymal stem cells (MSCs) to eradicate residual cancer cells in surgically removed patients, with the aim of extending cancer-free survival. In a separate trial, bispecific anti-CD33-anti-CD3 antibody was delivered to AML patients using MSCs housed in cryogel [2, 45]. Anti-cancer biomaterials can be created. Gliadel is one of the most successful biomaterials in brain cancer interstitial therapy. Gliadel is a biodegradable polifeprosan implant that delivers carmustine over 2–3 weeks. Gliadel improves survival in patients undergoing brain tumour surgery [5]. Recent research has found a thermo-responsive biodegradable paste that improves glioma patient survival. Once biomaterial composition and design are perfected, they may be used with stem cells to release anti-cancer chemicals. Biomaterial-based MSC treatments are a possible cancer treatment that warrants more study [48].

CONCLUSION AND FUTURE PERSPECTIVE

MSCs' role as guardians against excessive inflammation explains many of the beneficial effects shown in animal models for lung injury, diabetes, sepsis, MI, sterile corneal injury, and stroke. Recent information on cell-produced anti-inflammatory factors opens the door to safer, more widely applicable therapies than using the cells themselves. MSCs control anti-inflammatory actions based on tissue damage [40].

Numerous diseases are frequently treated with mesenchymal stem cells due to their ability to migrate to injured tissues, differentiate into numerous cell types, and pleiotropic effects. Contradictory preclinical results have hindered the use of MSCs in cancer therapy. MSC-based therapies offer highly effective, individualised anti-cancer therapy despite this. Utilizing MSCs as therapeutic Trojan horses is a step toward more effective cancer treatment. Next, better comprehend the interactions between MSCs and cancer cells in order to develop MSC-based therapy techniques. As a cell-free therapy, MSC-derived extracellular vesicles may circumvent safety issues associated with living cells. More research will show

the limitations of cell-free cancer therapy. We are getting closer to developing a cancer therapy that is both safe and effective and will boost survival and quality of life [18].

Recent research demonstrates MSC therapy has modest therapeutic results, showing their direct regeneration capacity isn't as successful as expected. MScs' safety, extensive differentiation capability, and great paracrine capabilities, including EV release, make them an important material for future cell-based therapeutics. Preclinical and clinical research is needed. New MSC information will help decide cell therapy efficacy. More research would also benefit stem cell biology.

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