

An overview of mesenchymal stem cells and their potential therapeutic benefits in cancer therapy (Review)

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Abstract. There has been increased interest in using stem cells for regenerative medicine and cancer therapy in the past decade. Mesenchymal stem cells (MSCs) are among the most studied stem cells due to their unique characteristics, such as self-renewal and developmental potency to differentiate into numerous cell types. MSC use has fewer ethical challenges compared with other types of stem cells. Although a number of studies have reported the beneficial effects of MSC-based therapies in treating various diseases, their contribution to cancer therapy remains controversial. The behaviour of MSCs is determined by the interaction between intrinsic transcriptional genes and extrinsic environmental factors. Numerous studies continue to emerge, as there is no denying the potential of MSCs to treat a wide variety of human afflictions. Therefore, the present review article provided an overview of MSCs and their differences compared with embryonic stem cells, and described the molecular mechanisms involved in maintaining their stemness. In addition, the article examined the therapeutic application of stem cells in the field of cancer. The present article also discussed the current divergent roles of MSCs in cancer therapy and the future potential in this field.

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1. Introduction

The human body contains numerous different cell types, which make up tissues and organs with specific functions that play a role in ensuring sustainability. It was discovered long ago that differentiated cells in some tissues, e.g., skin, intestinal epithelium and blood, have a short lifecycle and are incapable of self-renewal (1). Stem cells are able to self-renew and possess developmental potency to differentiate into numerous cell types of an organism. This finding led to the concept of stem cells as small unspecialized cells in the human body devoid of a number of phenotypic traits commonly found in cells from adult tissues for maintaining static and transient cell types (2). Potency with each differentiation step classifies stem cells into totipotent, pluripotent, multipotent, oligopotent and unipotent stem cells (3). As potency decreases, the possible cell types that stem cells can differentiate into also decrease accordingly.

Stem cells are generally categorized into two main groups: embryonic and nonembryonic (somatic stem cells). Embryonic stem cells (ESCs) are pluripotent, while somatic stem cells, e.g., mesenchymal stem cells (MSCs), are multipotent (4,5). ESCs were first isolated from mouse embryos (6), while MSCs were discovered in monolayer cultures of guinea pig bone marrow (7). Following their initial discovery, human stem cells were isolated and cultured, whereby ESCs were derived from human blastocysts (8) while MSCs were derived from human bone marrow (9). These achievements in isolating and culturing human stem cells opened new possibilities to better understand the basic molecular mechanisms behind human development and differentiation, leading to potential new treatments for various diseases. While the potential benefits of research on human ESCs are immense, there is a major ethical issue to address, e.g., the derivation of human ESCs results in the destruction of an embryo. In addition, reliance on human embryos may also lead to the commodification and exploitation of women (10-12). Indeed, the potential exploitation of women involving the donation or sales of oocytes or embryos for research and the purposeful creation of embryos for research remain huge ethical issues that need to be addressed. This ethical dilemma negatively impacts the benefit-to-risk ratio, and hence, research has moved towards

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somatic stem cells instead. Despite the focus on ESCs, MSCs have been extensively researched in clinical settings during the past decade (13-24) because MSCs can be easily obtained and cultured for clinical use from multiple tissue sources that are easily accessible using minimally intrusive methods, reducing the ethical dilemmas surrounding human stem cell research (25). Additionally, MSCs can differentiate into a variety of cell types that confer pleiotropic effects when used for therapeutic purposes (26). MSCs were initially discovered in bone marrow, and studies have reported that these stem cells can also be found in other postnatal organs and tissues, e.g., brain, kidney, liver, lung, spleen, adipose tissue, muscle, hair follicles, teeth, placenta, and umbilical cord (27,28). The International Society for Cellular Therapy (ISCT) defines three minimal criteria that need to be fulfilled for MSCs to overcome the issue of different characteristics due to isolation from different tissue types (29):

1. MSCs must adhere to plastic surfaces when cultured *in vitro*.
2. The surface anti-genes CD73, CD90, and CD105 must be expressed by MSCs, while CD34, CD45, CD14 or CD11b, CD79 α or CD19, and HLA-DR surface molecules should be absent.
3. MSCs must be able to differentiate into different mesodermal cell types, e.g., adipocytes, chondrocytes, and osteoblasts, when cultured *in vitro* under certain conditions.

In addition to these criteria, the ISCT recommended three additional conditions in 2019 to further clarify the nomenclature of MSCs to avoid confusion between mesenchymal stem cells and mesenchymal stromal cells (30). The tissue-source origin of MSCs should be documented to highlight tissue-specific properties, e.g., phenotypic, functional and secretome behaviour. Comprehensive *in vitro* and *in vivo* data demonstrate the stemness of MSCs associated with a robust matrix of functional assays that test the functionality of MSCs *in vitro* and *in vivo* based on their proposed utility.

Previous studies have reported that MSCs are multipotent and capable of differentiating into cells of mesodermal, ectodermal, and endodermal lineages (29,31-33). This plasticity of MSCs and their self-renewal capacity make these cells promising therapeutic targets for various diseases, including cancer treatment and tissue regeneration. MSCs undeniably offer immense potential in the field of medicine; however, the cells also present potential danger due to their ability to differentiate into tumour-associated fibroblasts (34-36), which support tumour growth through their secretome (37,38) and resistance to apoptosis (39). Due to their conflicting role in cancer progression and regression, efforts to utilize MSCs in anticancer therapies have been unsuccessful. Therefore, it is important to understand the underlying molecular mechanisms of MSCs to fully utilize their therapeutic potential.

2. Genetic regulators for multipotency of MSCs

Significant advancements in DNA sequencing, computational biology, and bioinformatics have been made to identify

transcriptional processes associated with the multipotency of MSCs. Based on previous studies, cyclin L2 (CCNL2), stromal cell-derived factor 1 (CXCL12), podocalyxin-like protein (PODXL), and ubiquitin carboxyl-terminal hydrolase 1 (USP1) were identified as four genes responsible for maintaining multipotency, chromosomal integrity, and MSC functions (40-42). CCNL2 was reported to inhibit proliferation and cell specialization while promoting apoptosis upon upregulation in mouse embryonic carcinoma P19 cells. In the same study, CCNL2-overexpressing P19 cells had a remarkably decreased S phase and reduced expression levels of myocardial cell differentiation-related genes, e.g., cardiac actin, GATA binding protein 4 (GATA4), myocyte-specific enhancer factor 2C (Mef2C), homeobox protein Nkx-2.5 (Nkx2.5), and B-type natriuretic peptide (BNP) (43). On the other hand, CXCL12 is a chemokine protein that induces the migration of stem cells. It functions by binding to CXC chemokine receptor (CXCR) 4, CXCR7 and atypical chemokine receptor 3 (ACKR3) (44,45). CXCL12 has been reported to be responsible for cell survival, growth and migration during tissue/organ development (46). While the exact mechanism by which CXCL12 helps maintain the stemness of MSCs has not been elucidated, there are numerous reports on its function in other stem cells. The CXCL12-CXCR4 axis was found to be responsible for cell migration, while the CXCL12-CXCR7 axis promotes cell adhesion in cardiac stem cells. Similar findings also reported the importance of CXCL12-mediated CXCR4 signalling in controlling the position of haematopoietic stem cells in bone marrow niches, which contain limiting lymphoid-instructive cytokines that are responsible for the multipotency of HSCs and their maintenance (47). A study confirmed that CXCL12-mediated CXCR4 signalling promotes the proliferation, survival, and migration of mesenchymal stromal cells *in vitro* (48). It is also likely that CXCL12 acts through a similar mechanism to help MSCs maintain their stemness.

PODXL is mainly involved in cell proliferation and oncosphere formation (49). However, the exact mechanism of action in maintaining the multipotency of MSCs is currently not well understood. A previous study reported that higher expression of PODXL and CD49f in MSCs increased the clonogenic potential, viability, and differentiation capabilities of MSCs (41). There may also be an interaction between PODXL and CCNL2, whereby both genes work together to help maintain the multipotency of MSCs. Nonetheless, further studies are warranted before this phenomenon can reach a suitable conclusion. USP1 encodes a deubiquitinating enzyme. USP1 was also found to stabilize inhibitors of DNA binding, which play a role in inhibiting cell specialization while enhancing proliferation (42). As interest in using MSCs for therapeutic purposes grows. Moreover, previous studies have reported other genes and novel mechanisms by which the stemness of MSCs is maintained (50-52). The therapeutic potential of MSCs mostly stems from their ability to self-renew and differentiate. The exact mechanism by which MSC multiplicity is maintained remains ambiguous, and likely, these genes work together in a balancing act to ensure the renewal and stemness of MSCs. Therefore, a clearer understanding should be made available to ensure the safety and efficacy of treatments using MSCs. After all, both the potential therapeutic benefits

and danger come from the self-renewal ability, migration, and stemness of MSCs.

3. Extrinsic regulators for multipotency of MSCs

The niche microenvironment strongly influences the behaviour of stem cells. As mentioned, CXCL12 maintains multipotency by directing MSCs to specific niches, where secreted factors influence their self-renewal and stemness (53). This phenomenon indicates that the behaviour of MSCs is determined by the interaction between intrinsic transcriptional genes and extrinsic factors of the environment. It has been established that the protein kinase B (Akt) and extracellular-signal-regulated kinase (Erk) signalling pathways control both stem cell proliferation and survival, while the Wnt, Notch, and Sonic hedgehog (Shh) signalling pathways regulate stem cell renewal and differentiation (54-57). A study also proposed two novel mechanisms that help to maintain the stemness of MSCs via the scrapie responsive gene 1 (SCRG1)/bone marrow stromal cell anti-gene 1 (BST1) ligand-receptor combination and cell-cell adhesion through N-cadherin (52). An improved understanding of the underlying mechanism involved in stem cell renewal and differentiation is important because the original abilities are lost at a high rate during long-term *in vitro* culture (58,59). Therefore, current work should develop novel techniques to ensure that MSCs maintain their multipotency despite long-term *in vitro* culture. This would, in turn, maintain the potential of MSCs to be used in regenerative medicine and cell therapy.

Epigenetic factors influence the differential gene expression in MSCs that causes cell differentiation. Hence, the DNA sequences of MSCs and their specialized cell types are similar, with almost no difference. Commonly studied epigenetic modifications include DNA methylation and histone modification, e.g., methylation, acetylation, ubiquitylation, and microRNAs. Once epigenetic modifications occur, gene expression can be influenced by changing the availability of gene promoters, thus affecting the recruitment of supplementary chromatin-modifying enzymes or transcriptional regulators that drive stem cell differentiation (60). For example, runt-related transcription factor 2 (Runx2) regulates most osteoblast-specific genes by working together with numerous coactivators and corepressors that alter the binding of Runx2 to the osteocalcin promoter. This binding modification occurs through DNA methylation and acetylation of histones H3 and H4 (61). Additionally, Runx2 changes the expression of its target in response to other signals, e.g., transforming growth factor-beta (TGF- β), bone morphogenetic protein (BMP) and Wnt signalling pathways (60), is responsible for the osteogenic lineage. MSCs can also undergo adipogenic differentiation, whereby hypomethylation of the genes encoding peroxisome proliferator-activated receptors gamma-2 (PPAR γ 2), fatty acid-binding protein 4 (FABP4), leptin (lep) and lipoprotein lipase (lpl) was reported to be responsible for these mechanisms (61,62).

In addition to secreted factors, the cyclic tensile strain that can alter cell behaviour should be considered another microenvironmental factor. MSCs have been observed to lose multipotency and spontaneously differentiate after prolonged passaging *in vitro* (25,63). Therefore, *in vitro* culture conditions

must be optimized to maintain the multipotency of MSCs for their therapeutic potential in clinical settings. A study found that low actomyosin contractility induced by restricting the cells to small islands during initial culture is necessary to ensure the stemness of MSCs (64). A disparity in differential gene expression when MSCs are cultured in 2D and 3D culture systems is likely due to the interaction between the cells in an intricate 3D structure compared to that in a monolayer 2D culture (65). Recent studies have also found that cyclic tensile strain promotes bone marrow-derived MSCs (BMSCs) to differentiate into cardiomyocyte-like cells (66) and adipose stem cells to differentiate into the osteogenic lineage (67). However, the regulatory pathways and epigenetic factors that might be involved seem to depend on the source of MSCs and the desired cell lineage.

4. Clinical applications of MSCs

MSCs have been the subject of clinical trials for the past decade, but the outcomes have fallen short of expectations despite promising data in animal models. Studies continue to emerge, as there is no denying the potential of MSCs to treat a wide variety of human afflictions, e.g., neurodegeneration, ageing, blindness, diabetes, and cancers (1). It is crucial to realistically assess the time and effort required to establish new clinical settings for numerous therapeutic applications. The same concern regarding the efficacy and safety of treatment must also always be at the forefront when considering the usage of MSCs, as there are crucial biological and pharmacological discrepancies in preclinical and clinical studies. The first clinical trial using MSCs as a therapeutic agent was in 1995 (68). Since then, MSCs have become the most widely clinically studied cell-based therapy worldwide (69). MSCs are currently classified as advanced therapy medicinal products (ATMPs), which follow the Good Manufacturing Practices (GMP) guidelines of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to authenticate and ensure the quality of cells before their administration to patients (70). This compliance with GMP includes the sources of MSCs, reagents, equipment, packaging materials, procedures, laboratory staff, environment, and final cellular medicine (71).

It is of the utmost importance that GMP conditions are maintained according to the international and national medicinal governing framework. This act ensures the quality of the administered MSCs and prevents possible contamination issues that may cause adverse reactions in patients and even death. However, there is currently a lack of unified and standard criteria for manufacturing MSCs as a therapeutic agent due to some differences over specific issues depending on the USA, Europe, Canada, Singapore, Japan and so forth. Despite this challenge, consistent physical and microbiological testing of the MSC production laboratory and cleanrooms to ensure the sterility of the production process is also warranted (72). This act fulfils the requirement of International Standard Organization (ISO) standard 14644.

Currently, 1,088 studies registered as clinical trials list MSCs as a clinical intervention. The majority of these trials, whether ongoing or completed, are phase 1 or 2 studies that evaluate the safety and efficacy of MSCs in humans. Despite

the most promising results, MSC-based therapies still have significant limitations due to the nature of the stem cells, e.g., MSCs markedly differ in gene expression profile, cell differentiation ability, growth rate, and therapeutic capacity, depending on their tissue source (63). Therefore, it may be vital to isolate and culture homogenous populations of MSCs to improve the efficacy and safety of the treatment. The method of transplanting MSCs isolated and grown in large batches from unrelated donor tissues is known as allogeneic transplantation; in contrast to autologous therapy, MSCs are extracted and grown from treated patients. The benefits of allogeneic transplantation include:

1. Efficiency, such as the isolation, expansion, and validation of MSCs from the patient, is not required.
2. The therapeutic functions of allogeneic MSCs remain the same, unlike autologous MSCs, which have been reported to have impaired functions when isolated from elderly individuals (73,74).
3. A well-established stock of MSCs following strict GMP requirements reduces the variability of donors and improves the success rate of the treatment.

Allogeneic transplantation, however, may induce an immunogenic response (75), especially when administered repeatedly at the same site (76). This phenomenon makes allogeneic therapy less desirable, especially when it needs to be administered for an extended period. At the same time, *in vitro* studies have reported on the hypoimmunogenic properties (immune-privileged) of MSCs, while the findings of *in vivo* studies were less conclusive (77). It was theorized that MSCs lose their hypoimmunogenic properties upon differentiation, which triggers the immune response and rejection after implantation into the host (77,78). A study also reported that different transplantation routes and microenvironments could influence the immunogenicity of implanted MSCs (79). Because of such inconclusive *in vivo* results, a paper suggested the term immune evasive be used instead of immune-privileged to describe the immunogenicity of MSCs. It was also reported that while MSCs may not be truly immune-privileged, the rejection of allogeneic MSCs occurs at a slower rate than that of other cell types (80). This phenomenon means that future studies should also examine strategies to maintain or prolong the immunogenicity of allogeneic MSCs to maximize the therapeutic benefits.

In contrast, autologous transplantation, which triggers less risk of immunogenic response, is an alternative. Autologous MSCs are easily available without identifying a suitable donor (81). Autologous MSCs also overcome the limitation of long-term *in vitro* culture for allogeneic MSCs, leading to loss of multipotency, morphological changes, and an increased risk of malignancy (25,74). Nonetheless, the challenge and reliance on autologous MSC transplantation mean that a well-optimized and established protocol for the isolation and *ex vivo* preparation of MSCs will be required. Such precise standardization may be difficult, as several exogenous factors greatly affect the biological properties of MSCs (70). Autologous MSCs may not be suitable for treating certain genetic diseases due to the mutations present in stem cells. Flaws in the genetic sequence hinder both the immunomodulatory function and

regenerative traits of MSCs. For example, MSCs isolated from patients suffering from systemic lupus erythematosis have a senescent phenotype with diminished capabilities to differentiate, migrate and regulate the immune system (79,82-84). Therefore, more preclinical and clinical studies are required to obtain more information related to the utility of MSCs as a therapeutic approach. Supplementary studies on the basic biology of MSC maintenance and the regulators of MSC differentiation would also provide a clearer picture of how to better administer MSCs as therapeutic agents in the future.

Most of the published clinical studies employing MSCs for diseases have specific treatments with positive outcomes. In neurology, ischaemic stroke patients treated with MSCs yielded positive results, whereby the patients showed significantly improved neurological and motor functions (85-88). Among all of the studies conducted, serious adverse events that were reported included transient ischaemic attack, seizure, asymptomatic subdural haematoma/hygroma, urinary tract infection, sepsis, pneumonia, hyperglycaemia, neutrophilia, shingles, ischaemic stroke, cellulitis, muscle cramps, fracture neck femur, and peripheral vascular disease (89). However, these side effects were attributed to the procedure rather than cell therapy. The study also reported promising results in the field of cardiology. Studies have shown that diseases, e.g., dilated cardiomyopathy and ischaemic or nonischaemic heart failure, have had clinical and pathophysiological improvements; no serious adverse effects were reported, demonstrating the treatment's safety profile (19,90-92). Patients suffering from cartilage lesions and/or osteoarthritis, especially in the knee, were reported to have a clinical improvement in pain, stiffness, and functionality when treated with MSCs. These results show the broad potential of MSCs for clinical usage with no serious adverse effects linked to cell therapy.

5. Therapeutic potential of MSCs

Interest in developing MSCs as therapeutic agents has not waned in the slightest, despite the obstacles faced, largely due to their immense therapeutic potential. In addition to being multipotent with self-renewing capabilities, MSCs also have the added benefits of migrating to the injury site and promoting tissue regeneration (26). This phenomenon means that MSCs can be a form of personalized therapy (when opting for autologous therapy) that is site-directed, promotes tissue restoration, and replaces damaged cells through differentiation. It is, therefore, unsurprising that scientists are so invested in advancing this field of research since the therapeutic agent reaches the targeted tissue for effective disease treatment. As MSCs have a natural tendency to be attracted towards damaged sites and the tumour microenvironment, the cells are a prime candidate for further investigation, as MSCs seem to be independent of the type of tumour, immunocompetence and delivery route (93).

Insight into the mechanism underlying the mobilization of MSCs to the injury site is still limited, but CXCL12-mediated CXCR4 signalling is most likely involved as a pathway that mediates cell migration (94). Secreted chemokines can mediate inflammation in the tumour microenvironment, and wounds are responsible for attracting MSCs (95). As the chemotactic properties of MSCs seem to be similar to those of other immune cells, the established model of leukocyte migration

can be used as a template to study the factors involved in MSC migration (95). Other chemokine receptors that react to signals from the injury site or tumour microenvironment induce CCR1-2, CXCR1-2, CCR4, CXCR4-6, CCR7-10, and CX3R1 expression in MSCs (95). In addition, cell adhesion molecules expressed by MSCs, e.g., CD44, CD49d, CD54, CD102 and CD106, are thought to be involved in MSC migration to injury sites (26,96).

A wide variety of trophic mediators and growth factors are secreted to initiate tissue regeneration once MSCs arrive at the injury site. The pleiotropic effects conferred by MSCs towards damaged tissues include anti-inflammation, immunomodulation, and enhanced cell survival and angiogenesis (97,98). Among these therapeutic effects, anti-inflammation and immunomodulation are key elements that make MSCs an attractive target to study because the immune system plays an integral role in regulating tissue repair and regeneration through healing, scarring and fibrosis (99). The immunomodulatory process of MSCs occurs through the secretion of several soluble factors that interfere with the immune system, and the inflammation process takes place through cell-cell interactions (100,101). The immunosuppressive effect of MSCs was enhanced by increasing the binding between MSCs and T-cells through intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (102). A similar phenomenon was reported when MSCs were shown to heighten the suppressive regulation of T-cells and macrophages regarding proinflammatory macrophages (103).

The flexibility of multipotent MSCs to differentiate into a wide variety of cells would then allow the cells to replace damaged or dead cells. However, reports on this mechanism are inconclusive, as the engraftment of MSCs is transient, and instead, MSCs secrete specific factors that grow and differentiate into local precursor cells (26). The potential of MSCs in tissue repair and regeneration is undeniable, regardless of the exact mechanisms.

6. MSCs in cancer therapy

Over the years, multiple reports have been published that strongly suggest the mechanism of action of MSCs. These actions are mainly attributed to the ability to migrate to the injury site (104-106), the paracrine effect of the secretome (107,108), and the immunomodulatory ability (109,110). The benefits of MSCs are enticing, and it is important to consider the potential side effects and major risk factors that are often associated with stem cell transplantation. There have been contradictory results in describing the anti- and pro-tumour effects of MSCs. As mentioned above, the therapeutic role of MSCs in cancer therapy is similar to that in other diseases; tumours secrete similar chemoattractants to damaged tissues, which initiate the migration of MSCs to the target site through the CXCL12-CXCR4 signalling pathway (111-114). MSCs have also been reported to interact with cancer cells, directly and indirectly, affecting tumour development (26). Moreover, MSCs secrete various cytokines and growth factors, which alter cellular activities, e.g., cell proliferation (cell cycle), angiogenesis, cell survival, and immunomodulation, to indirectly influence tumour growth. For example, BMSCs were described to enhance the proliferation of B16-LacZ cells and

increase tumour size when both cell lines were co-injected into syngeneic mice via enhanced angiogenesis (115). In contrast, BMSCs were also reported to inhibit proliferation, migration, and invasion and induce cell cycle arrest, which led to apoptosis of human glioma U251 cells by downregulating the PI3K/Akt pathway (116).

Indeed, such paradoxical results are not uncommon, as divergent effects on cell growth, invasion, and migration have been reported when MSCs sourced from the human umbilical cord were cocultured with glioblastoma cancer stem cells, e.g., direct contact between both cell lines caused an inhibitory response (117). At the same time, the release of soluble factors triggered a stimulatory reaction (117). Similar opposing effects were observed during an *in vivo* study investigating whether coinjection and distant injection of MSCs with breast tumour 4T1 cells exerted different effects on tumour growth (118). Coinjection supported tumour growth, while in the distant injection model, it inhibited tumour growth by promoting host antitumour immunity (118). Likewise, MSCs derived from umbilical cord blood and adipose tissue also had divergent effects on the proliferation of glioblastoma multiforme. The former inhibited and promoted the proliferation process (119).

Several studies have found that upon being recruited to tumour sites, the multipotency of MSCs enables their self-differentiation into carcinoma-associated fibroblasts, which directly contribute to cancer progression (120-122). In addition, MSCs were reported to promote tumour growth and angiogenesis through the secretion of proangiogenic cytokines, e.g., interleukin (IL)-6, vascular endothelial growth factor (VEGF), and transforming growth factor- β (TGF- β) (123-125) (Fig. 1). MSCs also enhanced the metastasis of human breast cancer cells by promoting *de novo* production of lysyl oxidase (LOX) by cancer cells (126). In addition, MSCs are able to modulate the production of regulatory T-cells and inhibit the activity of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), protecting breast cancer cells from the immune system (127). Similar immunosuppressive effects were observed when MSCs were reported to promote lung cancer metastasis (128). It was suggested that MSCs have the ability to form a cancer stem cell niche *in vivo* where tumour cells can preserve the potential to proliferate, thus sustaining the malignant process (129).

In contrast, MSCs increased the sensitivity of breast cancer cells to radiotherapy and impeded tumour progression by downregulating the signal transducer and activator of transcription 3 (Stat3) signalling pathway (130). Another study found that MSCs hampered hepatic cancer growth through the secretion of paracrine factors that lowered the insulin-like growth factor 1 receptor (IGF-1R), phosphatidylinositol 3-kinase (PI3K) and Akt signalling pathways (131). In addition, microRNA-4461 isolated from BMSCs was reported to inhibit tumour pathogenesis in colorectal cell lines and tissues by downregulating the expression of COPB2 (132). MSCs also inhibited vascular growth in glioma cells by downregulating the platelet-derived growth factor (PDGF)/PDGFR axis (133). Antiproliferative effects and apoptosis were observed when ovarian cancer cell lines were cocultured with conditioned media of MSCs derived from human bone marrow, adipose

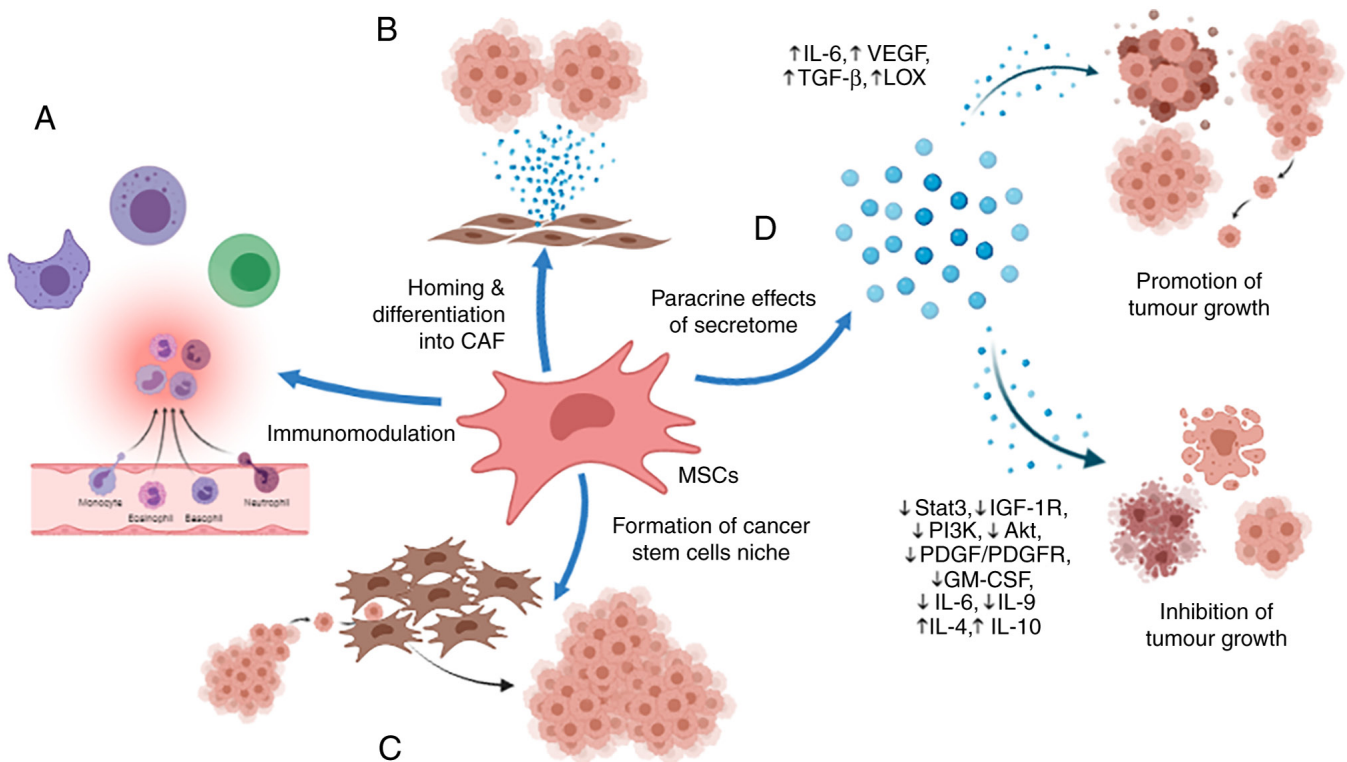


Figure 1. Summary of the mechanism of action of MSCs on the modulation of tumour cell growth. (A) MSCs regulate the immunomodulatory process by secreting several soluble factors that interfere with the immune system. MSCs also reveal their immunomodulatory potential through cell-cell interaction by activating monocytes, eosinophils, basophils and neutrophils. (B) MSCs are multipotent progenitors able to migrate, home and differentiate into CAFs. (C) MSCs have the ability to form a cancer stem cell niche *in vivo* where tumour cells can preserve the potential to proliferate and sustain the malignant process. (D) Paracrine effects of the secretome contributes to the duality function of MSCs. For example, they decrease levels in Stat3 and IGF-1R, and increase levels of IL-4 and IL-10 to inhibit tumour growth, while also increasing levels of IL-6 and VEGF to promote tumour growth. <https://biorender.com/> created the figure. MSCs, mesenchymal stem cells; CAF, cancer-associated fibroblasts; Stat3, signal transducer and activator of transcription 3; IGF-1R, insulin-like growth factor 1 receptor; IL-4, interleukin-4; IL-10, interleukin-10; IL-6, interleukin-6; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; GM-CSF, granulocyte/macrophage colony stimulating factor.

tissue, and umbilical cord (134). The study found that the conditioned media of MSCs showed an increase in IL-4 and IL-10 but a decrease in granulocyte/macrophage colony-stimulating factor (GM-CSF), IL-6, and IL-9. It is undeniable that anti-inflammatory cytokines play an important role in cancers (135-137). However, controversial findings have been reported regarding whether cytokines support or hinder tumour progression (138-141). Regardless, MSCs have been shown to modulate the immune response through the balanced secretion of proinflammatory and anti-inflammatory cytokines (142). Therefore, this duality of function found in the secretome of MSCs and the complex cell-to-cell interaction between MSCs and cancer cells might be the reason for the conflicting reports regarding the role of MSCs in cancers.

Although the underlying mechanisms are not yet fully understood, there is a consensus that the differences in experimental design, e.g., tumour models used, route of cell administration, control group, tissue source, dosage use, and timing of the treatment that may affect the final results, should be considered (37,117-119,143,144). Research should not make conclusions about the utility of MSCs in cancer therapy based on a single study. Instead, standardized protocols should be established to ensure that the data obtained are more comparable to understand the interaction of MSCs with cancer cells. Additionally, precautions should

be taken before the clinical introduction of MSCs for treating cancers since the heterogeneous characteristics of MSCs are easily susceptible to different pathological conditions present in patients, which can hinder the therapeutic mechanisms.

7. Potential strategy in utilizing MSCs for cancer therapy

MSCs are recognized for their ability to migrate towards tumour sites (145,146), but the literature to support the direct use of MSCs to treat cancer patients remains insufficient. MSCs can play a prominent role in reducing cancer progression since efficient intracellular tracking and directed delivery to the targeted site improve the pharmacological properties of anti-cancer drugs (147,148). One of the earliest studies developing MSCs for the delivery of biological agents found that MSCs genetically modified to express interferon- β (IFN- β) lowered tumour growth and doubled the survival rate of mice compared to the control group (149). In addition, IFN- β -transfected MSCs administered cisplatin triggered a high level of apoptosis in a melanoma xenograft mouse model (150). IFN- β -modified MSCs derived from the human umbilical cord were also reported to induce apoptosis in MDA-MB-231 cells (151). Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a promising target that selectively induces

apoptosis in cancer cells. TRAIL-modified MSCs have been reported to exert antitumour effects in different cancer cell lines and a mouse melanoma model (152-156). In addition, MSCs have been genetically modified to deliver other cytokines, e.g., IFN- γ (156), IL-2 (157), IL-12 (158), and IL-24 (159), for antitumour effects.

Numerous studies have been conducted to explore the possibility of enhancing the inherent therapeutic properties of MSCs using genetic engineering. These studies mainly focused on four crucial points: improving migration, adhesion, and survivability while reducing the cell senescence of transplanted MSCs (160-162). This phenomenon is accomplished by inserting a vector loaded with a constructed genetic cassette into MSCs; the cassette expresses certain genes constantly or can be controlled with a gene switch (163). For example, adipose-derived MSCs (AdMSCs) were transduced with a retroviral vector to upregulate the expression of CXCR4. The study reported that the transduced MSCs showed increased motility, invasion, and placement in the bone marrow when injected into nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice (164). In addition to CXCR4, other genes involved in MSC migration, e.g., aquaporin-1, can be modified. It was reported that the overexpression of aquaporin-1 and CXCR4 promoted the migratory ability of MSCs via the Akt and Erk pathways (165). MSCs have also been genetically engineered to overexpress integrin-linked kinase (ILK). The study found that genetically modified MSCs had 1.5-fold higher survivability and a 32.3% higher adhesion rate when engrafted into an ischaemic myocardium model, with a higher retention rate of ~4-fold (166). In addition, BMSCs and AdMSCs were reported to have increased proliferation and differentiation potential when engineered to overexpress Oct4 and Sox2 (167,168). Genetic engineering has the potential to circumvent the current problems that limit the application of MSCs in clinical settings and improve their potential therapeutic properties. Despite the immense benefits, this technique also has potential drawbacks, e.g., the risk of insertional oncogenesis due to viral vectors to introduce plasmid DNA, adverse immune reactions, and high production costs (169). Great precautions should be taken when considering the use of genetically modified MSCs for cancer therapy.

In addition, previous studies have established a connection between specific Toll-like receptors (TLRs) and the immunomodulatory properties of MSCs (170-172). Interestingly, a study reported that TLR-4-primed MSCs (MSC1) exhibited a proinflammatory phenotype, while TLR-3-primed MSCs (MSC2) secreted immunosuppressive mediators (173). Indeed, the polarization of MSCs into specific immunomodulatory phenotypes is a promising strategy as well. For example, macrophages cocultured with MSCs showed evidence of alternatively activated macrophages with high levels of CD206 and IL-10 but low levels of IL-12, which displayed a higher level of phagocytic activity (174). Studies have also reported that TL-3- and TL-4-primed MSCs preserved and enhanced the function of neutrophils through the combined action of IL-6, IFN- β , and GM-CSF (175,176). Furthermore, MSC1 was observed to recruit lymphocytes by activating T-cells and secreting macrophage inflammatory protein-1 (MIP-1), CCL5, CXCL9, and CXCL9 (177). In contrast, MSCs can change macrophages from a TNF α -secreting MSC1 phenotype to an immunosuppressive IL-10-expressing phenotype through a

prostaglandin-(PGE)-2-based mechanism (178). MSCs have also been reported to inhibit IL-2-induced NK cell proliferation and prevent the initiation of effector functions, e.g., cytotoxic activity and cytokine production, with the production of the soluble factors indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2) (179). MSCs influence tumour growth through immunomodulation, and as discussed earlier, the polarization of MSCs for cancer treatment warrants further investigation. After all, it is widely accepted that chronic inflammation is a critical hallmark of cancer that elevates the risk of malignancy (180). The anti-inflammatory cytokines secreted by MSCs can circumvent these effects. On the other hand, tumour cells evade the immune system by avoiding immune recognition and developing an immunosuppressive microenvironment (181), which can be overcome with the help of MSCs boosting the innate immune system. Therefore, careful and purposeful polarization will benefit the field of cancer therapy and facilitate manipulation of the immunomodulatory capacity of MSCs.

Studies have also investigated the potential of MSCs to act as vectors for oncolytic viruses. For example, MSCs were used as vectors to deliver oncolytic herpes simplex virus to human brain melanoma metastasis models grown in immunodeficient and immunocompetent mice. This study reported that the intervention significantly prolonged the life of the mice through immunomodulatory actions compared to the control group (182). A recent *in vivo* study also explored the possibility of using MSCs derived from menstrual blood as a vector for CRA5/F11 chimaeric oncolytic adenovirus to treat colorectal cancer. It was reported that the chimaeric oncolytic adenovirus was successfully delivered and accumulated at the tumour site, and it inhibited tumour growth (183). A mathematical model to quantitatively predict the efficacy of MSCs acting as vectors for virotherapeutic agents *in vivo* has been developed, indicating that MSCs are a promising strategy that improves the efficacy and safety profile of the treatment (184).

MSCs can also be primed with anticancer drugs for targeted delivery due to their preferential migration towards the tumour site and relative resistance to cytostatic and cytotoxic drugs (185-187). For example, MSCs acquire strong antitumour activity after packaging and delivering paclitaxel (PTX) through extracellular vesicles (188). The same study also demonstrated that it is possible to produce drugs with higher cell-target specificity by utilizing MSCs as a factory to package the drugs. Similar studies reported that MSCs isolated from different sources were primed with PTX and tested against different cancer cell lines (187,189-191). Other drugs were also tested for priming MSCs, e.g., doxorubicin and gemcitabine. A study reported similar results whereby MSCs effectively incorporated the active form of the drugs and released sufficient quantities to produce a significant inhibition of squamous cell carcinoma growth *in vitro* (192). Researchers have explored the possibility of using nanoparticles to improve the payload and delivery capacity of MSCs (193,194). All of these studies indicate that MSCs are able to take up and subsequently release drugs in a targeted and gradual manner, which improves the efficacy of anticancer drugs.

Due to the short half-life of most anticancer drugs in the body and their high toxicity to healthy cells, direct

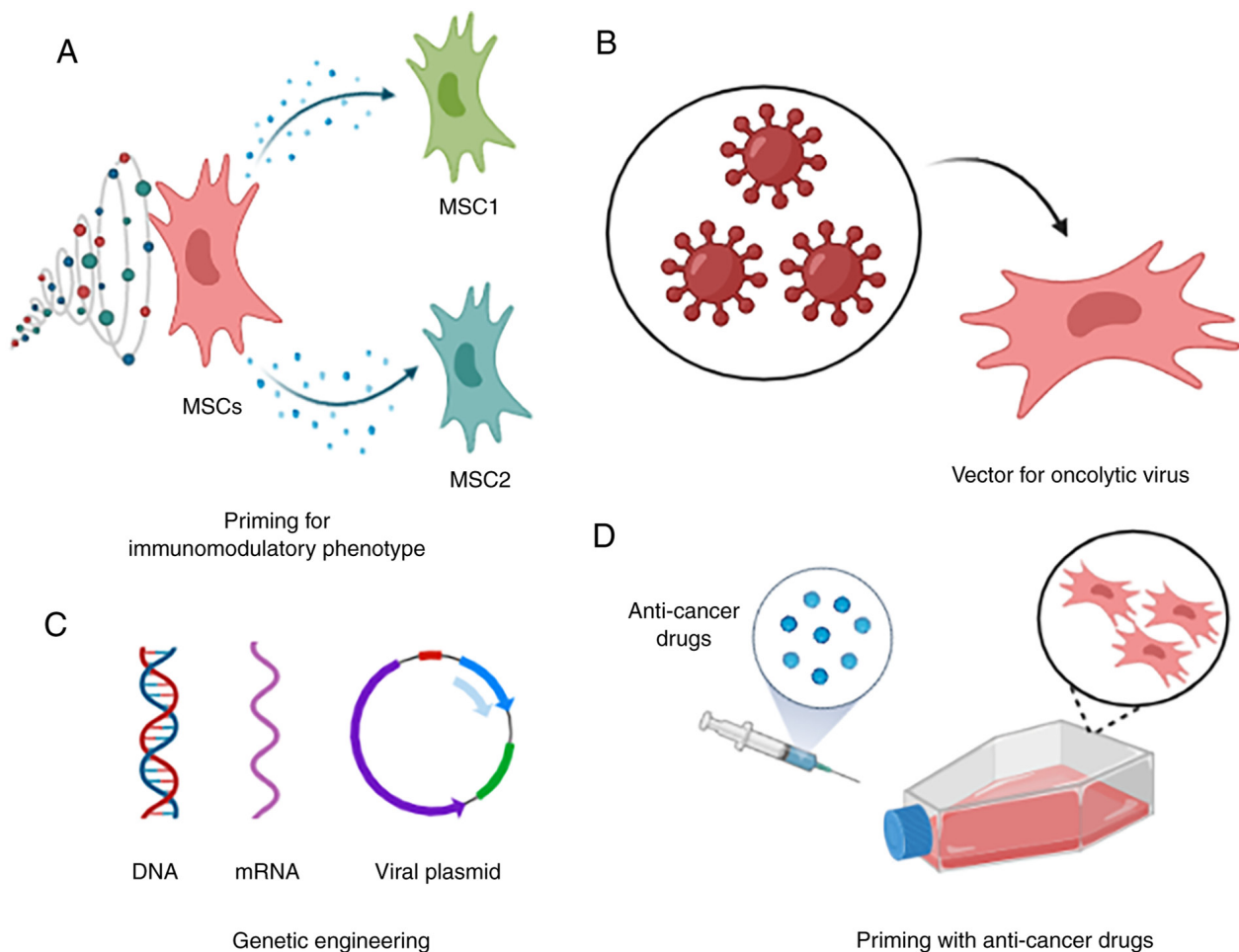


Figure 2. Potential therapeutic strategies of MSCs in cancer therapy. (A) Priming TLR-4-primed MSCs (MSC1) and TLR-3-primed MSCs (MSC2) for the immunomodulatory phenotype. (B) Vector delivers the oncolytic virus to the tumour site for growth inhibition. (C) Genetic engineering using viral vectors to introduce plasmid RNA and DNA. (D) Priming MSCs with anticancer drugs to improve their pharmacological properties. <https://biorender.com/> created the figure. MSCs, mesenchymal stem cells; TLR, Toll-like receptor.

administration of these drugs is often associated with unwanted side effects. For example, nausea and vomiting, tiredness, changes in taste, dry mouth, loss of appetite, constipation, and hair loss are common side effects faced by chemotherapy patients (195). Thus, using MSCs as vectors to deliver therapeutic proteins or anticancer drugs can help to solve this issue advantageously. MSCs can exert therapeutic effects locally due to selective migration and accumulation in tumour sites, increasing treatment efficacy and reducing systemic toxicity. Currently, divergent drugs are being investigated for different cancer therapeutic purposes. For example, MSCs were reported to enhance the therapeutic capabilities of tendon repair when pretreated with pioglitazone (196). Other studies using pioglitazone as the priming agent also found similar results, where pretreated MSCs had greater therapeutic effects on lung regeneration in an emphysema mouse model (197,198). Pioglitazone has been administered indirectly to breast cancer cells via stem-and-cancer cell interaction (199). Through this process, modified and viable pretreated stem cells are subsequently administered to patients, and pretreated stem cells are allowed to interact with cancer cells in the patients' bodies. Considering that pioglitazone has been reported to possess anticancer effects (200-202),

it may be beneficial to examine the possibility of priming MSCs with pioglitazone for cancer therapy. After all, using MSCs pretreated with pioglitazone as a strategy to improve the overall therapeutic effects, as reported in our study (199), remains rare. Despite the study on cardiomyogenic transdifferentiation and cardiac function (203), as mentioned above, MSCs pretreated with pioglitazone for cancer therapy remain to be characterized. A similar strategy was conducted using AdMSCs pretreated with a peroxisome proliferator-activated receptor gamma (PPAR γ) agonist to improve the regeneration effects in an elastase-induced emphysema mouse model (197). Indeed, human umbilical cord-derived mesenchymal stem cells pretreated with IL-6 were also found to abolish the stem cell growth-promoting effect on gastric cancer cells (204). The potential therapeutic strategies of MSCs in cancer therapy are summarized in Fig. 2.

Although the potential benefit is undeniable, there are potential risks in using MSCs for cancer treatments. These risks can be categorized as acute issues, e.g., inflammatory reaction or embolic phenomenon, intermediate issues, e.g., graft-versus-host disease (GVHD) or secondary infection, or long-term issues, e.g., risk of tumour growth (142). It was reported in a clinical study that patients treated

with MSCs commonly died due to infection (205). This phenomenon, coupled with the fact that MSCs can potentially promote tumour growth instead of inhibiting it, as previously discussed, makes it a risky treatment option. However, more studies must be conducted to provide future evidence and improve the therapeutic effects of modified MSCs in cancer treatments. These cells hold great potential to revolutionize the current cancer therapies that are available.

8. Concluding remarks and future perspectives

It is undeniable that stem cells are promising therapeutic alternatives for numerous human diseases. While the motivation to benefit human health is noble, researchers should take precautions in this field to prevent the potential exploitation of vulnerable groups. Efforts should also be directed towards using MSCs in autologous and allogeneic transplantation, as they do not raise the same ethical concerns as ESCs. In addition, MSCs benefit from their ability to carry anticancer payloads through genetic manipulation or pretreatment of the cells, leading to use in regenerative medicine and potentially oncology. Therefore, it is important to obtain as much information as possible to ensure that stem cell-based therapy is reliable, effective, efficient, safe, and affordable. It should be developed with the physiological condition of the patients in mind to truly benefit humanity.

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Authors' contributions

SKL and BYK contributed to the conception and design of the study. SKL drafted the manuscript and BYK revised the manuscript. Both authors have read and approved the final manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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