Mesenchymal Stem Cells

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A Boon or Bane in Cancer Progression and Metastasis

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Abstract

Tumor microenvironment (TME) is a complex network with a heterogeneous ensemble of cancer cells, mesenchymal stromal/stem cells (MSCs), inflammatory cells, immune cells, secreted factors, and extracellular matrix proteins. The interaction between cancer cells and its microenvironment decides the fate of tumors. This justifies the present impetus to target the components of the TME for better therapeutic responses. MSCs are integral components of the TME that play an active role in tumor initiation, progression, and metastasis. MSCs, owing to their antitumorigenic activity, ease of isolation, and inherent migratory capabilities, have emerged as effective anticancer therapeutics. In the present chapter, we discuss recent advances on the role of MSCs as potent antitumor agents. Additionally, we explore the therapeutic potential of MSCs and MSC-derived extracellular vesicles as carriers for anticancer agents at the preclinical and clinical levels. Therefore, it is anticipated that the new insights into the use of MSCs as

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anticancer agents will lead to the development of novel stem cell-based therapeutic strategies that enhance the safety and survivability of cancer patients.

Keywords

Cancer · Tumor heterogeneity · Tumor microenvironment · Mesenchymal stromal/ stem cells · Extracellular vesicles · Pro-tumor activity · Antitumor activity · Anticancer therapeutics · Cancer-associated fibroblasts · Tumor-associated macrophages

Introduction

Cancer is the leading cause of mortality across the globe with approximately 10 million deaths reported in the year 2020. There has been tremendous improvement in the understanding of tumor biology. However, the lack of efficacious approaches to treat cancer remains the major obstacle. While new approaches are paving the way forward for the development of efficacious anti-therapeutics, the use of conventional therapies has taken a back seat owing to their adverse side effects and varied receptivity. Conventional therapies usually focus on cancer cells and overlook the importance of components found in the tumor microenvironment (TME) thereby failing in the clinical trials. The varied receptiveness can be attributed to tumor heterogeneity, also leading to cancer progression. The plethora of cells present in the TME that differ from each other in their phenotype and genotype are responsible for tumor complexity, drug resistance, metastasis, and angiogenesis (Quail and Joyce 2013). The cross-talk mechanism occurring within the components of TME also plays a crucial role in tumor progression. Among the various cellular and non-cellular components that participate in the TME, mesenchymal stromal/stem cells (MSCs) play a distinct role (Sun et al. 2014). Over the past decade, MSCs have been explored as delivery vehicles for anti-cancer therapies due to their potent antitumor activities. However, recent studies have depicted a pro-tumorigenic role of MSCs in the TME (Karnoub et al. 2007). Although few studies suggest the pro-tumorigenic effects of MSCs, the use of MSCs as anti-cancer therapeutics remains alluring due to the ease of MSC harvesting, their inherent migratory capabilities, and potent antitumorigenic properties. To overcome the pro-tumorigenic effects of MSCs as well as to decrease the cell-based effects, extracellular vesicles derived from MSCs have emerged as an effective alternative (Rani et al. 2015). This chapter will briefly focus on the cancer epidemiology, limitations of the present anticancer therapeutics, the components of TME, the role of MSCs in TME, and the therapeutic potential of MSCs as anticancer therapeutics.

Cancer Epidemiology

Among all human diseases, cancer represents the highest clinical risk with reference to premature mortality and the years lived with a disability. According to the world health organization (WHO), breast cancer is reported to be the most common cancer

with 2.26 million cases, followed closely by 2.21 million cases of lung cancer and 1.93 million cases of colon and rectum, in the year 2020. Prostate cancer closely trailed by non-melanoma skin cancer occupies the fourth and fifth most common cancers with an estimate of 1.41 and 1.20 million cases, respectively. However, the highest number of cancer-related casualties in a year is recorded in the case of lung cancer with 1.80 million deaths, followed by colon and rectum with 935,000 deaths, liver with 830,000 deaths, and 769,000 deaths caused due to stomach cancer. Interestingly, there is a sharp decrease in the number of breast cancer deaths (685,000 deaths) as compared with the recorded breast cancer cases. A study revealed that there was a sharp surge of 1.59-fold times in cancer prevalence for the year 2017 as compared to the year 1990. In terms of cancer prognosis, prostate and thyroid cancers have been reported to have the best prognosis (Mattiuzzi and Lippi 2019), while the worst prognosis is reported in the case of the esophagus, liver, and especially pancreatic cancers with typically less than 20% of 5-year survival.

Though the overall risk of cancer is 20.2%, men are more at risk with 22.4%, while the risk for women accounts for 18.2% (Mattiuzzi and Lippi 2019). The risk of mortality due to cancer in individuals below 74 years is 12.7% in men and 8.7% in women. Similarly, the cancer-related load is faintly but non-significantly higher in men (9.6%) than in women (8.6%). While lung cancer is the leading cause of cancer-related mortality in men, breast cancer has been reported to be the leading cause of cancer deaths among women. In the case of many individual cancer types, age is the most important risk factor. The incidence rates for cancer steadily surge with age. The risk of individual cancers also differs with the age group, for example, in subjects below 14 years of age; leukemia is the predominant malignant disease. It is closely trailed by the nervous system and brain-related cancers and lymphomas. Breast cancer is the most frequent malignancy in people aged 15 to 49 years, followed by liver and lung cancers (Bray et al. 2018), while in subjects aged 50 to 59 years, lung, and liver cancers are the most common malignancies followed by breast cancers. Lung, colorectal, stomach, and liver cancers are reported to be the most common malignancies in people aged 60 and above (Bray et al. 2018). Overall, breast cancer occurrence is most frequent, succeeded by prostate, lung, colorectal, cervix uteri, and stomach cancer cases (Li et al. 2019).

Current Challenges in Cancer Treatment

The conventional strategies to treat cancer include chemotherapy, radiotherapy, and hormone therapy. The use of nitrogen mustards and anti-folate drugs marked the beginning of cancer chemotherapy (DeVita and Chu 2008). The practice of cancer medicine for the past few decades has transformed dramatically resulting in better therapeutic approaches to treat various cancers. Additionally, combinatorial approaches involving adjuvant chemotherapy and hormonal therapy have resulted in increased life expectancy and decreased cancer recurrence (Reza et al. 2017). Despite advancements in cancer research, chemotherapy's success has been limited by difficulties in dosage selection, rapid drug metabolism, lack of specificity, cytotoxicity to non-cancerous cells, intrinsic and acquired drug resistance, varying

inpatient status, and a variety of harmful side effects. Radiation therapy, like other treatment strategies, treats many types of cancer effectively, but it also leads to various side effects in patients (Bentzen 2006). The type of cancer and its location, general health of the patient, and other factors also determine the severity of these side effects. The requirement of high doses of radiation can cause most of the side effects as the healthy tissues surrounding the tumor are also vulnerable to these radiations. Few tissue-specific cancers, such as breast and prostate cancers depend upon hormones for growth and survival. In such cases, hormone therapy plays a crucial role in preventing tumor growth and spread. Breast cancers may have either estrogen or progesterone receptors, or both, whereas prostate cancer relies on testosterone and other male sex hormones, such as dihydrotestosterone for growth and survival (Risbridger et al. 2010). This therapy also results in some common yet less severe side effects like rashes and fatigue to adverse effects like dizziness and seizures.

Nanomedicine, extracellular vesicles, selective surgery, immunotherapy, gene therapy, thermal removal, radiomics, and pathomics are emerging developments in cancer treatment (Pucci et al. 2019). Nanomedicine is the use of biocompatible nanoparticles to address some of the limitations of traditional medicines, such as low specificity and bioavailability (Martinelli et al. 2019). Nanoparticles are being explored for diverse functions in the field of tumor biology such as cancer diagnosis and cancer therapy. The diversity in the characteristics of nanoparticles is a major drawback as each nanoparticle has to be evaluated independently. Furthermore, these particles are dependent on their surroundings to aggregate or disintegrate, resulting in a variety of anomalies, including toxicity. Unforeseen interactions of these particles and inadvertent breaching of other cell membranes are some of the drawbacks (Shubhika 2012). Chemical compositions, structure, surface charge, and solubility are some of the other factors that are responsible for toxicity. Recent advances have led to exploring the vast potential of extracellular vesicles such as exosomes in cancer treatment as cancer vaccines. A phase II clinical trial demonstrated improved overall survival in non-small cell lung cancer patients administered with exosomes derived from dendritic cells (Viaud et al. 2011). The major limitation precluding the use of exosomes is that the clinical translation is still under developmental stages. They are also associated with heterogeneity challenges during isolation. Although the drug-targeted therapies have shown outstanding successes so far, these are mostly limited to treating selected cancers. Clinically, combinatorial approaches of targeted molecules and traditional cytotoxic agents have depicted a strong synergy in treating cancer. Immunotherapy works by enhancing the patient's immune system to fight cancer (Rosenberg et al. 2008). The major limitation of immunotherapy is that there are instances of the immune system attacking the healthy cells thereby causing side effects. This in turn can lead to fatal autoimmune diseases. Thermal ablation, magnetic hyperthermia, radiomics, and pathomics approach are other emerging potential approaches for cancer therapy (Aerts 2016). The term "thermal ablation" refers to a set of procedures that use hyperthermia or hypothermia to eliminate cancerous tissues (Aerts 2016). Magnetic hyperthermia uses superparamagnetic or ferromagnetic nanoparticles to create heat after being stimulated with an alternating magnetic field. Thus, this results in the

destruction of the cancerous tissue. Radiomics refers to the high-throughput quantification of tumor attributes derived from medical image processing, while pathomics is dependent on the creation and analysis of high-resolution tissue images. Studies focusing on the development of novel image processing techniques are being conducted in order to extrapolate information through quantification and disease classification (Aerts 2016).

Despite the fact that these advancements in cancer research have led to more effective, accurate, and less invasive cancer therapies, these chemoprevention strategies often have a number of drawbacks. Literature suggests that when cancer progresses, tumors become increasingly heterogeneous, resulting in a mixed population of cells with varied molecular traits. This ultimately leads to a wide range of therapeutic responses (Meacham and Morrison 2013). Furthermore, the molecular cues secreted by the cells and reorganization of the components of the TME resulting in the crosstalk mechanisms influence the process of tumor formation and progression (Quail and Joyce 2013).

Components of the TME

As discussed earlier, tumor heterogeneity is a crucial factor for tumor progression. This heterogeneity is mostly owing to a large number of physiologically, genetically, and functionally varied cells (Fig. 1) (Tang 2012). These can be classified into cellular and non-cellular components.

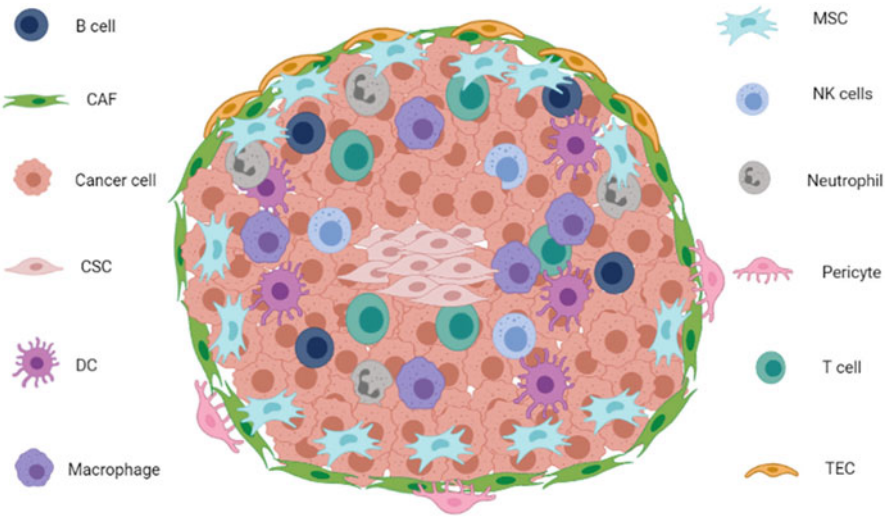

Fig. 1 *Cellular components present in the TME.* TME is heterogeneous with a complex ensemble of cancer cells, cancer stem cells (CSCs), B cells, dendritic cells (DCs), macrophages, natural killer cells (NK cells), neutrophils, T cells, mesenchymal stromal/stem cells (MSCs), cancer-associated fibroblasts (CAFs), pericytes, and tumor endothelial cells (TECs). "Created with BioRender.com"

Cellular Components Tumor cells display diverse nature with respect to genotype as well as phenotype. Immune cells, pericytes, circulating tumor cells, tumor endothelial cells, and cancer-associated fibroblasts are few among the cellular components. They play a major role in cancer development and progression (Baghban et al. 2020).

Immune Cells TME consists of a diverse ensemble of immune cells that are crucial for tumor initiation and progression. They either contribute to tumor progression or actively interfere with its development. Cytotoxic T cells (CTLs), macrophages, natural killer (NK) cells, neutrophils, and dendritic cells (DCs) possess antitumor activities (Flavell et al. 2010). The CTLs are considered as the major subset of lymphocytes, and their main function is to present the cancer cells to major histocompatibility complex class I molecules (Hewitt 2003). The secretion of certain chemokines by DCs facilitates the migration of activated CTLs expressing C-X-C chemokine receptor type 3 (CXCR3) to the tumor milieu (Spranger et al. 2017). CTL's priming depends on molecular cues secreted from CD4+ T cells, besides signals from DCs (Ahrends et al. 2017).

Expression of programmed death-ligand 1 (PD-L1) by cancer cells inhibits CTLs ensuing tumor development, thus evading immune responses (Gonzalez et al. 2018). NK cells exhibit potent antitumor cytotoxicity by secreting various cytokines and chemokines in the tumor milieu (Guillerey et al. 2016). NK cell-mediated cytotoxicity makes the tumor susceptible. Thus, tumor infiltrates prevent NK-cell recruitment to the tumor site as an evasion mechanism. Interaction of DCs with NK cells and B cells results in the recruitment of other immune cells. However, in vitro studies demonstrated that the supplementation of DCs with conditioned media obtained from culturing human colorectal tumors inhibited the maturation of the former cells (Michielsen et al. 2011). Studies have also reported that the expression of programmed cell death protein 1 (PD-1) by tumors can inactivate DCs. Secretion of cytokines and reactive oxygen/nitrogen species upon activation of macrophages results in tumor cytotoxicity (Krempski et al. 2011). In vitro studies demonstrated the activated neutrophils could exhibit antitumorigenic functions to lyse the tumor cells. However, the neutrophils present in the TME exhibit pro-tumorigenic effects and help in tumor progression (Coffelt et al. 2016).

Pericytes Pericytes are dynamic cells that play a key role in the basement membrane remodeling during angiogenesis. Therefore, antiangiogenic therapies to treat cancer implement various approaches that target pericytes. Several studies have shown the dual functionality of pericytes, i.e., their coverage parallels to a better diagnosis, while other studies showed that targeting pericytes may aggravate the tumor progression by promoting tumor metastasis (Xian et al. 2006). Semb et al. demonstrated that pericyte deficiency leads to the metastatic spread of insulinoma-derived cells in a PDGF Bret/ret. mouse model (Xian et al. 2006). In contrast to this report, the growth of glioma tumors was enhanced by the production of pericytes by cancer cells. Glioblastoma stem cells migrate along the stromal cell-derived factor

1α (SDF1α)/C-X-C chemokine receptor type 4 (CXCR4) axes in response to transforming growth factor-β (TGF-β) secretion from endothelial cells. These stem cells then generate pericytes and promote tumor growth (Cheng et al. 2013).

Tumor Endothelial Cells Tumor-derived endothelial cells (TECs) have a distressed phenotype as compared to normal ECs (Salazar and Zabel 2019). Reports suggest that certain CSCs like glioblastoma stem cells can give rise to TECs upon transdifferentiation. They have also been reported to promote tumor angiogenesis, and metastasis, leading to the progression of the disease (Dudley 2012). In this line, studies have reported that TECs generate glioma-initiating cells that in turn maintain stemness property by activating Notch signaling. In vitro studies depicted that the presence of these tumor-initiating cells expresses high levels of ATP binding cassette subfamily B member 1 and aldehyde dehydrogenase (Hida et al. 2017). Thus, these distorted TECs impair efficient drug delivery and impart drug resistance to tumor cells (Dianat-Moghadam et al. 2018). Expression of various chemokine receptors like glycoprotein D, chemokine (C-X-C Motif) receptor type 7, SDF1 receptor, and monocyte chemotactic protein 1 receptor by TECs also facilitates tumor progression. TECs not only provide nutrients to the tumor but also aid in the infiltration of immune cells (Abbasi et al. 2015).

Circulating Tumor Cells Cancer cells that enter the bloodstream after detaching from the primary tumor site are categorized as circulating tumor cells (CTCs) (Krol et al. 2018). CTCs are responsible for cancer recurrence as they migrate to distant organs and generate secondary tumors (Shishido et al. 2019). Clinically, these are very hard to detect and therapeutically intervene in a timely and precise manner. In vivo studies have revealed that CTCs preferentially mediate self-seeding at the primary tumor site such as breast, melanoma, and colon cancers. They also mediate metastasis towards the bone, brain, or lung resulting in tumor recurrence. CTCs migrate in response to cytokines like interferon beta-2 and C-X-C motif chemokine ligand 8 (CXCL8) secreted by tumors, while infiltration of CTCs into mammary tumors is enabled through the expression of matrix metallopeptidase 1 and fascin actin-bundling protein 1. Clinical evaluation in a cohort of 2026 breast cancer patients showed that the detection rate of CTCs after chemotherapy escalated from 21.5 to 22.1% (Yan et al. 2017). This increase has been associated with a poor prognosis. The presence of CTCs and their expression profiles improve the staging sensitivity and treatment specificity. Therefore, the clinical relevance of CTCs provides a new approach towards an improved prognosis of cancer therapy.

Cancer-Associated Fibroblast In the TME, cancer-associated fibroblasts (CAFs) are heterogeneous cells and can be involved in pro- or antitumor activities. They act as pro-tumorigenic mediators in TME by enhancing the proliferation and migration of cancer cells and simultaneously reducing apoptosis (Kalluri 2016). They express surface markers like alpha-actin-1, kinase-related protein, type V collagenase, proteoglycan core protein, and epididymis secretory sperm-binding protein (Nishishita et al. 2018). In vitro studies on breast cancer depicted that CAFs secrete ECM

proteins that promote immunosuppression of tumor cells through the recruitment of monocytes and induction of PD-1+ tumor-associated macrophages (Yavuz et al. 2019). In various cancers, CAFs facilitate angiogenesis through the secretion of heparin-binding growth factor 2, vascular permeability factor, and lactose-binding lectin 1 (Tang et al. 2016). In vivo studies depicted that the cytokines released from the CAFs like interleukin 6 (IL6) increase nicotinamide adenine dinucleotide phosphate (NADP) synthesis of ovarian cancer cells. This in turn enables tumor progression and recurrence (Curtis et al. 2019).

Tumor-Associated Macrophage Tumor-associated macrophages (TAMs) may possess tumor-enhancing or repressing roles. TAMs secrete migration-stimulating factors aiding motility and metastasis of cancer cells. An in vitro co-culture study of human colorectal cancer cells with TAMs revealed the induction of EMT and enhanced invasion, migration, and CTC-mediated metastasis that occurred via activation of Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling axis and IL6 production. This promotes macrophage infiltration in response to chemokine (C-C motif) ligand 2 (CCL2) secretions. Inhibition of IL6 reduced the metastasis driven by CTCs, while CCL2 inhibition decreased the migration of macrophages (Wei et al. 2019). Another study revealed the contrasting antitumorigenic role of TAMs while interacting with apoptotic cancer cells that led to inhibition of EMT and thus decreased the tumor invasion (Kim et al. 2019). TAMs secrete various cytokines like vascular endothelial growth factor-A (VEGF-A), tumor necrosis factor-α (TNF-α), urokinase plasminogen activator (uPA), fibroblast growth factor (FGF), adrenomedullin, and thymidine phosphorylase fueling cancer angiogenesis, invasion, and metastasis (Chen et al. 2019a). Various reports also suggest that TAM-derived cytokines like TGF-β, IL-6, IL-10, and TNF-α promote EMT, enhancing cancer stemness (Chen et al. 2018). Thus, therapeutic treatments aimed at reducing and depleting TAMs are being considered. Recently, combinatorial targeting of TAMs and immune control point inhibition by administering ligand/receptor-specific neutralizing antibodies such as PD-1 resulted in improved efficacy. Similarly, TAM targeting can be achieved by blocking certain receptors that take part in the TAM recruitment and survival (Mantovani et al. 2017).

Mesenchymal Stromal/Stem Cells Mesenchymal stromal/stem cells (MSCs) are unique cellular components that are widely distributed within the TME. They play a key role in tumor development via cross-talk with other cells present in the tumor milieu. This crosstalk of MSCs within the TME has been reported to either suppress or promote the tumor progression which is dependent on the number of MSCs, source of MSCs, their differentiation level, and tumor type. Although most of the reports focus on the antitumorigenic properties of MSCs, they also have the potential to promote tumor progression, promote metastasis, contribute to epithelial-to-mesenchymal transition (EMT), and evade immune surveillance (Karnoub et al. 2007). The pro-tumorigenic behavior of MSCs has been identified in an array of cancers like ovarian cancer, colon cancer, and gastric cancer.

Additionally, in vivo studies performed on mice models of osteosarcoma depicted that human MSCs enhanced tumorigenesis and metastasis (Xu et al. 2009). Moreover, few studies suggest that MSCs give rise to CAFs. However, the heterogeneous nature of TME and lack of substantial experimental evidence conceal the origin of CAFs. Shi et al. demonstrated that MSCs present in tumors stimulate tumor growth and angiogenesis and promote chemoresistance due to the secretion of certain cytokines like chemokine C–C motif ligand 5 (CCL5), IL-8, and IL-6 (Shi et al. 2017). In most solid tumors, MSCs present in the TME can also modulate the resident macrophages upon direct contact. Studies depicted that MSCs induce an anti-inflammatory phenotype in macrophages via cell-to-cell interaction, with high secreting levels of IL-10 and TNF-α and low levels of IL-6 and nitric oxide (Khosrowpour et al. 2017). Co-culture studies with macrophages exhibited a profound decrease in the secretion levels of TNF-α along with the enhanced secretion of pro-angiogenic and pro-tumoral chemokines. The role of MSCs as a pro- or antitumorigenic factor in TME has been critically explored in the chapter later.

Non-cellular Components The TME also consists of the non-cellular components, whose interaction with the plethora of cells in the tumor milieu also determines the phenotype of a tumor and governs the tumor metastasis. These non-cellular components include extracellular matrix (ECM), exosomes, small RNAs, DNA, and apoptotic bodies which in turn promote the progression of the tumor.

ECM The role of ECM in TME is unique, and its synthesis, the organization, is mostly derived through CAFs (Walker et al. 2018). In tumor cells, ECM increases tissue stiffness, acts as a barrier for drug delivery, and induces chemoresistance. Additionally, the ECM may facilitate the homing of metastatic cancer cells at the secondary tumor site by remotely remodeling itself with the aid of cytokines/chemokines secreted from primary tumors (Eble and Niland 2019). Collagen, a predominant component of ECM, can influence the fate of the tumor cells via its interaction with tyrosine kinase receptors, microRNAs (miRNAs), and exosomes. Further, cancer cell activity is also dependent on the interaction of collagen with other components of ECM (Natarajan et al. 2019). A dense ECM reduces the diffusion of drugs effectively into the cells resulting in chemoresistance. Interaction of the ECM with cancer cells leads to the activation of survival pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI_3K/AKT), tumor protein p53 (p53), and mitogen-activated protein kinases (MAPK) in the latter thereby promoting chemoresistance (Sato et al. 2016).

Exosomes These are vesicles secreted into the extracellular space that stimulate signaling pathways in various cells, while their role in cancer cells is mostly restricted to promoting pro-tumorigenic activities. Exosomes contain proteins, DNAs, mRNAs, microRNAs, long noncoding RNAs, and/or circular RNAs that play a critical role in tumor growth, metastasis, and angiogenesis during cancer development. These are utilized as a prognostic marker and/or grading for tumor

patients. Information transmitted through the bidirectional release of exosomes between tumor cells or cancer-initiating cells and the TME enriched with fibroblasts ultimately results in promoting tumor progression and recurrence. In vitro studies demonstrated that exosomes are partially responsible for the acquired drug resistance, as exosomes carrying the MET oncogene regulated the transfer of the oncogene. This resulted in the generation of icotinib-resistant lung cancer cells with enhanced migration and invasion properties of these cells (Yu et al. 2019). Exosomes play a crucial role in metastasis. Exosomes from tumors are taken up by organ-specific cells, preparing them to function as a pre-metastatic habitat. Exosomes produced from lung-tropic models caused bone-tropic tumor cells to metastasize in this investigation. As a result, a number of preclinical and clinical studies looked into the therapeutic potential of exosomes by focusing on pathways involved in exosome production. Exosomes have been effectively used as efficient drug carriers to enhance DOX absorption in HER2+ cells in a mouse tumor model (Gomari et al. 2018).

Apoptotic Bodies In pathological circumstances such as cancer, apoptotic bodies are secreted from cells that are undergoing apoptosis. A wide range of cell components, including nucleic acids, inhibitory RNAs, and proteins, are found in these apoptotic aggregates. Apoptotic bodies play a critical role in tumor cell genetic heterogeneity and aid in the DNA horizontal transfer resulting in malignancy (Trejo-Becerril et al. 2012). Studies depicted that the exosomal phosphatase and tensin homolog (PTEN) levels were elevated by apoptotic 344SQ cell-induced peroxisome proliferator-activated receptor (PPAR) activation in macrophages, which was then taken up by lung cancer cells (Kim et al. 2019). In vivo mice, tumor model studies suggested that both tumor cells and TAMs exhibited enhanced PPARγ/PTEN signaling upon a single injection of apoptotic 344SQ cells that resulted in inhibition of lung metastasis (Kim et al. 2019). As a result, when used in conjunction with other cancer therapies, the delivery of these apoptotic bodies can provide an additional antitumorigenic approach.

Circulating-Free DNA Circulating-free DNA (cfDNA) is a by-product of live and apoptotic eukaryotic cells and is made up of small double-stranded DNA fragments. cfDNA found in the TME is derived from both cancerous cells and non-cancer cells like endothelial and immune cells (Gomari et al. 2018). They are responsible for horizontal gene transfer and are involved in the tumor progression by facilitating tumor metastasis (Bronkhorst et al. 2019). cfDNA is also responsible for the enhanced resistance of cancer cells to conventional therapies, as well as genometastasis. On the other hand, cfDNAs comprise information on the genetic alterations, allowing for more personalized therapeutic examination, which could lead to the generation of better cancer treatment approaches. The difficulty in extraction and amplification of cfDNA due to high DNA fragmentation is a major stumbling block to utilize cfDNA as an effective therapeutic approach to treat cancer.

Role of MSCs in the TME

Among the cellular and non-cellular components of TME, MSCs play diverse roles in the TME. MSCs are the most common adult stem cell types that can be extracted from a variety of human tissues, including bone marrow, adipose tissue, umbilical cord, and blood (Kaushik and Das 2020). MSCs can be isolated from these tissues using specific approaches. Initially, MSCs from bone marrow have been isolated based on their plastic adherence capability that resulted in contamination with fibroblastic cells. Density gradient centrifugation, a preparatory method, was often used for the isolation of MSC from bone marrow. The mononuclear cells in the collected fraction were washed and seeded on a petri dish for proliferation. A number of potential markers like CD146 and STRO-1 have also been used so far to isolate bone marrow-derived MSCs using fluorescent-activated cell sorting (FACS) technique (Sacchetti et al. 2007). Immunodepletion of CD11b-, CD34-, or CD45-expressing cells has also been used. Isolation with a single surface marker, on the other hand, resulted in hematopoietic stem cell contamination. Recent studies showed the successful isolation of MSCs from bone marrow cells upon sequential immunodepletion using CD11b and Ter119 antibody-coated magnetic microbeads in a magnetic-activated cell sorting (MACS) system (Dhoke et al. 2016). Adipose tissue-derived MSCs have been isolated from the adipose tissue severed during liposuction, lipoplasty, or lipectomy procedures by enzymatic digestion with collagenase IV followed by centrifugation and washing (Secunda et al. 2015). Similarly, the umbilical cord-derived MSCs have been isolated from the severed umbilical cord placed in phosphate buffered saline with antibiotics, making them devoid of blood. The dices of umbilical cord were also subjected to explant method or enzymatic method to isolate MSCs (Secunda et al. 2015). Ficoll-hypaque gradient technique has been used to separate mononuclear cells from umbilical cord blood, which were then cultured in DMEM-low glucose (Secunda et al. 2015). Interestingly, MSCs isolated from various tissues exhibit similar properties, such as fibroblast-like appearance, trilineage differentiation capability, and expression of specific cell surface antigens like CD90 and CD105, but lack the expression of markers such as CD11b, CD34, and CD45. However, functional diversities have been reported for these MSCs based on the source of isolation. These are influenced by the differences in the extracellular milieu, presence of cell-cell communications, protease exposure, hypoxic microenvironment, and the expression levels of microRNAs. Additionally, MSCs derived from umbilical cord exhibited an increased proliferative capacity under hypoxic conditions as compared with MSCs derived from other adult tissues. Furthermore, MSCs from the human placenta have been reported to have a higher expansion and engraftment capacity as compared with bone marrow-derived MSCs (Barlow et al. 2008). These characteristics of MSCs led to explore the role of MSCs as vehicles to deliver anticancer treatment. MSC recruitment contributes to either inhibition or promotion of tumor growth through immune modulation, tumor angiogenesis, and direct and/or indirect interactions with the TME components. Thus, we have explored the pleiotropic effects of MSCs in the following section.

Pro-tumor Activity of MSCs Studies have exemplified the function of MSCs in promoting tumor growth and recurrence. This is attributed to the various cytokines secreted by MSCs or through the cellular cross-talk within the TME. In this line, studies have reported that primary ovarian tissue-derived MSCs secrete high levels of IL-6 resulting in enhanced tumor growth (Ding et al. 2016). Intereukin-8 secretion by these tumor-derived MSCs enhanced gastric tumorigenesis and metastasis. Compelling evidence indicates that MSCs also contribute to tumor angiogenesis via the secretion of pro-angiogenic factors. Additionally, MSCs secreted TGFβ, VEGF, and IL-6 upon their recruitment to the TME, which contributed to breast and prostate tumor cell proliferation and angiogenesis. A strong correlation between denser microvessels and induction of TGFβ1 in MSCs supported its role in enhancing tumor angiogenesis.

Furthermore, activated MSCs within the TME exhibit extensive immunosuppression through the secretion of various soluble factors, cytokines, and chemokines. MSCs also interact with the repertoire immune cells, such as B cells, NK cells, and macrophages, to display their immune-suppressive functions. Kalluri et al. reported that MSCs can differentiate into CAFs, which in turn promotes tumor progression (Kalluri 2016). The production of the CCL5 by MSCs has been shown to increase tumor invasion in metastatic breast cancer cells (Zhong et al. 2017). Pro-survival factors such as VEGF and basic FGF (bFGF) secreted from MSCs aid the tumor cells to evade apoptosis. MSCs also secrete TGFβ, which enables macrophage recruitment to the tumor location and facilitates the tumor to evade the host immune surveillance.

Few studies have demonstrated that MSCs are differentiated into CAFs that promote tumorigenesis due to the secretion of soluble factors including TGFβ from cancer cells. Furthermore, the secretion of immune-modulating agents, pro-angiogenic factors, pro-survival factors, and extracellular matrix modulators by MSCs facilitates the differentiation of MSCs to CAFs (Kalluri 2016). Chen et al. reported that the interaction between MSCs and breast cancer cells resulted in MSC engulfment, which caused changes in the transcriptome profile of tumor cells, most of which were linked to tumor-associated pathways (Chen et al. 2019b). The consequence of this MSC engulfment was the induction of EMT and breast cancer progression.

Antitumor Activity of MSCs MSCs have also been used as cancer therapeutics as they possess potent tumor-suppressive effects. Reports suggest that MSCs within the TME suppress breast cancer cell proliferation and inhibit certain signaling pathways leading to cancer cell susceptibility to conventional therapies (He et al. 2018). Furthermore, MSCs, as well as its conditioned media, inhibited the proliferation of ovarian cancer cells (Khalil et al. 2019). TNF-related apoptosis-inducing ligand (TRAIL) secretion by MSCs selectively induces apoptosis in a wide array of cancers (Fakiruddin et al. 2018). Downregulation of PI_3K/AKT signaling in bone marrow-derived MSCs suppresses the proliferation and induces apoptosis of glioma cells. Intravenous transplantation of MSCs primed with AKT pathway blockers resulted in

tumor suppression in a mouse model (Lu et al. 2019). MSCs derived from the umbilical cord impaired cell growth and promoted apoptosis of mammary carcinoma cells via inhibition of ERK1/2 and AKT signaling pathways. Studies focusing on the inhibitory effect of MSCs demonstrated that the protein Dickkopf-1 secreted by MSCs limits tumor growth via suppression of Wnt signaling (Qiao et al. 2008).

MSCs are also reported to act as inhibitors of tumor angiogenesis in contrast to the investigations described earlier. In this line, a study focusing on the glioma xenograft model described that MSCs derived from bone marrow attenuated the platelet-derived growth factor (PDGF)/PDGF receptor (PDGFR) axis that in turn markedly decreased the vascular growth. In vivo murine model studies depicted that the transplanted MSCs suppressed angiogenesis, resulting in decreased tumor development (Ho et al. 2013). MSCs have also generated antitumor immune responses by releasing inflammatory mediators including TGFβ. TGFβ signaling exhibits tumor-suppressive effects, for example, during breast cancer progression, the expression of the TGFβ receptor III (TGFβRIII) diminishes, while the reinforcement of TGFβRIII expression suppresses tumorigenicity.

Pro-metastatic Activity of MSCs The role of MSCs is multifaceted, not only in its development but also progression. MSCs promote metastasis resulting in cancer relapse. In a variety of malignancies, MSCs release a plethora of paracrine factors, including chemokines, cytokines, and growth factors, which regulate tumor metastasis. In vivo studies demonstrated that MSCs when injected with hepatocellular carcinoma cells developed metastatic nodules at liver sites (Chen et al. 2019c). MSC-derived extracellular vesicles enhanced breast cancer cell migration and proliferation by increasing Wingless-related integration site (Wnt)/β-catenin signaling (Lin et al. 2013). Bone marrow-derived MSCs attract and interact with breast cancer cells via the SDF1α/CXCR4 axis (Karnoub et al. 2007). This preferentially promotes the metastasis of breast cancer cells towards bone marrow. MSCs induce the expression levels of mir-199 and mir-214 in breast cancer cells leading to the suppression of FoxP2 expression. This, in turn, promotes breast cancer cell metastasis and the maintenance of the cancer stemness phenotype (Cuiffo et al. 2014). MSCs release CCL5 that downregulates the androgen receptor signaling and increases hypoxia inducible factor 2 expression in prostate cancer cells thereby promoting its metastasis (Luo et al. 2015). The interaction of umbilical cord-derived MSCs with cholangiocarcinoma cells resulted in activation of Wnt/β-catenin signaling in the latter. Furthermore, this promotes metastasis of cholangiocarcinoma cells (Wang et al. 2015). These studies evidently provide the plausible role of MSCs on cancer cell metastasis.

Anti-metastatic Activity of MSCs Contrasting to this, some studies have demonstrated that MSCs limit tumor development and metastasis by reducing immunological responses, along with decreasing angiogenesis. Rhee et al. reported that MSCs inhibited Akt and Wnt signaling to trigger apoptosis or cell cycle arrest (Rhee et al. 2015). Interestingly, reports also suggest that human bone marrow-derived MSCs

when injected *intravenously* along with breast cancer cells in vivo delayed and inhibited the formation of lung metastasis (Meleshina et al. 2015). In another instance, using an in vivo model of breast and lung malignancies, human MSCs transduced with an adenoviral expression vector encoding the human *Interferon* gene inhibited the growth of lung metastases (Studeny et al. 2004). Utilizing animal models, Chen et al. demonstrated that MSCs expressing IL-12 inhibited metastasis into lymph nodes and other internal organs as well as increase tumor cell apoptosis (Chen et al. 2008). Liu et al. have demonstrated that human umbilical cord MSCs expressing IL-18 reduced the growth and metastasis of breast cancer in mice (Liu et al. 2018).

Anticancer Therapeutic Potential of MSCs

The scientific world has seen a rapid development of cell-based therapies and their application in the field of tumor biology over the last decade, with the use of MSCs at the forefront of this new propensity (Fig. 2). MSCs have a slight edge for being used as personalized cell-based therapies over other approaches owing to their ease in procurement as well as the requirement of minimally invasive procedures and rapid large-scale expansion. Moreover, MSCs have also garnered a lot of attention as delivery vehicles for anticancer treatments because of their innate ability to migrate to various tissues. Various studies have utilized the genetically engineered MSCs to

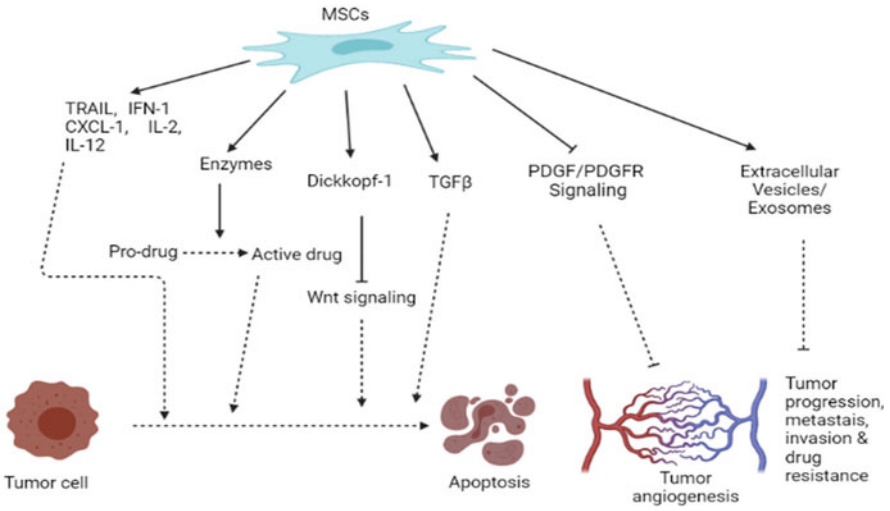

Fig. 2 *MSCs as potent anticancer therapeutics.* MSCs present in the TME secrete various cytokines, chemokines, and enzymes that induce tumor cell apoptosis. MSCs also inhibit signaling pathways like PDGF/PDGFRβ axis in tumor cells resulting in inhibition of tumor angiogenesis. MSC-derived exosomes play a crucial role in inhibition of various processes including chemoresistance, metastasis, and angiogenesis. "Created with BioRender.com"

either carry or express certain tumor-antagonizing mediators such as TRAIL, chemokines, and nanoparticles. In the case of prostate cancer treatment, engineered MSCs expressing enzymes like prostate-specific membrane antigen, which catalyze the inactive prodrugs to active cytotoxic drugs, reducing potential systemic toxicity, depicted an efficacious approach in facilitating the chemotherapeutic activity within the tumor. Genetically engineered MSCs produce more effective tumor-suppressive activities as they increase the expression of tumor-antagonizing agents, as compared with their effects when administered as a systemic therapy (Nakamizo et al. 2005). Reports also suggested an affirmative role of MSCs expressing TRAIL that inhibits cancer-initiating cells in the lung, resulting in reduced chemoresistance, tumor aggressiveness, and recurrence. MSC-derived nanovesicles aid in homing of MSCs to tumors. Additionally, lung and prostate tumor development was inhibited by MSC-derived nanovesicles containing specific inhibitory RNA molecules.

Chemotherapeutic agents are known to cause oxidative stress in cancer cells which results in lipid peroxidation and produces a large number of electrophilic aldehydes that target a variety of downstream cellular processes. These oxidative stress-causing agents lead to generation of reactive oxygen species (ROS) that delays the cancer cell cycle progression and triggers cell cycle checkpoint arrest, which can make anticancer drugs less effective. Interestingly, MSCs are resistant to oxidative stimuli in vitro, due to constitutive expression of antioxidant enzymes like superoxide dismutases 1 and 2, catalase, and glutathione peroxidase, as well as high levels of intracellular glutathione (Valle-Prieto and Conget 2010). MSCs express heat-shock protein 70 and sirtuin 3 that may in turn play a role in their resistance to oxidative damage (Gorbunov et al. 2013). Sirtuin 1 has been reported to be essential for MSC survival in the presence of hydrogen peroxide (H_2O_2), and its overexpression provides protection. Sirtuin 6 has been shown to offer resistance to oxidative stress and basal ROS generation in MSCs by producing antioxidants (Pan et al. 2016). Moreover, studies have also suggested that preconditioning of MSCs with low concentrations of H_2O_2 resulted in higher cell proliferation in vitro, and transplantation of these pre-conditioned MSCs depicted enhanced engraftment and expansion leading to tissue regeneration in vivo (Dhoke et al. 2018). These studies suggest MSCs as ideal candidates for anticancer therapeutics.

Most of the clinical trials pertaining to MSCs are in the initial stages of assessing the safety and efficacy (i.e., either in phase I or II) (Table 1). The first clinical trial in humans using genetically modified MSCs for gastrointestinal cancers was reported with a successful outcome of phase I/II clinical trial (TREATME1) (Niess et al. 2015). Further, clinical trials primarily focused on ovarian cancer utilized genetically engineered human MSCs expressing interferon-beta (IFNβ) to evaluate the clinical safety and to determine the best tolerable dose that can be administered. In ovarian cancer patients, a phase I/II clinical trial was initiated to assess the adverse effects and optimal dose of MSCs infected with oncolytic measles virus expressing sodium iodine symporter. Allogeneic MSCs have been employed as gene-therapeutic vehicles to deliver the full-length version of TRAIL to lung cancer patients. Furthermore, in a phase I clinical trial, men with localized prostate cancer were infused intravenously with allogeneic bone marrow-derived MSCs 4–6 days prior to prostatectomy

Table 1 List of clinical trials of MSCs as anticancer therapeutics and their status

S. No	Title of the study	Pathological condition	Interventions	Status
1.	Mesenchymal stem cells for ovarian cancer	Ovarian cancer	MSC-INFβ	Completed
2.	Allogeneic human bone marrow derived mesenchymal stem cells in localized prostate cancer	Prostate cancer	Allogeneic human mesenchymal stem cells	Terminated
3.	Tissue and hematopoietic/ mesenchymal stem cell for humanized xenograft studies in melanoma and squamous head and neck cancer	Malignant melanoma and head and neck cancer	Drug: Filgrastim	Recruiting
4.	Mesenchymal stem cells in cisplatin-induced acute renal failure in patients with solid organ cancers	Solid tumors	Mesenchymal stromal cell infusion	Withdrawn
5.	Safety and efficacy of repeated infusion of CELYVIR in children and adults with metastatic and refractory Tumors.	Solid tumors	CELYVIR	Completed
6.	Mesenchymal stem cell infusion as prevention for graft rejection and graft-versus-host disease	Hematological malignancies	Mesenchymal stem cell infusion	Completed
7.	Using mesenchymal stem cells to fill bone void defects in patients with benign bone lesions	Bone neoplasms	Trinity multipotent stem cells	Withdrawn
8.	Safety and efficacy of mesenchymal stem cell for radiation-induced hyposalivation and xerostomia in previous head and neck cancer patients	Xerostomia following radiotherapy	Mesenchymal stem cells	Recruiting
9.	Donor mesenchymal stem cell infusion in treating patients with acute or chronic graft-versus-host disease after undergoing a donor stem cell transplant	Cancer	Mesenchymal stem cell infusion	Completed
10.	Stem cell injection in cancer survivors	Cardiomyopathy due to anthracyclines	Allo-MSCs	Completed
11.	Mesenchymal stem cells for radiation induced xerostomia	Xerostomia	Mesenchymal stem cell	Completed

(continued)

Table 1 (continued)

S. No	Title of the study	Pathological condition	Interventions	Status
12.	Intracavernous bone marrow stem-cell injection for post prostatectomy erectile dysfunction	Prostate Cancer & Erectile Dysfunction	Injection of bone marrow mononucleated cells	Completed
13.	OTI-010 for graft-versus-host disease prophylaxis in treating patients who are undergoing donor peripheral stem cell transplantation for hematologic malignancies	Leukemia	Autologous expanded mesenchymal stem cells OTI-010	Withdrawn
14.	Cord blood expansion on mesenchymal stem cells	Leukemia	Cord blood infusion	Completed
15.	MSC and HSC co-infusion in mismatched mini transplants	Leukemia, myeloid, acute	Mesenchymal stem cells	Recruiting

to evaluate the safety of these MSCs. Nevertheless, the inhibition of tumor growth did not occur due to the failed homing of MSCs at the primary sites. A phase I/II clinical trial demonstrated that using multidose of MSCs infected with the oncolytic adenovirus ICOVIR5 (CELYVIR) to treat solid tumors depicted a good safety profile with potent antitumor effects (NCT01844661) (Melen et al. 2016). A few additional registered clinical trials employing MSCs to treat solid tumors are now on-going around the world. MSCs have also been explored to treat the various side effects that surface during cancer treatment. In these lines, about nine registered clinical trials evaluated the use of MSCs to treat various cancer-related side effects such as cardiomyopathy, radiation-induced hemorrhagic cystitis, and xerostomia. Thus, MSC-based therapeutic approaches provide a good platform not only for directly targeting cancer but also for reducing cancer therapy side effects. Moreover, MSCs are being loaded with anticancer drugs and thus are explored as effective drug delivery tools. Altogether, these emerging approaches display a great potential of MSCs as efficacious tumor antagonizing agents as they address the limitations with decreased cytotoxicity and improved specificity.

However, the lack of published results involving clinical studies delays further advancements in this field, thus limiting the therapeutic application of MSCs at the clinics. Moreover, the precise role of MSCs in the TME remains controversial. Researchers have genetically engineered MSCs to resolve the problem of the tumor-promoting effects, thus making them irrefutable therapeutic agents for the development of efficacious anti-cancer therapeutics. These genetically engineered MSCs either deliver or express specific cytokines, drugs, nanoparticles, and siRNAs that particularly target cancer cells, reducing off-target effects. Furthermore, MSCs can be modified to carry particular anticancer miRNA to promote tumor-suppressive behavior.

Conclusion and Future Perspective

Recent advances in the field of tumor biology helped us to understand the complexity of cellular and molecular mechanisms of tumor heterogeneity. The inherent plasticity, as well as the ability to home to various tissues, makes MSCs a prominent component among the others in the TME. Also, the interaction between MSCs and the other cellular components of the TME is important in supporting the EMT and metastatic processes. These interactions also result in immune evasion and facilitate the progression of cancer. MSCs display multifaceted roles in the TME and are currently being utilized as vehicles to deliver anticancer treatment. In contrast, few recent preclinical studies have reported the pro-tumorigenic role of MSCs. This is attributed to its ability to secrete various cytokines and growth factors. Few studies have exemplified that the transdifferentiation of MSCs leads to the generation of CAFs and TAMs. Nevertheless, this transdifferentiation of MSCs in the TME is not supported by substantial evidence other than their shared markers. Also, the degree of plasticity of MSC post-recruitment to the TME poses a crucial challenge. Thus, there is a necessity to identify unique markers to distinguish MSCs apart from other cells within tumors that will enable researchers to precisely conclude the role of MSCs in tumor initiation and progression. Additionally, it will help to understand the factors that trigger the pro-tumorigenic effects of MSCs.

Although the role of MSCs as CAFs or TAMs is still under critical scrutiny, owing to the potent antitumorigenic activity of MSCs, MSC-based therapies are still being considered as effective targeted therapies against certain types of cancers. MSC-based therapies are associated with limitations such as their ability to undergo physiological differentiation and transdifferentiation into different lineages that result in eliciting immunogenicity, induce tumorigenesis, and reduce the therapeutic potential that may probably reduce the expected clinical benefit. Additionally, the lack of critical understanding of the complex cross-talk between MSCs and cancer cells limits the therapy. Thus, it necessitates the development of a more cellular and molecular mechanistic understanding of the tumor heterogeneity, the complexity of TME, and the cross-talk within the TME at a preclinical and translational level. To overcome this, extracellular vesicles derived from MSCs that can be loaded with chemotherapeutics, small molecules, siRNAs, miRNAs are being explored to bring more efficacies to these MSC-based approaches. MSC-derived extracellular vesicles/exosomes have emerged as a promising option as it is a cell-free therapy that evades the risks associated with live cell therapy. This cell-free therapy will also aid MSC-based therapeutic techniques to be more clinically safe. These novel and beneficial anti-neoplastic approaches enhance the safety and survivability of cancer patients.

In conclusion, MSCs/MSC-derived exosomes have great efficacy as antitumor agents. However, more advanced research is warranted to expedite the process of transition from preclinical research to clinical application with better safety and greater efficacy. Nevertheless, in clinical settings, MSC-based anticancer therapies are being explored to provide new hope by enabling effective personalized treatment to cancer patients. Thus, by far, MSCs are certainly the most prominent therapeutic

agents in not only wound healing, tissue engineering, and regenerative medicines but also as an anticancer therapy.

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