Role of mesenchymal stem cells and their derived exosomes in cervical cancer: Bidirectional mechanisms and research progress (Review)

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Abstract. Cervical cancer (CC) is one of the most common malignant tumors among women worldwide and it imposes a notable clinical burden. Current traditional treatment methods have certain limitations. Mesenchymal stem cells (MSCs), due to their notable biological properties, have shown broad application prospects in the field of regenerative medicine. The unique tumor homing characteristics and immune regulatory capabilities of MSCs have made them an important research direction for targeted cancer treatment. As the key mediator of MSC functions, their derived exosomes serve an important role in intercellular communication and disease regulation. However, MSCs and their exosomes, as important components of the tumor microenvironment, may have potential tumorigenic risks, which also restrict the progress of related therapies towards clinical application. Therefore, the present review aimed to systematically elaborate on the molecular mechanisms by which MSCs and their exosomes exert both promoting and inhibitory effects in CC and further explore the possible reasons behind this contradictory phenomenon.

Contents

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1. Introduction

Cervical cancer (CC) is the third most common malignant tumor among women worldwide (1). It has been reported that ~600,000 novel cases are diagnosed annually, leading to ~340,000 mortalities (2). Human papillomavirus (HPV)-based screening and prophylactic vaccination have become critical interventions. Despite continuous advancements in screening technologies, 5-11% of CC cases are unassociated with HPV infection (3). These cases, characterized by distinct histopathological, molecular and clinical features, are referred to as HPV-independent CCs, with major subtypes including gastric-type adenocarcinoma, clear cell, mesonephric and endometrioid carcinoma (4). Current treatment strategies for CC vary by disease stage, with surgical intervention being the primary approach for early-stage disease, while advanced-stage disease relies on chemotherapy, radiotherapy and immunotherapy (5). However, challenges such as surgery-related complications, damage to normal tissues caused by chemotherapy, radiotherapy and immunotherapy, as well as the pervasive issue of drug resistance, remain notable obstacles in the clinical management of CC (6,7). Therefore, the exploration of novel therapeutic strategies has emerged as a critical direction in current research.

Mesenchymal stem cells (MSCs) are a type of adult stem cells with self-renewal and multi-directional differentiation potential (8). Over the past 3 decades, their unique biological properties and broad therapeutic potential have garnered extensive attention in various diseases (9). For instance, MSCs have demonstrated potential therapeutic value in fields such as tuberculosis (10), osteoarthritis (11), and oral (12), neurodegenerative (13), kidney (14) and rheumatic diseases (15). More importantly, MSCs possess innate tumor-homing capabilities

and potent immunomodulatory functions, positioning them as notable research subjects in cancer therapy (16). As key mediators of MSC function, their derived exosomes can serve a central role in regulating the tumor microenvironment (TME) (17,18) and influencing resistance to cancer therapies, including chemotherapy, radiotherapy, targeted therapy and immunotherapy (19,20), by mediating intercellular communication (21).

Selecting CC as a model to investigate the role of MSCs and their derived exosomes is supported by unique scientific rationale. Firstly, persistent infection with high-risk HPV, particularly HPV-16 and HPV-18, is the primary driver of cervical carcinogenesis (22,23). This viral oncogenic mechanism fundamentally shapes the TME of CC. HPV oncoproteins, such as E6 and E7, while disrupting cell cycle regulation, also compromise host immune surveillance, thereby establishing a chronic inflammatory and immunosuppressive microenvironment conducive to tumorigenesis (24). The potent immunomodulatory properties of MSCs offer distinct advantages in this context for CC therapy (25). Secondly, the TME of CC is characterized by complex interactions between infected epithelial cells and various stromal components, including cancer-associated fibroblasts and infiltrating immune cells (26,27). MSCs and their derived exosomes are known to be recruited to tumor sites and can differentiate into cancer-associated fibroblasts, promoting tissue remodeling and tumor progression (16). In CC, persistent viral stimulation further complicates these interactions, potentially inducing plasticity in the functions of MSCs and their derived exosomes, leading to dual pro-tumorigenic or antitumorigenic effects (28,29).

This dualistic and paradoxical role inherent to MSCs and their derived exosomes underscores the complexity that must be addressed prior to their clinical translation. Therefore, the present review aims to systematically elucidate the specific mechanisms of action of MSCs and their derived exosomes in cervical carcinogenesis and progression, delve into the underlying reasons for their dual effects and summarize recent advances in therapeutic research based on these findings.

2. MSCs and MSC exosomes (MSC-Exos)

MSCs. The origin of MSCs can be traced back to the mid-to-late 20th century (30). After decades of exploration, researchers have now developed a relatively systematic understanding of these cells (Fig. 1). As early as 1960-1975, researchers first identified a type of non-hematopoietic stem cell in the bone marrow with clonogenic capacity and adherence-dependent growth (31). Friedenstein *et al* (32) were the first to systematically isolate and characterize these cells, which is considered the starting point of research on MSCs. This discovery demonstrated for the first time that within the complex hematopoietic microenvironment of the bone marrow, there exists a unique group of non-hematopoietic precursor cells, laying the theoretical foundation for subsequent studies on MSCs.

From 1975 to 1980, research further elaborated on the biological characteristics of MSCs, such as the cloning formation characteristics and radiation resistance (33). Further studies gradually revealed the multi-lineage differentiation potential of these cells. In 1988, Grigoriadis *et al* (34) found that a subset of mesenchymal progenitor cells could differentiate into four distinct cell types, namely, muscle, adipose tissue, cartilage and bone, *in vitro* under the induction of glucocorticoids. This discovery suggested that MSCs possessed multi-directional differentiation capabilities, thus opening up the possibility of application in regenerative medicine. In 1995, research further confirmed the presence of MSCs in periodontal tissues (35). This finding indicated that the source of MSCs expanded from bone marrow to other tissues, providing an important basis for the subsequent isolation of MSCs from various tissues, such as fat and the umbilical cord, and also revealed the extensive distribution of MSCs in the body.

From 2000 to 2015, the mechanisms of MSCs were extensively explored and researchers gradually recognized that MSCs possessed multiple functions in disease contexts, including immunomodulation, inflammation suppression, promotion of repair (for example, repairing bones, cartilage, tendons and cardiac muscle) and specific homing to tumor sites (36,37). In 2006, the International Society for Cellular Therapy proposed the minimal defining criteria for MSCs: i) Adherence to plastic; ii) specific expression of CD105, CD73 and CD90; iii) lack of expression of surface markers CD45, CD34, CD14, CD11b, CD79α, CD19 and human leukocyte antigen-DR isotype; and iv) multi-lineage differentiation potential. This criteria established a foundation in standardizing research on MSCs (38). The proposal of this standardized definition marks a notable milestone in the development of this field. It enables the results of different researchers to be similar and establishes standards for the basic research of MSCs.

Between 2015 and 2020, extracellular vesicles (EVs) secreted by MSCs, particularly exosomes, were identified as key carriers mediating their effects and gradually became a research hotspot in regenerative medicine as an alternative to cell therapy (39). From 2020 to the present, clinical trials associated with MSCs have been widely conducted. Certain studies have demonstrated that MSCs exhibit notable therapeutic efficacy (40,41), while others have reported potential negative effects; for instance, there are complex interactions between MSCs and tumor cells, which can create a microenvironment conducive to tumor cell proliferation, angiogenesis, migration, invasion and metastasis, thereby promoting tumor progression (42). Furthermore, in another study, it was found that MSCs co-cultured with colorectal cancer cells exhibited enhanced invasiveness and proliferation ability due to changes in their tumor protein p53/transforming growth factor β1 (p53/TGF-β1) levels (43). The core contribution of this stage is that it has pushed the research on MSCs to enter a novel phase from 'verification of effectiveness' to 'precision of treatment' (44). These results have prompted researchers to reflect, suggesting that this bidirectional nature of effects may be associated with factors such as cell source, route of administration and dosage (45,46). Of note, MSCs can be isolated from various biological tissues. In addition to common sources such as bone marrow, adipose tissue, umbilical cord, amniotic fluid, placenta and menstrual blood (47-51), several studies have also reported that MSCs can be successfully extracted and isolated from teeth (52), tonsils (53), as well as visceral tissues including the brain, spleen, kidney and liver (54-56).

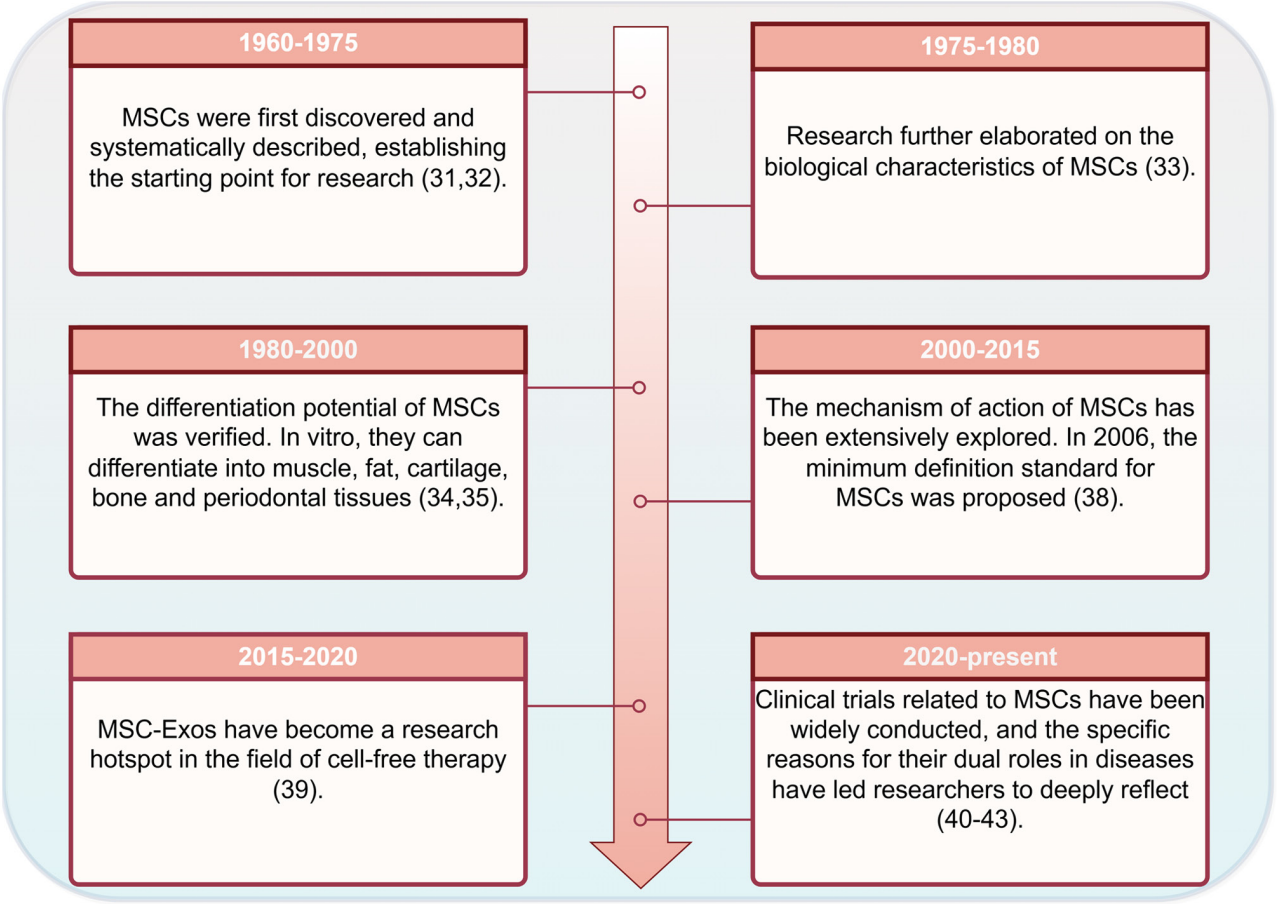

Figure 1. Development history of MSCs. The figure was generated using Figdraw (www.figdraw.com). MSCs, mesenchymal stem cells; MSC-Exos, exosomes derived from mesenchymal stem cells.

Exosomes. EVs are heterogeneous collections of particles enclosed by a lipid bilayer membrane. EVs are typically classified into three main types based on their biogenesis pathways and size (57). Among them, exosomes are small nanovesicles (diameter, 30-150 nm) derived from the endosomal system (58), which distinguishes them from the larger microvesicles (diameter, 100-1,000 nm) and the distinctively originating apoptotic bodies (diameter, 500-5,000 nm) (59,60) (Fig. 2A). The biogenesis of exosomes is a complex process (Fig. 2B). It begins with endocytosis at the cell membrane surface, forming early endosomes. Early endosomes further mature, receive transport vesicles from organelles such as the Golgi apparatus and undergo processes such as acidification to transform into late endosomes. Within late endosomes, the membrane invaginates inwardly a second time, forming multiple intraluminal vesicles (ILVs) through budding (61-63). Late endosomes containing numerous ILVs are termed multivesicular bodies (MVBs). MVBs undergo either of two pathways: Most MVBs fuse with lysosomes, leading to the degradation of the ILVs, while a small portion of MVBs fuse with the plasma membrane, releasing the ILVs into the extracellular environment. These released ILVs are termed exosomes (61,64,65). Similar to MSCs, the sources of exosomes are diverse (Fig. 3). Besides being present in MSCs and various immune cells (66-68), exosomes are also widely found in tumor cells (69,70). Furthermore, exosomes exist in various bodily fluids, including blood, urine, breast milk and semen (71,72). Exosomes have also been detected in certain foods and plants (73-77).

3. Tumor-promoting mechanism of MSCs and their derived exosomes in CC

In the initiation and progression of CC, the role of MSCs appear to be more extensively documented compared with that of their derived exosomes. MSCs primarily exert pro-tumorigenic effects through multiple mechanisms, including promoting tumor cell proliferation, inducing tumor angiogenesis and suppressing the immune response of the body, working in synergy (78-80) (Table I).

Promoting the proliferation of tumor cells. The abnormal proliferation of tumor cells is a central aspect of tumor progression. A study based on *in vitro* cell models found that MSCs derived from CC cells (CC-MSCs) upregulated the expression level of CD73 in tumor cells, thereby accelerating the progression of CC (78). Another study using both *in vitro* and *in vivo* models further revealed that the expression level of the transcription factor NANOG in CC cell-derived MSCs can promote the proliferation of CC SiHa cells, thereby driving CC growth (81). Notably, further research has observed that the effect of bone marrow-derived MSCs (B-MSCs) on the proliferation of CC cells exhibits a dose-dependent pattern:

Table I. Mechanisms by which MSCs promote the occurrence and development of CC.

Source	Research type	Mechanism of action	(Refs.)
Bone marrow	*In vitro* cell model	At low doses, MSCs can promote the proliferation of CC cells	(46)
CC	*In vitro* cell model	Increases the expression level of CD73 in tumor cells	(78)
Adipose tissue	*In vitro* cell models and *in vivo* animal models	Activates the NF-κB signaling pathway and promotes angiogenesis in CC	(79)
CC	*In vitro* cell model	Promotes the secretion of TGF-β1 and the expression level of PD-L1, thereby inhibiting the antitumor activity of $CD8^+$ T lymphocytes	(80)
CC	*In vitro* cell models and *in vivo* animal models	Expression level of transcription factor NANOG can promote the proliferation of CC SiHa cells	(81)
Umbilical cord	*In vitro* cell models and *in vivo* animal models	Secretion of VEGF to enhance *in vivo* angiogenesis of CC HeLa cells	(83)
CC	*In vitro* cell model	Enhances the ability of M2 type macrophages to polarize	(84,85)
CC	*In vitro* cell model	High expression levels of CD39 and CD73, promoting the occurrence of immune escape	(86)

CC, cervical cancer; MSCs, mesenchymal stem cells; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor β1; PD-L1, programmed death-ligand 1.

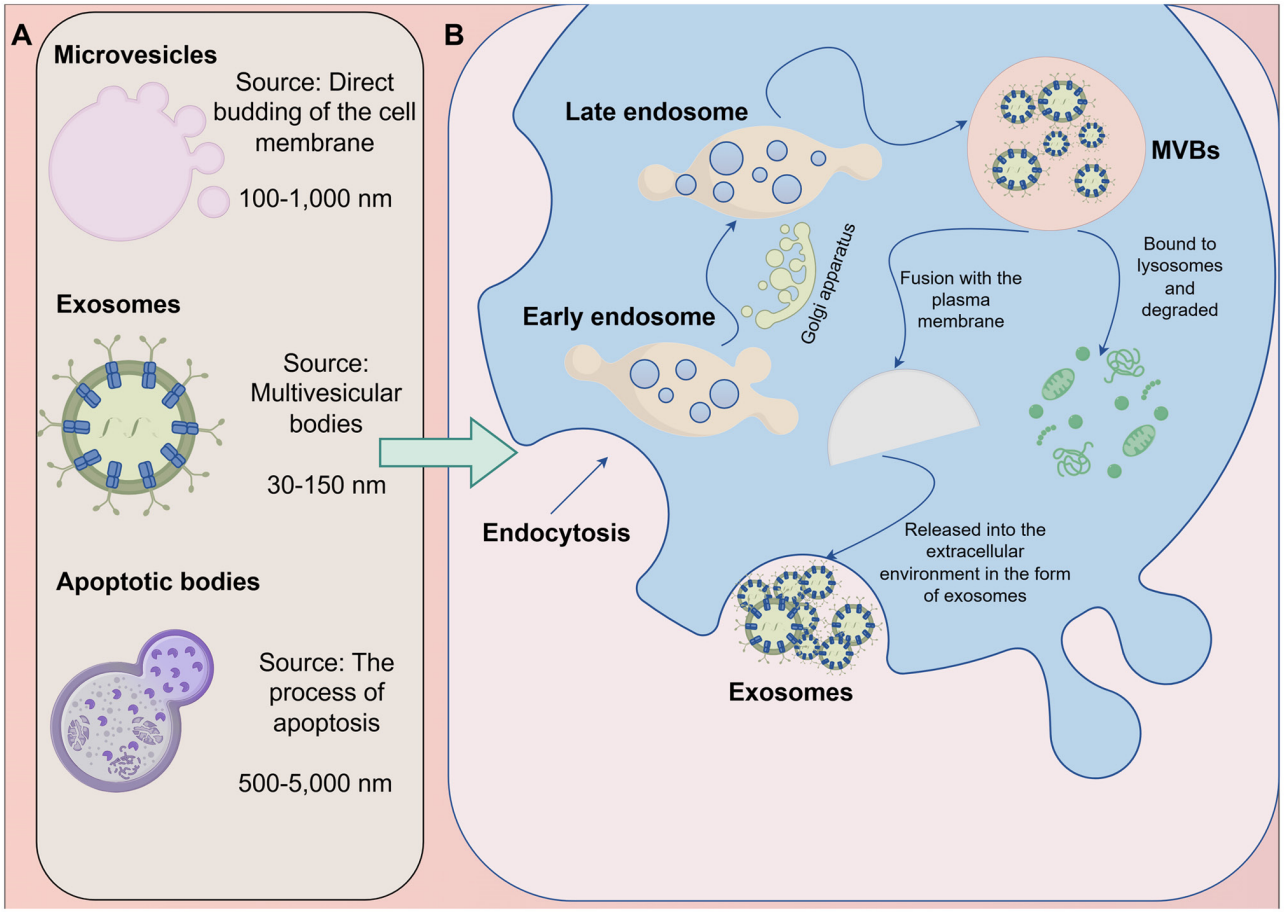

Figure 2. Classification of extracellular vesicles and the biogenesis of exosomes. (A) Classification of extracellular vesicles. (B) Biological occurrence process of exosomes. The figure was generated using Figdraw (www.figdraw.com). MVBs, multivesicular bodies.

Low doses can promote proliferation, whereas high doses inhibit proliferation; this phenomenon may be associated with the modulation of the mitogen-activated protein kinase/phosphatidylinositol 3-kinase (PI3K) signaling pathways (46). This

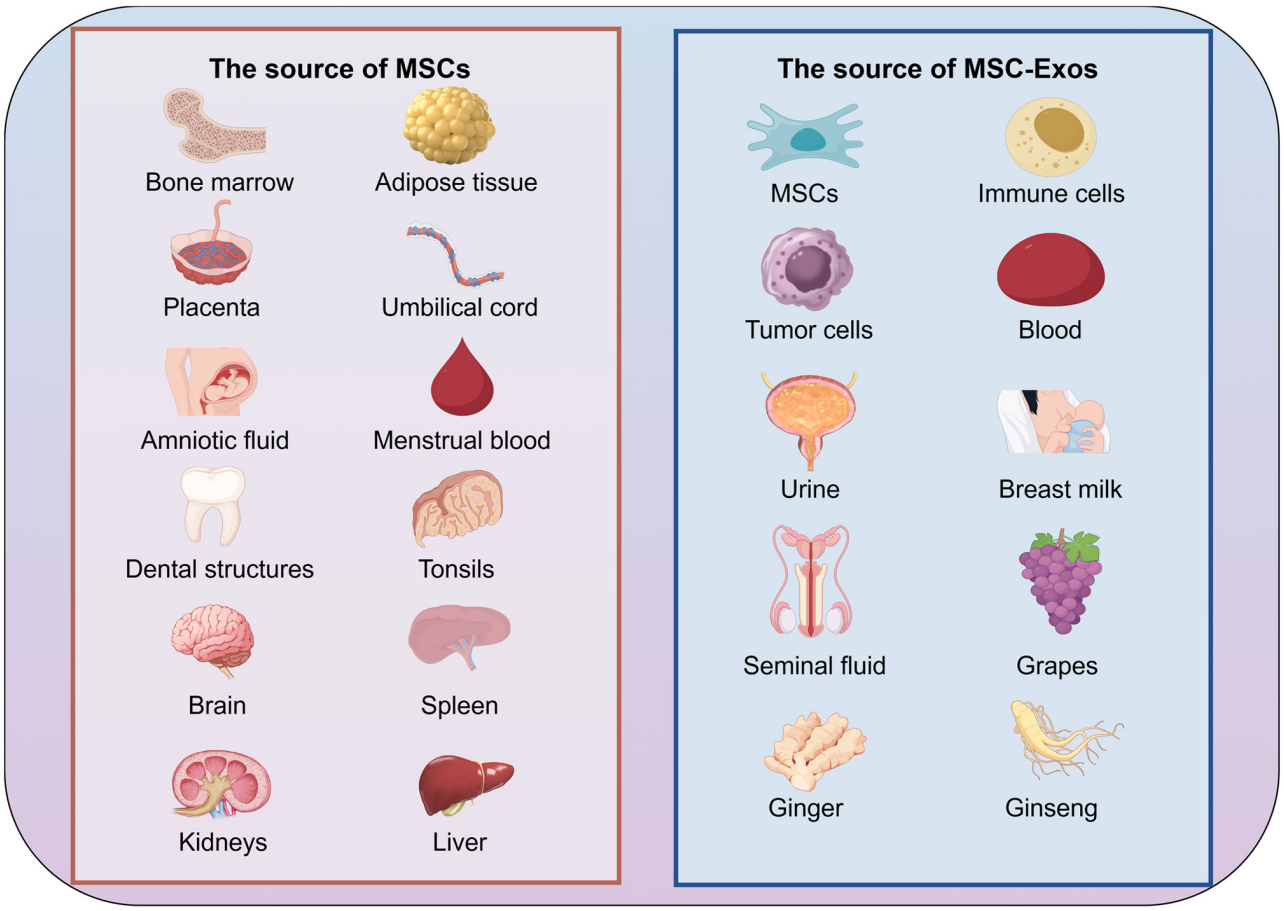

Figure 3. Sources of MSCs and exosomes. The figure was generated using Figdraw (www.figdraw.com). MSCs, Mesenchymal stem cells; MSC-Exos, exosomes derived from mesenchymal stem cells.

finding suggested that the dosage of MSCs used may be one of the key factors influencing whether MSCs exert pro-tumor or antitumor effects.

Promoting tumor angiogenesis. Due to the high demand for oxygen and nutrients by tumor cells, tumor angiogenesis is key to sustaining the early stages of tumor development and its progression (82). Previously, a study based on *in vitro* and *in vivo* models reported that adipose tissue-derived MSCs (AD-MSCs) may promote CC angiogenesis by activating the nuclear factor κ-light-chain-enhancer of activated B cells signaling pathway, thereby accelerating tumor growth and metastasis (79). Similarly, umbilical cord-derived MSCs (UC-MSCs) may enhance *in vivo* angiogenesis in CC HeLa cells by secreting vascular endothelial growth factor (VEGF), thereby promoting the progression of CC (83).

Suppressing the immune response. MSCs can promote cancer progression by modulating the immune response within the TME. For instance, CC-MSCs exhibit a stronger ability to induce M2 macrophage polarization compared with MSCs derived from normal cervical tissue, thereby fostering an immunosuppressive microenvironment (84,85). Furthermore, it has been reported that CC-MSCs can promote the secretion of TGF-β1 and the expression level of programmed death-ligand 1 through an adenosine-dependent pathway, subsequently inhibiting the antitumor activity of $CD8^+$ T lymphocytes and contributing to cancer promotion (80). Another study also revealed that, compared with MSCs from normal cervical cells, MSCs derived from CC cells highly express CD39 and CD73 on their cell membrane. These molecules serve a notable role in extracellular adenosine generation and immune evasion (86). However, the aforementioned mechanisms are primarily based on *in vitro* experiments and their *in vivo* effects require further validation.

4. Antitumor mechanisms of MSCs and their derived exosomes in CC

Consistent with their tumor-promoting effects, MSCs and their derived exosomes can, under specific conditions, exert anti-tumor effects by inhibiting tumor cell proliferation, inducing apoptosis, regulating immune responses and suppressing tumor angiogenesis (Table II).

Inhibiting the proliferation of tumor cells and inducing tumor cell apoptosis. MSCs and their derived exosomes can inhibit the growth of CC through multiple signaling pathways. For example, *in vitro* cell models have reported that UC-MSC-Exos can induce apoptosis in CC HeLa cells and suppress the expression levels of epithelial-mesenchymal transition (EMT)-related proteins, thereby exerting anti-tumor effects (87). Additionally, microRNA (miR)-370-3p carried by such exosomes can inhibit the proliferation and

Table II. MSCs in inhibiting the occurrence and development of CC.

First author, year	Source	Product administered	Research type	Mechanism of action	(Refs.)
Abas *et al*, 2022	Umbilical cord	MSC-Exos	*In vitro* cell model	Induces apoptosis in CC HeLa cells and inhibits the expression levels of proteins associated with epithelial-mesenchymal transition and as an effective delivery carrier for paclitaxel, it enhances its antitumor efficacy	(87)
Li *et al*, 2024	Umbilical cord	MSC-Exos	*In vitro* cell model	miR-370-3p inhibits the proliferation and migration of CC cells by targeting DHCR24	(88)
Li *et al*, 2023	Umbilical cord	MSC-Exos	*In vitro* cell model	Activates the Notch signaling pathway, promotes the squamous differentiation of CC CaSki cells, thereby inhibiting tumor proliferation and metastasis	(89)
Kenarkoohi *et al*, 2020	Adipose tissue	MSCs	*In vitro* cell models and *in vivo* animal models	Carries the HSV-TK lentiviral vector to induce apoptosis in CC cells	(90)
Meng *et al*, 2021	Bone marrow	MSC-Exos	*In vitro* cell models and *in vivo* animal models	miR-144-3p inhibits the proliferation and invasion of CC cells and promotes their apoptosis by targeting CEP55	(91)
Liu *et al*, 2019	Menstrual blood	MSCs	*In vitro* cell models and *in vivo* animal models	Inhibition of CC HeLa cell proliferation through the TGF-β1-mediated JNK/p21 signaling pathway	(92)
Yi *et al*, 2024	Umbilical cord	MSC-Exos	*In vitro* cell model	Reduces the expression levels of pro-inflammatory factors while increasing the expression levels of anti-inflammatory factors	(96)
Zhou *et al*, 2023	Amniotic fluid	MSCs	*In vitro* cell model	Inhibits tumor angiogenesis	(97)
Yang *et al*, 2022	Bone marrow	MSC-Exos	*In vitro* cell models and *in vivo* animal models	Delivers miR-331-3p to regulate the methylation level of LIMS2 in CC cells	(99)

CC, cervical cancer; MSCs, mesenchymal stem cells; MSC-Exos, exosomes derived from mesenchymal stem cells; DHCR24, 24-dehydrocholesterol reductase; HSV-TK, herpes simplex virus thymidine kinase; CEP55, centrosomal protein 55; TGF-β1, transforming growth factor β1; JNK/p21, c-Jun N-terminal kinase/p21; LIMS2, LIM and senescent cell antigen-like domains 2; miR, microRNA.

migration of CC cells by targeting 24-dehydrocholesterol reductase in *in vitro* cell models (88). It has also been reported that UC-MSC-Exos can promote squamous differentiation of CC CaSki cells by activating the Notch signaling pathway, thereby inhibiting their growth and metastasis (89). In *in vivo* animal models, AD-MSCs carrying the herpes simplex virus thymidine kinase lentiviral vector can induce cancer cell apoptosis, thereby delaying CC progression (90). Furthermore, miR-144-3p in B-MSC-Exos can inhibit the proliferation and invasion of CC cells and promote their apoptosis by targeting centrosomal protein 55 (91). Menstrual blood-derived MSCs can inhibit the proliferation of CC HeLa cells through the TGF-β1-mediated c-Jun N-terminal kinase/p21 signaling pathway, thereby exerting antitumor effects (92).

Regulating immune responses and inflammatory microenvironment. Due to the immunosuppressive properties of MSCs, MSCs are often perceived more as tumor-promoting rather than antitumor agents (93-95). However, research has also suggested that MSCs may exert antitumor effects by modulating inflammatory responses. For example, a previous study by Yi *et al* (96) demonstrated that UC-MSC-Exos can markedly reduce the expression levels of pro-inflammatory factors such as tumor necrosis factor-α (TNF-α), IL-1β and IL-6, while increasing the expression of the anti-inflammatory factor IL-10, thereby alleviating cervical inflammation and potentially reducing the risk of carcinogenesis by inhibiting the EMT process. This finding indicated that the anti-inflammatory regulatory functions of MSCs and their derived exosomes may be associated with their antitumor effects.

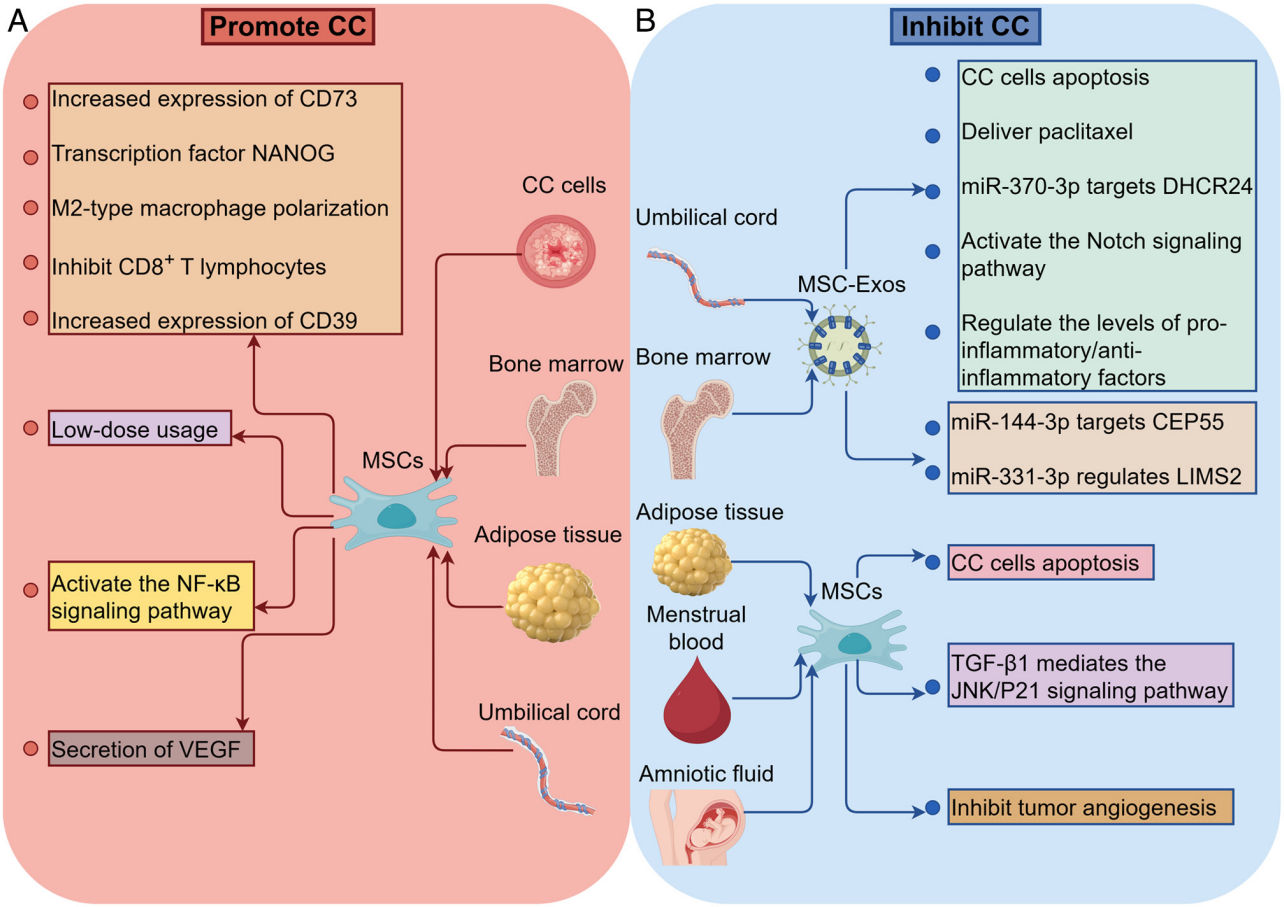

Figure 4. Bidirectional regulatory mechanism of MSCs and their derived exosomes in CC. (A) Mechanism by which MSCs and their derived exosomes promote the development of CC. (B) Mechanism by which MSCs and their derived exosomes inhibit the development of CC. The figure was generated using Figdraw (www.figdraw.com). CC, cervical cancer; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; VEGF, vascular endothelial growth factor; MSCs, mesenchymal stem cells; MSC-Exos, exosomes derived from mesenchymal stem cells; DHCR24, 24-dehydrocholesterol reductase; CEP55, centrosomal protein 55; LIMS2, LIM and senescent cell antigen-like domains 2; TGF-β1, transforming growth factor β1; JNK/p21, c-Jun N-terminal kinase/p21.

Inhibiting tumor angiogenesis. In contrast to the pro-angiogenic effects of AD-MSC-Exos (79) and UC-MSC-Exos (83), a previous study based on an *in vitro* cell model indicated that amniotic fluid-derived MSC-Exos can inhibit the proliferation of CC HeLa cells by suppressing tumor angiogenesis, thereby exerting antitumor effects (97). This opposing role in tumor vascular regulation exhibited by MSCs and their exosomes derived from different tissues suggests that the cellular source may be a key factor in determining their functional direction.

Delivering active substances. MSC-Exos inherently carry various bioactive substances, such as lipids, proteins and nucleic acids, serving as crucial mediators in intercellular communication (98). Furthermore, following engineering modifications, MSC-Exos can also function as drug delivery systems to enhance therapeutic precision. For example, UC-MSC-Exos can serve as effective delivery vehicles for paclitaxel, augmenting its antitumor efficacy (79). Furthermore, B-MSC-Exos can regulate the methylation level of LIM zinc finger domain 2 in CC cells by delivering miR-331-3p, thereby inhibiting tumor progression (99).

In summary, MSCs and their exosomes exhibit a distinct dual role in CC (Fig. 4): MSCs and their exosomes can both promote tumor cell proliferation, angiogenesis and immune escape, as well as inhibit tumor cell proliferation, induce apoptosis and modulate the immune microenvironment. This bidirectional effect is likely closely associated with their tissue origin, dosage, administration route and the specific signaling molecules carried by the exosomes. These aspects will be discussed in detail in the following sections.

5. Analysis of the bidirectional role of MSCs and their derived exosomes in CC

During the initiation and progression of CC, MSCs and their derived exosomes serve a complex and dual-functional role. Although, MSCs and their derived exosomes can promote tumor progression through various mechanisms (78-80); by contrast, under specific conditions, MSCs and their derived exosomes exhibit antitumor effects (87,96,97,99). This functional paradox suggests that their dual role may be regulated by multiple factors, potentially including tissue origin, dosage and administration methods (46,100,101).

Influence of organizational origin. The differences in tissue origin may be an important factor influencing the direction of the role of MSCs and their derived exosomes in CC. A previous study by Song *et al* (102) demonstrated that MSCs

from different sources exhibited notable differences in their chemotactic ability towards CC cells. This research conducted a series of *in vitro* experiments to compare the chemotactic effects of MSCs from adipose tissue, umbilical cord, amniotic membrane and chorion on CC cells. The results demonstrated that the MSCs from chorion had the strongest chemotactic ability. Underlying this phenomenon may involve the epigenetic signatures carried by MSCs from different tissue origins. A previous study demonstrated that MSCs retain the epigenetic characteristics of their tissue of origin during development, thereby influencing their gene expression profiles and secretome (103). For instance, B-MSCs may be more inclined to express factors associated with osteogenesis, whereas AD-MSCs are enriched in molecules associated with lipid metabolism and angiogenesis (104). This finding suggested that although MSCs from different tissue sources are similar in morphology, immunophenotype and basic activity, their biological functions may differ, which was consistent with the conclusion of Kern *et al* (100).

Influence of dosage. The different dosages used may also result in opposite effects of the same source of MSCs on CC cells. Long *et al* (46) conducted co-culture experiments of B-MSCs with CC cells HeLa *in vitro*. The results indicated that a low proportion of B-MSCs could promote the proliferation of CC cells, while a high proportion inhibited their proliferation. This dose-dependent effect may be associated with a threshold effect in signaling pathways. Specifically, at low doses, growth factors secreted by MSCs (such as VEGF and TGF-β) might primarily activate pro-survival signaling pathways (for example, PI3K/protein kinase B) in tumor cells, thereby promoting proliferation. However, when the MSCs dose increases to a certain level, the concentration of their secreted factors also rises, potentially exceeding a threshold and instead activating pro-apoptotic or anti-proliferative signaling pathways (involving molecules such as interferon-γ or TNF-α). Nevertheless, this hypothesis requires further investigation for confirmation. The aforementioned phenomenon suggests that when applying MSCs in CC therapy, the selection of dosage is critically important and may directly impact therapeutic outcomes.

Differences in functions between MSCs and their exosomes. Although exosomes are derived from MSCs and share high functional similarity with MSCs, they may exert different or even opposing effects during the development of CC. For instance, UC-MSCs can promote tumor progression by inducing tumor angiogenesis (83), whereas their derived exosomes demonstrate antitumor effects (87). This functional discrepancy is closely associated with the distinct mechanisms of action between the two. Specifically, MSC-Exos can modulate their secretion and uptake behavior through various means and interventions, thereby exhibiting functional characteristics that differ from those of their parent cells (105). This understanding suggests that in future research, the relationship between the two should be regarded as both interconnected and independent, warranting separate investigation rather than being simplistically treated as a single entity.

Influence of the administration route. MSCs and their derived exosomes can be administered through various routes and the method of administration may influence their ultimate effects. A previous study has reported that in mouse models, local injection of B-MSCs exacerbate tumor growth, whereas no notable difference was observed between the treatment and control groups after intravenous injection (101). Although this study was based on an ascites cancer cell model, the results suggested that the route of administration may affect the function of MSCs. Based on this phenomenon, the present review hypothesizes that local injection may result in a high concentration of MSCs aggregating at the tumor site, yet the sphere of action may be limited and MSCs might be induced to exhibit pro-tumorigenic effects due to pro-tumoral signals within the local microenvironment. Furthermore, different routes of administration lead to distinct patterns of contact between MSCs and the immune system of the host, potentially triggering different rates of immune recognition and clearance (106). This could, in turn, affect their persistence and functional duration *in vivo*, which may also contribute to their differential effects. Therefore, using CC models in future research is necessary to further elucidate the differential impacts of various administration routes in CC.

6. Challenges and prospects

Although MSCs and their derived exosomes demonstrate potential for application in CC treatment, their translation to clinical practice faces a series of notable challenges. Currently, the large-scale and standardized production of exosomes remains a considerable challenge (107). While various isolation and extraction methods exist, such as ultracentrifugation (108), ultrafiltration (109), size-exclusion chromatography (110), precipitation-based separation (111), immunoaffinity capture (112) and microchip-based techniques (113), each of these approaches has its respective advantages and drawbacks (114). None of the currently available methods can simultaneously meet the requirements for high purity and efficiency, operational simplicity and low cost. Therefore, achieving efficient, accurate and economical isolation of high-purity exosomes remains a critical issue that urgently needs to be addressed (115,116). Regarding *in vivo* application, the pharmacokinetic profiles, targeted delivery efficiency and tissue distribution patterns of MSCs and their derived exosomes are still not well understood, which markedly compromises the precision and controllability of their therapeutic use. Furthermore, the long-term safety and potential tumor-promoting risks require thorough evaluation through systematic and rigorous preclinical and clinical studies.

To address the aforementioned challenges, future research could focus on the following directions: First, leveraging multi-omics technologies to gain deeper insights into the molecular composition and mechanisms of action of MSCs and their derived exosomes, thereby providing a theoretical foundation for their precise application. Second, developing efficient and standardized isolation and extraction methods to enable the large-scale, standardized production of MSC-Exos. Additionally, *in vivo* experimental studies should

be strengthened to further elucidate their pharmacokinetic behavior, targeted delivery characteristics and tissue distribution patterns, providing a basis for optimizing administration strategies. Notably, although MSCs and their derived exosomes from natural sources hold potential in cancer therapy, their targeting specificity remains limited. The emergence of engineering modification techniques offers a novel strategy to address this issue. MSCs and their derived exosomes can be modified to express specific tumor-suppressive miRNAs or cytokines by engineering, thereby enhancing their antitumor activity (117). Concurrently, the feasibility and efficacy of MSCs and their derived exosomes, whether employed as monotherapy or as part of combination treatment strategies for CC, should be systematically evaluated through well-designed preclinical and clinical trials. This is essential to facilitate their translation into clinical application. Beyond therapeutic applications, MSC-Exos also demonstrate marked potential in the diagnosis and prognosis of CC. As novel tools for liquid biopsy, the molecular information carried by exosomes can reflect tumor initiation, progression and response to therapy (118).

7. Conclusion

MSCs and their derived exosomes serve a complex and dual-regulatory role in the initiation, progression and metastasis of CC. Their functions are closely associated with multiple factors such as tissue origin, dosage and route of administration. A systematic and comprehensive understanding of this bidirectional regulatory mechanism not only contributes to further insight into their biological behavior but also provides a theoretical foundation in developing novel diagnostic and therapeutic strategies based on MSCs and their exosomes. Although numerous challenges remain in their current clinical application for CC, with the aid of advanced technologies such as engineering modifications, MSCs and their derived exosomes are expected to become important tools integrating both diagnostic and therapeutic functions, thereby opening new avenues for the diagnosis and treatment of CC in the future.

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Authors' contributions

XL and DW contributed to the conception and overall design of the present review. XL and DW drafted the manuscript and prepared the figures and tables. DW reviewed and revised the manuscript. Both authors read and approved the final version of the manuscript. Data authentication 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.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Ferrara P, Dallagiacoma G, Alberti F, Gentile L, Bertuccio P and Odone A: Prevention, diagnosis and treatment of cervical cancer: A systematic review of the impact of COVID-19 on patient care. Prev Med 164: 107264, 2022.
3. Giannella L, Grelloni C, Natalini L, Sartini G, Bordini M, Delli Carpini G, Di Giuseppe J, Dugo E, Piva F and Ciavattini A: Molecular features of HPV-Independent cervical cancers. Pathogens 14: 668, 2025.
4. Hurjui RM, Hurjui IA, Buțureanu TA, Popovici D, Avădănei ER and Balan RA: HPV-independent cervical cancer-a new challenge of modern oncology. Int J Mol Sci 26: 10051, 2025.
5. Cohen PA, Jhingran A, Oaknin A and Denny L: Cervical cancer. Lancet 393: 169-182, 2019.
6. Dilruba S and Kalayda GV: Platinum-based drugs: Past, present and future. Cancer Chemother Pharmacol 77: 1103-1124, 2016.
7. Duska LR, Podwika SE and Randall LM: Top advances of the year: Cervical cancer. Cancer 130: 2571-2576, 2024.
8. Zhidu S, Ying T, Rui J and Chao Z: Translational potential of mesenchymal stem cells in regenerative therapies for human diseases: Challenges and opportunities. Stem Cell Res Ther 15: 266, 2024.
9. Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM and Caplan AI: Mesenchymal stem cell perspective: Cell biology to clinical progress. NPJ Regen Med 4: 22, 2019.
10. Zhang X, Xie Q, Ye Z, Li Y, Che Z, Huang M and Zeng J: Mesenchymal stem cells and tuberculosis: Clinical challenges and opportunities. Front Immunol 12: 695278, 2021.
11. Yu H, Huang Y and Yang L: Research progress in the use of mesenchymal stem cells and their derived exosomes in the treatment of osteoarthritis. Ageing Res Rev 80: 101684, 2022.
12. Smojver I, Katalinić I, Bjelica R, Gabrić D, Matišić V, Molnar V and Primorac D: Mesenchymal stem cells based treatment in dental medicine: A narrative review. Int J Mol Sci 23: 1662, 2022.
13. Mattei V and Delle Monache S: Mesenchymal stem cells and their role in neurodegenerative diseases. Cells 13: 779, 2024.
14. Huang Y and Yang L: Mesenchymal stem cells and extracellular vesicles in therapy against kidney diseases. Stem Cell Res Ther 12: 219, 2021.
15. Wang Y, Ma D, Wu Z, Yang B, Li R, Zhao X, Yang H and Zhang L: Clinical application of mesenchymal stem cells in rheumatic diseases. Stem Cell Res Ther 12: 567, 2021.
16. TomyTomcy A and Sindhu ER: Mesenchymal stem cells-an excellent therapeutic agent for cancer. Asia Pac J Clin Oncol 20: 7-15, 2024.
17. Vakhshiteh F, Atyabi F and Ostad SN: Mesenchymal stem cell exosomes: A two-edged sword in cancer therapy. Int J Nanomedicine 14: 2847-2859, 2019.
18. Wang Y, Wang H, Tan J, Cao Z, Wang Q, Wang H, Yue S, Li W and Wang D: Therapeutic effect of mesenchymal stem cells and their derived exosomes in diseases. Mol Biomed 6: 34, 2025.
19. Weng Z, Zhang B, Wu C, Yu F, Han B, Li B and Li L: Therapeutic roles of mesenchymal stem cell-derived extracellular vesicles in cancer. J Hematol Oncol 14: 136, 2021.

20. Lyu T, Wang Y, Li D, Yang H, Qin B, Zhang W, Li Z, Cheng C, Zhang B, Guo R and Song Y: Exosomes from BM-MSCs promote acute myeloid leukemia cell proliferation, invasion and chemoresistance via upregulation of S100A4. Exp Hematol Oncol 10: 24, 2021.
21. Xunian Z and Kalluri R: Biology and therapeutic potential of mesenchymal stem cell-derived exosomes. Cancer Sci 111: 3100-3110, 2020.
22. Ahmed HG, Bensumaidea SH, Alshammari FD, Alenazi FSH, ALmutlaq BA, Alturkstani MZ and Aladani IA: Prevalence of Human Papillomavirus subtypes 16 and 18 among Yemeni Patients with Cervical Cancer. Asian Pac J Cancer Prev 18: 1543-1548, 2017.
23. Brandt HM, Footman A, Adsul P, Ramanadhan S and Kepka D: Implementing interventions to start HPV vaccination at age 9: Using the evidence we have. Hum Vaccin Immunother 19: 2180250, 2023.
24. Moody CA and Laimins LA: Human papillomavirus oncoproteins: Pathways to transformation. Nat Rev Cancer 10: 550-560, 2010.
25. Wang Y, Fang J, Liu B, Shao C and Shi Y: Reciprocal regulation of mesenchymal stem cells and immune responses. Cell Stem Cell 29: 1515-1530, 2022.
26. Lin Z, Zhou Y, Liu Z, Nie W, Cao H, Li S, Li X, Zhu L, Lin G, Ding Y, *et al*: Deciphering the tumor immune microenvironment: single-cell and spatial transcriptomic insights into cervical cancer fibroblasts. J Exp Clin Cancer Res 44: 194, 2025.
27. Ou Z, Lin S, Qiu J, Ding W, Ren P, Chen D, Wang J, Tong Y, Wu D, Chen A, *et al*: Single-Nucleus RNA sequencing and spatial transcriptomics reveal the immunological microenvironment of cervical squamous cell carcinoma. Adv Sci (Weinh) 9: e2203040, 2022.
28. Taheri M, Tehrani HA, Dehghani S, Rajabzadeh A, Alibolandi M, Zamani N, Arefian E and Ramezani M: Signaling crosstalk between mesenchymal stem cells and tumor cells: Implications for tumor suppression or progression. Cytokine Growth Factor Rev 76: 30-47, 2024.
29. Ramírez Idarraga JA and Restrepo Múnera LM: Mesenchymal stem cells: Their role in the tumor microenvironment. Tissue Eng Part B Rev 29: 681-691, 2023.
30. Bianco P, Robey PG and Simmons PJ: Mesenchymal stem cells: Revisiting history, concepts, and assays. Cell Stem Cell 2: 313-319, 2008.
31. Maloney MA and Patt HM: On the origin of hematopoietic stem cells after local marrow extirpation. Proc Soc Exp Biol Med 149: 94-97, 1975.
32. Friedenstein AJ, Chailakhjan RK and Lalykina KS: The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet 3: 393-403, 1970.
33. Friedenstein AJ, Gorskaja JF and Kulagina NN: Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol 4: 267-274, 1976.
34. Grigoriadis AE, Heersche JN and Aubin JE: Differentiation of muscle, fat, cartilage, and bone from progenitor cells present in a bone-derived clonal cell population: Effect of dexamethasone. J Cell Biol 106: 2139-2151, 1988.
35. Lang H, Schüler N, Arnhold S, Nolden R and Mertens T: Formation of differentiated tissues in vivo by periodontal cell populations cultured in vitro. J Dent Res 74: 1219-1225, 1995.
36. Patel SA, Sherman L, Munoz J and Rameshwar P: Immunological properties of mesenchymal stem cells and clinical implications. Arch Immunol Ther Exp (Warsz) 56: 1-8, 2008.
37. Porada CD and Almeida-Porada G: Mesenchymal stem cells as therapeutics and vehicles for gene and drug delivery. Adv Drug Deliv Rev 62: 1156-1166, 2010.
38. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj and Horwitz E: Minimal criteria for defining multipotent mesenchymal stromal cells. The International society for cellular therapy position statement. Cytotherapy 8: 315-317, 2006.
39. Keshtkar S, Azarpira N and Ghahremani MH: Mesenchymal stem cell-derived extracellular vesicles: Novel frontiers in regenerative medicine. Stem Cell Res Ther 9: 63, 2018.
40. Li X, Liu H, Han C, Luo J, Guan X, Wang L, Li Y, Wang J, Piao H, Zou W and Liu J: A Human brain model mimicking umbilical cord mesenchymal stem cells for the treatment of hypoxic-ischemic brain injury. Int J Mol Sci 24: 14208, 2023.
41. da Silva KN, Marim FM, Rocha GV, Costa-Ferro ZSM, França LSA, Nonaka CKV, Paredes BD, Rossi EA, Loiola EC, Adanho CSA, *et al*: Functional heterogeneity of mesenchymal stem cells and their therapeutic potential in the K18-hACE2 mouse model of SARS-CoV-2 infection. Stem Cell Res Ther 16: 15, 2025.
42. Antoon R, Overdevest N, Saleh AH and Keating A: Mesenchymal stromal cells as cancer promoters. Oncogene 43: 3545-3555, 2024.
43. Oh IR, Raymundo B, Kim M and Kim CW: Mesenchymal stem cells co-cultured with colorectal cancer cells showed increased invasive and proliferative abilities due to its altered p53/TGF-β1 levels. Biosci Biotechnol Biochem 84: 256-267, 2020.
44. Lu W and Allickson J: Mesenchymal stromal cell therapy: Progress to date and future outlook. Mol Ther 33: 2679-2688, 2025.
45. Kresse JC, Gregersen E, Atay JCL, Eijken M and Nørregaard R: Does the route matter? A preclinical review of mesenchymal stromal cell delivery to the kidney. APMIS 131: 687-697, 2023.
46. Long X, Matsumoto R, Yang P and Uemura T: Effect of human mesenchymal stem cells on the growth of HepG2 and Hela cells. Cell Struct Funct 38: 109-121, 2013.
47. Park S and Jung SC: New sources, differentiation, and therapeutic uses of mesenchymal stem cells. Int J Mol Sci 22: 5288, 2021.
48. Patel AN, Park E, Kuzman M, Benetti F, Silva FJ and Allickson JG: Multipotent menstrual blood stromal stem cells: Isolation, characterization, and differentiation. Cell Transplant 17: 303-311, 2008.
49. Igura K, Zhang X, Takahashi K, Mitsuru A, Yamaguchi S and Takashi TA: Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta. Cytotherapy 6: 543-553, 2004.
50. Reyhani S, Abbaspanah B and Mousavi SH: Umbilical cord-derived mesenchymal stem cells in neurodegenerative disorders: From literature to clinical practice. Regen Med 15: 1561-1578, 2020.
51. Joerger-Messerli MS, Marx C, Oppliger B, Mueller M, Surbek DV and Schoeberlein A: Mesenchymal stem cells from Wharton's Jelly and amniotic fluid. Best Pract Res Clin Obstet Gynaecol 31: 30-44, 2016.
52. Entezami S and Sam MR: The role of mesenchymal stem cells-derived from oral and teeth in regenerative and reconstructive medicine. Tissue Cell 93: 102766, 2025.
53. Jung N, Park S, Choi Y, Park JW, Hong YB, Park HH, Yu Y, Kwak G, Kim HS, Ryu KH, *et al*: Tonsil-Derived mesenchymal stem cells differentiate into a Schwann cell phenotype and promote peripheral nerve regeneration. Int J Mol Sci 17: 1867, 2016.
54. Pombero A, Garcia-Lopez R and Martinez S: Brain mesenchymal stem cells: Physiology and pathological implications. Dev Growth Differ 58: 469-480, 2016.
55. Wang Y, Yu X, Chen E and Li L: Liver-derived human mesenchymal stem cells: A novel therapeutic source for liver diseases. Stem Cell Res Ther 7: 71, 2016.
56. da Silva Meirelles L, Chagastelles PC and Nardi NB: Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J Cell Sci 119 (Pt 11): 2204-2213, 2006.
57. Kao CY and Papoutsakis ET: Extracellular vesicles: Exosomes, microparticles, their parts, and their targets to enable their biomanufacturing and clinical applications. Curr Opin Biotechnol 60: 89-98, 2019.
58. Kowal J, Tkach M and Théry C: Biogenesis and secretion of exosomes. Curr Opin Cell Biol 29: 116-125, 2014.
59. Zhang Y, Liu Y, Liu H and Tang WH: Exosomes: Biogenesis, biologic function and clinical potential. Cell Biosci 9: 19, 2019.
60. Farooqi AA, Desai NN, Qureshi MZ, Librelotto DRN, Gasparri ML, Bishayee A, Nabavi SM, Curti V and Daglia M: Exosome biogenesis, bioactivities and functions as new delivery systems of natural compounds. Biotechnol Adv 36: 328-334, 2018.
61. Colombo M, Raposo G and Théry C: Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol 30: 255-289, 2014.
62. Simons M and Raposo G: Exosomes-vesicular carriers for intercellular communication. Curr Opin Cell Biol 21: 575-581, 2009.
63. Stoorvogel W, Strous GJ, Geuze HJ, Oorschot V and Schwartz AL: Late endosomes derive from early endosomes by maturation. Cell 65: 417-427, 1991.
64. Hanson PI and Cashikar A: Multivesicular body morphogenesis. Annu Rev Cell Dev Biol 28: 337-362, 2012.

65. Sahu R, Kaushik S, Clement CC, Cannizzo ES, Scharf B, Follenzi A, Potolicchio I, Nieves E, Cuervo AM and Santambrogio L: Microautophagy of cytosolic proteins by late endosomes. Dev Cell 20: 131-139, 2011.
66. Zhang S, Duan Z, Liu F, Wu Q, Sun X and Ma H: The impact of exosomes derived from distinct sources on rheumatoid arthritis. Front Immunol 14: 1240747, 2023.
67. Xu F, Zhang Q, Liu Y, Tang R, Li H, Yang H and Lin L: The role of exosomes derived from various sources in facilitating the healing of chronic refractory wounds. Pharmacol Res 216: 107753, 2025.
68. Si C, Gao J and Ma X: Natural killer cell-derived exosome-based cancer therapy: From biological roles to clinical significance and implications. Mol Cancer 23: 134, 2024.
69. Dai X, Ye Y and He F: Emerging innovations on exosome-based onco-therapeutics. Front Immunol 13: 865245, 2022.
70. Liang B, Peng P, Chen S, Li L, Zhang M, Cao D, Yang J, Li H, Gui T, Li X and Shen K: Characterization and proteomic analysis of ovarian cancer-derived exosomes. J Proteomics 80: 171-182, 2013.
71. Panfoli I, Granata S, Candiano G, Verlato A, Lombardi G, Bruschi M and Zaza G: Analysis of urinary exosomes applications for rare kidney disorders. Expert Rev Proteomics 17: 735-749, 2020.
72. Di SJ, Cui XW, Liu TJ and Shi YY: Therapeutic potential of human breast milk-derived exosomes in necrotizing enterocolitis. Mol Med 30: 243, 2024.
73. Cao M, Diao N, Cai X, Chen X, Xiao Y, Guo C, Chen D and Zhang X: Plant exosome nanovesicles (PENs): green delivery platforms. Mater Horiz 10: 3879-3894, 2023.
74. Yi Q, Xu Z, Thakur A, Zhang K, Liang Q, Liu Y and Yan Y: Current understanding of plant-derived exosome-like nanoparticles in regulating the inflammatory response and immune system microenvironment. Pharmacol Res 190: 106733, 2023.
75. Li Q, Zhang Y, Shi B, Lin C, Feng Q, Zhou H, Hao M, Ding Y, Ma C, Mu J and Wang D: Galangin exosomes induce cell apoptosis through miR-10b/P53 axis in gastric cancer. Sci Rep 15: 12876, 2025.
76. Kim NH, Kim J, Lee JY, Bae HA and Kim CY: Application of milk exosomes for musculoskeletal health: Talking points in recent outcomes. Nutrients 15: 4645, 2023.
77. Karabay AZ, Barar J, Hekmatshoar Y and Rahbar Saadat Y: Multifaceted therapeutic potential of plant-derived exosomes: Immunomodulation, anticancer, anti-aging, anti-melanogenesis, detoxification, and drug delivery. Biomolecules 15: 394, 2025.
78. Ávila-Ibarra LR, Mora-García ML, García-Rocha R, Hernández-Montes J, Weiss-Steider B, Montesinos JJ, Lizano Soberon M, García-López P, López CAD, Torres-Pineda DB, *et al*: Mesenchymal stromal cells derived from normal cervix and cervical cancer tumors increase CD73 expression in cervical cancer cells through TGF-β1 production. Stem Cells Dev 28: 477-488, 2019.
79. Castro-Oropeza R, Vazquez-Santillan K, Díaz-Gastelum C, Melendez-Zajgla J, Zampedri C, Ferat-Osorio E, Rodríguez-González A, Arriaga-Pizano L and Maldonado V: Adipose-derived mesenchymal stem cells promote the malignant phenotype of cervical cancer. Sci Rep 10: 14205, 2020.
80. Marín-Aquino LA, Mora-García ML, Moreno-Lafont MC, García-Rocha R, Montesinos-Montesinos JJ, López-Santiago R, Sánchez-Torres LE, Torres-Pineda DB, Weiss-Steider B, Hernández-Montes J, *et al*: Adenosine increases PD-L1 expression in mesenchymal stromal cells derived from cervical cancer through its interaction with A2AR/A2BR and the production of TGF-β1. Cell Biochem Funct 42: e4010, 2024.
81. Gu TT, Liu SY and Zheng PS: Cytoplasmic NANOG-positive stromal cells promote human cervical cancer progression. Am J Pathol 181: 652-661, 2012.
82. Burlacu A, Grigorescu G, Rosca AM, Preda MB and Simionescu M: Factors secreted by mesenchymal stem cells and endothelial progenitor cells have complementary effects on angiogenesis in vitro. Stem Cells Dev 22: 643-653, 2013.
83. Lin L, Sun W and Wang L: Effects of mesenchymal stem cells on angiogenesis of cervical cancer HeLa cancer cell line HeLa in vivo. Zhonghua Yi Xue Za Zhi 95: 1175-1178, 2015 (In Chinese).
84. Cortés-Morales VA, Chávez-Sánchez L, Rocha-Zavaleta L, Espíndola-Garibay S, Monroy-García A, Castro-Manrreza ME, Fajardo-Orduña GR, Apresa-García T, Gutiérrez-de la Barrera M, Mayani H and Montesinos JJ: Mesenchymal stem/stromal cells derived from cervical cancer promote M2 macrophage polarization. Cells 12: 1047, 2023.
85. Bautista-Sebastián E, Cortés-Morales VA, Fajardo-Orduña GR, Monroy-García A, Castro-Manrreza ME, Saucedo-Campos AD, Barrera MG, Mayani H and Montesinos JJ: Interaction between mesenchymal stromal cells and tumor cells present in cervical cancer influences macrophage polarization. Cancers (Basel) 17: 3099, 2025.
86. de Lourdes Mora-García M, García-Rocha R, Morales-Ramírez O, Montesinos JJ, Weiss-Steider B, Hernández-Montes J, Ávila-Ibarra LR, Don-López CA, Velasco-Velázquez MA, Gutiérrez-Serrano V and Monroy-García A: Mesenchymal stromal cells derived from cervical cancer produce high amounts of adenosine to suppress cytotoxic T lymphocyte functions. J Transl Med 14: 302, 2016.
87. Abas BI, Demirbolat GM and Cevik O: Wharton jelly-derived mesenchymal stem cell exosomes induce apoptosis and suppress EMT signaling in cervical cancer cells as an effective drug carrier system of paclitaxel. PLoS One 17: e0274607, 2022.
88. Li W, Zhang C, Gao T, Sun Y, Yang H, Liu L, Shi M, Ding L, Zhang C, Deng DYB and Li T: Human umbilical cord mesenchymal stem cells small extracellular vesicles-derived miR-370-3p inhibits cervical precancerous lesions by targeting DHCR24. Stem Cells Transl Med 14: szae087, 2025.
89. Li W, Zhang X, Gao T, Liu L, Zhang C, Yang H, Xie J, Pan W, Deng DYB, Zhang C and Li T: Jagged1 contained in MSC-derived small extracellular vesicles promotes squamous differentiation of cervical cancer by activating NOTCH pathway. J Cancer Res Clin Oncol 149: 18093-18102, 2023.
90. Kenarkoohi A, Bamdad T, Soleimani M, Soleimanjahi H, Fallah A and Falahi S: HSV-TK expressing mesenchymal stem cells exert inhibitory effect on cervical cancer model. Int J Mol Cell Med 9: 146-154, 2020.
91. Meng Q, Zhang B, Zhang Y, Wang S and Zhu X: Human bone marrow mesenchymal stem cell-derived extracellular vesicles impede the progression of cervical cancer via the miR-144-3p/CEP55 pathway. J Cell Mol Med 25: 1867-1883, 2021.
92. Liu QY, Ruan F, Li JY, Wei L, Hu P, Chen HW and Liu QW: Human menstrual blood-derived stem cells inhibit the proliferation of HeLa cells via TGF-β1-Mediated JNK/P21 signaling pathways. Stem Cells Int 2019: 9280298, 2019.
93. Ridge SM, Sullivan FJ and Glynn SA: Mesenchymal stem cells: Key players in cancer progression. Mol Cancer 16: 31, 2017.
94. Melzer C, Yang Y and Hass R: Interaction of MSC with tumor cells. Cell Commun Signal 14: 20, 2016.
95. Norozi F, Ahmadzadeh A, Shahrabi S, Vosoughi T and Saki N: Mesenchymal stem cells as a double-edged sword in suppression or progression of solid tumor cells. Tumour Biol 37: 11679-11689, 2016.
96. Yi C, Wang H, Din MAU, Xia Y, Akanyibah FA and Mao F: Human umbilical cord mesenchymal stem cells derived-exosomes alleviate LPS-induced cervical inflammation and epithelial-mesenchymal transition. Am J Transl Res 16: 6903-6913, 2024.
97. Zhou J, Liang T, Wang D, Li L, Cheng Y, Guo Q and Zhang G: IFNα-expressing amniotic fluid-derived mesenchymal stem cells migrate to and suppress HeLa cell-derived tumors in a mouse model. Stem Cells Int 2018: 1241323, 2018.
98. Veziroglu EM and Mias GI: Characterizing extracellular vesicles and their diverse RNA contents. Front Genet 11: 700, 2020.
99. Yang S, Wang L, Gu L, Wang Z, Wang Y, Wang J and Zhang Y: Mesenchymal stem cell-derived extracellular vesicles alleviate cervical cancer by delivering microRNA-331-3p to reduce LIM zinc finger domain containing 2 methylation in tumor cells. Hum Mol Genet 31: 3829-3845, 2022.
100. Kern S, Eichler H, Stoeve J, Klüter H and Bieback K: Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells 24: 1294-1301, 2006.
101. Mostafa A, Mohamed Abdelsalam S, S Sabbah W and Mekawey D: Mesenchymal stem cells treatment aggravates tumor growth regardless its route of administration: An in vivo study. Asian Pac J Cancer Prev 23: 3309-3315, 2022.
102. Song Y, Li R, Ye M, Pan C, Zheng L, Wang ZW and Zhu X: Differences in chemotaxis of human mesenchymal stem cells and cervical cancer cells. Apoptosis 27: 840-851, 2022.
103. Godini R, Karami K and Fallahi H: Genome imprinting in stem cells: A mini-review. Gene Expr Patterns 34: 119063, 2019.

104. Costela-Ruiz VJ, Melguizo-Rodríguez L, Bellotti C, Illescas-Montes R, Stanco D, Arciola CR and Lucarelli E: different sources of mesenchymal stem cells for tissue regeneration: A guide to identifying the most favorable one in orthopedics and dentistry applications. Int J Mol Sci 23: 6356, 2022.
105. Liu Z, Liu Y, Li Y, Xu S, Wang Y, Zhu Y, Jiang C, Wang K, Zhang Y and Wang Y: ECM stiffness affects cargo sorting into MSC-EVs to regulate their secretion and uptake behaviors. J Nanobiotechnology 22: 124, 2024.
106. Galipeau J and Sensébé L: Mesenchymal stromal cells: Clinical challenges and therapeutic opportunities. Cell Stem Cell 22: 824-833, 2018.
107. van Niel G, Carter DRF, Clayton A, Lambert DW, Raposo G and Vader P: Challenges and directions in studying cell-cell communication by extracellular vesicles. Nat Rev Mol Cell Biol 23: 369-382, 2022.
108. Johnstone RM, Bianchini A and Teng K: Reticulocyte maturation and exosome release: Transferrin receptor containing exosomes shows multiple plasma membrane functions. Blood 74: 1844-1851, 1989.
109. Yu LL, Zhu J, Liu JX, Jiang F, Ni WK, Qu LS, Ni RZ, Lu CH and Xiao MB: A comparison of traditional and novel methods for the separation of exosomes from human samples. Biomed Res Int 2018: 3634563, 2018.
110. Lathe GH and Ruthven CR: The separation of substances on the basis of their molecular weights, using columns of starch and water. Biochem J 60: xxxiv, 1955.
111. Cheng H, Fang H, Xu RD, Fu MQ, Chen L, Song XY, Qian JY, Zou YZ, Ma JY and Ge JB: Development of a rinsing separation method for exosome isolation and comparison to conventional methods. Eur Rev Med Pharmacol Sci 23: 5074-5083, 2019.
112. Yoo CE, Kim G, Kim M, Park D, Kang HJ, Lee M and Huh N: A direct extraction method for microRNAs from exosomes captured by immunoaffinity beads. Anal Biochem 431: 96-98, 2012.
113. Wunsch BH, Smith JT, Gifford SM, Wang C, Brink M, Bruce RL, Austin RH, Stolovitzky G and Astier Y: Nanoscale lateral displacement arrays for the separation of exosomes and colloids down to 20 nm. Nat Nanotechnol 11: 936-940, 2016.
114. Li P, Kaslan M, Lee SH, Yao J and Gao Z: Progress in. exosome isolation techniques Theranostics 7: 789-804, 2017.
115. Royo F, Théry C, Falcón-Pérez JM, Nieuwland R and Witwer KW: Methods for separation and characterization of extracellular vesicles: Results of a worldwide survey performed by the ISEV rigor and standardization subcommittee. Cells 9: 1955, 2020.
116. Ramirez MI, Amorim MG, Gadelha C, Milic I, Welsh JA, Freitas VM, Nawaz M, Akbar N, Couch Y, Makin L, *et al*: Technical challenges of working with extracellular vesicles. Nanoscale 10: 881-906, 2018.
117. Ye M, Liu T, Miao L, Ji H, Xu Z, Wang H, Zhang J and Zhu X: Cisplatin-encapsulated TRAIL-engineered exosomes from human chorion-derived MSCs for targeted cervical cancer therapy. Stem Cell Res Ther 15: 396, 2024.
118. Alen BO, Estévez-Pérez LS, Otero Alén M, Domínguez Hormaetxe S, Simón L and Concha Á: Expression of epithelial and mesenchymal markers in plasmatic extracellular vesicles as a diagnostic tool for neoplastic processes. Int J Mol Sci 24: 3578, 2023.