RESEARCH PAPER

Mesenchymal Stem Cells in High-Grade Serous Ovarian Cancer: Dual Roles in Tumor Progression and Therapeutic Potential

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Abstract

As the most dangerous form of epithelial ovarian cancer, high-grade serous ovarian cancer (HGSC) spreads quickly, responds poorly to treatment, and offers limited choices for patients. Some recent studies have shown that mesenchymal stem cells (MSCs) play key roles in the tumor microenvironment of HGSC and demonstrate both helpful and detrimental effects. On the one hand, it helps the growth of tumors by supporting their ability to avoid the immune system, change in structure, develop new blood vessels, and keep cancer stem cells alive, which leads to platinum resistance and relapse. On a different note, their preference for tumors, minimal reaction by the immune system, and easy genetic manipulation make them good for targeted treatments, including both engineered cytokine and prodrug technology. This review covers how MSCs and HGSC cells interact, reviews possible ways HGSCs evade therapy through mitochondrial transfer and reprogramming the stroma, and looks at the benefits and potential dangers involved in MSC treatments. Combining data from preclinical studies with new translational techniques, we stress how observing the functions of MSC subsets carefully can benefit treatment while limiting their risk of helping cancer growth. The use of MSCs in HGSC brings both difficulties and potential benefits to developing precision treatments.

Keywords: High-grade serous ovarian cancer (HGSC), Mesenchymal stem cells (MSCs), Platinum resistance, Precision treatments.

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1. INTRODUCTION

High-grade serous ovarian cancer (HGSC) is the most common and lethal subtype of epithelial ovarian cancer (EOC), accounting for 70–80% of EOC-related deaths. Ovarian cancer subtypes aid accurate diagnosis and classification (1). Ovarian cancer ranks as the eighth leading cause of cancer mortality among women worldwide, with BRCA1/2 mutations representing a significant subset (2). Growing evidence indicates that HGSC primarily develops from the secretory epithelial cells in the fallopian tube, particularly at the fimbrial end, supported by identically present TP53 mutations in both serous tubal intraepithelial carcinoma (STIC) and HGSC tumors (3,4). The disease usually spreads through coelomic fluid, predominantly affecting the omentum and often resulting in the formation of malignant ascites (5). HGSC is characterized by nearly universal TP53 mutations (~96%) and frequent homologous recombination defects from BRCA1/2 or other DNA repair gene alterations, driving its aggressiveness and informing targeted treatments (6). Molecular subtyping has classified the tumors into immune, mesenchymal, proliferative, and differentiated groups, each exhibiting different clinical outcomes and responses to treatment (7). The standard treatment for HGSC involves maximal cytoreductive surgery followed by platinum- and taxane-based chemotherapy. Despite initial responses, recurrence rates are high, highlighting the need for better therapies. Recent guidelines endorse adding targeted agents like PARP inhibitors and, for some patients, HIPEC to improve outcomes (8). Recently, mesenchymal stem cells (MSCs) have become known as important elements within the tumor microenvironment (TME) of HGSC, exhibiting functions that can both facilitate and hinder tumor development. MSCs, which are capable of differentiating into various mesenchymal cell types such as osteoblasts, adipocytes, and chondrocytes, are appealing for clinical applications because they have a lower tendency to form teratomas compared to embryonic or induced pluripotent stem cells. In their natural state, MSCs are relatively infrequent and noted for their ability to modulate the immune response: they can inhibit T cells, B cells, NK cells, macrophages, and dendritic cells by releasing various factors, including nitric oxide, prostaglandin E2, TSG-6, and indoleamine 2,3-dioxygenase(9,10). Moreover, MSCs produce

growth factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), and interleukin-6 (IL-6), which facilitate angiogenesis, protect against cell death, and assist in tissue repair. By responding to chemokines, adhesion proteins, and matrix metalloproteinases, MSCs can move to areas of inflammation and injury, further influencing tissue recovery and immune modulation. Within the TME, MSCs work in concert with other stromal components, including cancer-associated fibroblasts (CAFs), extracellular matrix (ECM), and tumor-associated macrophages, to enhance immune suppression, tumor cell migration, invasion, angiogenesis, and the remodeling of the extracellular matrix (11,12). Immunosuppressive mechanisms, such as the PD-1/PD-L1 pathway and the presence of regulatory T cells and myeloid-derived suppressor cells, further weaken the effectiveness of anti-tumor immune responses and therapies (13). Factors such as hypoxia, chronic inflammation, metabolic alterations, and communications via exosomes within the TME also play a role in escalating tumor aggressiveness and reducing treatment efficacy (14,15). Considering their diverse functions, targeting the TME, particularly the dual nature of MSCs (Fig.1), might provide novel approaches for successfully treating HGSC. This review seeks to emphasize the significance of MSCs in HGSC by examining their relationships within the cancer microenvironment and assessing their potential as future therapeutic targets.

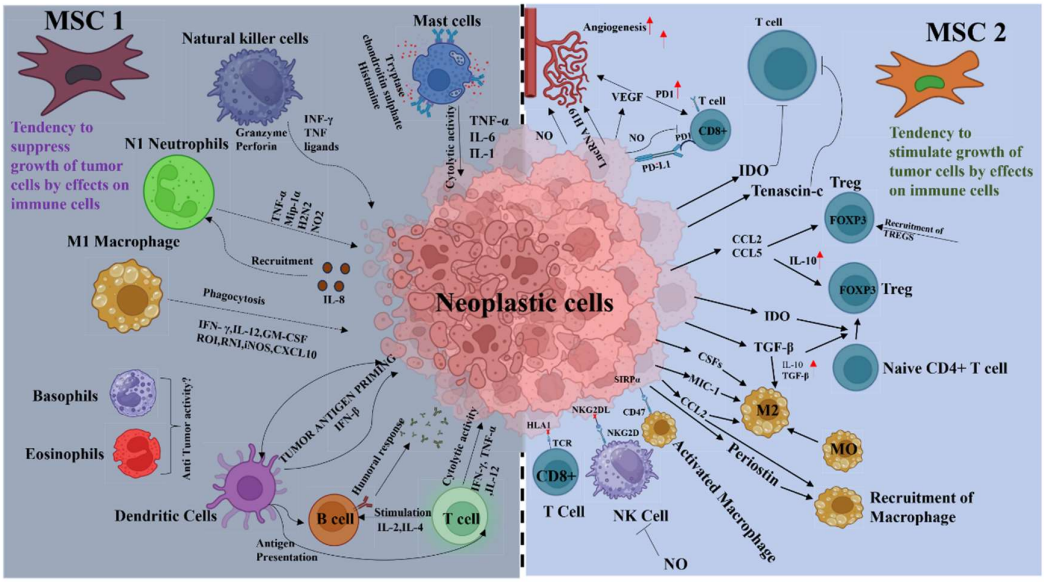

Figure 1: (MSCs 1) Mesenchymal stem cells bolster the immune system to fight against tumors (MSCs 2). The immune system, with its immunomodulatory and anti-inflammatory abilities, can inadvertently suppress its own response, resulting in tumor advancement

The illustration depicts the opposing roles of MSCs within the TME, focusing on the contrasting MSC1 and MSC2 phenotypes. On the left, MSC1 (activated through TLR4) displays anti-tumor effects by boosting the activity of immune effector cells. MSC1 promotes the recruitment and activation of M1 macrophages, which produce pro-inflammatory cytokines such as TNF-α, IL-12, GM-CSF, and inducible nitric oxide synthase (iNOS), thereby facilitating tumor cell destruction via phagocytosis and nitric oxide (NO) generation. It also enhances the function of N1-type neutrophils, leading to the release of TNF-α, MIP-1α, and H_2O_2, which further aids in tumor cell elimination. MSC1 stimulates natural killer (NK) cells and CD8+ cytotoxic T cells to secrete granzyme, perforin, and IFN-γ, boosting their cytolytic activity. Under the influence of MSC1, dendritic cells (DCs) are activated, improving antigen presentation and the priming of T and B cells, thereby strengthening adaptive immune responses. Additionally, MSC1 inhibits angiogenesis, curtailing tumor growth by diminishing vascular endothelial growth factor (VEGF) and PDGF signaling. On the other hand, the right side of the illustration represents MSC2, which assumes a pro-tumorigenic profile after TLR3 activation. MSC2 produces immunosuppressive mediators such as indoleamine 2,3-dioxygenase (IDO), TGF-β, and IL-10, which convert naïve CD4+ T cells into FOXP3+ regulatory T cells (Tregs). These Tregs subsequently secrete IL-10 and TGF-β, reinforcing immunosuppression and inhibiting effector T cell responses. MSC2 also attracts and polarizes macrophages toward the M2 phenotype, promoting tumor growth, extracellular matrix remodeling, and angiogenesis via periostin and chemokines like CCL2 and CCL5. Factors

derived from MSC2, such as PGE2 and IL-6, impede the functions of NK cells and dendritic cells, thereby weakening cytotoxic immunity and antigen presentation. Moreover, MSC2 increases PD-L1 expression, leading to T cell exhaustion through PD-1/PD-L1 interaction. The release of VEGF, MIP-2, and IL-6 enhances neovascularization, supporting tumor survival and metastasis. The combined immunosuppressive and pro-angiogenic actions of MSC2 play a significant role in tumor progression within the TME (16) (Fig.1).

2. CROSSTALK BETWEEN MSCS AND HGSC CELLS

2.1. Mechanisms of MSC Recruitment to Tumors

HGSC tends to metastasize more often to the omentum, indicating that this fat-rich tissue creates a conducive environment for tumor colonization. Inside the omental fat pads are "milky spots," which consist of immune cell clusters that include adipocytes, macrophages, MSCs, and lymphocytes. These formations act as attractors for tumor cells and help dampen local immune responses, thereby aiding in tumor establishment and growth. (17,18). MSCs, particularly adipose-derived stem cells (ADSCs), are drawn to tumor locations by chemotactic signals. Ovarian cancer cells release substances such as CXCL10 and CCR5, which guide ADSCs towards the TME. Once they arrive, ADSCs can secrete IL-10, which further suppresses immune responses and attracts regulatory T cells to the location, enhancing the tumor's ability to avoid immune detection. (19). Moreover, substances like LL-37 can promote MSC recruitment, encourage their movement, and increase the production of tumor-supportive molecules, including IL-6, VEGF, IL-10, CCL5, and MMP-2. This reciprocal interaction allows ovarian cancer cells to direct MSCs into becoming cancer-associated ADSCs (ca-ADSCs), which subsequently offer greater support for tumor advancement. These ca-ADSCs exhibit a heightened capacity to foster tumor development and secrete factors such as BMP2 and BMP4, potentially contributing to microcalcification at metastatic locations. (20). In summary, these interactions between stromal cells are essential in developing the distinct metastatic niche for HGSC within the omentum.

2.2. MSC-Mediated Signalling Pathways

Carcinoma-associated mesenchymal stem cells (CA-MSCs) enhance the survival, spread, and chemotherapy resistance of ovarian cancer stem-like cells (CSCs) by releasing various cytokines and growth factors, including IL-6, CXCL12, TGF-β, BMP2/4, and CCL5. These factors promote CSC characteristics, epithelial-mesenchymal transition (EMT), and the ability to evade immune responses. (21,22). The CXCL12/CXCR4 pathway aids in the migration of CSCs and their spread to other sites. PDGF-BB secreted by CA-MSCs activates PDGFR-β on CSCs, helping to maintain stemness and resistance to platinum-based therapies. Reducing PDGF-BB levels lowers PDGFR-β expression, diminishes the population of ALDH+ CSCs, and restores sensitivity to carboplatin. PDGF signaling occurs before the activation of the Hedgehog pathway, which includes elements like SHH, PTCH1, and GLI1; drugs that inhibit PDGFR-β and Hedgehog can reverse chemoresistance caused by MSCs (23). Recent research has also shown that mitochondrial transfer from CA-MSCs to ovarian cancer cells can promote both metastasis and drug resistance. (24). Furthermore, CA-MSCs play a role in tumor angiogenesis and sustain a pro-tumor cytokine environment, particularly through their secretion of IL-6. (25). In summary, CA-MSCs regulate several pathways, including IL-6/JAK-STAT, CXCL12/CXCR4, PDGF, and Hedgehog, that drive CSC characteristics, EMT, metastasis, and chemoresistance in HGSC.

2.3. Paracrine Effects Promoting Tumorigenesis

CA-MSCs are crucial in supporting the survival, metastasis, and chemotherapy resistance of ovarian cancer stem-like cells (CSCs) through the release of significant cytokines and growth factors. These include bone morphogenetic proteins (BMP2/4) and platelet-derived growth factor-BB (PDGF-BB), which activate signaling pathways that boost CSC stemness, facilitate epithelial-mesenchymal transition (EMT), and enable immune evasion. Notably, BMPs derived from CA-MSCs regulate the maintenance of CSCs and the process of tumorigenesis. (20). The PDGF-BB released by CA-MSCs interacts with PDGFR-β on CSCs, which perpetuates stemness and chemoresistance; blocking this pathway reduces the populations of ALDH+ CSCs and reestablishes sensitivity to platinum-based treatments (26,27). Furthermore, recent studies of Frisbie et al. indicate that mitochondrial transfer from CA-MSCs to ovarian cancer cells enhances metabolic adaptability, fosters metastasis, and contributes to resistance against chemotherapy (24). Collectively, these findings position CA-MSCs as fundamental regulators of ovarian tumor development and highlight various therapeutic strategies aimed at targeting MSC-mediated signaling pathways.

3. ROLE OF MSCS IN TUMOR PROGRESSION

3.1. Enhancement of EMT and Metastasis

MSCs, especially carcinoma-associated MSCs (CA-MSCs), play crucial roles in facilitating epithelial-to-mesenchymal transition (EMT), metastasis, and resistance to chemotherapy in ovarian cancer. CA-MSCs release EMT-promoting transcription factors such as Twist and Snail, which aid in tumor cell detachment, invasion, and plasticity

(28). They activate important signaling pathways like IL-6/JAK2/STAT3 and PI3K/AKT, which not only enhance EMT but also increase the population of cancer stem-like cells (CSCs) and contribute to chemotherapy resistance (29,30). Chemokines such as CCL5 and CXCL12 produced by CA-MSCs interact with CCR5 and CXCR4 receptors on tumor cells, leading to enhanced migration and metastasis. Signals from the TME affect MSC polarization through Toll-like receptors (TLRs), with TLR3-activated MSCs adopting a pro-metastatic phenotype, while different priming can reduce tumor progression (31). Notably, mitochondrial transfer from CA-MSCs to ovarian cancer cells alters tumor metabolism to facilitate EMT, invasion, and chemoresistance, indicating a potential novel target for therapy (24). In summary, these various MSC-driven mechanisms coordinate the progression of ovarian cancer by enhancing plasticity, spread, and resistance to therapy.

3.2. Promotion of Angiogenesis

MSCs play a significant role in tumor angiogenesis through various mechanisms, including the secretion of pro-angiogenic cytokines and growth factors, the release of extracellular vesicles (EVs), and their differentiation into cells that support blood vessels. EVs derived from hypoxic MSCs carry microRNAs such as miR-21-5p, which facilitate epithelial-mesenchymal transition (EMT), promote tumor growth, and lead to the polarization of M2 macrophages, ultimately reshaping the TME to aid neovascularization and tumor advancement (32). MSC-derived EVs also boost tumor development and blood vessel formation by transferring pro-angiogenic components (33). Important cytokines produced by MSCs, including interleukin-6 (IL-6), trigger the secretion of endothelin-1 (ET-1) from tumor cells, which activates the downstream Akt and ERK signaling pathways in endothelial cells, promoting angiogenesis (34). The transforming growth factor-β (TGF-β)/Smad signaling pathway serves as another vital mediator through which MSCs encourage the formation and stabilization of tumor blood vessels (35). Furthermore, the long non-coding RNA H19 expressed by MSCs modulates angiogenesis epigenetically by influencing the expression of EZH2 and vasohibin-1, thus preventing excessive blood vessel growth and ensuring vascular homeostasis (36). Together, these modalities establish MSCs as key regulators of tumor angiogenesis and potential targets for anti-angiogenic treatments.

3.3. MSCs and Cancer Stem Cell Niches in Ovarian Cancer

MSCs play a critical role in establishing and maintaining the cancer stem cell (CSC) niche in ovarian cancer through dynamic bidirectional communication with CSCs and remodeling of the TME. CSCs recruit MSCs, which secrete key factors including transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), prostaglandin E2 (PGE2), and chemokines, supporting CSC survival, self-renewal, and expansion. These interactions occur via direct cell contact, paracrine signaling, and exosome-mediated transfer, sustaining CSC stemness and promoting epithelial-mesenchymal transition (EMT) (37,38). MSC-derived TGF-β activates Notch and Wnt/β-catenin pathways (Fig. 3), upregulating EMT transcription factors such as ZEB1, Snail, Slug, and Twist (Fig. 2), thereby enhancing CSC invasiveness. (39). The IL-6/STAT3 axis is central to maintaining CSC proliferation and stemness, with MSCs producing CXCL7 in response to tumor IL-6, creating a feedback loop that amplifies pro-stemness cytokine secretion (Fig. 4) (40). MSC-derived exosomes transfer oncogenic microRNAs and proteins that induce matrix metalloproteinases, remodeling the extracellular matrix and facilitating tumor invasion (39). These processes collectively elevate CSC marker expression, increase metastatic potential, and promote chemoresistance (41). Recent ovarian cancer-specific studies highlight MSC modulation of bone morphogenetic protein (BMP) signaling pathways to sustain CSC traits and chemoresistance, with BMP inhibition suppressing tumor stemness and growth (42). Additionally, engineered MSCs delivering therapeutic miRNAs and oncolytic viruses show promise in disrupting ovarian CSC niches and reducing tumor progression in preclinical models, suggesting novel therapeutic strategies (43).

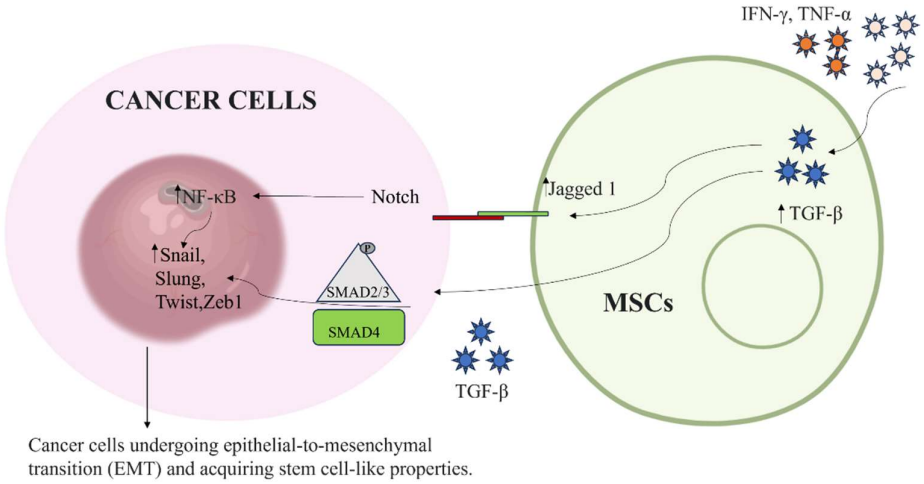

Figure 2: MSCs and induction of the CSC phenotype in cancer cells

Pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) stimulate MSCs to overexpress transforming growth factor-beta (TGF-β). This elevated TGF-β activates Notch and TGF-β/Smad signaling pathways in adjacent cancer cells, leading to the induction of the cancer stem cell (CSC) phenotype. Specifically, TGF-β signaling upregulates key epithelial-mesenchymal transition (EMT)-associated transcription factors, including ZEB1, Twist, Slug, and Snail, which are critical for EMT and CSC traits (44) Fig 2

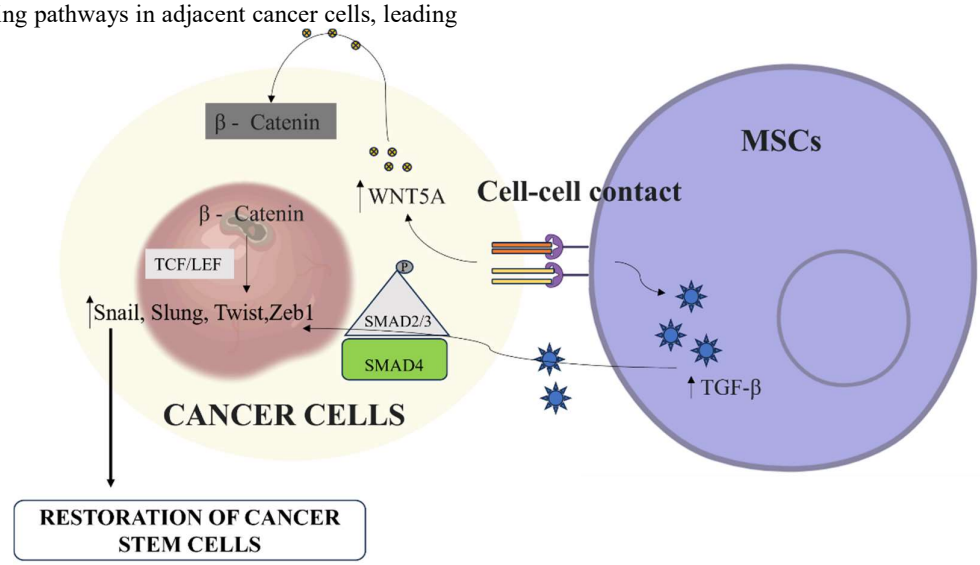

Figure 3: Cell contact and restoration of CSC populations

Direct cell-cell contact between MSCs and cancer cells increases TGF-β expression in MSCs and induces WNT5A expression in cancer cells. The paracrine effects of MSC-derived TGF-β and the autocrine WNT5A signaling within cancer cells synergistically promote the restoration and expansion of CSC populations. This process involves the upregulation of Snail-family transcription factors, including Slug, Snail, Twist1, and Twist2, reinforcing EMT and stem-like characteristics in tumor cells (44) Fig 3

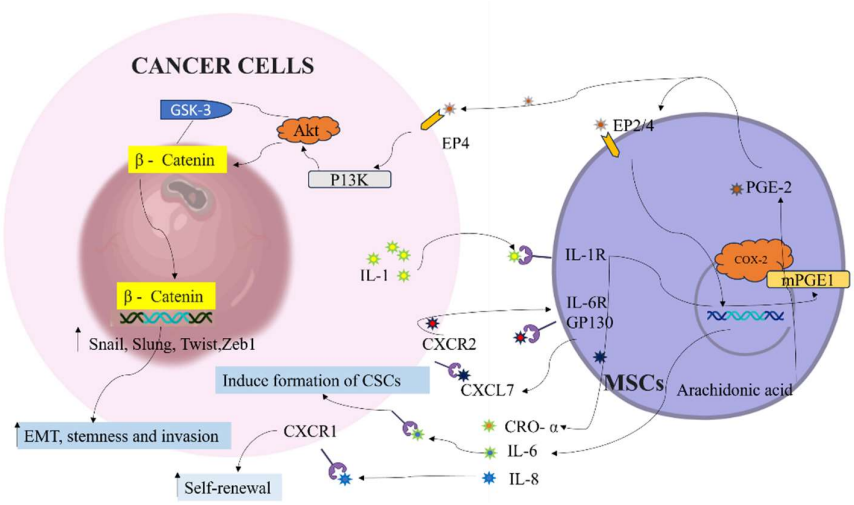

Figure 4: MSC-mediated enhancement of CSCs and EMT via pro-inflammatory signalling

MSC-derived prostaglandin E2 (PGE2), stimulated by tumor-released interleukin-1 (IL-1), promotes increased secretion of cytokines and chemokines such as IL-6, IL-8, CXCL1, and RANTES within the TME. This cytokine cascade enhances CSC self-renewal and epithelial-mesenchymal transition, contributing to tumor progression and metastasis (38) Fig. 4.

4. MSCS AND CHEMORESISTANCE IN HGSC

4.1 Mechanisms of Therapy Evasion

CA-MSCs play a crucial role in the development of chemoresistance in HGSC by transferring mitochondria to tumor cells that lack these organelles. This transfer of mitochondria boosts the proliferation, survival, and resistance of tumor cells to platinum-based chemotherapy agents such as cisplatin (26). The hypoxic and spheroid-like conditions typical of the HGSC tumor microenvironment further enhance mitochondrial transfer through increased interactions between cells, which in turn elevate oxidative metabolism and ATP production, aiding in the survival of tumor cells during chemotherapy (27,45). Additionally, the mitochondria that are taken up stimulate the production of angiopoietin-like protein 3 (ANGPTL3), which activates the MAPK/ERK signaling pathway that supports tumor growth and progression (46). The transferred mitochondria remain within the recipient tumor cells and continue to replicate over extended periods, sustaining the metabolic reprogramming and phenotypic changes associated with resistance to therapy. Intervening in the mitochondrial trafficking mechanisms, such as targeting the mitochondrial motor protein MIRO1, effectively reduces mitochondrial transfer, which in turn decreases tumor growth and restores sensitivity to chemotherapy (47). Furthermore, CA-MSCs contribute to the clonal heterogeneity observed within tumors, partly through mitochondrial heteroplasmy and the spread of harmful mitochondrial DNA mutations, complicating therapeutic approaches and enabling long-term resistance to chemotherapy (27). These results highlight mitochondrial transfer as an essential mechanism through which CA-MSCs bolster tumor survival and evolution in response to chemotherapeutic pressure.

4.2 Influence on Platinum-Based Chemotherapy Response

HGSC often becomes resistant to chemotherapy based on platinum, such as carboplatin, resulting in tumor recurrence. The TME, especially CA-MSCs, significantly contributes to this resistance by influencing cancer stem-like cells (CSCs). The co-culture of CSCs with CA-MSCs leads to an increase in ALDH+ CSC populations, which correlate with chemoresistance and unfavorable prognosis. This phenomenon is mainly driven by platelet-derived growth factor-BB (PDGF-BB) signaling via PDGFR-β on CSCs, which enhances stemness, induces epithelial-mesenchymal transition (EMT), and escalates drug resistance. Inhibiting PDGF signaling through genetic silencing or pharmacological agents like sunitinib decreases CSC prevalence and restores sensitivity to platinum-based treatments (26). The PDGF-BB/PDGFR-β signaling pathway also leads to the upregulation of EMT-associated transcription factors such as TWIST, SNAIL, ZEB1, and ZEB2, promoting invasion and metastasis (48). Simultaneous activation of the Hedgehog (HH) pathway further supports CSC stemness and resistance to chemotherapy. Combined inhibition of the PDGF

and HH pathways has been demonstrated to enhance sensitivity to platinum drugs, underlining the critical interactions between stromal and cancer cells (49). From a clinical perspective, evaluating tumor-stroma proportion (TSP) acts as a predictive biomarker. Patients whose tumors show a high stromal content have significantly higher rates of platinum resistance and exhibit poorer progression-free and overall survival, indicating that TSP assessment can assist in identifying patients who might benefit from therapies targeting the stroma (50,51).

4.3 Role of MSCs in Tumor Dormancy

MSCs play a crucial role in regulating tumor dormancy, which is an important aspect of cancer recurrence and metastasis. MSCs derived from bone marrow promote dormancy by releasing factors like TGF-β2, GAS6, and BMP7, activating signaling pathways such as p38 MAPK and AXL receptor, which results in reduced ERK activity and the upregulation of genes associated with dormancy (52,53). The CXCL12/CXCR4 chemokine pathway assists in the homing and maintenance of dormant cancer cells in the bone marrow microenvironment. Exosomes from MSCs that contain microRNAs such as miR-127 and miR-222 further strengthen dormancy by targeting TGF-β and CXCL12 signaling (54,55). Interplay between nutrient scarcity and MSCs fosters quiescence in cancer cells, which is reflected in the elevated expression of TWIST1 and LOX, indicators of micro metastatic dormancy (56). Factors associated with the senescence-associated secretory phenotype, including IL-6 and IL-8, aid in immune evasion and the maintenance of dormancy (56). Environmental challenges such as hypoxia and detachment from the extracellular matrix trigger JNK signaling that supports dormant states. Furthermore, human umbilical cord MSCs inhibit the β-catenin and c-Myc pathways to induce a halt in tumor cell growth (57). Tumor-associated MSCs enhance dormancy through the secretion of CXCL12, TGF-β, and specific exosomal microRNAs related to dormancy (58). These discoveries underline the significance of MSCs as fundamental contributors to tumor dormancy and their potential as targets for therapeutic approaches designed to avert cancer relapse.

5. THERAPEUTIC APPLICATIONS OF MSCS IN HGSC

5.1 MSCs as Drug/Gene Delivery Vehicles

MSCs have been recognized as promising carriers for drugs and genes in HGSC because of their natural ability to target tumor locations and their low immunological response. These characteristics make MSCs appealing transporters for cytokines, enzymes that convert prodrugs, immune modifiers, and small-molecule medications (59). For instance, MSCs obtained from amniotic fluid or umbilical cord have been genetically modified to produce interleukins such as IL-2 and IL-21, which boost immune-mediated tumor elimination in ovarian cancer studies. Furthermore, MSCs that express anti-angiogenic agents, such as endostatin, effectively hinder tumor growth and angiogenesis. Utilizing MSCs for suicide gene therapy allows for localized activation of prodrugs within the tumor's microenvironment, enhancing the therapeutic margin while reducing systemic side effects (60). Menstrual blood-derived MSCs, recognized for their quick growth and ease of collection, have demonstrated promising capabilities in targeting tumors in preclinical investigations. Notably, certain populations of MSCs, including endometrial MSCs, have shown inherent anti-tumor activity against ovarian cancer cells (61). Nonetheless, there are ongoing concerns regarding the possible tumor-promoting effects of MSCs, highlighting the need for thorough preclinical assessments to ensure safety. In light of the obstacles presented by metastasis and chemotherapy resistance in HGSC, MSC-based delivery methods provide a beneficial approach for targeting tumor environments and resistant cell groups that are generally hard to reach with standard treatments.

5.2 Use of Engineered MSCs

Engineered mesenchymal stem cells (eMSCs) exploit the natural tumor-homing abilities of MSCs to transport therapeutic agents that trigger apoptosis in cancer cells, modify immune responses, and inhibit oncogenic pathways. eMSCs that produce TRAIL specifically activate apoptotic pathways in tumor cells through the death receptors DR4 and DR5 and show improved effectiveness when used alongside chemotherapy, effectively addressing tumor resistance (62). Moreover, eMSCs designed to release immunostimulatory cytokines such as IL-2, IL-12, and IL-21 enhance the cytotoxic capabilities of CD8+ T cells and natural killer (NK) cells, significantly hindering tumor progression (63). Type I interferon–producing eMSCs stimulate antitumor immunity and facilitate cancer cell apoptosis, although it is essential to carefully regulate IFN-γ expression to prevent potential immunosuppressive effects. Advanced eMSC platforms are also capable of delivering oncolytic viruses, siRNAs, miRNAs, nanoparticles, and enzymes that convert prodrugs, thereby improving the precision of targeted chemotherapy and gene therapy. The integration of inducible gene circuits,

tumor-specific promoters, and safety switches like iCasp9 further refines the control over therapeutic payload activation, enhancing both treatment safety and effectiveness. A recent thorough review underscores these innovative engineering approaches and highlights the dual function of eMSCs in targeting the TME while modulating immune responses to enhance outcomes in ovarian and other solid tumors (43). Despite encouraging preclinical and early clinical findings, current research continues to focus on addressing delivery challenges, ensuring biosafety, and reducing any tumor-supportive characteristics associated with MSCs.

5.3 Safety and Translational Challenges

Mesenchymal stem cell (MSC) therapies for HGSC encounter significant challenges regarding safety, regulatory approval, and large-scale production, which currently hinder their broad clinical use. The inherent diversity among MSC populations, resulting from variations in donors, tissue sources, as well as methods of culture and expansion, can affect the consistency and effectiveness of treatments. Importantly, some MSC subsets may develop pro-tumorigenic characteristics within the TME, highlighting the necessity for thorough characterization (63). Extended in vitro culture raises concerns about chromosomal instability and genetic changes, which increase the risks of unforeseen tumorigenicity or abnormal differentiation following transplantation. MSCs' immunomodulatory adaptability presents another obstacle; for instance, stimulating MSCs with interferon-γ can increase the expression of immunosuppressive factors like PD-L1 and indoleamine 2,3-dioxygenase (IDO), potentially suppressing anti-tumor immune responses if not managed carefully (64). Therefore, fine-tuning the timing, dosage, and combinations with immune checkpoint inhibitors is crucial to optimize efficacy while reducing adverse effects. Acellular therapies utilizing MSC-derived extracellular vesicles (EVs) present promising alternatives with potentially enhanced safety profiles; however, issues remain concerning their rapid clearance and inconsistent distribution in vivo. Strategies such as PEGylation and glycosylphosphatidylinositol (GPI) anchoring have shown preclinical success in improving EV stability and targeting, but clinical validation is still necessary (63). Furthermore, the absence of standardized, good manufacturing practice (GMP)-compliant procedures for MSC isolation, engineering, and quality control has resulted in variability from batch to batch, complicating clinical application. Global regulatory authorities and professional organizations are working to standardize guidelines for evaluating potency, ensuring sterility, maintaining genetic stability, and conducting safety tests to bridge this gap. Addressing these safety and translational obstacles through thorough characterization, standardized production practices, and extensive preclinical assessments is vital to realizing the complete therapeutic potential of MSC-based treatments in HGSC.

6. CONTROVERSIES AND CHALLENGES

6.1 MSC Heterogeneity and Source-Dependent Effects

MSCs utilized in research related to HGSC exhibit considerable diversity influenced by their tissue source, characteristics of the donor, and the conditions under which they are cultured (65,66). MSCs can be sourced from various origins such as bone marrow, adipose tissue, umbilical cord, placenta, and endometrium, each presenting unique gene expression profiles, secretome characteristics, and immunomodulatory abilities. For instance, bone marrow-derived MSCs (BM-MSCs) mainly support the niches for osteogenic and hematopoietic cells, while adipose-derived MSCs (AD-MSCs) demonstrate strong growth-factor promotion and immune-suppressive actions. Umbilical cord MSCs (UC-MSCs) proliferate quickly and exhibit reduced immunomodulatory effects, making them favorable for allogeneic applications but less suitable for immune-based therapies. In spite of the application of minimal standards for MSC identification (CD73+, CD90+, CD105+, and negative for CD14, CD34, CD45, and HLA-DR), there remains intra-source variability with subpopulations differing in their abilities to differentiate, proliferate, and secrete substances. Extended culture durations can lead to clonal drift and cellular aging, affecting the reliability of therapeutic outcomes. Additionally, factors related to the donor, including age, biological sex, and existing health conditions, impact MSC quality; cells derived from older or metabolically unhealthy individuals may have diminished regenerative abilities and produce cytokines that could inadvertently encourage tumor development. The lack of source-specific biomarkers makes it challenging to assess quality, scale up manufacturing, and reproduce preclinical results consistently. As a result, it is crucial to develop good manufacturing practice (GMP) compliant procedures, dependable donor-specific tests, and standardized potency evaluations to enhance uniformity and support the clinical advancement of MSC-based therapies for HGSC. (65,67).

6.2 Tumor-Promoting vs. Tumor-Suppressing Roles

MSCs display both supportive and inhibitory roles in cancer, functioning as either tumor suppressors or enhancers depending on the context. On the tumor-suppressing front, MSCs can cause cancer cells to halt their cycle by downregulating cyclins and releasing factors such as interferon-alpha (IFN-α), DKK-1, and TRAIL, which restrict tumor growth through the modulation of pathways like Wnt/β-catenin and MAPK (68). Furthermore, genetically modified MSCs have shown potential as targeted therapies against cancer (69). On the other hand, in the TME associated with HGSC, MSCs frequently promote tumor advancement through various mechanisms, including immune evasion, triggering of epithelial-mesenchymal transition (EMT), the formation of new blood vessels (neoangiogenesis), chemoresistance, and the growth of cancer stem cell populations. Important mediators of these pro-tumorigenic actions comprise transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), prostaglandin E2 (PGE2), and oncogenic microRNAs conveyed through MSC-derived extracellular vesicles (68). MSCs stimulate survival signaling pathways such as PI3K/Akt and Notch pathways, thereby promoting anti-apoptotic proteins such as Bcl-2, enhancing the survival and resistance of tumor cells (69). Recent developments have enriched the understanding of MSCs' roles as cancer-associated stromal cells (CA-MSCs) that create specialized environments aiding in the maintenance of cancer stem cells and driving drug resistance through the secretion of cytokines, chemokines, and metabolic modulators. Additionally, MSC-derived extracellular vesicles have been recognized as crucial carriers for delivering oncogenic microRNAs and proteins that reshape tumor and immune cells into pro-tumor phenotypes. Cutting-edge investigations emphasize the adaptability of MSCs in the tumor environment, showing their role in suppressing immune cells through the modulation of dendritic cells, natural killer cells, and the induction of immunosuppressive subsets of macrophages and regulatory T cells (43). This enhanced mechanistic understanding has sparked the creation of therapeutic strategies that combine MSC engineering with suicide gene systems and tumor-specific promoters to reduce the risks associated with tumor support while boosting anti-tumor efficacy (69). The functional significance of MSCs is heavily affected by their origin from specific tissues, the conditions of culture, including passage numbers, and the experimental context, such as whether the models are immunocompetent or immunodeficient. Due to this complexity, careful characterization and context-sensitive engineering remain essential to fully utilize MSCs' therapeutic capabilities while steering clear of tumorigenic risks (43,68). Table 1 gives the Summary of Dual Functional Roles of MSCs in Ovarian Cancer.

Table 1: Dual Functional Roles of MSCs in Ovarian Cancer: Tumor-Suppressing and Tumor-Promoting Effects (62,68,69)

Functional Role	Tumor-Suppressing Effects	Tumor-Promoting Effects
Proliferation	Induction of cell cycle arrest (G0/G1), downregulation of cyclins (e.g., cyclin D1)	Secretion of IL-6, VEGF, and TGF-β enhances tumor proliferation and growth.
Apoptosis	TRAIL-mediated and IFN-α/β-induced apoptosis in tumor cells	Activation of PI3K/Akt and Notch pathways promotes survival and chemoresistance
Angiogenesis	Inhibition via DKK-1, IL-12, and endostatin expression	Secretion of VEGF, IL-8 promotes neovascularization
Immune Modulation	Enhanced antitumor immunity via IL-12, IFN-γ, and IL-2, promoting T cell and NK cell activity	Immunosuppressive cytokines (PGE2, IL-10, TGF-β) supporting immune evasion
Cancer Stemness	Downregulation of stemness genes (e.g., SOX2, NANOG)	Increase of ALDH+ cancer stem cells via Wnt/β-catenin and IL-6/CXCL7 signaling
Chemosensitivity	Sensitization to drugs like cisplatin via metabolic signalling	MSC-derived EVs confer resistance through miRNA-mediated pathways
Metastasis & EMT	Downregulation of EMT markers such as SNAIL and ZEB1 in some models	Promotion of EMT via TGF-β and matrix remodeling enzymes (MMPs)
Delivery Vehicle	Safe delivery of antitumor genes like TRAIL, IFN-β, and IL-12 with targeted effects	Risk of off-target effects or transformation during gene delivery

6.3 Risks of MSC-Based Therapy

Mesenchymal stem cell (MSC) treatments for HGSC involve various biological and clinical risks that necessitate meticulous assessment. Extended in vitro culturing beyond early passages can lead to chromosomal instability and heighten the risk of malignant transformation, particularly in

immunocompromised patients, emphasizing the need to utilize low-passage MSCs with genomic oversight during production (70). The intravenous administration of MSCs poses a risk of thrombosis due to the expression of tissue factor (CD142), which activates coagulation pathways and can result in potentially life-threatening embolic events in cancer patients who are already at a higher risk for hypercoagulability (71). Under inflammatory or hypoxic conditions, MSCs have the potential to differentiate into myofibroblasts, leading to fibrosis and organ damage, as demonstrated by cases of interstitial fibrosis and tubular atrophy following MSC infusion in kidney transplant recipients (72). Infectious dangers arise from latent viruses such as parvovirus B19, Epstein-Barr virus, and human herpesvirus 7 that can remain present within MSCs, posing significant risks primarily to immunosuppressed individuals; additionally, mycoplasma contamination during culture expansion is a critical issue (73). Notably, recent research has pinpointed “high-risk” MSC subsets concentrated near premalignant serous tubal intraepithelial carcinoma lesions and fallopian tubes in BRCA mutation carriers, which can inflict DNA damage in epithelial cells and facilitate the onset and spread of ovarian cancer in preclinical models (74). While clinical trials predominantly report mild adverse events, there have been instances of serious complications, including organ failure and tumor progression, with MSC co-administration associated with increased relapse rates in hematological malignancies, suggesting possible tumor-promoting implications (75). To alleviate such risks, emerging safety protocols incorporate inducible suicide gene switches (e.g., iCasp9), utilization of MSC-derived extracellular vesicles as safer substitutes for whole-cell therapy, and thorough product screening to improve clinical safety and effectiveness (43). Considering the limited long-term safety information, MSC therapies for HGSC must be applied judiciously under strict clinical trial supervision.

7. AUTHORS' REVIEW ON FUTURE PERSPECTIVES

This section summarizes significant safety issues, developing therapeutic strategies, and translational obstacles associated with mesenchymal stem cell (MSC)-based treatments in HGSC. Its brief yet thorough nature aims to inform future research and clinical practices.

7.1 Precision Targeting of MSC–Tumor Interactions

While MSCs are utilized clinically, such as in combination therapies for hematological cancers, research indicates an association with increased tumor recurrence and lower relapse-free survival, suggesting unintended tumor-promoting implications (75). To mitigate these concerns, innovative safety strategies like inducible suicide gene switches (e.g., iCasp9), the application of MSC-derived extracellular vesicles (EVs) as safer alternatives, and improved product evaluations are currently in development (76). Given the scarcity of long-term safety information, stringent clinical supervision within well-structured trial protocols is crucial.

7.2 Combining MSC-Based Therapies with Immunotherapy

Merging MSC-based strategies with immune checkpoint inhibitors and adoptive T cell therapies shows promise in addressing the immunosuppressive TME typically observed in HGSC. Engineered MSCs that produce immunostimulatory cytokines (e.g., IL-12, IL-21, IFN-β) could improve the recruitment and activation of cytotoxic lymphocytes. Precisely refining dosing, timing, and therapeutic combinations through thorough preclinical investigations is vital to optimizing effectiveness and reducing adverse reactions prior to clinical implementation.

7.3 Need for Advanced In Vivo Models and Clinical Trials

Despite promising preclinical results, translating MSC-based therapies into clinical practice encounters considerable hurdles. Establishing physiologically relevant, immunocompetent orthotopic HGSC models is essential for accurately assessing MSC biodistribution, persistence, and systemic effects. Early-phase clinical trials involving MSC-derived EVs or genetically modified MSCs must carefully assess immunomodulatory effects and the risk of tumor recurrence. Advancement relies on aligning regulatory standards, applying robust potency assessments, and complying with Good Manufacturing Practice (GMP) guidelines.

8. CONCLUSION

Mesenchymal stem cells (MSCs) play a dual role in HGSC that is dependent on the context. They aid tumor development by facilitating immune escape, epithelial-mesenchymal transition, angiogenesis, and resistance to chemotherapy, all of which worsen the aggressiveness of the disease. On the other hand, their natural ability to home to tumors, low immunogenic profiles, and capacity for genetic modification position MSCs as promising candidates for targeted therapies. Evidence from

preclinical studies shows that engineered MSCs, which express pro-apoptotic proteins, immunostimulatory cytokines, or anti-angiogenic factors, can improve treatment effectiveness, particularly when used in conjunction with chemotherapy or immune checkpoint inhibitors. However, potential risks such as the possibility of malignant transformation, suppression of immune responses, and promotion of metastasis necessitate careful management through enhanced safety engineering and accurate delivery techniques. Therefore, MSCs in high-grade serous ovarian cancer represent a complicated interaction of stromal elements that not only aid in tumor growth but also present new therapeutic opportunities. As advancements in functional profiling, gene editing methods, and delivery systems progress, MSCs could transition from being promoters of cancer progression to valuable instruments in precision oncology for managing high-grade serous ovarian cancer.

REFERENCES

1. Mehra P, Aditi S, Prasad KM, Bariar NK. Histomorphological Analysis of Ovarian Neoplasms According to the 2020 WHO Classification of Ovarian Tumors: A Distribution Pattern in a Tertiary Care Center. Cureus. 2023;
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3).
3. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. American Journal of Surgical Pathology. 2007;31(2).
4. Kuhn E, Kurman RJ, Vang R, Sehdev AS, Han G, Soslow R, et al. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous ovarian cancer-evidence supporting the clonal relationship of the two lesions. Journal of Pathology. 2012;226(3).
5. Lengyel E. Ovarian cancer development and metastasis. Vol. 177, American Journal of Pathology. 2010.
6. Bowtell DD, Böhm S, Ahmed AA, Aspuria PJ, Bast RC, Beral V, et al. Rethinking ovarian cancer II: Reducing mortality from high-grade serous ovarian cancer. Vol. 15, Nature Reviews Cancer. 2015.
7. Verhaak RGW, Tamayo P, Yang JY, Hubbard D, Zhang H, Creighton CJ, et al. Prognostically relevant gene signatures of high-grade serous ovarian carcinoma. Journal of Clinical Investigation. 2013;123(1).
8. González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆. Annals of Oncology. 2023;34(10).
9. Ren G, Su J, Zhang L, Zhao X, Ling W, L'Huillie A, et al. Species variation in the mechanisms of mesenchymal stem cell-mediated immunosuppression. Stem Cells. 2009;27(8).
10. Polchert D, Sobinsky J, Douglas GW, Kidd M, Moadsiri A, Reina E, et al. IFN-γ activation of mesenchymal stem cells for treatment and prevention of graft versus host disease. Eur J Immunol. 2008;38(6).
11. Arneth B. Tumor microenvironment. Vol. 56, Medicina (Lithuania). MDPI AG; 2020.
12. Barrett RL, Pure E. Cancer-associated fibroblasts and their influence on tumor immunity and immunotherapy. Elife. 2020;9.
13. Jiang X, Wang J, Deng X, Xiong F, Ge J, Xiang B, et al. Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. Vol. 18, Molecular Cancer. 2019.
14. Neophytou CM, Panagi M, Stylianopoulos T, Papageorgis P. The role of tumor microenvironment in cancer metastasis: Molecular mechanisms and therapeutic opportunities. Vol. 13, Cancers. 2021.
15. Wang W, Han Y, Jo HA, Lee J, Song YS. Non-coding RNAs shuttled via exosomes reshape the hypoxic tumor microenvironment. Vol. 13, Journal of Hematology and Oncology. 2020.
16. Afkhami H, Mahmoudvand G, Fakouri A, Shadab A, Mahjoor M, Komeili Movahhed T. New insights in application of mesenchymal stem cells therapy in tumor microenvironment: pros and cons. Vol. 11, Frontiers in Cell and Developmental Biology. 2023.
17. Clark R, Krishnan V, Schoof M, Rodriguez I, Theriault B, Chekmareva M, et al. Milky spots promote ovarian cancer metastatic colonization of peritoneal adipose in experimental models. American Journal of Pathology. 2013;183(2).
18. Robinson-Smith TM, Isaacsohn I, Mercer CA, Zhou M, Van Rooijen N, Husseinzadeh N, et al. Macrophages mediate inflammation-enhanced metastasis of ovarian tumors in mice. Cancer Res. 2007;67(12).
19. Rezaeifard S, Razmkhah M, Robati M, Momtahan M, Ghaderi A. Adipose-derived stem cells isolated from omentum: A novel source of chemokines for ovarian cancer growth. J Cancer Res Ther. 2014;10(1).
20. McLean K, Gong Y, Choi Y, Deng N, Yang K, Bai S, et al. Human ovarian carcinoma-associated mesenchymal stem cells regulate

cancer stem cells and tumorigenesis via altered BMP production. Journal of Clinical Investigation. 2011;121(8).
21. McLean K, Gong Y, Choi Y, Deng N, Yang K, Bai S, et al. Human ovarian carcinoma-associated mesenchymal stem cells regulate cancer stem cells and tumorigenesis via altered BMP production. Journal of Clinical Investigation. 2011;121(8).
22. Wang KH, Ding DC. Role of cancer-associated mesenchymal stem cells in the tumor microenvironment: A review. Vol. 35, Tzu Chi Medical Journal. 2023.
23. Coffman LG, Choi YJ, McLean K, Allen BL, Di Magliano MP, Buckanovich RJ. Human carcinoma-associated mesenchymal stem cells promote ovarian cancer chemotherapy resistance via a BMP4/HH signaling loop. Oncotarget. 2016;7(6).
24. Frisbie LG, Pressimone CA, Baruwal R, Garcia GL, Javed Z, Croix C St., et al. Abstract B085: Carcinoma-associated mesenchymal stem cells promote high-grade serous ovarian cancer metastasis and drive tumor heterogeneity at the metastatic site through direct mitochondrial transfer. Cancer Res. 2024;84(5_Supplement_2).
25. Hazrati A, Malekpour K, Mirsanei Z, Khosrojerdi A, Rahmani-Kukia N, Heidari N, et al. Cancer-associated mesenchymal stem/stromal cells: role in progression and potential targets for therapeutic approaches. Vol. 14, Frontiers in Immunology. 2023.
26. Coffman LG, Choi YJ, McLean K, Allen BL, Di Magliano MP, Buckanovich RJ. Human carcinoma-associated mesenchymal stem cells promote ovarian cancer chemotherapy resistance via a BMP4/HH signaling loop. Oncotarget. 2016;7(6).
27. Raghavan S, Snyder CS, Wang A, McLean K, Zamarin D, Buckanovich RJ, et al. Carcinoma-associated mesenchymal stem cells promote chemoresistance in ovarian cancer stem cells via PDGF signaling. Cancers (Basel). 2020;12(8).
28. Battula VL, Evans KW, Hollier BG, Shi Y, Marini FC, Ayyanan A, et al. Epithelial-mesenchymal transition-derived cells exhibit multilineage differentiation potential similar to mesenchymal stem cells. Stem Cells. 2010;28(8).
29. Shi Y, Zhang J, Li Y, Feng C, Shao C, Shi Y, et al. Engineered mesenchymal stem/stromal cells against cancer. Vol. 16, Cell Death and Disease. Springer Nature; 2025.
30. Jackson GA, Adamson DC. Similarities in Mechanisms of Ovarian Cancer Metastasis and Brain Glioblastoma Multiforme Invasion Suggest Common Therapeutic Targets. Vol. 14, Cells. Multidisciplinary Digital Publishing Institute (MDPI); 2025.
31. Waterman RS, Henkle SL, Betancourt AM. Mesenchymal Stem Cell 1 (MSC1)-Based Therapy Attenuates Tumor Growth, Whereas MSC2-Treatment Promotes Tumor Growth and Metastasis. PLoS One. 2012;7(9).
32. Ren W, Hou J, Yang C, Wang H, Wu S, Wu Y, et al. Extracellular vesicles secreted by hypoxia pre-challenged mesenchymal stem cells promote non-small cell lung cancer cell growth and mobility, as well as macrophage M2 polarization via miR-21-5p delivery. Journal of Experimental and Clinical Cancer Research. 2019;38(1).
33. Zhu W, Huang L, Li Y, Zhang X, Gu J, Yan Y, et al. Exosomes derived from human bone marrow mesenchymal stem cells promote tumor growth in vivo. Cancer Lett. 2012;315(1).
34. Huang WH, Chang MC, Tsai KS, Hung MC, Chen HL, Hung SC. Mesenchymal stem cells promote growth and angiogenesis of tumors in mice. Oncogene. 2013;32(37).
35. Li GC, Zhang HW, Zhao QC, Sun L, Yang JJ, Hong L, et al. Mesenchymal stem cells promote tumor angiogenesis via the action of transforming growth factor β1. Oncol Lett. 2016;11(2).
36. Yuan Z, Bian Y, Ma X, Tang Z, Chen N, Shen M. LncRNA H19 Knockdown in Human Amniotic Mesenchymal Stem Cells Suppresses Angiogenesis by Associating with EZH2 and Activating Vasohibin-1. Stem Cells Dev. 2019;28(12).
37. Liu S, Ginestier C, Ou SJ, Clouthier SG, Patel SH, Monville F, et al. Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks. Cancer Res. 2011;71(2).
38. Li HJ, Reinhardt F, Herschman HR, Weinberg RA. Cancer-stimulated mesenchymal stem cells create a carcinoma stem cell niche via prostaglandin E2 Signaling. Cancer Discov. 2012;2(9).
39. Lindoso RS, Collino F, Camussi G. Extracellular vesicles derived from renal cancer stem cells induce a pro-tumorigenic phenotype in mesenchymal stromal cells. Oncotarget. 2015;6(10).
40. Hossain A, Gumin J, Gao F, Figueroa J, Shinojima N, Takezaki T, et al. Mesenchymal Stem Cells Isolated from Human Gliomas Increase Proliferation and Maintain Stemness of Glioma Stem Cells Through the IL-6/gp130/STAT3 Pathway. Stem Cells. 2015;33(8).
41. Zhang LN, Kong CF, Zhao D, Cong XL, Wang S Sen, Ma L, et al. Fusion with mesenchymal stem cells differentially affects tumorigenic and metastatic abilities of lung cancer cells. J Cell Physiol. 2019;234(4).
42. Alizadeh H, Akbarabadi P, Dadfar A, Tareh MR, Soltani B. A comprehensive overview of ovarian

cancer stem cells: correlation with high recurrence rate, underlying mechanisms, and therapeutic opportunities. Vol. 24, Molecular Cancer. BioMed Central Ltd; 2025.
43. Shi Y, Zhang J, Li Y, Feng C, Shao C, Shi Y, et al. Engineered mesenchymal stem/stromal cells against cancer. Vol. 16, Cell Death and Disease. Springer Nature; 2025.
44. Pandi K, Ramasamy J, Kasimayan K, Sakthivel P, Thirupathi R, Aravindhan K, Kumaravel, H, Binoy Varghese Cheriyan & Cheriyan, B. V. Capsaicin from Capsicum annuum var. Cayenne: Isolation, GC-MS Analysis, Anticancer Activity on MG63 Osteosarcoma Cells, and In Silico Interaction with 6T2W. *Journal of Natural Remedies.* 2025;*25*(5):1139–1150.
45. Pandi, K., Binoy Varghese Cheriyan, Vishali Ramesh, Sowparnika Murugavel, & Jaya Surya Venkatesan. Overcoming chemoresistance in mucinous adenocarcinoma: the impact of tumor microenvironment and genetic alterations. *Journal of Applied Pharmaceutical Research*. 2025;*13*(3):76-93.
46. Cascio S, Chandler C, Zhang L, Sinno S, Gao B, Onkar S, et al. Cancer-associated MSC drive tumor immune exclusion and resistance to immunotherapy, which can be overcome by Hedgehog inhibition. Sci Adv. 2021;7(46).
47. Vijayan N, Thanikachalam PV, Patel S. Decoding of the Role of TREM2 in Neuropathic Pain: Molecular Pathway and Neuroinflammatory Mechanism. Drug Dev Res. 2025 Jun;86(4):e70111. doi: 10.1002/ddr.70111. PMID: 40488255.
48. Devarajan E, Song YH, Krishnappa S, Alt E. Epithelial-mesenchymal transition in breast cancer lines is mediated through PDGF-D released by tissue-resident stem cells. Int J Cancer. 2012;131(5).
49. Levanat S, Sabol M, Musani V, Ozretić P, Trnski D. Hedgehog Signaling Pathway as Genetic and Epigenetic Target in Ovarian Tumors. Curr Pharm Des. 2016;22(999).
50. Lou E, Vogel RI, Hoostal S, Klein M, Linden MA, Teoh D, et al. Tumor-Stroma Proportion as a Predictive Biomarker of Resistance to Platinum-Based Chemotherapy in Patients with Ovarian Cancer. Vol. 5, JAMA Oncology. 2019.
51. Kim S, Han Y, Kim SI, Kim HS, Kim SJ, Song YS. Tumor evolution and chemoresistance in ovarian cancer. Vol. 2, npj Precision Oncology. 2018.
52. Widner DB, Park SH, Eber MR, Shiozawa Y. Interactions Between Disseminated Tumor Cells and Bone Marrow Stromal Cells Regulate Tumor Dormancy. Vol. 16, Current Osteoporosis Reports. 2018.
53. Yumoto K, Eber MR, Wang J, Cackowski FC, Decker AM, Lee E, et al. Axl is required for TGF-β2-induced dormancy of prostate cancer cells in the bone marrow. Sci Rep. 2016;6.
54. Bliss SA, Sinha G, Sandiford OA, Williams LM, Engelberth DJ, Guiro K, et al. Mesenchymal stem cell-derived exosomes stimulate cycling quiescence and early breast cancer dormancy in bone marrow. Cancer Res. 2016;76(19).
55. Ono M, Kosaka N, Tominaga N, Yoshioka Y, Takeshita F, Takahashi RU, et al. Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells. Sci Signal. 2014;7(332).
56. Özcan S, Alessio N, Acar MB, Toprak G, Gönen ZB, Peluso G, et al. Myeloma cells can corrupt senescent mesenchymal stromal cells and impair their anti-tumor activity. Oncotarget. 2015;6(37).
57. Yuan Y, Chen D, Chen X, Shao H, Huang S. Human umbilical cord-derived mesenchymal stem cells inhibit proliferation but maintain survival of Jurkat leukemia cells in vitro by activating Notch signaling. Nan Fang Yi Ke Da Xue Xue Bao. 2014;34(4).
58. Li P, Gong Z, Shultz LD, Ren G. Mesenchymal stem cells: From regeneration to cancer. Vol. 200, Pharmacology and Therapeutics. 2019.
59. Amara I, Touati W, Beaune P, De Waziers I. Mesenchymal stem cells as cellular vehicles for prodrug gene therapy against tumors. Vol. 105, Biochimie. 2014.
60. Dembinski JL, Wilson SM, Spaeth EL, Studeny M, Zompetta C, Samudio I, et al. Tumor stroma engraftment of gene-modified mesenchymal stem cells as anti-tumor therapy against ovarian cancer. Cytotherapy. 2013;15(1).
61. Bu S, Wang Q, Zhang Q, Sun J, He B, Xiang C, et al. Human endometrial mesenchymal stem cells exhibit intrinsic anti-tumor properties on human epithelial ovarian cancer cells. Sci Rep. 2016;6.
62. Kim SM, Lim JY, Park SI, Jeong CH, Oh JH, Jeong M, et al. Gene therapy using TRAIL-secreting human umbilical cord blood-derived mesenchymal stem cells against intracranial glioma. Cancer Res. 2008;68(23).
63. Bae J, Liu L, Moore C, Hsu E, Zhang A, Ren Z, et al. IL-2 delivery by engineered mesenchymal stem cells re-invigorates CD8+ T cells to overcome immunotherapy resistance in cancer. Nat Cell Biol. 2022;24(12).
64. Shi Y, Hu G, Su J, Li W, Chen Q, Shou P, et al. Mesenchymal stem cells: A new strategy for immunosuppression and tissue repair. Vol. 20, Cell Research. 2010.
65. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4).

66. Khatun M, Sorjamaa A, Kangasniemi M, Sutinen M, Salo T, Liakka A, et al. Niche matters: The comparison between bone marrow stem cells and endometrial stem cells and stromal fibroblasts reveal distinct migration and cytokine profiles in response to inflammatory stimulus. PLoS One. 2017;12(4).
67. Campioni D, Lanza F, Moretti S, Ferrari L, Cuneo A. Loss of Thy-1 (CD90) antigen expression on mesenchymal stromal cells from hematologic malignancies is induced by in vitro angiogenic stimuli and is associated with peculiar functional and phenotypic characteristics. Cytotherapy. 2008;10(1).
68. Zhu Y, Sun Z, Han Q, Liao L, Wang J, Bian C, et al. Human mesenchymal stem cells inhibit cancer cell proliferation by secreting DKK-1. Leukemia. 2009;23(5).
69. Wang XJ, Xiang BY, Ding YH, Chen L, Zou H, Mou XZ, et al. Human menstrual blood-derived mesenchymal stem cells as a cellular vehicle for malignant glioma gene therapy. Oncotarget. 2017;8(35).
70. Røsland GV, Svendsen A, Torsvik A, Sobala E, McCormack E, Immervoll H, et al. Long-term cultures of bone marrow-derived human mesenchymal stem cells frequently undergo spontaneous malignant transformation. Cancer Res. 2009;69(13).
71. Moll G, Drzeniek N, Kamhieh-Milz J, Geissler S, Volk HD, Reinke P. MSC Therapies for COVID-19: Importance of Patient Coagulopathy, Thromboprophylaxis, Cell Product Quality and Mode of Delivery for Treatment Safety and Efficacy. Front Immunol. 2020;11.
72. Večerić-Haler Ž, Kojc N, Sever M, Zver S, Švajger U, Poženel P, et al. Case Report: Capillary Leak Syndrome With Kidney Transplant Failure Following Autologous Mesenchymal Stem Cell Therapy. Front Med (Lausanne). 2021;8.
73. Sundin M, Lindblom A, Örvell C, Barrett AJ, Sundberg B, Watz E, et al. Persistence of Human Parvovirus B19 in Multipotent Mesenchymal Stromal Cells Expressing the Erythrocyte P Antigen: Implications for Transplantation. Biology of Blood and Marrow Transplantation. 2008;14(10).
74. Coffman L, et al. Identification of high-risk mesenchymal stem cells promoting ovarian cancer initiation and metastasis.
75. Ning H, Yang F, Jiang M, Hu L, Feng K, Zhang J, et al. The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: Outcome of a pilot clinical study. Leukemia. 2008;22(3).
76. Krasilnikova OA, Klabukov ID, Baranovskii DS, Shegay P V., Kaprin AD. The new legal framework for minimally manipulated cells expands the possibilities for cell therapy in Russia. Cytotherapy. 2021;23(8).