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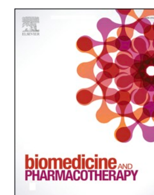

Review

Roles of mesenchymal stromal cells in the head and neck cancer microenvironment

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ABSTRACT

Head and neck cancer (HNC), a common malignancy worldwide, is associated with high morbidity and mortality rates. Squamous cell carcinoma is the most common HNC type, followed by salivary gland carcinomas, head and neck sarcomas, and lymphomas. The microenvironment of HNCs comprises various cells that regulate tumor development. Recent studies have reported that the tumor microenvironment, which modulates cancer progression, regulates cancer treatment response. However, the presence of different types of stromal cells in cancers is a major challenge to elucidate the role of individual cells in tumor progression. The role of mesenchymal stromal cells (MSCs), which are a component of the tumor microenvironment, in HNC is unclear. The major impediment for characterizing the role of MSCs in cancer progression is the lack of MSC-specific markers and their phenotypic similarity with stromal cells. This review aimed to summarize the latest findings on the role of MSCs in the progression of HNC to improve our understanding of HNC pathophysiology.

1. Introduction

Head and neck cancers (HNCs) are a common type of malignancy associated with high mortality and morbidity rates [1–5]. At this anatomical site, squamous cell carcinoma (SCC) is the most common neoplasia in adults and accounts for 3% of all cancers and 1.5% of all cancer-related deaths in the United States of America [1,5–7]. SCC, which is typically observed in tobacco and alcohol users, is associated with a poor prognosis [1,8]. Lately, human papillomavirus (HPV) infection has increased the oropharyngeal SCC incidence in middle-aged patients with different progression and treatment responses, and better prognosis [9]. Lymph node-regional metastasis in head and neck SCC (HNSCC) decreases the overall survival rate by approximately 40–50% [10]. The elucidation of various signaling pathways involved in the induction of metastasis can aid in mitigating the poor prognosis of patients with HNSCC. Previous studies have reported that the tumor microenvironment has a critical role in the metastasis of cancer cells [11–15].

The tumor microenvironment is the ecosystem that surrounds and includes the tumor; it comprises the extracellular matrix (ECM), blood and lymph vessels, immune cells, fibroblasts/myofibroblasts, endothelial cells, pericytes, multipotent cells, and signaling molecules [16,17]. Recent studies have demonstrated that the modulation of the tumor microenvironment is a promising therapeutic strategy for cancer [14,18,19]. However, the role of many of the tumor microenvironment components in tumorigenesis is unclear. In particular, mesenchymal stromal cells (MSCs) are reported to exhibit dual roles in tumor progression [20,21].

MSCs, which are multipotent, mobile cells, are involved in tissue homeostasis, tissue/organ repair, and immune modulation [22–25]. Inflammatory signals promote the migration of MSCs to the lesion site, where they secrete signaling molecules and differentiate into various cell types. Chronic inflammatory sites, such as tumors, promote the homing of MSCs, and these cells can be recovered from different cancer tissues [20,26]. These cells can be recognized *in vitro* based on several markers and their capacity to differentiate into different cell types [27]. However, these markers are not MSC-specific, which is a major

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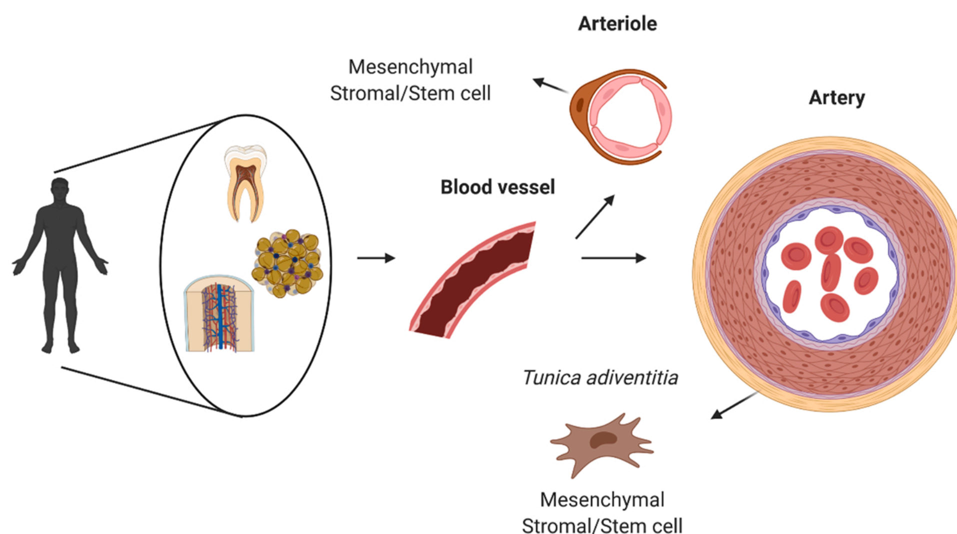

Fig. 1. Mesenchymal stromal cell (MSC) distribution. The major sources of MSCs are the bone marrow,adipose tissue, and dental pulp, although they can be obtained from differentorgans. MSCs are postulated to be localized in proximity to the blood vessels,such as permeating arterioles and inside the tunica adventitia in arteries. Stimulatory signals promote themigration of MSCs to the injured/inflamed site and regulate the host responseor promote MSC differentiation

impediment to examine MSC behavior in situ. This review aimed to summarize the role of the MSCs in the progression of HNCs, especially SCC.

2. MSCs identification

First identified in the bone marrow, the mesenchymal stem cells have the ability to differentiate into muscular, bone, and cartilage tissue *in vivo* [28,29]. Later, cells with similar capacities were recovered from different tissues; however, the true transdifferentiating capacity of these cells is still controversial [24]. Hence, the International Society for Cellular Therapy proposed that mesenchymal stroma cells are the best terminology for these cells. The term mesenchymal stem cells only should be used to indicate cells satisfying specific stemness criteria [30].

BM and adipose tissue stromal vascular fraction are the most common tissue sources for human MSC extraction [22,31,32]. BM-derived MSCs (BMMSCs) and adipose-derived MSCs (AMSCs) share several characteristics, such as the ability to divide symmetrically (generating two stem cells or two differentiated cells) or asymmetrically (generating one stem cell and one differentiated cell), differentiate into some tissue lineages, and migrate [23,27]. Stem cell populations are heterogeneous and often behave as individual cells.

MSCs are identified based on the expression of a subset of surface protein markers *in vitro* and the ability to adhere in culture, form colonies, and differentiate into at least three cell lineages after stimulation [22,27,33]. These features of MSCs are analyzed *in vitro* using a population of cells. Currently available markers cannot delineate the physiological roles of the MSCs in a specific tissue or disease, making the identification of MSCs *in loco* challenging. MSCs derived from different tissues are more closely related than those derived from other mesodermal lineages [34,35]. Crisan et al. reported that the morphology, proliferation kinetics, differentiation capacity, and surface markers of MSCs are similar to those of BMMSCs [36]. However, the phenotypic signatures of MSCs are similar to those of other cell lines, such as perivascular cells and fibroblasts [37,38].

Previous studies have reported that the surface markers of fibroblasts and microvascular pericytes are similar to those of MSCs, which further hinders the identification of MSCs [39–41]. MSC-specific markers were observed in perivascular spaces around large arteries and veins, where fibroblast-like cells were identified in the outermost tunica adventitia (Fig. 1) [42]. The proximity to the vasculature enables the MSCs to respond rapidly to injury or disease. Additionally, MSCs may have a distinct role in the tumor maintenance phase. The major challenge to elucidate the role of MSCs during the natural course of a disease is the lack of specific markers for differentiating different mesenchymal cell types.

Among the several markers proposed for MSC identification, some are strategic markers. For example, smooth muscle actin (SMA) can differentiate MSCs from activated fibroblast/myofibroblast [43,44]. However, the physiological levels of SMA have not been reported and SMA may exhibit varying protein and mRNA levels in MSCs *in vitro* [45]. It was reported that the expression of SMA in non-activated dermal fibroblasts was higher than that in matched MSCs ($\log_2$ (fold change) $= 2.036$, adjusted p-value $= 1.1487 \times 10^{-4}$; RNAseq) [38]. The upregulated expression of SMA promotes the differentiation of MSCs into myofibroblasts and cancer-activated fibroblasts (CAFs), which are involved in the development of various pathologies [43,46,47]. The co-expression of fibroblast activation protein alpha and fibroblast specific protein 1 (FSP, also known as S100A4) has been successfully used to differentiate fibroblasts from mesenchymal cells [48,49]. RNAseq analysis of MSCs and dermal fibroblasts revealed that the expression of *S100A4* was downregulated in MSCs ($\log_2$ (fold change) $= -2.808$, adjusted p-value $= 4.92 \times 10^{-6}$) [38]. Gremlin-1 (GREM1) is also reported to be a candidate marker of MSCs [50,51]. RNAseq analysis revealed that the expression of *GREM1* was not markedly different between MSCs and dermal fibroblasts ($\log_2$ (fold change) $= 0.644$, adjusted p-value $= 0.5182$) [38]. However, a refined analysis must be performed to exclude post-translation modifications of GREM1. Several studies have also proposed various markers, such as Meflin (ISLR), PDPN (podoplanin), STRO-1, and stage-specific embryonic antigen 4 (SSEA-4) [51–55]. However, these markers are associated with some limitations and may be expressed in other cell lineages. The limitations and reliability of MSC markers have been reviewed by Lv et al. [55].

3. Physiological role of MSCs

In addition to tissue repair, MSCs are involved in various biological processes, including tissue homeostasis regulation and maintenance of blood vessel integrity [23,36]. Tissue injury induces the immune cells, endothelial cells, and fibroblasts to secrete several chemokines and mediators, which promote the mobilization of MSCs. These MSCs can undergo differentiation in several stromal components. Additionally, MSCs can produce factors that stimulate innate tissue repair and modulate the immune response and inflammation.

Table 1
Effects of the secretome on head and neck cancer.

Secretome origin	Molecule	Phenotype	Target cell
BMMSC	IL-6	Proliferation	FaDu/ HLaC78
	B2M	Invasion / Migration	TE1/Eca109
	CCN2	Invasion / Migration / ↑MMP9 / ↑MMP2 / EMP	TSCCa/ Cal27
	FGF19	Proliferation	CNE2/5-8F/ 6–10B
	EV	Migration	CNE1/ CNE2/5-8F
		EMP	CNE2
	POSTN	Proliferation	Cal27
		Death resistance	Cal27/HN4
	CCL5	↑MMP9 / ↑MMP2 / ColA1	HSC3
	Not identified	Decreased proliferation / decreased invasion	Eca109
Gingival-MSC	SCGF-β	Death resistance	ISCCI24
	Not identified	Decreased proliferation / Cell death	NH6/Cal27
AMSC	TGF-β	↑MMP14	PCI13
HNSCC	IL-6	Invasion / Migration	BMMSC
(JHU-011/ −012/−019)	PDGF	Invasion / Migration	
ACC	TGF-β / SDF-1	Migration	BMMSC

BMMSC – bone marrow mesenchymal stromal cell; PDGF – plated-derived growth factor; B2M – beta 2 microglobulin; CCN2 – cellular communication network factor 2; FGF19 – fibroblast growth factor 19; EV – extracellular vesicle; POSTN – periostin; SCGF-β – stromal cell growth factor-beta; TGF-β – transforming growth factor-beta; SDF-1 – stromal cell-derived factor 1; MMP – matrix metalloproteinases; EMP – epithelial-mesenchymal plasticity; MSC – mesenchymal stromal cell; AMSC – adipose-derived mesenchymal stromal cell; ACC – acinic cell carcinoma-derived cell.

MSCs can be detected at the injured tissue site (virtually in every blood vessel) or mobilized from the BM through a poorly understood mechanism [23,56]. Endothelial cell selectins are reported to promote MSC homing [57,58]. CD44 and CD24 expressed on the MSC surface can interact with yet unknown endothelial selectins and initiate the rolling of the MSCs after chemotaxis [59,60]. The identification of vascular selectin is an active area of research. P-selectin (CD24/CD44 binding) and Galectin-1 (CD44 binding) are reported to promote MSC-endothelial cell interaction [58,61,62]. Integrins, such as α4β1 are activated after chemotaxis and bind to VCAM-1 on endothelial cells, which results in MSC arrest [63,64]. The release of matrix metalloproteinases (MMPs) promotes the transmigration of MSCs into the fenestrated endothelium of the stromal tissue [64]. The inflammatory cytokines released from the injured tissue can upregulate MMP expression in MSCs and consequently promote cell migration. The knockdown of *MMP2*, *MMP14* (MT-MMP), and *TIMP2* inhibits the migration of MSCs through the interstitium [65]. Mediators, such as interleukin-8 (IL-8), platelet-derived growth factor-AB (PGDF-AB), insulin-like growth factor (IGF)−1, and vascular endothelial growth factor (VEGF) can promote the migration of MSCs into the stroma [66–68].

At the lesion site, the MSCs and surrounding cells modulate each other. For example, interferon-gamma (INF-γ), which enhances macrophage activation and M1 polarization, neutrophil mobility, and CD8^{+} T cell and natural killer (NK) cell activity, promotes the defense response against infection and tumors [69]. INF-γ-stimulated MSCs exert immunosuppressive effects and induce the expression of indoleamine 2, 3-dioxygenase (IDO1), which results in the mitigation of inflammation and the stimulation of anti-inflammatory proteins [70–72]. Moreover, the co-culture of MSCs with lymphocytes inhibits T cell proliferation without apoptosis induction [73]. Additionally, MSCs shift the activity of mature immune cells toward an anti-inflammatory state, which results in the augmentation of T regulatory (Treg) cells, T helper-2 (Th2) cells, and type 2 dendritic cells (DC2) polarization. Furthermore, MSCs decrease the number of Th1 and NK cells, promote M2 polarization of macrophages, and inhibit the secretion of immunoglobulin from plasma cells [74–82].

4. Dual roles of MSCs in the HNC microenvironment

The solid tumor is a complex system comprising heterogeneous transformed cells, stromal cells, immune cells, blood vessels, and lymph vessels. The variability of individual tumors can be attributed to their non-structured, variable, and pathological microenvironment, which is responsible for poor treatment response and cancer progression [17,19,83–86]. Each cell can communicate with the microenvironment components through cytokines and mediators in a paracrine fashion or cell-cell interaction [87]. Cytokines and mediators confer plasticity, variability, and uniqueness to the microenvironment. Recent studies have shown that the tumor microenvironment content is a part of the repertoire for cancer treatment [88].

MSCs associated with the tumor exert dual effects on tumor progression in different models [20,89,90]. The role of MSCs in disease progression has not been completely elucidated. MSCs can contribute to HNC formation through distinct mechanisms. For example, MSCs can exert their activity by secreting biomolecules, promoting cell-cell contact, suppressing protective activities of immune cells, enhancing angiogenesis, or undergoing differentiation in other tumor stroma components, such as CAF.

5. Effect of the crosstalk between MSCs and HNC cells: paracrine signaling, cell-cell interaction, and immunomodulation

Various studies have characterized the biomolecules secreted from MSCs and cancer cells, which are termed secretome [60,91,92]. The crosstalk between cancer cells and MSCs can modify the secretion of biomolecules involved in altering cell behavior (Table 1) [68,93–96]. Watts et al. characterized the secretion profile of HNSCC (JHU-011, JHU-012, and JHU-019 cells), which included stromal cell-derived factor 1 (SDF-1 or CXCL-12), VEGF, growth-regulated alpha protein (Gro-α or CXCL1), IL-8, IL-6, and platelet-derived growth factors (PDGF). The exposure of BMMSCs to the HNSCC-derived secretory molecules increased the migration and invasion of the MSCs toward cancer cells. Conversely, the inhibition of IL-6 and PDGF receptor alpha decreased the migration and invasion of MSCs toward the cancer cells [93]. These results indicate that cancer cell-secreted IL-6 and PDGF in the tumor microenvironment are sufficient to induce MSC migration into the head and neck tumor stroma. Kansy et al. reported the presence of IL-1β, IL-2, IL-4, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), INF-γ, macrophage inflammatory protein 1β (MIP1β or CCL4), SDF-1, and tumor necrosis factor-alpha (TNF-α) in the secretome of MSCs derived from primary HNSCC [97]. Ji et al. reported a similar secretome profile of MSCs derived from gingival tissue upon supplementation of IL-10, a potent anti-inflammatory cytokine [98,99].

Wang et al. identified beta-2-microglobulin (B2M) in the secretome of BMMSCs. The knockdown of B2M-encoding gene on BMMSCs inhibited the invasion and migration of HNSCC cells (TE1 and Eca109 cells) exposed to the MSC secretome [100]. Similarly, the exposure of HNSCC cells (TSCCa and Cal-27 cells) to the MSC secretome upregulated the levels of cellular communication network factor 2 (CCN2) in BMMSCs. *CCN2* knockdown in MSCs inhibited cancer cell migration and invasion and downregulated the levels of MMP9, MMP2, and epithelial-mesenchymal plasticity markers. The expression of CCN2 in HNSCC tissues was higher than that in the adjacent non-tumorous tissues [101]. The inhibition of IL-6 in the BMMSC secretome decreased HNSCC cell (FaDu and HLaC78 cells) proliferation, which was partly dependent on the MAPK (ERK) signaling pathway [96].

AMSCs secrete high levels of VEGF and tumor growth factor-beta (TGF-β) [102]. TGF-β promoted the invasion of HNSCC cells by

Table 2
In vitro role of MSC on HNC.

Observed effect	Effector cells	Publication
Migration and invasion of BMMSC	JHU-011/012 derived IL-6	[93]
Migration and invasion of TE-1 and Eca109 HNSCC	BMMSC derived beta-2-microglobulin	[100]
Proliferation of FaDu and HlaC78 cells	BMMSC derived IL-6	[96]
BMMSC migration	Acinic-cell carcinoma derived TGF-β and SDF-1	[104]
Anti-apoptotic effect on SCC154 cells	SCGF-β secreted by gingival derived MSC exposed to paclitaxel or gemcitabine	[105]
Anti-apoptotic effect on JHU-012 cells	BMMSC cultured with cisplatin	[106]
Anti-apoptotic effect on Eca109 and TE-1	BMMSC cultured with carboplatin	[100]
Cell proliferation, EMP, and paclitaxel resistance (SCC25)	BMMSC	[107]
Proliferation, survival, and EMP of HN4 and Cal27 cells	BMMSC derived POSTN	[108]
Increased expression of MMP9, MMP2, and collagen (1A2, 6A3, 1A1, 3A1)	BMMSC derived CCL5	[95]
EMP on ameloblastoma cells	IL-6, IL-8, angiogenin from MSC isolated from ameloblastoma	[109]
Migration and invasion of SSC15 cells	miR-8485 on EV-Leukoplakia-MSC and EV-HNSCC	[110]
Proliferation (CNE2, 5–8F, 6–10B), migration (CNE1, CNE2, 5–8F) and EMP (CNE2)	FGF-19 on EV-BMMSC	[111]
Inhibition of proliferation, induction of cell death of Cal27 and HN6 cells	Gengival derived-MSC	[98]
Inhibition of proliferation and cell death of Eca109 cells	BMMSC	[112]
Proliferation, migration, and invasion (Eca109, TE-1))	MSC derived GREM-1	[113]
Invasion of TE-9 cells	AMSC	[114]
Proliferation of TPC1 cells	BMMSC	[115]
Increased expression of DUSP6, cell death	Umbilical cord MSC-HNSCC fusion	[116]
Reduction on TCD4$^+$ and TCD8$^+$ cells; reduction of INF-γ and TNF-α expression	BMMSC-IDO	[117]
Reduction on T cell proliferation	HNSCC-MSC-IDO and IL4I1	[118]
Reduction on T cell (CD3$^+$) cell proliferation	MSC	[119]
Reduction on CD73 expression, reduction on T cell proliferation	HNSCC derived MSC	[120]

BMMSC – Bone marrow mesenchymal stromal cell; AMSC – Adipose tissue derived-mesenchymal stromal cell; TGF-β – Transforming growth factor-beta; SDF-1 – Stromal cell-derived factor 1; SCGF-β – Stromal cell growth factor-beta; EMP – Epithelial-mesenchymal plasticity; POSTN – Periostin; MMP – Matrix metalloproteinases; EV – Extracellular vesicles; FGF-19 – Fibroblast growth factor 19; GREM-1 – Gremlin 1; DUSP6 – Dual Specificity Phosphatase 6; IDO – Indoleamine 2,3-dioxygenase; IL4I1 – Interleukin 4 Induced 1.

upregulating the expression of MMP14 [103]. Previous studies have reported that TGF-β and SDF-1 induce BMMSC migration toward acinic cell carcinoma cell lineage [104].

Coccè et al. reported that paclitaxel or gemcitabine promoted the secretion of stem growth factor-beta (SCGF-β) from MSCs derived from gingival tissue, which protects cancer cells (SCC154 cells) against these anti-neoplastic drugs *in vitro* [105]. *In vitro* approaches related to the MSC effects on HNC are summarized in Table 2.

Wang et al. demonstrated that co-culturing JHU-012 cells with BMMSCs promoted cisplatin resistance and upregulated the expression of BCL-2, an anti-apoptotic protein [106]. BMMSCs also confers paclitaxel resistance in SSC25 cells with upregulation of BCL-2, periostin (POSTN), multidrug resistance-associated protein 1, and ABCG transporter [107]. Conversely, treatment with the secretome of doxorubicin-treated MSCs increased tumor cell death [105]. Additionally, the BMMSC secretome protects HNSCC against the growth-inhibitory effects of carboplatin [100]. These findings indicate that the stromal cells regulate the treatment response in patients with cancer.

Moreover, POSTN secreted by BMMSCs induced Cal27 cell proliferation and inhibited the death of HN4 and Cal27 cells through PI3K signaling and upregulation of epithelial-mesenchymal plasticity markers [108]. CCL5 secreted from BMMSCs upregulated the expression of MMP9, MMP2, and collagen (col1A2, col1A1, col6A3, and col3A1). The upregulated collagen expression (desmoplasia) in the tumor front is correlated with decreased patient survival [95]. Compared with those derived from the BMMSCs and oral mucosa-derived MSCs, the levels of MMP9 were higher and the levels of collagen IV were lower in MSCs obtained from the tissues of patients with leukoplakia comprising microscopically visible dysplasia or hyperplasia [121].

In addition to the SCC stroma, MSCs have been detected elsewhere. Jiang et al. (2017) isolated MSC-like cells from follicular ameloblastoma, an aggressive odontogenic tumor with high recurrence rates [4,109,122–124]. The secretome of ameloblastoma-derived MSCs comprised increased levels of IL-6, IL-8, and angiogenin, which contribute to mesenchymal-epithelial plasticity in ameloblastoma cells [109]. The cells can secrete biomolecules directly or through vesicles.

Extracellular vesicles (EVs) facilitate cell-cell communication and transport biomolecules, such as proteins, micro RNAs (miRNAs), long non-coding RNAs (lncRNAs), and messenger RNAs (mRNAs) [125]. EVs of MSC (MSC-EV) derived from a premalignant lesion and oral squamous cell carcinoma increased SCC15 cell migration and invasion by upregulating the levels of miR-8485. Although the miR-8485 interaction sites were not identified, transfection with the miR-8485 mimic restored the aggressive phenotype in the SCC cell line. This indicated that miR-8485 is involved in the carcinogenesis of HNC. The expression of miR-8485 was upregulated in both leukoplakia and carcinoma lesions [110]. As a limited number of these premalignant lesions progress to carcinoma, it would be interesting to understand if this microRNA correlates with malignization, validating its expression as an HNSCC progression marker. BMMSC-EV promoted pharyngeal SCC cell proliferation (CNE2, 5-8F, and 6-10B cells), migration (CNE1, CNE2, and 5–8F cells), and epithelial-mesenchymal plasticity (CNE2 cells) [111]. Fibroblast growth factor-19 (FGF-19) encapsulated within MSC-EV promotes cell proliferation by activating the ERK signaling pathway through FGF receptor 4 (FGFR4). However, MSC-EVs differentially affect the pharyngeal cell lineages, which indicates the diverse response of different cancers to the microenvironment.

In contrast, Ji et al. demonstrated that the MSC secretome decreased oral cancer cell proliferation and increased cell death (Cal27 and HN6 cells) [98]. Additionally, the MSC secretome downregulated the levels of Cyclin D1, phosphorylated STAT3, and ERK and upregulated the phosphorylation of JNK. Similar to treatment with the MSC secretome, treatment with the JNK signaling inhibitor promoted cell proliferation. However, the components of the MSC secretome slightly increased cell proliferation or did not consistently increase the proliferation of the cell lines. This can be attributed to the complex availability of each component in the conditioned media and the metabolic profiles of different cell lines. Li et al. reported similar results using BMMSC secretome, which decreased cell proliferation and invasion (Eca109 cells) and increased cell death. The downregulated expression of Cyclin E, phosphorylated Rb, and MMP2 was consistent with the phenotypic characteristics [112]. These findings suggest that both MSCs and HNC secretome comprise modulators that promote stromal MSC enrichment and modulate the proliferation and migration/invasion of cancer cells.

During migration, cancer cells are in close contact with stromal components. This cell-cell interaction can induce epithelial-mesenchymal plasticity, cell proliferation, and tumor invasion [105, 126–128]. Hong et al. reported that the expression of GREM1 was upregulated in esophageal SCC [149]. *GREM1* knockdown in MSCs downregulated the expression of epithelial-mesenchymal plasticity

markers, TGF-β, and activated Smad-2 and Smad-3 and the proliferation and invasion of Eca109 and TE-1 cells and upregulated the levels of bone morphogenic protein-4 (BMP4), phosphorylated Smad-1, Smad-5, and Smad-8. The inhibition of TGF-β mimics the *GREM1* knockdown phenotype. The authors suggest that MSC-GREM1 inhibits BMP4 that can activate Smad-1, Smad-5, and Smad-8 and consequently inhibit the protective effect of this pathway. The paracrine stimulation of TGF-β released by MSCs and cell contact-dependent pathway can increase cancer cell aggressive behavior. Additionally, direct contact between AMSCs and SCC cells (TE-9 cells) increased cancer invasion into the gel-collagen matrix and upregulated the expression of MMP9 and laminin 5 [114]. The invasive SSC tissues exhibited upregulated expression of laminin 5 (gamma-2 chain), co-localized with stromal vimentin-positive cells, and promoted the expression of MMP2 and MMP14 on cancer cells in contact with these mesenchymal cells [126]. The enhanced activation of IGF receptor beta followed by phosphorylation of ERK and AKT signaling pathway could explain the observed phenotype. Unpublished preliminary data from our group indicated that the contact between AMSCs and SCC (HN12 cells) promoted MMP9 bidirectional expression and the invasion of cancer cells into the collagen/Matrigel matrix, which was partly dependent on integrin alpha 6. Moreover, MSCs increased thyroid cancer cell (TPC1 cells) proliferation through the epidermal growth factor receptor (EGFR), ERK, c-Jun, and p38 MAPK pathways [115]. However, Wang et al. reported that MSCs and HNSCC can fuse, which leads to the upregulation of dual-specificity phosphatase 6 (DUSP6). The upregulated expression of DUSP6 promotes cell death in these fused cells and consequently regulates cancer growth [116].

MSC-mediated immunomodulation is an active area of research. Previous studies have reported that MSC-mediated immunomodulation supports cancer growth [26,85,90,131]. HNSCC-derived MSCs decreased the proliferation of $CD4^+$ and $CD8^+$ T cells and down-regulated the expression of INFγ and TNF-α [117]. The inhibition of IDO1 activity suppressed the HNSCC-derived MSC-mediated T cell proliferation arrest, which indicated that IDO1 of MSCs is involved in immunosuppression in HNC. Similarly, Mazzoni et al. reported that HNSCC-MSCs decreased T cell proliferation, which could be restored by IDO1 inhibition [118]. The inhibition of IL-4 induced gene 1 (IL4I1), which is secreted by HNSCC-MSCs and contributes to T cell proliferation inhibition, partially restores T cell proliferation capacity [118]. In contrast, treatment with the HNSCC secretome differentially affected the expression of CD39 and CD73 in MSCs and HNSCC-derived MSCs. CD39 and CD73 hydrolyze extracellular dNTP and AMP, respectively [120]. Extracellular ATP (eATP) and metabolites elicit an inflammatory response, promote cell proliferation, and activate immune cells [128, 129]. MSCs derived from HNSCC exhibit downregulated expression of CD73 and metabolism of ATP [120]. Consequently, the expression of extracellular adenosine (ADO), an eATP metabolite known to inhibit T cell proliferation, is downregulated. The authors suggest that MSCs generate an inflammatory and tumor-friendly microenvironment. This conclusion must be carefully interpreted as different concentrations of ATP and ADO can exert differential effects on the immune cell subtypes. For example, ADO favors the M2-like macrophage phenotype, while eATP, M1-like polarization, and M1 macrophages promote tumor destruction. Meanwhile, eATP modulates lymphocyte ($CD4^+$, $CD8^+$, and Treg cells) infiltration into the tumor microenvironment and promotes cancer growth [129]. A detailed analysis of the effect of eATP on HNSCC and MSCs is needed.

The interaction and secretome among tumor cells and MSCs are associated with the differentiation of the mesenchymal stromal cells in cancer-associated fibroblasts [130–132] These cancer-associated fibroblasts can release factors and interact with HNC cells, which turns the tumor more aggressive [132]. However, these CAFs can also be derived from resident fibroblasts, epithelial cells, endothelial cells, cancer stem cells, adipocytes, and pericytes in a complex system [131]. Hence, a detailed discussion on CAF is out of the scope of this review.

Table 3
In vivo evidence of MSC on HNC.

Observed effect	Effector cells	Publication
Increased tumor size (FaDU)	HNSCC-MSC	[97]
(Cal27)	BMMSC	[108]
(Eca109, TE-1)	BMMSC	[100]
Vascularization, increased tumor size, increased MMP2/9 expression (Cal27, SCC4)	AMSC	[134]
Vascularization, increased tumor size (Eca109)	BMMSC	[112]
Increased tumor size after radiation (UMSCC1)	MSC	[135]
Increased tumor size, lymph node metastasis (Cal27)	BMMSC	[108]
Increased tumor size (CCN2)	BMMSC	[101,113]
Increased tumor size (SCC25) and paclitaxel resistance	BMMSC	[107]
Reduced tumor size, cellular fusion, increased DUSP6 expression (EC9706)	MSC (commercial)	[116]
Reduced tumor size (Cal27)	Gingival derived-MSC	[98]
Increased tumor size (TPC1)	EV-BMMSC	[111]
No influence on tumor growth (FaDu)	EV-MSC-Myc	[136]
Increased MSC migration toward tumor enriched with myofibroblast (OE21)	BMMSC, myofibroblast	[137]
DMBA induced tumor – proliferation reduction and increased cell death	MSC	[138]
DMBA induced tumor nodule stage – tumor progression; DMBA induced tumor hyperplasia stage – tumor regression	MSC	[139]
4NQO induced tumor – reduction on $CD3^+$ and $CD45^+$ cells	MSC	[119]

MMP – Matrix metalloproteinases; AMSC – Adipose tissue derived-mesenchymal stromal cell; BMMSC – Bone marrow mesenchymal stromal cell; DUSP6 – Dual Specificity Phosphatase 6; EV – Extracellular vesicles; MSC-Myc – immortalized mesenchymal stromal cell; DMBA - 7,12-Dimethylbenz[*a*]anthracene; 4NQO – 4-Nitroquinoline-1-oxide.

6. *In vivo* studies in MSCs and HNC interactions

Various animal models have been used to study cancer microenvironments (Table 3). Studies on the xenograft tumor models have partially elucidated the role of the MSCs in a complex environment. In the *in vitro* models, the cells were exposed to a relatively homogeneous environment characterized by the same oxygen concentration and nutrients and limited interactions with different cells. Although *in vitro* models provided valuable information, they cannot completely mimic the cancer microenvironment. Mouse xenograft models can mimic the *in vivo* tumor microenvironment. This environment involves communication with stromal cells, such as cells from the innate immune system, even in immunodeficient mice [133]. A similar outcome was reported when HNC cells were co-injected with MSCs from different sources, including those derived from HNSCC although different protocols were used [97,100,108,134]. For example, Rowan et al. reported that compared with those in the HNC cell lines, the tumor volume and vascularization were higher and the expression of MMP2 and MMP9 was upregulated in HNSCC cells (Cal27 and SCC4 cells) co-cultured with AMSCs [137]. Li et al. reported that the growth and angiogenesis were upregulated in xenograft tumors derived from HNSCC cells (Eca-109 cells) co-cultured with BMMSCs although the *in vitro* paracrine communication revealed decreased tumor cell proliferation [112]. Additionally, MSC migration toward cancer increased in the xenograft HNSCC model after radiation therapy, which indicated the protective effect of the MSCs during radiotherapy [135].

Moreover, lymph node and distant metastases increased in tumors cultured with MSCs [108,140,141]. Several studies have proposed the molecular pathways involved in these outcomes. The mRNA levels of *POSTN* were upregulated in BMMSC-HNSCC (Cal27 cells) tumors with high proliferation rates, volume, and lymph node metastasis [108]. The downregulation of the expression of GREM1 and CCN2 in MSCs decreased tumor volume, which indicated that these proteins were

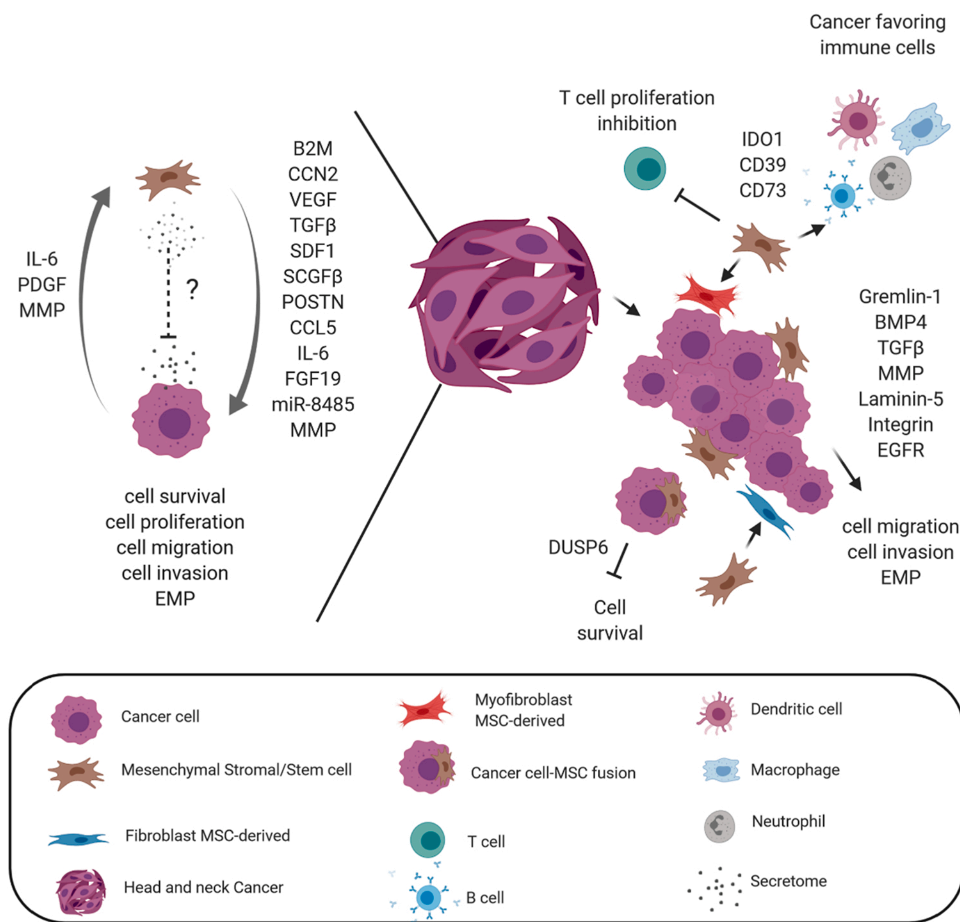

Fig. 2. Effect of mesenchymal stromal cells (MSCs) on head and neck cancer (HNC). MSCs can affect both tumor progression and arrest with a tendency to promote the former. Various molecules can regulate the progression of HNC by modulating MSC behavior. IL-6, platelet-derived growth factor (PDGF), and matrix metalloproteinase (MMP) secreted by HNC cells influence MSC behavior. Similarly, B2M, CCN2, vascular endothelial growth factor, TNFβ, SDF1, SCGFβ, POSTN, CCL5, IL-6, FGF19, miR-8485, and MMP modulate HNC progression and affect cell survival, proliferation, migration, invasion, and epithelial-mesenchymal plasticity (EMP). Additionally, MSCs regulate immune response (by regulating the expression of IDO, CD39, CD73), differentiate into specific cell types (fibroblasts and myofibroblasts), and consequently modulate HNC behavior. GREM1, BMP4, TGFβ, MMP, laminin-5, integrin, and EGFR promote cancer cell migration and invasion and EMP. The fusion of MSCs and cancer cells leads to the production of DUSP6 and decreased cancer cell survival.

involved in MSC-dependent HNSCC growth [109,149]. Conversely, overexpression of DUSP6 in MSC-SCC fusion decreased tumorigeneses, angiogenesis, proliferation, and metastasis [116]. Additionally, gingival-derived MSCs inhibited tumor formation in oral SCC [98]. However, the clinical contribution of these findings needs further clarification.

Shi et al. (2016) reported the contribution of EV to cancer progression using an *in vivo* model [111]. The authors reported that compared with those in animals injected with phosphate-buffered saline, the tumor growth was rapid and the tumor volume was higher in animals injected daily with BMMSC-EV. In contrast, Tan et al. reported no difference of intraperitoneally injected animals with EV of MYC-immortalized MSCs derived from HNSCC xenograft (FaDu cells) [136]. Kumar et al. isolated myofibroblasts from HNSCC and co-injected it with an esophageal SCC cell line (OE21) to examine the role of the stroma in MSC homing. Fluorescence probe-labeled BMMSCs were intravascularly injected to allow posterior analysis [137]. The authors reported that the MSCs in the tumor injected with myofibroblasts exhibited increased migration toward the xenograft tumor, which was dependent on chemerin (RARRES2) and its receptor chemR23.

Furthermore, animal studies have been performed to examine the role of MSC in HNSCC carcinogenesis. Bruna et al. used the Syrian golden hamsters treated with 0.5% 7,12-dimethylbenz[*a*]anthracene (DMBA) to examine the role of MSCs in oral carcinogenesis [138]. The hamster-derived MSCs were injected into the mucosa around the local nodule after DMBA treatment. MSC injection decreased the tumor size, reduced the number of Ki67-positive cells, and promoted cell death. The same research group also reported the effect of systemic administration of MSCs on oral carcinogenesis [139]. The experimental groups were defined as animals with hyperplasia (4–5 weeks) or hyperplasia and dysplasia during two different time points (6–8 and 9–13 weeks). MSCs dose-dependently promoted the progression of initial nodules to SCC after 13 weeks of treatment in all animals. Surprisingly, the tumor volume in animals injected with an intermediate MSC concentration was lower than that in control animals. Animals injected with low and intermediate MSC concentrations exhibited hyperplasia and dysplasia in approximately 25% of the samples. The terminal point analysis revealed that almost all hyperplasia plus dysplasia groups injected with MSCs did not progress to SCC. After 13 weeks, the control animals were diagnosed with SCC, which indicated the tumor-protective role of MSCs. The clinical manifestation of leukoplakia was observed only in tissues with hyperplasia + dysplasia, which does not completely mimic the clinical and microscopic characteristics of human patients [142]. The authors suggest that systemic administration of MSCs can influence tumor progression in later phases of carcinogenesis because chronic inflammation persists in the tissue, which augments MSCs homing. High doses of MSCs administration can elicit an immune response in healthy animals and promote tumor growth.

Female rats with oral lesions induced by administering 0.05 g/L 4-nitroquinoline-1-oxide (4NQO) for 22 weeks exhibited increased numbers of MSCs in premalignant SCC tissue with dysplasia [119]. Analysis of the MSC secretome profile derived from these tissues revealed upregulated secretion of CCL21 and SDF1. Interestingly, the cancer samples exhibited decreased numbers of lymphocytes ($CD3^+$) and leukocytes ($CD45^+$). The MSC content was weakly and inversely correlated with $CD3^+$ (R^2 = 0.1371; p-value = 0.2361) or $C45^+$ cells (R^2 = 0.0308; p-value = 0.5849). This indicated that MSCs and other stromal cells could contribute to the decreased $CD3^+$ number. The proliferation of $CD3^+$ cells was significantly inhibited upon co-culturing with cancer-derived MSCs. Ouchi et al. reported the potential role of

MSCs and their derivatives in HNC. They demonstrated the enrichment of $CD90^{+}/CD105^{+}/CD73^{+}$ cells in recurrent spindle cell carcinoma, a high-grade SCC subtype, of the tongue [143].

7. Role of MSCs in HNC progression: conclusions and perspectives

The findings of previous studies support the dual role of MSCs in HNC progression with a tendency to promote cancer aggressiveness. MSCs have a differential effect on different phases of carcinogenesis. However, this cannot be a conclusive finding as different studies use different models. In summary, MSCs isolated from different tissue sources exert their effects through the secretion of IL-6, VEGF, B2M, CCN2, TGF-β, SDF-1, POSTN, FGF19, miR-8485, IDO1, IL4I1, and EGF. These ligands act on PDGFR, VEGFR, FGFR, and EGFR on the cancer cell surface to exert various effects, inducing upregulation of *MMP9*, *MMP2*, *MMP14*, and epithelial-mesenchymal plasticity markers. The induction of MMP expression promotes the MSC-mediated and cancer cell-mediated ECM modifications and facilitates the migration of cancer cells into the stroma [11,144,145]. MMP may aid the extravasation of cancer cells from the blood and lymph vessels, which enables the migration of cancer cells to regional or distant sites [11,146]. Epithelial-mesenchymal plasticity is a cellular process in which epithelial cells lose the epithelial phenotype and acquire the mesenchymal phenotypes and behavior [147]. During this process, the expression of mesenchymal markers, such as vimentin and N-cadherin is upregulated, whereas that of epithelial markers (such as E-cadherin) is down-regulated in epithelial cells. Acquiring mesenchymal characteristics promotes the migration of cancer cells. The downregulation of adhesive epithelial proteins facilitates the detachment from other epithelial cells, which promotes cell migration. HNC exhibited partial epithelial-mesenchymal characteristics dependent on the stromal content and correlated with lymph node metastasis [49]. MSCs can induce the expression of laminin 5, which facilitates cancer cell migration. Additionally, MSCs can mitigate HNC progression through some unknown signaling pathways. These unknown signaling (non-exclusively dependent on TGFRIII, ERK, and AKT) pathways downregulate the expression of MMP and collagen IV, inhibit proliferation, and upregulate DUSP6 (in MSC-HNC fusion).

Previous studies have begun to elucidate the characteristics of the HNC microenvironment and the role of MSCs in tumor progression (Fig. 2). However, translational research could be conducted in the future to address various knowledge gaps, such as the role of MSCs in the molecular pathways involved in MSC-mediated metastasis induction, tumor radiotherapy resistance, and immunotherapy response in human cancers.

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CRediT authorship contribution statement

Marcelo Coutinho de Miranda did the conceptualization and wrote the original draft; Mariane Izabella Abreu de Melo, Pricila da Silva Cunha, Jovino Gentilini Júnior, and Michele Angela Rodrigues participated in data interpretation and discussion; Jerusa Araújo Quintão Arantes Faria and Dawidson Assis Gomes reviewed and edited the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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