BBA - Reviews on Cancer 1879 (2024) 189189

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review Article

The tumor microenvironment's gambit: Exosomal pawns on the board of head and neck cancer

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ARTICLE INFO

Keywords:
Head and neck cancers
Tumor microenvironment
Exosome
Intercellular communication
Cancer progression

ABSTRACT

The tumor microenvironment (TME) harbors a hidden universe of interactions that profoundly shape the behavior of head and neck cancers (HNCs). HNCs are not merely localized afflictions; they constitute a pressing global health crisis that impacts millions, frequently resulting in severe prognoses due to late-stage diagnosis and intrinsic resistance to conventional therapies. In this intricate interplay, cancer cells function as strategic players, adeptly manipulating their microenvironment to foster proliferation, evade immune detection, and withstand therapeutic interventions. Central to this dynamic play are exosomes, the enigmatic pawns of cellular communication, carrying vital messages across the board. This review elucidates the multifaceted roles of exosomes within the TME, highlighting their capacity to transmit critical signals that not only promote tumor progression but also modulate immune responses, ultimately playing a crucial role in the evolving narrative of HNC. Our insights aim to catalyze further research and exploration into exosome-targeted therapies, potentially transforming the landscape of HNC treatment and improving clinical outcomes in this formidable battle against cancer.

1. Introduction

The head and neck cancers (HNCs), encompassing malignancies of oral cavity, oropharynx, pharynx, hypopharynx, larynx, and thyroid, forces a massive burden on the life quality of their hosts, due to low sensitivity and severe resistance to treatments [1,2]. These cancers present considerable challenges primarily due to their often late-stage diagnosis, aggressive behavior, and the complexity of treatment modalities, which typically include surgery, radiation, and chemotherapy [3,4]. Despite significant advancements in therapeutic strategies—including targeted treatments and immunotherapy—a substantial number of patients still experience recurrence and treatment resistance [1]. This underscores the urgent need to enhance our understanding of the cellular and molecular interactions that drive tumor progression and influence patient outcomes in HNCs [5,6].

At the core of HNCs lies the tumor microenvironment (TME), a dynamic ecosystem that comprises malignant cells alongside various stromal and immune cells. These cellular components significantly influence tumor behavior and contribute to the cancer progression. Among the key players within the TME are cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), mesenchymal stem cells (MSCs), neutrophils, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, platelets, and mast cells, each playing critical roles in shaping the trajectory of head and neck cancers [7,8]. For these cells to exchange information, various signaling networks exists within the TME. These range from secreted factors including chemokines, cytokines, and extracellular vesicles such as exosomes, to juxtacrine interactions including desmosomes and cell-cell (CC) junctions [1]. In between, the complexity of dynamic CC interactions that generate the TME, are very well highlighted with exosomes and other extracellular vesicles.

In this review, we aim to provide a comprehensive examination of

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https://doi.org/10.1016/j.bbcan.2024.189189
Received 7 July 2024; Received in revised form 19 September 2024; Accepted 23 September 2024
Available online 27 September 2024

the critical role that exosomes play as essential mediators of intercellular signaling within the TME of HNCs. By shedding light on how exosomes facilitate communication among CAFs, TAMs, and MSCs, as predominant cell types within the TME, we hope to elucidate their roles in modulating the TME and enhancing cancer resilience. Understanding these complex cellular interactions is crucial for identifying novel biomarkers and therapeutic targets, ultimately paving the way for innovative treatment strategies that aim to improve patient outcomes in HNCs. We anticipate that this review will inspire further investigation into the role of exosomes in the TME and contribute to significant advancements in the management of HNCs.

2. Biogenesis and function of Exosome

The biogenesis of exosomes begins once the plasma membrane initiates inward budding to generate early endosomes. The membrane of endosomes further partly enfolds and buds into surrounding lumina with cytoplasmic elements to form intraluminal vesicles (ILVs) [9]. Multivesicular bodies (MVBs) are late endosomal structures encompassing numerous ILVs. MVBs are destined for either of the followings; i) they are delivered to lysosomes for degrading all carried components, ii) transported to the trans-Golgi network (TGN) for endosome recycling, or iii) fused with the plasma membrane and release exosomes into the extracellular space [10,11] (Fig. 1). Formation of an endosomal-sorting complex that is required for transport (ESCRT) is required for biogenesis and secretion of exosomes [12]. Four complexes (ESCRT-0, —I, -II, and -III) and associated proteins (VPS4, Tsg101 and ALIX) encompass ESCRT. Each complex and protein has its own responsibility; ESCRT-0 is responsible for sorting ubiquitinated cargo proteins into the lipid domain. Meanwhile, ESCRT-I and -II are responsible for generating the stable membrane neck through inducing the deformation of membrane. Afterwards, ESCRT-III recruits the Vps4 complex to drive the scission and the dissociation of vesicle neck and recycling of the ESCRT-III complex [11,13].

Exosomes mostly encompass the same molecules that are found in their originated cells. This enrichment of precise lipids and proteins in exosomes confirms a targeted cellular sorting mechanism. Exosomes contain cell-type specific E proteins (e.g., cytoskeletal proteins, adhesion molecules, enzymes, etc) [14], and lipids (e.g., sphingomyelin, phosphatidylserine, cholesterol, and saturated fatty acids) [15]. Exosomes also contain nucleic acids, such as genomic and mitochondrial DNA, functional mRNAs, non-coding RNA (including microRNA that are resistant to RNase digestion) [16], and exosomal RNA species [17–20]. Exosomal RNA species are different from cellular RNA, since they do not contain full-length ribosomal RNA (rRNA) that generates more than 95 % of the human transcriptome [21]. Altogether, the functional genomic component of exosome is context-specific and is being elucidated.

Moreover, exosomes serve a pivotal role in inter- and intra-cellular communications both locally and distantly [22]. The lipid bilayer-membrane of exosomes protect vulnerable biological molecules, such as proteins or miRNAs from degradation by proteinase or by RNases, respectively [23,24]. Once exosomes are liberated form their originated cells and attached to their recipient cells, their components are capable of modulating cell signaling events and biological processes [25]. For instance, tumor-derived microvesicles (oncosomes) are able to transmit the epidermal growth factor receptor (EGFR) vIII from aggressive brain tumor to another cancer cell lacking this oncogenic receptor [26]. Also, oncosomes encompassing miRNAs are found to be exchanged between cervical cancer cells to trigger cancer progression [27]. Exosome-mediated CC interactions is not only in cancer cells, rather it is also found within the TME locally and distantly [28]. Through transporting transforming growth factor beta (TGF-β) from cancers to normal fibroblasts, tumor-derived exosomes are capable of driving fibroblast into myofibroblast differentiation [29]. On the contrary, CAF-derived exosomes (CAF-E) are capable of modulating cancer cells metabolism through suppressing the mitochondrial oxidative phosphorylation

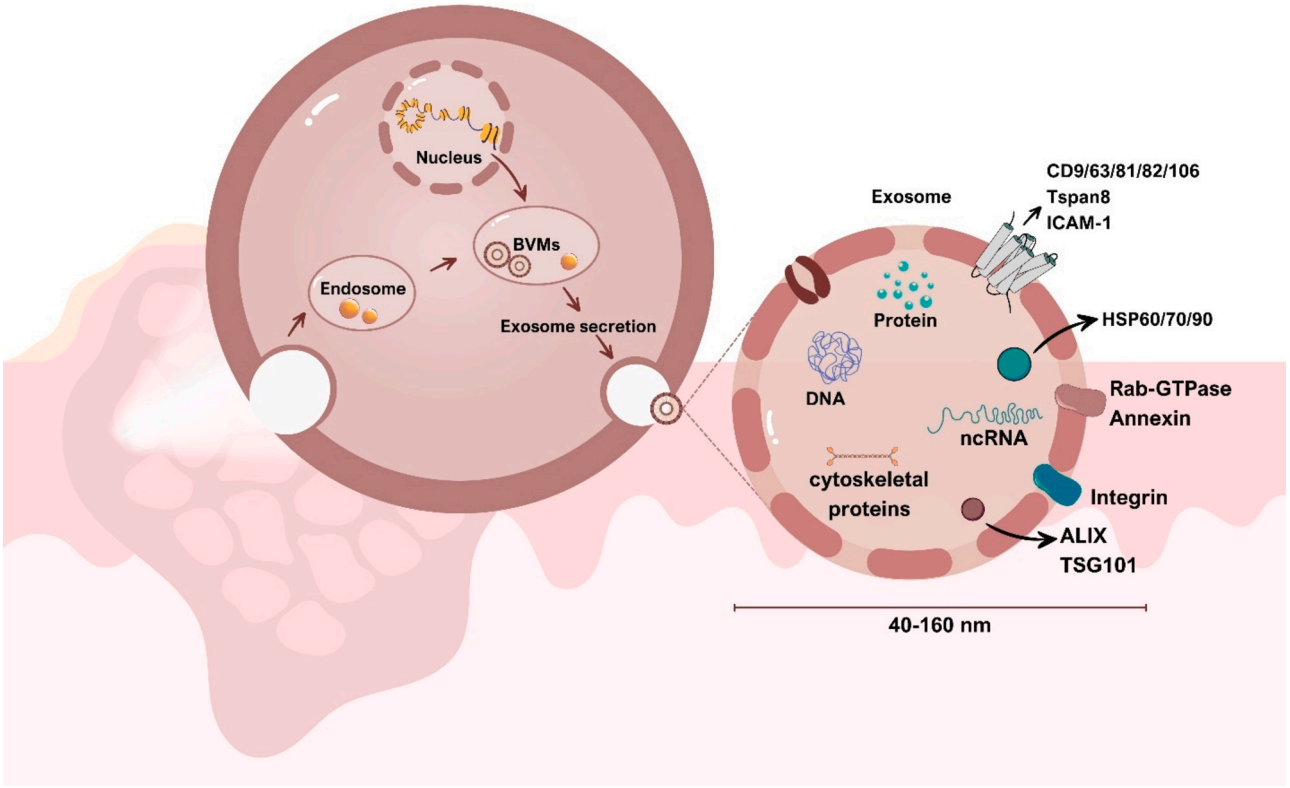

Fig. 1. Biogenesis of exosome and its components. Exosomes originated from MVBs, which comprise various types of proteins type and noncoding RNAs that participate in tumor development.

process [26,30]. Considering the contribution of exosomes in transferring biological molecules between cells at distant sites, malignant cancer cells, including breast or pancreatic, secrete exosomes encompassing bioactive molecules [31]. Transfer of these molecules that are capable of triggering telomerase activity or inhibiting macrophage migration [32,33], to the distant tumor-associated microenvironment will promote the formation of premetastatic niches [26].

3. Function of TME-derived exosome in HNC development

The TME is generated by the tumor comprises of tumor-induced interactions [34]. As alluded in ***Fig.*** 2, TME is comprised of extracellular matrix, different stromal cell types, and immunity cells. Each participating cell including fibroblasts, T and B lymphocytes, natural killer cells, tumor-associated macrophages (TAM), etc., plays a crucial role in tumor progression. In that regard, through this section we took a glance on the role of exosomes that are derived from these cells in HNC development (Table 1).

3.1. Cancer-associated fibroblasts

Between various stromal cell types in the TME, CAFs are the main elements of multiple cancer types such as HNC, prostate, and breast cancers [35–37]. CAFs are heterogeneous cell types, encompassing cells with cancer-restraining and cancer-promoting properties. In fact, CAFs can be categorized into multiple subtypes in accordance to their differential expression of specific biomolecular markers, and distinct subtypes exert distinct functions [35]. Fibroblasts are often inactive in normal tissues, and activated during tissue damage [38]. Activated fibroblasts are placed adjacent of cancer cells and are pivotal subtype of the CAF population [39]. CAFs regulate cancer development through affecting cancer cell invasion and metastasis, inducing immune evasion, promoting angiogenesis, and resistance to chemotherapy [40–42]. Beside ECM remodeling, CAFs can promote tumorigenesis through paracrine factors, including exosomes and cytokines.

As one of the main causes of global cancer death, oral squamous cell carcinoma (OSCC) has a high risk of mortality, so regardless of the therapeutic approach [43], site, or stage of the disease, >50 % of the individuals experience a relapse [44]. The CC interaction within the TME are pivotal contributors in OSCC progression [45]. CAFs are identified to serve a critical role in the OSCC progression, such as epithelial-to-mesenchymal transition (EMT) and metastasis [46]. However, the interaction between CAFs and OSCC cells is in need of more attention. In this regard, Li et al. [47] investigated the role of CAFs-derived exosomal miRNAs (CAF-*E*-miR) in OSCC. They observed a significant downregulation in the level of miR-34a-5p in CAF-derived exosomes. Fibroblasts are capable of transferring E-miR-34a-5p to OSCC cells. In xenograft experiments, upregulation of miR-34a-5p in CAFs could suppress the tumorigenesis of OSCC cells. miR-34a-5p attaches to its direct downstream target AXL receptor tyrosine kinase, to inhibit OSCC cell proliferation and metastasis. Mechanically, the miR-34a-5p/AXL cascade promotes OSCC progression through the protein kinase b (PKB or AKT)/GSK-3β/β-catenin axis, which promotes EMT to trigger cancer cell metastasis. Besides, the miR-34a-5p/AXL cascade enhances the nuclear translocation of β-catenin and subsequently upregulates SNAIL, which in turn activates both matrix metalloproteinase 2 and 9 (MMP-2/9). Overall, miR-34a-5p inhibits OSCC metastasis and proliferation and in return, CAF-Es contain downregulated miR-34a-5p OSCC metastasis and proliferation by targeting AXL. Similarly, miR-3188 inhibits HNC development by promoting apoptosis through negatively regulating Bcl-2, in return, CAF-E contain downregulated miR-3188 leads to induction of HNC development by inhibiting apoptosis [48]. In another study, Wang and colleagues [49] found that miR-34c-5p expression is significantly downregulated in CAF—Es. It also has been demonstrated that miR-34c-5p can control the stem-like properties of laryngeal cancer cells (LSCC), including proliferation, invasion, chemoresistance, sphere and plate colony formation, tumorigenicity in nude mice, along with the expression of cancer stem cell genes [49]. As a result, the loss of miR-34c-5p in CAF-E participates to maintaining stem-like phenotypes of LSCC. It should be mentioned

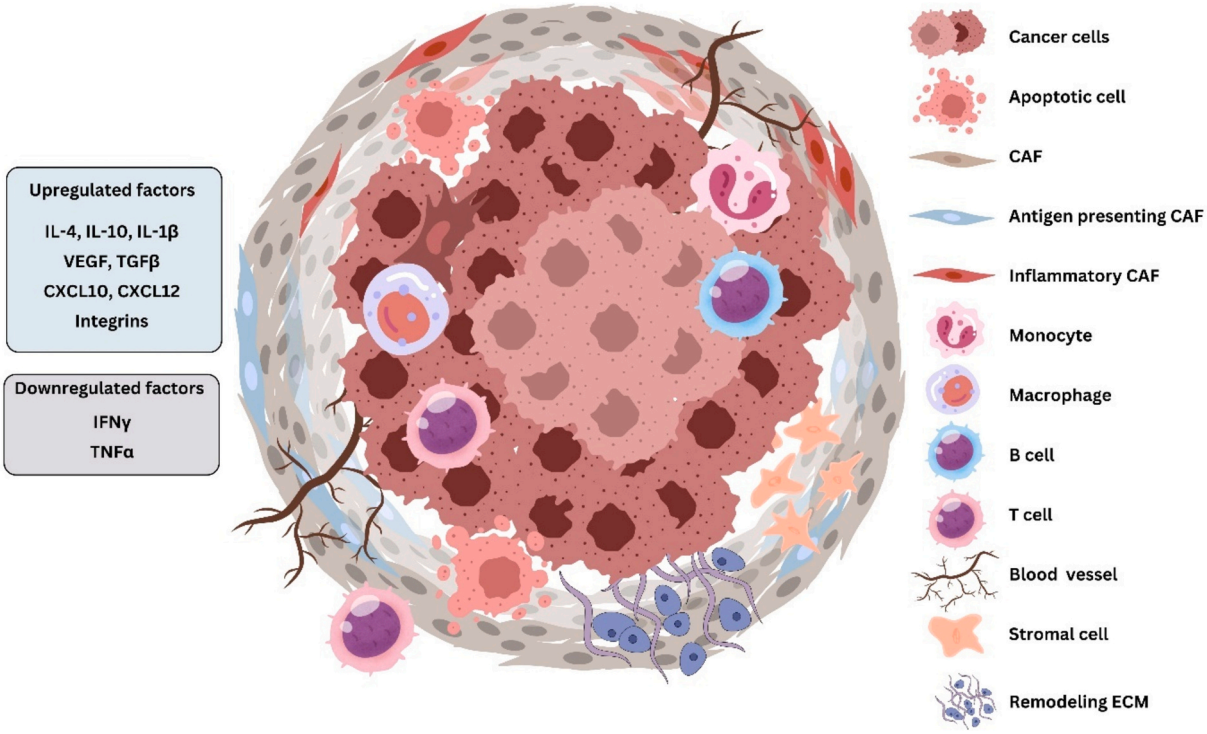

Fig. 2. The landscape of tumor microenvironment in cancer progression. TME is generated of extracellular matrix, immunity cells (e.g., natural killer cells, T and B lymphocytesand, tumor-associated macrophages) stromal cells (e.g., MSCs, fibroblasts, occasional adipocytes, pericytes, blood, and lymphatic network) that serve as signaling molecules between tumor cells and the surroundings cells of TME.

Table 1
TME-derived exosomes roles in HNCs.

Originating cells	Exosome Cargo	Receiving cells	Target	Function	Note	Ref
CAFs	Lnc-FLJ22447	OSCC	–	Promoting OSCC development	CAFs-derived exosomal lnc-FLJ22447 supported OSCC growth by CAFs activation through positively regulating IL-33 expression levels.	[153]
CAFs	miR-146b-5p	OSCC	HIPK3	Promoting OSCC development	CAFs-derived exosomal miR-146b-5p inducing OSCC development by negatively regulating HIPK3.	[37]
CAFs	miR-382-5p	OSCC	–	Promoting OSCC migration and invasion	CAFs-derived exosomal miR-382-5p aggregates OSCC development by inducing migration and invasion.	[51]
CAFs	miR-34a-5p (Down)	OSCC	AXL	Promoting the OSCC metastasis and proliferation	miR-34a-5p inhibits OSCC metastasis and proliferation and in return, CAFs-secreted exosomes contain downregulated miR-34a-5p OSCC metastasis and proliferation by targeting AXL.	[154]
CAFs	piR-35,462	OSCC	–	Promoting OSCC progression	CAFs-derived exosomal piR-35,462 enhances OSCC development by inducing the FTO expression levels by inhibiting m6A. In return, upregulated FTO leads to the induction of EMT through positively regulating Twist1.	[155]
CAFs	miR-3529-3	OSSC	–	Promoting OSCC development	CAFs-derived exosomal miR-3529-3 contributes to OSCC development maybe by inducing invasion, migration, and proliferation and by inhibiting apoptosis.	[36]
CAFs	miR-196a	HNC	CDKN1B and ING5	Promoting cisplatin resistance and proliferation	CAFs-derived exosomal miR-196a enhances resistance to cisplatin therapy and proloferation in HNC cells by targeting CDKN1B and ING5.	[55]
CAFs	miR-3188 (Down)	HNC	Bcl-2	Inhibiting HNC development	miR-3188 inhibits HNC development by promoting apoptosis through targeting Bcl-2, in return, CAFs-secreted exosomes contain downregulated miR-3188 leads to induction of HNC development by inhibiting apoptosis.	[48]
CAFs	miR-34c-5p (Down)	LSCC	–	The maintenance of LSCC stem-like phenotypes	miR-3188 inhibits laryngeal cancer cell development. In return, CAFs-secreted exosomes contain downregulated miR-34c-5p contributes to the maintenance of LSCC stem-like phenotypes.	[156]
Fibroblasts	TβRII	Oral cavity SCC	–	Promoting TGFβ signaling pathway	Exosomal TβRII derived from fibroblast can promote TGFβ signaling pathway in oral cavity SCC and maybe contribute to cancer development.	[157]
TAMs (M2)	miR-21–5p	HNSCC	LATS1 and VHL	Promoting HNC angiogenesis	TAMs-derived eoxosmal miR-21–5p contribute to tumor angiogenesis by negatively regulating expression level of LATS1 and VHL genes.	[158]
TAMs	miR-31–5p	OSCC	LATS2	Promoting OSCC development	TAMs-derived exosomal miR-31–5p enhances OSCC progression by targeting LATS2.	[159]
TAMs (RBPJ overexpressed-macrophages)	LBX1-AS1	OSCC	miR-182-5p	Inhibiting OSCC development	RBPJ overexpressed-macrophages-derived exosomal LBX1-AS1 inhibits OSCC progression by positively regulating FOXO3 through sponging miR-182-5p.	[160]
TAMs (M1)	HOTTIP	HNSCC	miR-19a-3p and -19b-3p	Inhibiting HNSCC development	M1 macrophages derived-exosomal HOTTIP inhibits HNSCC progression by activating TLR5/NF-κB pathway through sponging miR-19a-3p and -19b-3p.	[161]
TAMs (M2)	miR-23a-3p	OSCC	PTEN	Promoting OSCC development	TAM (M2)-derived exosomal miR-23a-3p enhances OSCC progression through inducing proliferation, migration, invasion and inhibiting apoptosis by targeting PTEN.	[70]
TAMs	ANXA3	LSCC	ATF2	Promoting LSCC metastasis and inhibits ferroptosis	TAMs-derived exosomal ANXA3 inhibits ferroptosis and promotes metastasis of LSCC cells by inhibiting ATF2.	[73]
TAMs (THP1 macrophages)	–	LSCC (BICR18 cell)	–	Promoting LSCC migration, PD-L1 expression and cisplatin resistance	THP1 macrophages-derived exosomes enhances the PD-L1 expression, migration and resistance to cispaltin in LSCC cells.	[162]
OLK-MSCs and Ca-MSCs	MMP1	HUVECs	–	Promoting angiogenesis	Exosomes derived from OLK-MSCs and Ca-MSCs contain MMP1, which induces angiogenesis.	[163]
LK-MSCs and Ca-MSCs	miR-8485	SCC15 cells	–	Promoting oral malignancy	Exosomes secreted from LK-MSC- and Ca-MSC cells contain miR-8485 inducing invasion, migration, and proliferation of SCC15 cells.	[114]
Cancer stem cell-like cells (CSCs)	CDKN2B-AS1	Thyroid cancer	miR-122-5p	Promoting PC metastasis and growth	CSCs-derived exosomal CDKN2B-AS1 aggregates thyroid cancer metastasis and growth by positively regulating P4HA1 through sponging miR-122-5p.	[164]
G-MSCs	–	Oral cancer	–	Inhibiting oral cancer cell proliferation	G-MSCs-derived exosomes inhibits oral cancer cell development by positively regulating the expression of pro-apoptotic genes.	[165]
BMSCs	miR-155	OSCC	PTEN12	Promoting OSCC development	BMSCs-derived exosomes contain upregulated miR-155 enhances OSCC development by promoting proliferation, migration and inhibiting apoptosis through targeting PTEN12.	[128]
BMSCs	miR-101-3p	Oral cancer	COL10A1	Inhibiting oral cancer development	BMSCs-secreted miR-101-3p inhibits oral cancer development by suppressing invasion, migration and proliferation through targeting COL10A1.	[127]
Adipose -MSCs	–	HNSCC	–	Anti-cancer effect	Adipose-derived mesenchymal stem cells-secreted exosomes decreases HNSCC cells viability by decreasing CRKI expression levels.	[129]
Menstrual- MSCs	–	OSCC	–	Inhibiting tumor cell angiogenesis and growth	Menstrual MSCs-derived exosomes inhibit OSCC development by inhibiting angiogenesis and inducing apoptosis.	[130]
Umbilical cord MSC	miR-181a	NPC	KDM5C	Retarding NPC progression	Human umbilical cord MSC-derived exosomal miR-181a alleviates NPC progression by targeting KDM5C.	[141]

that downregulation of CAF-*E*-miR is observed in distinct types of tumors function as tumor suppressors. They are also found to inhibit the metastasis of tumor cells by targeting their downstream genes. Therefore, upregulation of such miRNAs or downregulation of their target genes appears as an advantageous solution for preventing metastasis [50].

A fraction of miRNAs is overexpressed in CAFs, packed into the exosomes and released into the intercellular stroma. Upregulated CAF-*E*-miR promote the malignancy progression by triggering various signaling cascades in HNC. For instance, the expression of miR-146b-5p is elevated in CAF-E and CAFs compared with normal fibroblasts. On the other side, in OSCC cells downregulation of miR-146b-5p inhibits the proliferation, migration, and invasion capability in vitro and the growth in vivo. Mechanistically, overexpression of miR-146b-5p leads to the inhibition of HIKP3 through directly targeting the 3′-UTR of HIPK3. Altogether, CAF-E encompassing higher levels of miR-146b-5p which targets HIPK3 and subsequently induces the malignant phenotype of OSCC. Moreover, Sun et al. [51] confirmed that in tumor tissues, the density of CAF was relevant to OSCC lymph node metastasis. The group also established an overexpression in the miR-382-5p level within CAFs in comparison to fibroblasts of adjacent normal tissue, which results in OSCC cell migration and invasion. Finally, their results suggested that CAF-*E*-miR-382-5p aggregates OSCC development by inducing migration and invasion [51]. Likewise, miR-3529-3 is overexpressed in CAF-E and contributes to OSCC development by inducing invasion, migration, and proliferation and by inhibiting apoptosis [36]. Therefore, upregulation of CAF-E-miR is correlated with a positive feedback loop for tumor progression. Counteracting the upregulated miRNAs, such as those aforementioned, can be the first zone of action to encounter this loop of progression.

The effect of CAFs in the regulation of chemoresistance is attracting more attention in various cancer types [52]. CAFs are capable of secreting growth factors or cytokines to elevate tumorigenesis and chemoresistance in breast cancer [53]. Also, CAFs-derived interleukin 6 (IL6) significantly contributes to chemoresistance through increasing C-X-C motif chemokine receptor 7 (CXCR7) expression [54]. Recently, Qin et al. [55] confirmed a resistance in CAFs toward cisplatin. They also established the essential role of CAF-E in regulation of HNC cell survival and proliferation through delivering functional miR-196a to tumor cells. They demonstrated that *E*-miR-196a can binds to CDKN1B and ING5, to promote cisplatin resistance in HNC cells.

In return, depletion of CAF-E-miR-196a functionally restored HNC cisplatin sensitivity. Importantly, they found that generation of CAF-E-miR-196a may be mediated through heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) (Fig. 3) [55]. In addition to chemoresistance, high levels of plasma E-miR-196a was found to be associated with poor overall survival and [55]. Altoghter, indicates miR-196a as a promising predictor and therapeutic target for cisplatin resistance in HNC. As well, this established the pivotal role of TME in anti-apoptotic phenotype and chemoresistance of tumor cells through delivering exosomes.

3.2. *Tumor associated macrophages*

Derived from precursor cells in the bone marrow (BM), monocytes are the ancestor of macrophages that are described as white blood cells located in tissues. However, not all macrophages are originated form circulating monocytes during local self-renewal, instead, those present in brain, heart, liver, lung, kidney, and skin are originated from embryonic precursors in the yolk sac and fetal liver (Fig. 4) [56]. In fact, diverse populations of tissue-specific macrophages exhibit varied transcriptional profiles and epigenetic markers, which are defined by tissue-specific factors [57].

Macrophages are categorized based on their function, activation status, and secreted cytokines into one of the two reversible subtypes: i) classically activated, pro-inflammatory, M1 macrophages, and ii) alternatively activated, anti-inflammatory, M2 macrophages [58,59]. M1 phenotype is exhibited by TAMs in early-stage cancer, and have high levels of CD40, −80, and − 86, which affect antitumor immunity. M1

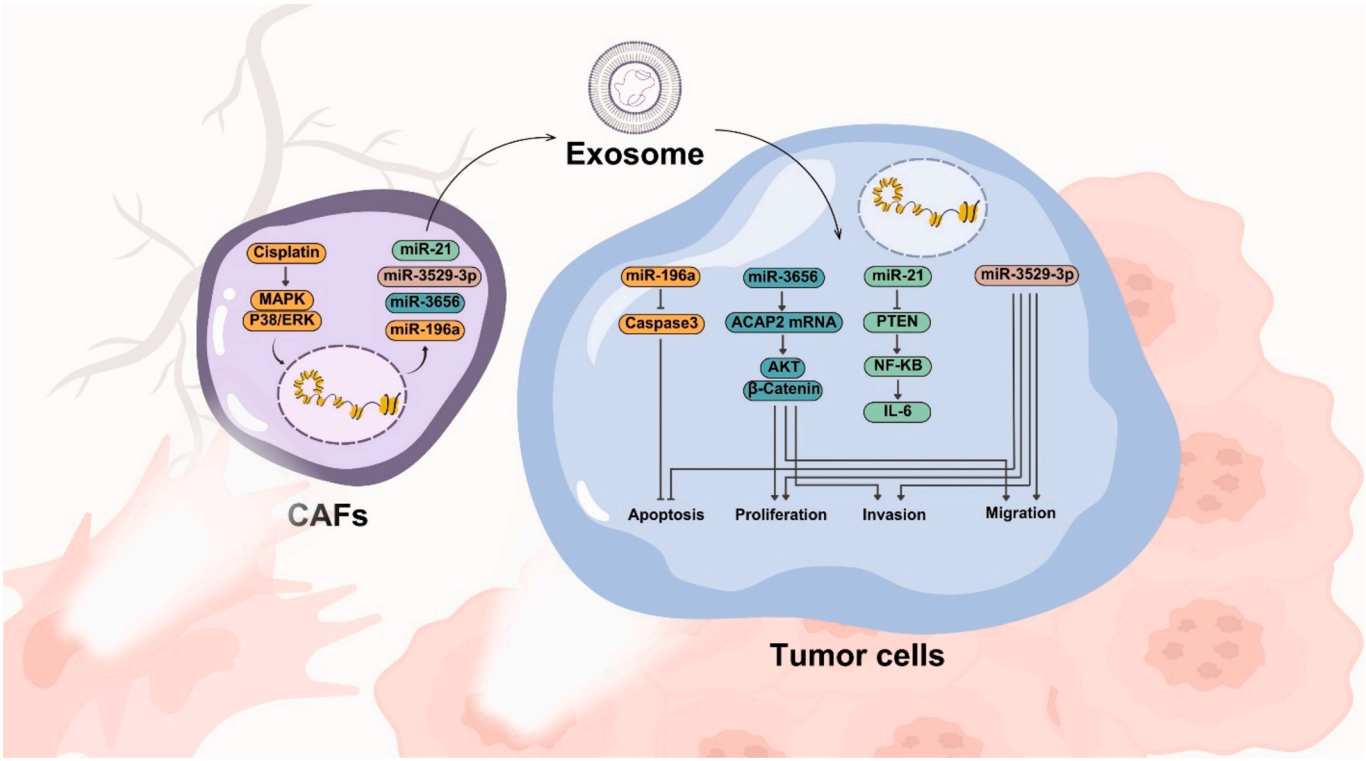

Fig. 3. CAF-derived exosomal microRNAs trigger tumor progression. CAF cells transcribe different miRNAs that regulate different signaling transduction pathways within the recipient cell.

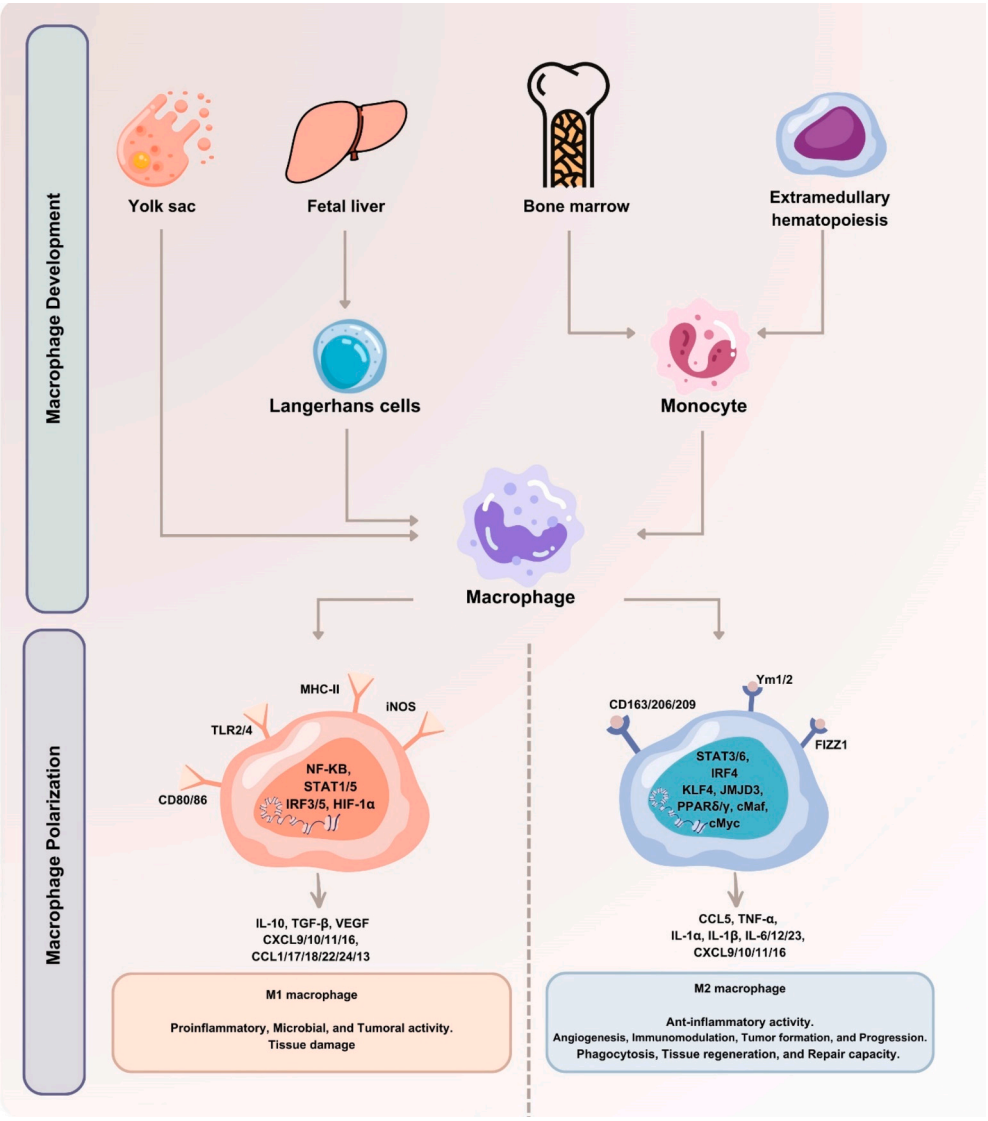

Fig. 4. Generation of macrophages from ancestor cells. Macrophages can be derived from monocytes of various origins.

macrophages secrete pro-inflammatory cytokines, and tumor necrosis factor (TNF)-β, which elevate inflammatory responses and suppress tumor growth. They are further promoted by Th2 cytokines to polarize at the tumor site and eventually activated into M2-type that generate anti-inflammatory cytokines [60]. M2-type macrophages mostly suppress the inflammatory response, hence elevating tumor growth and metastasis *(*Fig. 4*)* [61].

Within the TME, BM-derived macrophages are abundant which enter tumor tissues through peripheral blood [62]. In the OSCC TME, TAMs are dynamic assembly of varied macrophage subtypes. During the early stage of tumor progression, M1 is the predominant phenotype present at the TAMs [63]. Considering the high antigen-presentation ability of M1 phenotype, it can elevate the proliferation of CD8 + T and NK cells by IL-6, −12, and TNF, and promote their cytotoxicity to trigger apoptosis in tumor cells (Fig. 5) [64]. Secreted colony-stimulating factor-1 (CSF-1), also known as macrophage-CSF (M-CSF) [65], from tumor cells binds to the CSF-1 receptor (CSF-1R) on the surface of TAMs to shift their polarization to M2. The simultaneous activity of hypoxia-inducible factor-1 and 2 (HIF-1/2) in the TME and nuclear factor kappa B (NF-κB) signaling cascade can switch the M2 polarization [66]. Beside BM -derived monocytes, TAMs are also found to be originated form tissue-resident macrophages in different tumor types, including OSCC [67]. However, more studies are required to establish that in OSCC tissue-resident macrophages are a component of TAMs.

Increasing evidence indicates that TAM-derived exosomes (TAM-E) from play a critical role in tumor growth and metastasis of HNC. For example, Yan et al. [68] reported that TAM-*E*-miR21–5p promotes tumor angiogenesis through regulating the Yes1 associated transcriptional regulator (YAP1)/HIF-1α axis in HNSCC. Angiogenesis is a complicated process that significantly contributes in tumor initiation, progression, and metastasis. HIF-1α is a critical transcriptional factor that is capable of regulating the expression of target genes implicated in angiogenesis. HIF-1α is able to directly control the transcription of vascular endothelial growth factor (VEGF) at the gene level and as a result, lead to induce angiogenesis [69]. In that context, Yan et al. found that TAM-E significantly enhance the angiogenic potential of pHUVECs and successfully promoted the formation of perfusable blood vessels [68]. Besides, targeting miR-21–5p of TAMs could successfully suppress angiogenesis induced by TAM-E. Also, exosomal miR-21–5p derived from TAM downregulates large tumor suppressor kinase 1 (LATS1) and von Hippel-Lindau tumor suppressor von Hippel-Lindau tumor suppressor (VHL) levels but upregulates YAP1 and HIF-1α levels. Suppression of YAP1 and HIF-1α are able to suppress the miR-21–5p enhanced angiogenesis in HUVECs. The in vivo experiments further established that TAM-*E*-miR-21–5p elevates angiogenesis through the YAP1/HIF-1α axis in HNSCC [68]. Conclusively, M2-derived exosomes transferred

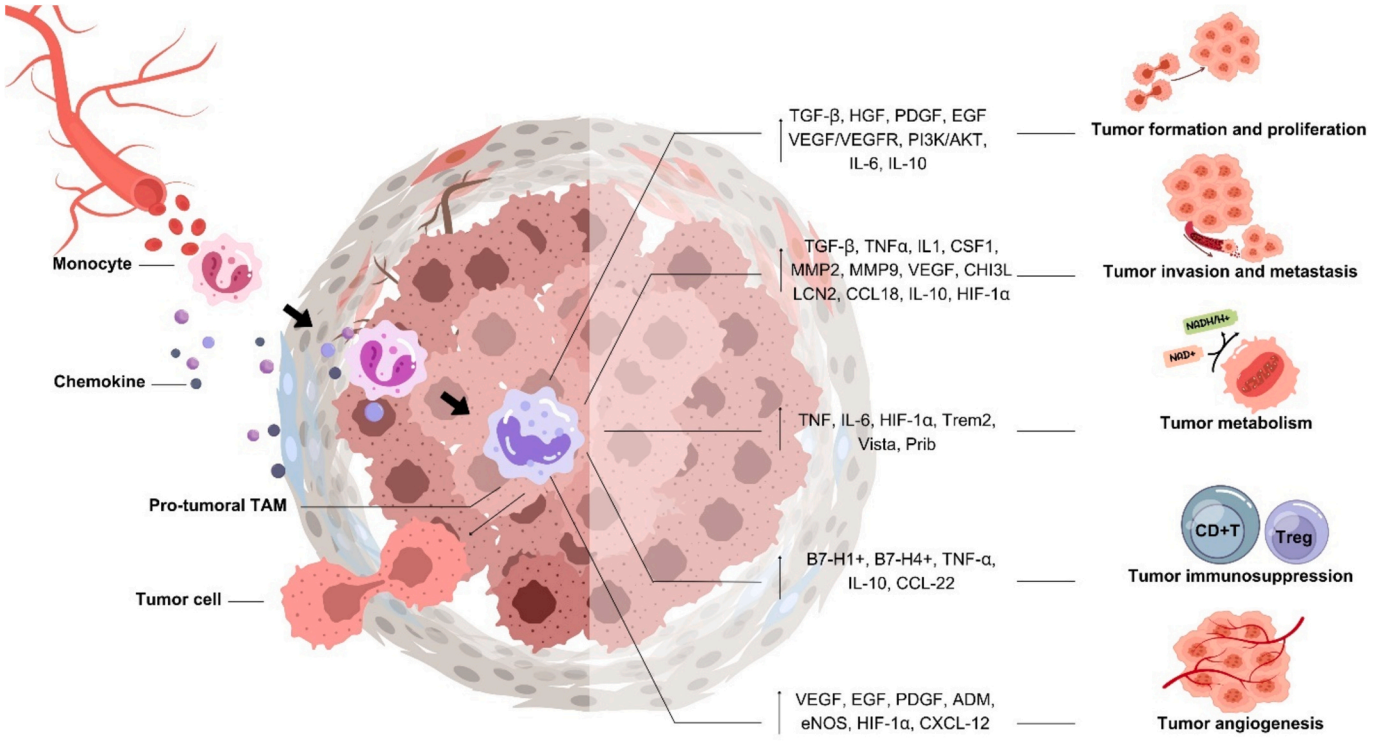

Fig. 5. Generation of tumor associated macrophages and their contribution to tumor generation and progression. TAMs can promote cancer metastasis, regulate tumor metabolism, and influence immune response within the TME.

miR-21–5p to endothelial cells to target LATS1 and VHL the mRNA level, which suppresses the phosphorylation of YAP1 and consequently enhances YAP1-mediated HIF-1α transcription and reduces HIF-1α ubiquitination mediated by VHL, contributing to HNSCC angiogenesis. In other research, Yi et al. have shown that M2 macrophages and M2 macrophage-derived *E*-miR-31–5p can induce tumorigenicity and OSCC growth. Delivery of miR-31–5p by M2-secreted exosomes to recipient OSCC cells results in its complementary pairing with the large tumor suppressor 2 (LATS2) coding sequence. This further results in the suppression of the LATS2 expression and blockade of the Hippo signaling cascade to support OSCC growth. These data demonstrated that M2 macrophage-derived *E*-miR-31–5p is capable of inhibiting tumor suppressor LATS2 gene and promote OSCC progression through downregulating the Hippo cascade, providing new targets for the OSCC molecular therapy. Similarly, Li and colleagues [70] found that in comparison to M0 macrophages-derived exosomes, exosomes from M2 macrophages trigger proliferation and invasion and inhibit apoptosis in OSCC cells. Besides, miR-23a-3p, which is capable of targeting phosphatase and tensin homolog (PTEN), exhibit a distinct expression pattern in exosomes derived from M0 and M2 macrophages. E-miR-23a-3p derived from M2 macrophages trigger the OSCC malignant progression by targeting PTEN [70,71]. Therefore, miR-23a-3p, an M2 macrophage-derived exosome, appears as a possible target for future OSCC therapy.

In TAMs, through activating the AKT–GSK3β–β-catenin axis, annexin A3 (ANXA3) promotes macrophages to polarize to an M2-like phenotype [72]. Surprisingly, TAMs-derived ANXA3-rich exosomes inhibit ferroptosis in laryngeal cancer cells through an activating transcription factor-2 (ATF2)/ ChaC glutathione-specific γ-glutamylcyclotransferase 1 (CHAC1) axis. This process is correlated with lymphatic metastasis [73]. Mechanistically, ANXA3 in exosomes inhibits ATF2 ubiquitination, whereas ATF2 acts as a transcription factor to regulate the CHAC1 expression, thereby downregulation ferroptosis in LSCC cells. Altoghter, indicates that aberrant ANXA3 expression is capable of triggering TAM reprogramming and elevate an immunosuppressive TME in LSCC. At the same time, ANXA3-rich exosomes suppress ferroptosis, induce lymphatic metastasis, thereby promots tumor progression of LSCC cells [73].

The Notch pathway is involved in several cancer progressions [74,75], and is in charge of differentiation and activation of macrophages [76,77]. The recombination signal binding protein for immunoglobulin kappa J region (RBPJ) is frequently used as a marker for the activation of Notch pathway [78]. Following the ligand binding, the intracellular domain of Notch translocates into the nucleus and accompanies RBPJ to generate a complex for activating the expression of Notch target genes [78]. Loss of the Notch effector RBPJ elevates tumorigenesis [23]. Moreover, Notch-RBPJ pathway appears to control the polarization of Toll-like receptors (TLRs)-induced inflammatory macrophage by indirectly regulating M1-specific genes [79]. Recently, Ai et al. [80] investigated the effect of RBPJ overexpression macrophages on OSCC cells. They found that RBPJ overexpression (RBPJ-OE) macrophage-derived exosomes can suppress cell proliferation and invasion of OSCC cells. In addition, they discovered that long noncoding RNA LBX1 (lncRNA LBX1) LBX1-AS1 is upregulated in RBPJ-OE macrophage-derived exosomes. Then they demonstrated that the inhibitory effects of RBPJ-OE macrophage-derived exosomes on the proliferation and invasiveness of OSCC cells (SCC-4 and CAL-27) are downregulated when LBX1-AS1 is knocked down in exosomes. On the other hand, overexpression of LBX1-AS1 inhibits proliferation and invasiveness of OSCC by sponging miR-182-5p [80]. Moreover, miR-182-5p is found to interact with Forkhead Box O3 (FOXO3), a well-characterized tumor suppressor gene [81–83]. Additionally, reactivation of FOXO3a mediates the synergistic cytotoxic effects of cisplatin and rapamycin in OSCC cells [84]. It also has been demonstrated that overexpression of LBX1-AS1 upregulates FOXO3 and inhibits cells from proliferating and invading, while transfection of miR-182-5p mimics in OSCC cells reversed these effects. In fact, the expression of FOXO3 exhibit a is negative and positive correlation with the level of miR-182-5p and LBX1-AS1 in OSCC tissues, respectively. Besides, RBPJ-OE macrophage-derived exosomes suppress tumor growth via LBX1-AS1/

miR-182-5p/FOXO3 axis in xenograft tumor models [80]. Taken as a whole, RBPJ overexpressed-macrophages-derived exosomal LBX1-AS1 inhibits OSCC progression by positively regulating FOXO3 through sponging miR-182-5p.

HOXA transcript at the distal tip (HOTTIP), located on chromosome 7 and transcribed from the 5′ end of the HOXA locus, is a lncRNA with the ability to trigger numerous HOXA genes. HOTTIP is a pivotal oncogene, associated with several malignant tumors, such as liver cancer [85], esophageal squamous cell carcinoma [86], and lung small cell carcinoma [87]. However, a recent study has found that HOTTIP also possesses antitumor properties, which shows that HOTTIP inhibits glioma proliferation by promoting apoptosis by downregulating the BRE gene [88]. HOTTIP is also established to serve in a bidirectional manner in the progression of distinct tumors. A bidirectional function has also been established for exosomal HOTTIP. For instance, the upregulated serum exosomal HOTTIP is found to have a significant correlation with poor overall survival in gastric cancer individuals [89]. On the other hand, low levels of serum exosomal HOTTIP is found to be significantly correlated with poor overall survival in colorectal cancer individuals [90]. With that context, more studies are required to clarify the role and mechanism of HOTTIP in HNSCC progression. Jiang et al. [91] recently demonstrated that HOTTIP levels is upregulated in M1-derived exosomes. Furthermore, M1 exosomes suppress proliferation, invasion, and migration while it induces apoptosis of HNSCC cells. HOTTIP-overexpressed M1 exosomes are found to enhance this function. In that regard, HOTTIP-knockdown suppressed these effects, indicating a pivotal role for HOTTIP in M1 exosomes [91]. Moreover, overexpression of HOTTIP inhibits proliferation, invasion, and migration but induces apoptosis of HNSCC cells in vitro. It is established that M1 exosomes and HOTTIP activated the TLR5/NF-κB axis by competitively adsorbing miR-19a-3p and -19b-3p [91]. Taken together, M1 exosomal lncRNA HOTTIP downregulates HNSCC progression by elevating the TLR5/NF-κB axis through competitively adsorbing miR-19a-3p and -19b-3p. Particularly, M1 exosomes and HOTTIP promote the polarization of M1 in circulating monocytes, thereby creating new understanding into HNSCC immunotherapy.

3.3. Mesenchymal stem cells

3.3.1. Promoting HNC development by MSCs

As multipotent cells, mesenchymal stem cells (MSCs) are a promising regenerative medicine population, considering their high differentiation potential and self-renewal capability [92]. Besides, acquiring MSCs is easy from a wide range of tissues. In fact, BM are considered as the major source of MSCs [93], which supports hemopoiesis and control immune activity [94]. Furthermore, MSCs can be isolated from adipose tissue of individuals experiencing liposuction. Adipose tissue-derived stem cells play a crucial role in reconstructive or tissue engineering medicine [95]. Also, MSCs can be extracted from other tissues, including peripheral blood, lung muscle, placenta, umbilical cord, umbilical cord blood, and amniotic membrane [96–102]. MSCs have various functions in these organs, such as contributing to organ homeostasis as well as tissue-specific healing [103]. Additionally, three basic characterizations have been described for MSCs. Form the morphological point of view, MSCs encompass a heterogeneous cell population with multiple shapes (e.g., spindle-form fibroblast-like, spherical, or flattened) [104–106]. From the functional and differentiation point of view, MSCs can differentiate into various cell types (e.g., osteoblasts, adipocytes, fibroblasts, and chondrocytes) with multiple functions, in response to the appropriate stimuli [107]. Finally, MSCs are capable of expressing the cell surface markers CD105, −90, and − 73 but lack CD45, −34, −14, −11b, −79a, or − 19, as well as HLA-DR [108]. Furthermore, an immune-suppressive properties have been characterized MSCs [92]. In fact, MSCs is found to modulate immunity through producing cytokines and regulating various immune functions [109]. For instance, MSCs serve an effectual role in treating graft disease versus host disease and some autoimmune diseases [110,111]. Also, MSCs are able to migrate to tumor and inflammatory areas. Numerous chemokines and related receptors might be implicated in the process of MSC migration, including growth factors, angiogenic factors, chemokines, inflammatory factors, and other cytokines [112]. Recently, it has been reported that cancer cell-derived exosomes can control the migration and homing of MSCs through promoting the expression of circular RNAs (circRNAs). In oral leukoplakia (OLK), for instance, OLK-MSCs-derived exosomes (OLK-MSCs-E) and OSCC-MSCs-derived exosomes (OSCC-MSCs-E) treatment significantly promotes HUVEC invasion, migration, and tube-formation ability. Mechanically, OLK and OSCC-OLK-MSCs-derived exosomes contain MMP1 which it induces angiogenesis in receiving cells such as HUVEC [113]. In that regard, Li et al. [114] investigated the contribution of MSCs oral carcinogenesis development. The result established that the oral leukoplakia with dysplasia (LK)-MSCs exhibited suppressed proliferation and migration, in comparison with the normal oral mucosa (N-MSCs) and oral carcinoma-MSCs [114]. Moreover, LK-MSCs-derived-exosomes (LK-MSCs-E) significantly contribute to proliferation, migration, and invasion in vitro. This is similar to the oral carcinoma-MSC-derived exosomes which both derived exosomes enhance cancer progression through miR-8485. The exosomal miR-8485 is able to promote proliferation, migration, and invasion of tumor cells [114]. These findings showed that exosomes can promote MSC migration to multiple types of tumor sites, thereby elevating or suppressing tumor growth.

Thyroid cancer is the leading endocrine malignancy worldwide [115,116]. Differentiated thyroid cancers with good prognosis generate most thyroid cancers. However, small percentage will develop into aggressive form, resulting in distant metastasis and a poor prognosis [115,117]. Despite all the efforts for treatment of individuals with aggressive thyroid cancer, such as tumor resection, drug-targeted therapy, chemo-, and radio-therapy, several issues including poor prognosis during the treatment still occur [118,119]. Consequently, revealing the mechanism of occurrence and progression of thyroid cancer, as well as advances in specific molecular markers and therapy targets are crucial for diagnosis and treatment. The researchers report that the exosomes derived by thyroid cancer stem cell-like cells (CSCs) play a critical role in the occurrence and progression of tumor cells [120,121]. As a subgroup of self-renewing cells, CSCs, are capable of triggering chemo- and radiotherapy resistance, along with recurrence and metastatic disease [122,123]. Recently, Wu et al. [124] reported a high level of lncRNA-CDKN2B-AS1 in CSCs and CSCs-derived exosomes. They found that exosomal CDKN2B-AS1 silencing could transfer to thyroid cancer cells to upregulate E-cadherin, and downregulate prolyl 4-hydroxylase subunit alpha 1 (P4HA1), N-cadherin, and Vimentin, thereby hindering cell migration and invasion [124]. On the other side, they observed that miR-122-5p inhibitor overturned the function of exosomal CDKN2B-AS1. Whereas, P4HA1 silencing decreased the effect of miR-122-5p inhibitor [124]. Overall, CSCs-derived exosomal CDKN2B-AS1 aggregates thyroid cancer metastasis and growth by upregulating P4HA1 through adsorbing miR-122-5p.

3.4. Inhibiting HNC development by MSCs

As mentioned above, BM-derived mesenchymal stem cells (BMSCs) are multipotent stromal cells that are recruited to cancers and serve a critical role in tumor progression [125]. It has been established that BMSCs-derived exosomes downregulate oral cancer development. Also, human BMSCs are found to transfer *E*-miR-101-3p to human TSCC cells TCA8113, and miR-101-3p downregulate collagen type X alpha 1 chain (COL1A1). MiR-101-3p suppress the proliferation, invasion, and migration of TCA8113 cells through downregulating COL1A1. Injection of human BMSCs-miR-101-3p in nude mice resulted in suppression of tumor volume and weight, confirming the inhibitory effect of BMSCs-E-miR-101-3p on tumor growth in vivo [126]. Similarly, BMSCs-secreted miR-101-3p suppresses oral cancer development by suppressing invasion, migration and proliferation through targeting COL10A1 [127]. In

contrast, promotional effects of BMSCs-derived exosomes on oral cancer have been suggested. For example, Ma et al. [128] reported that co-culture of BMSCs with upregulated miR-155 with OSCC cells can elevate cell proliferation, cell migration, and MMP-9 secretion while reducing apoptosis, and PTEN12 expression. Besides, they found that miR-155 is upregulated in OSCC individuals, and BMSCs of high expression miR-155 can elevate the proliferation and metastasis by regulating PTEN12 [128]. Altogether, BMSCs-derived exosomes contain upregulated miR-155 enhances OSCC development by promoting proliferation, and migration and inhibiting apoptosis through targeting PTEN12.

Adipose tissue derived MSCs (AMSCs) are at the center of attention, among the applications of MSCs for cancer treatment, considering their easy collection and production (Fig. 6). It has been demonstrated that co-culture of AMSCs with human TSCC cell (HSC-3), did not promote proliferation, migration, and invasion of tumor cells. This suggests that AMSCs might be more suitable for tumor therapy compared to other types of MSCs. In that context, Shafiaa and colleagues found that adipose-derived mesenchymal stem cells-secreted exosomes decreases HNSCC cells viability by decreasing CRKI expression levels [129]. Considering the limited number of experiments on interaction of AMSCs and tumors, more investigations are required before further applications.

It has been demonstrated that MSCs are able to affect tumor progression through controlling intra-tumor angiogenesis. Anti-angiogenic therapy can be effective for treating tumors in the future. Treatment of TSCC CAL27 cells with exosomes secreted from human deciduous exfoliated teeth and established a significant downregulation in the tumor volume. These exosomes are capable of downregulating VEGF-A expression through miR-100-5p and − 1246, which results in a significant reduction of microvasculature around TSCC. Similarly, menstrual MSCs-derived exosomes inhibits OSCC development by inhibiting angiogenesis and inducing apoptosis [130].

Another type of self-renewing and multipotent cells are human umbilical cord mesenchymal stem cells (HUC-MSCs) that are present in the umbilical cord tissue (Fig. 6). These cells are capable of renewing themselves continuously and, in certain circumstances, differentiate into one or more cell types creating tissues and organs [131]. Considering the self-renewal, multi-potency, and immunomodulatory properties of HUC-MSCs, they appear as a great candidate in tumor therapies [132,133]. In fact, considering the unique secretome and exosomes, the cell lysate and conditioned medium (CM) of HUC-MSCs they have been used of cell-free tumor therapy [134]. UCMSCs-CM encompass various exosomes, growth agents, and cytokines. However, the anti-cancer effects of UCMSCs-CM are yet unknown. It has been demonstrate that the human UCMSCs extracts are capable of suppressing the proliferation of ovarian cancer cells in vitro [135,136], UCMSCs-CM is also found to suppress the growth of mammary carcinoma, bladder cancer, osteosarcoma, and lymphoma cells both in vitro and in vivo [135,137,138]. It also has been found that UCMSCs-CM has the ability to promote the proliferation and migration of glioblastoma cells, MDA-MB-231 cells, and few subtypes of lung cancer stem cells [139,140]. These opposing results are mostly due to the distinct sensibility of different tumor cell types. Recently, Liu et al. [141] established that HUC-MSCs-derived exosomes are capable of restraining NPC cell growth in vivo and in vitro. They found that depletion or restoration of exosomal miR-181a can promote or delay NPC cell progression. Besides, KDM5C, as the miR-181a target, silencing suppresses NPC cell progression [141]. The conclusion of these results is that hUC-MSCs-*E*-miR-181a retards NPC development through down-regulating KDM5C, appearing as a great candidate for NPC treatment.

4. Conclusion and Future Perspective

The pivotal role of TME in the initiation and development of HNC has been significantly suggested through different experiments. Exosomes are critical elements of the TME and serve as messengers of intercellular network. This review gathers information about the role of exosomes in the interaction between HNC cells and TME cells, along with the clinical value of exosomes [142,143]. Though existing literature are incapable of elaborating the functions of exosomes, the current studies highlight the importance and potential application of exosomes in the TME of HNC.

The TME-derived exosomes reflect the nature of their originated cells, and the molecules that they carry can reflect the differences between cancer and normal cells. These differences can be adopted for identifying the most suitable targets and biomarkers [144,145]. The

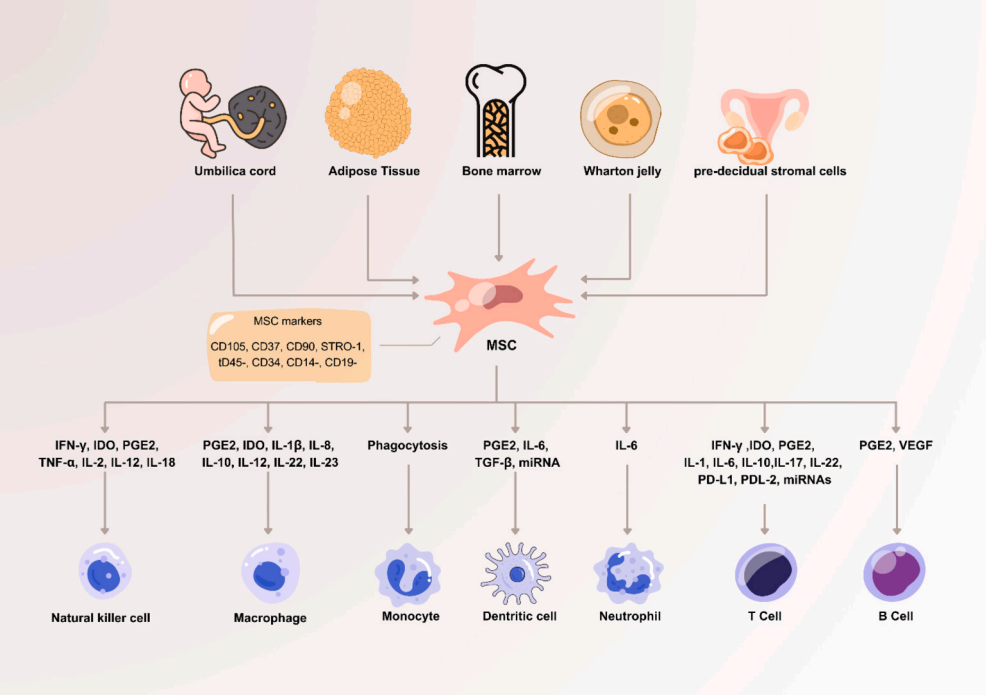

Fig. 6. Generation of mesenchymal stem cells and their evolvement to immune cells.

interaction between the TME and TME-derived exosomes is complex, and they constantly affect one another. TME influences the production and secretion of these exosomes, and they influence tumor progression through delivering, further affecting TME [144]. Noteworthy, not all the elements within the TME-associated exosomes can promote cancer, and more regulatory processes are required to be elucidated. Additionally, exosomes can contribute to tumor drug resistance and affects treatment outcomes. Recently, several RNAs from exosomes, including miRNA, lncRNA, and circRNA are found to be implicated in tumor drug resistance through targeting distinct signaling cascades. However, very few studies have investigated the role of exosome and exosome compounds in HNC chemoresistance and should be given more attention. Exosomes also appear as an effectual drug delivery system for cancer therapy [30,146,147].

In addition to noncoding RNAs, exosomes derived from cancer cells and/or TME cells can encompass different contents such as proteins, DNA, and mRNA that can serve as biomarkers for early detection and prognosis. Some of the contents are capable of serving as mediators of signal transduction between cancer cells, or cancer cells with TME cells, and participate in tumor development, invasion, metastasis, and drug resistance [148,149]. This allows for developing novel strategies based on engineered exosomes carrying tumor-suppressing proteins, nucleic acid components or drugs [150]. However, several issues must be addressed, such as the need for a complete understanding of the composition and function of exosomes, the immunogenicity and safety, and efficiency and stability of the delivery. In that context and considering the importance of a comprehensive view for proposing an effective application, this review was dedicated for providing a deeper understanding on this matter. Investigating the heterogeneity, long-distance delivery, and diverse mediation network of exosomes in TME, more studies are required for HNC treatment. In fact, the heterogeneity of exosomes promotes intricate biological reactions, acting as a barrier in the way of understanding their biogenesis, bio-distribution, contents, and roles in the TME. Besides, the abundancy and size of other extracellular vesicles also make it hard to purely acquire and characterize exosomes [151,152]. Various methods are developed for extraction of exosomes, including tangential flow filtration, ultracentrifugation, ultrafiltration devices, and size exclusion chromatography. However, some of these methods might degrade the functionality and structural integrity of exosomes. Therefore, no established method has been developed for isolation of exosome as a gold standard, which appears as an obstacle for exploring the role of exosomes in tumor development and searching for specific clinical indicators [21,30]. More in depth investigations are required to provide a comprehensive overview of exosomes for distinguishing them from other extracellular vesicles and identifying specific exosome populations.

Funding

No funding was received.

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.

Data availability

No data was used in this study.

Acknowledgments

None declared.

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