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Review article

Role of exosomes in the communication and treatment between OSCC and normal cells

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is a prevalent cancer that needs new therapeutic targets due to the poor postoperative prognosis in patients. Exosomes are currently one of important research areas owing to their unique properties. Exosomes are capable of acting as drug transporters, as well as facilitating interactions between OSCC and normal cells. Exosomes can be detected in body fluids such as blood, urine, cerebrospinal fluid, and bile. When exosomes are released from donor cells, they can carry various bioactive molecules to recipient cells, where these molecules participate in biological processes. This review highlights the mechanisms of exosome transfer between normal and OSCC cells. Exosomes isolated from donor OSCC cells can carry circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs) and play a role in signaling processes in the recipient OSCC cells, human umbilical vein endothelial cells, and macrophages. Exosomes secreted by carcinoma-associated fibroblasts, macrophages, and stem cells can also enter the recipient OSCC cells and modulate signaling events in these cells. Exosomes isolated from OSCC plasma, serum, and saliva are also associated with OSCC prognosis. Furthermore, while exosomes were shown to be associated with chemotherapy resistance in OSCC, they can also be used for drug delivery during OSCC treatment. In this paper, we reviewed the molecular mechanisms and functions of exosomes from different cell sources in OSCC cells, providing a basis for diagnosis and prognosis prediction in OSCC patients, and offering guidance for the design of molecular targets carried by exosomes in OSCC.

1. Introduction

Oral cavity is one of the most important organs in the human body and is often affected by oral cancer (OC). When the oral cavity is affected by cancer, functions such as speech, swallowing, and expression are severely affected [1]. OC can occur in the lining of the lips and cheeks, floor of the mouth, soft and hard palates, tongue, and gums [2]. Many patients have a reduced quality of life owing to impaired facial function after surgery. Currently, tissue biopsy and histopathological analyses are commonly used to diagnose OC; however, they have some limitations. A tissue biopsy sample does not represent the entire tumor tissue, and collection of

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histopathological evidence is time-consuming and expensive [3]. As a new diagnostic tool, liquid biopsy is widely used today and is expected to contribute to personalized OC treatment [4,5]. Liquid biopsies have the advantage of being less invasive, less risky, and able to overcome the problem of hard-to-obtain tissue samples that can be monitored in real time and reflect the heterogeneity of the tumor. However, liquid biopsies also have limitations, including low sensitivity, non-standard analytical workflows, and small sample sizes [121]. Circulating tumor cells, circulating tumor DNA, and exosomes are the three main markers used in liquid biopsy examination; in recent years, exosomes extracted from the blood [6] and saliva [7–10] of patients with OC are increasingly being used for its diagnosis [11]. At the same time, it has also been reported that tissue autofluorescence, narrowband imaging, high-frequency ultrasound, and other non-invasive imaging techniques can be used for the detection of OC [122]. However, the gold standard for diagnosis remains tissue biopsy and histological examination [12]. OSCC has a high local recurrence rate, poor prognosis and represents 90% of OCs [13]. Advanced OSCC can metastasize to the lymph nodes [14], and the 5-year survival rate in patients with OSCC does not exceed 60%, owing to the metastasis and recurrence of the tumor [15]. Therefore, identification of molecular therapeutic targets and diagnostic markers for OSCC is a major research direction.

Donor cells can release exosomes, which can transport various bioactive chemicals to recipient cells to participate in biological processes [16]. Exosomes have become a novel type of cancer biomarkers in recent years and can influence tumor therapy by controlling the sensitivity of malignancies to therapy [17]. Exosomes secreted by OSCC cells can interact with other cells and OSCC cells, and those secreted by other cells can interact with OSCC cells as well. In this study, we have highlighted the exosome transport process between normal and OSCC cells. We have also examined recent developments in the field of exosome research, especially regarding the biogenesis, development, clinical and therapeutic importance of exosomes, and their effects on OSCC.

2. Composition and delivery of exosomes

Extracellular vesicles are secreted by donor cells, and their lipid bimolecular structure is rich in proteins and nucleic acids [18]. Based on their morphological characteristics, extracellular vesicles can be classified as microvesicles, exosomes, or apoptotic bodies [19,20]. Exosomes are uniform in size with diameters of approximately 40–100 nm [21–23]. Exosomes are formed by invagination of the endoplasmic membrane or endocytosis, where extracellular components such as functional proteins, RNA, and lipids are taken up to form vesicles. The vesicles fuse to form early-sorting endosomes; most of them form late-sorting endosomes, a small fraction of which can directly form exosomes that are released into the cytoplasm. Late-sorting endosomes accumulate in the cell to form multivesicular bodies (MVBs) that contain many intracellular vesicles [24,25]. Eventually, MVBs fuse with lysosomes and are degraded, whereas intraluminal vesicles are released into the extracellular space to form exosomes [26–28] (Fig. 1).

Exosomes are released from various cell types and contain lipids, DNA, RNA, proteins, and metabolites [29–31]. The main components of exosomes are lipids, including cholesterol, diglycerides, glycerolipids, phospholipids, and sphingolipids, as well as RNA

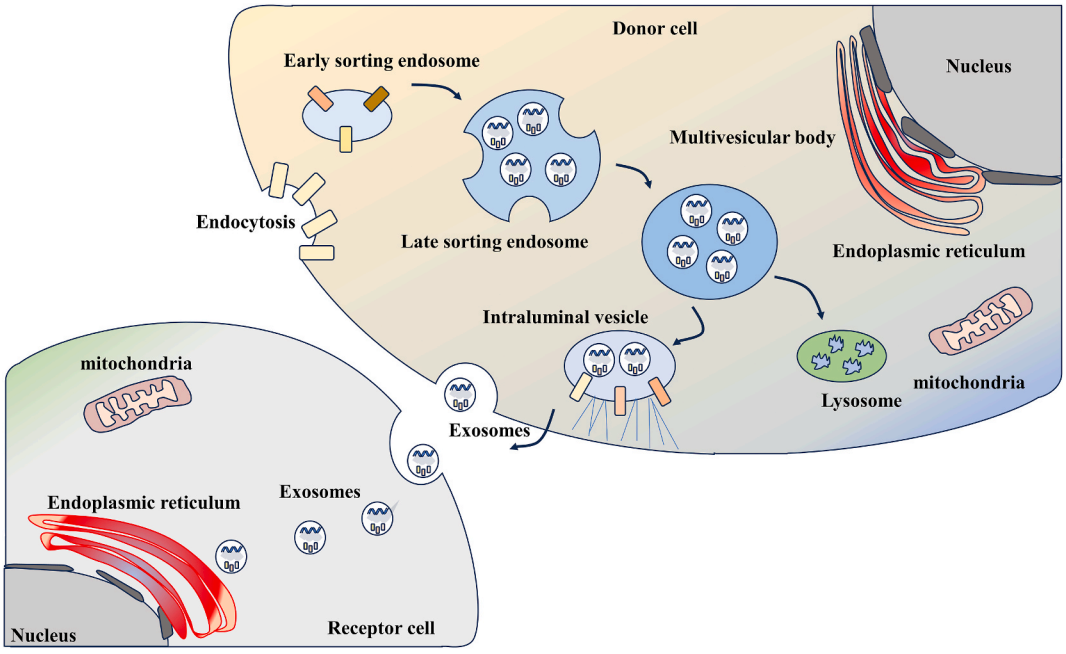

Fig. 1. Exosomes are produced by donor cells and transported into recipient cells.
Extracellular components in donor cells, such as functional proteins, RNA, and lipids, are combined to form vesicles, and then to form early-sorting endosomes, which can assemble into late-sorting endosomes, and finally form MVBs, which can then combine with lysosomes or autophagosomes for degradation, or release ILVs as exosomes. Exosomes secreted by the donor cell can be absorbed by the recipient cell where they play their specific roles. ILV, intraluminal vesicles; MVB, multivesicular bodies.

fragments and various proteins [32]. The internal components of the exosomes include RNA fragments and various proteins. Exosomal RNA fragments include messenger RNAs (mRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). The protein components of exosomes include some universal and cell type-specific proteins [33], as well as some membrane proteins and soluble proteins [2,34]. Exosomes are important carriers of intracellular signaling molecules and may promote tumor metastasis and growth in situ [32]. Exosomes secreted from different cells carry a number of molecular targets that can be released into the extracellular space of various cell types to regulate tumor progression [35,36] (Fig. 2). Bioactive substances that are carried and delivered by exosomes can reprogram the functioning of recipient cells and regulate the tumor microenvironment (TME) [37].

3. Extraction methods of exosomes

Exosomes can be detected in body fluids such as blood, urine, cerebrospinal fluid, and bile [38]. They are involved in the intercellular transport of materials and information to regulate the physiological functions of cells, including antigen presentation, immune escape, induction of normal cell transformation, promotion of tumorigenesis, and metastasis. Because exosomes carry miRNA, mRNA and other bioactive substances, some of which can predict prognosis, they are also considered novel biomarkers for disease diagnosis. Furthermore, exosomes are polyvesicular bodies with lipid bilayer membranes and are distributed in the extracellular matrix [39]. To obtain high-purity exosomes, effective removal of cell debris and other unwanted contaminants is necessary. Currently, several methods are commonly used to isolate exosomes, including ultracentrifugation, density gradient centrifugation, ultrafiltration centrifugation, size exclusion chromatography, magnetic bead-based immunoassays, polyethylene glycol (PEG)-based precipitation, and microfluidic technology [40]. In the extraction process, ultracentrifugation is the most commonly used method, but to obtain exosomes of higher purity, density gradient centrifugation is usually employed. The principle of this procedure is to enrich different substances in media with different densities by centrifugation, based on the density difference between exosomes and impurity particles, to obtain exosomes of high purity [123].

4. Exosomes extracted from OSCC cells

Exosomes secreted by tumor cells are known as tumor-derived exosomes (TDEs). TDEs can alter the TME and promote tumor progression [41]. Typical TDE components include proteins, lipids, DNA, and a variety of RNAs, which can be taken up by the recipient cells to regulate recipient cell gene expression, tumorigenesis, vascularization, and other functions, thereby promoting metastasis, recurrence, and resistance to treatment [42]. TDEs can contribute to tumor progression in several ways, including promotion of tumor metastasis, invasion, and proliferation and induction of drug resistance and immunosuppression [43]. For example, Sento et al. found that OSCC cells can take up exosomes secreted by donor OSCC cells; however, heparin can inhibit this process [44]. In addition, studies have shown that exosomes released from tumor cells have anti-tumor properties by participating in apoptosis and immune-related processes of tumor cells [45]. For example, exosomal miR-181a-3p secreted by OSCC cells transmitse endoplasmic reticulum stress and reaches muscle cells, where it causes apoptosis and atrophy [46].

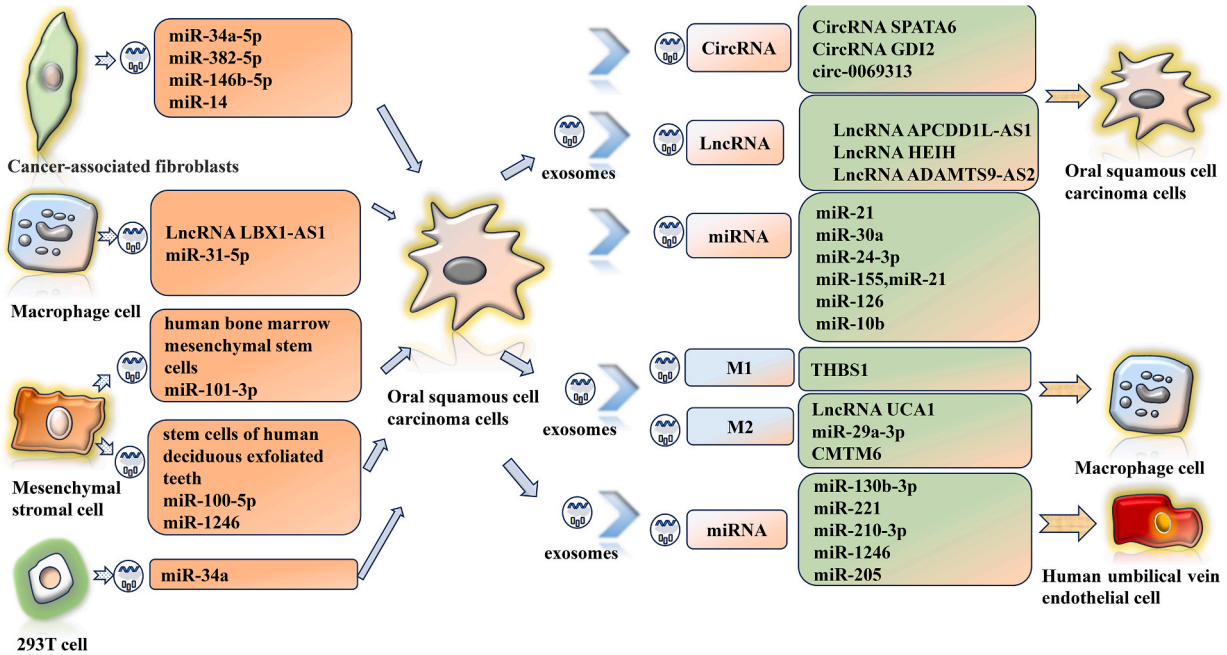

Fig. 2. Exosomes play an important role when OSCC cells interact with other cells. OSCC, Oral squamous cell carcinoma.

4.1. Exosomes extracted from OSCC cells can enter OSCC cells and play an important role

4.1.1. Exosomes secreted by OSCC cells carry circRNA to play a role in OSCC cells

Exosomes deliver nucleic acids to recipient cells to promote or inhibit diseases [47]. CircRNAs carried by exosomes are highly stable in cancer cells. CircRNAs carried by TDEs can be transported to target cells or organs; thus, exosomes participate in the regulation of tumor metastasis [48]. Some studies have shown that exosomes derived from donor cells carry circRNAs that act on recipient cells. The expression level of the circRNA SPATA6 in the serum of patients with OSCC was significantly lower than that in healthy individuals. Subsequently, a CAL27/HSC6 circRNA SPATA6 exosome set was constructed and transfected into HSC6 and CAL27 cells. Compared with that in the control group, the migratory and invasive abilities of the cells transfected with the circRNA SPATA6 exosome were significantly reduced, and cell cycle arrest and apoptosis were enhanced [49]. Although the expression level of circRNA GDI2 is reduced in OSCC cells, these cells transfer the circRNA to receptor OSCC cells via exosomes, regulate the miR-424–5p/SCAI axis, and influence the proliferation, migration, invasion, and glycolysis of receptor cells [50]. Chen et al. observed that has-circ-0069313 expression was upregulated after treatment with OSCC cell-derived exosomes, which induced immune escape in OSCC and Treg cells via the miR-325–3p/FOXP13 axis [51]. Compared with linear RNA, circRNA shows better stability and resistance to RNase activity, making it a potentially attractive biomarker. In addition, exosomal circRNAs secreted by donor cells can reach neighboring and distant cells and transfer information via exosomal circular RNAs to regulate recipient cells. Therefore, exosomal circRNAs have potential as diagnostic and therapeutic markers.

4.1.2. Exosomes secreted by OSCC cells carry lncRNA to play a role in OSCC cells

Exosomal lncRNAs play significant roles in the regulation of physiological processes and communication between cells. They are also associated with chemotherapy resistance, proliferation, migration, apoptosis, and other processes in tumor cells. The expression level of the lncRNA APCDD1L-AS1 is notably elevated in OSCC cells as well as in 5-fluorouracil (5-FU)-resistant OSCC cells; by extracting exosomes from the culture medium of 5-FU-resistant OSCC cells and co-incubating OSCC cells, it was found that exosomes increased APCDD1L-AS1 levels in OSCC cells to confer 5-FU resistance [52]. Wang et al. observed that the lncRNA HEIH exhibited increased expression in cisplatin-resistant SCC4 cells. Exosomes produced in cisplatin-resistant SCC4 cells are taken up by cisplatin-sensitive SCC4 cells, and the exosomal lncRNA HEIH secreted by the cisplatin-resistant cells promotes drug resistance, proliferation of cisplatin-sensitive SCC4 cells and inhibits apoptosis via the miR-3169–5p/HDGF axis [53]. The exosomal lncRNA ADAMTS9-AS2 secreted from the culture medium of SCC9 and CAL27 cells inhibits the protein kinase B (AKT) signaling pathway and the growth, migration, and invasion of recipient OSCC cells, which also regulates the process of epithelial mesenchymal transformation (EMT) [54]. Exosomes serve as a means of communication between cells. They can contain lncRNAs that act as messengers for intercellular communication and help regulate the cell microenvironment [54]. Compared with protein-coding mRNAs, lncRNAs are more tissue-specific [55]. This is useful for identifying cancer subtypes, biomarkers, and potential therapeutic targets. A clinical trial (NCT03102268) has been initiated by the Second Affiliated Hospital of Nanjing Medical University (China) to test the diagnostic and predictive value of non-coding RNAs derived from exosomal weight in cholangiocarcinoma [55]. However, further in-depth studies are required to determine the function of exosomal lncRNAs or their specific expression in specific tumors. Therefore, the clinical application of exosomal lncRNAs as biomarkers is still under development.

4.1.3. Exosomes secreted by OSCC cells carry miRNA to play a role in OSCC cells

Exosomes have considerable diagnostic value owing to their distinct expression levels in cancerous and non-cancerous cells [56]. Owing to the presence of the lipid bilayer of exosomes, miRNAs can be protected from RNase degradation in body fluids (including serum and plasma), thereby stabilizing the miRNAs present in body fluids [57]. The constructed cell lines (HSC-3-R and SCC-9-R) were resistant to cisplatin, and exosomes derived from drug-resistant OSCC cells carried miR-21, which was shown to regulate phosphatase and tensin homolog (PTEN) and programmed cell death 4 (PDCD4) expression in non-resistant OSCC cells, resulting in drug resistance in normal OSCC cells [58]. Kulkarni et al. analyzed the expression levels of miR-30a in the serum of patients with OSCC and cisplatin-resistant OSCC cells and found that its levels in these cells were lower than those in cisplatin-sensitive cells. After the overexpression of miR-30a in the exosomes of cisplatin-resistant cells, it was found that the exosomal miR-30a played an important role in the transfer by restoring the sensitivity of cisplatin-resistant OSCC cells, enhancing the apoptosis of cisplatin-resistant cells, and reducing autophagy [59]. Compared with that in normal controls, higher expression levels of miR-24–3p were observed in salivary exosomes and tissues of patients with OSCC; miR-24–3p directly regulated PER1 expression in the recipient OSCC cells to affect the proliferation of the recipient cells [60]. Chen et al. found that exosomal miR-155 and miR-21 served as an oncogene, and exosomal miR-126 served as a tumor suppressor gene, which could be used as a marker for OSCC detection [61]. The exchange of exosomal miRNAs between cells promotes communication between different cells and helps in physiological and pathological processes such as tumor immune response, TME remodeling, and tumor metastasis. Thus, exosomal miRNAs may serve as biomarkers for the diagnosis of OSCC. In addition, hypoxia may affect tumor glycolysis, angiogenesis, immortalization, and other processes that promote tumor progression [62]. TDEs transfer miRNAs between cancer cells under normoxic and hypoxic conditions. In a hypoxic environment, OSCC cells are stimulated to produce exosomes rich in miR-21, which are transported to cells under normoxic conditions; In addition, hypoxic cell exosomes express HIF-1α and HIF-2α is involved in OSCC cell invasion and migration in a dependent manner [63]. These miRNAs, derived from OSCC cells, can serve as non-specific biomarkers for OSCC. Their application can guide the sensitivity and treatment of OSCC diagnosis. Therefore, the use of related biomarkers in exosomes for the diagnosis and treatment of OSCC still has extensive research prospects and exploration space.

Table 1
OSCC cell-derived exosomal trafficking to OSCC cells, Macrophage,HUVECs.

	Author/ year	Donor cells/body fluids/tissues	Exosome carrier molecule	Receptor cell	Molecular/ signaling pathways in receptor cells	The function of exosomes acting on receptor cells
1	Fan et al., /2021	CAL-27; HSC-6	CircSPATA6	CAL-27; HSC-6	_	The exosomes carry the overexpressed CircSPATA6 to the receptor OSCC cells, inhibit their migration and invasion, and increase cell cycle arrest and apoptosis
2	Zhang et al., /2020	CAL-27; SCC-15	CircGDI2	CAL-27; SCC-15	CircGDI2/miR-424–5p/SCAI	Overexpression of CircGDI2 inhibits the glycolysis, proliferation, migration and invasion of OSCC cells
3	Chen et al., /2022	UM1; SCC-9	Circ-0069,313	CAL-27; UM2; Treg cells	Circ-0069313/ miR-325–3p/ FOXP3	Knockdown of Circ-0069313 inhibited tumor growth through miR-325–3p/ FOXP3 axis in OSCC cells; Invasion of Treg cells is impaired by miR-325–3p/ FOXP3 axis in receptor Treg cells
4	Li et al., /2021	5-FU resistant HSC-3 cells; 5-FU resistant HN-4 cells	LncRNA APCDD1L-AS1	HSC-3; HN-4	LncRNA APCDD1L-AS1/ miR-1224–5p/ NSD2	Exosomes secreted by 5-FU-resistant OSCC cells make receptor cells resistant by increasing APCDD1L-AS1 level in receptor OSCC cells. In 5-FU-resistant donor OSCC cells, silencing APCDD1L-AS1 inhibited proliferation and accelerated apoptosis of donor OSCC cells
5	Wang et al., /2020	DDP resistant SCC-4 cells	LncRNA HEIH	DDP sensitive SCC-4 cells	LncRNA HEIH/ miR-3169–5p/ HDGF	After the exosomes overexpressing HEIH enter the DDP sensitive SCC-4 receptor cells, they promote the proliferation and drug resistance of the receptor cells, and inhibit their apoptosis
6	Zhou et al., /2021	CAL-27; SCC-9	LncRNA ADAMTS9-AS2	CAL-27; SCC-9	Akt signaling pathway	Exosomes carrying overexpressed LncRNA ADAMTS9-AS2 inhibit the proliferation, migration and invasion of OSCC cells
7	Liu et al., /2017	Cisplatin resistant HSC-3 cells; Cisplatin resistant SCC-9 cells	miR-21	Normal HSC-3 cells and SCC-9 cells	PTEN/PDCD4	Eexosome miR-21 derived from cisplatin resistant HSC-3 donor cells, can induce cisplatin resistance in OSCC cells after reaching the recipient HSC-3 cells
8	Kulkarni et al., /2020	Cisplatin resistant OSCC cells; Serum of patients with OSCC	miR-30a	Na ï ve cisplatin resistant OSCC cells	Beclin1/Bcl2	It can restore the sensitivity of cisplatin resistant cells to cisplatin
9	He et al., /2020	Saliva of OSCC patients; Saliva from healthy controls; Stable overexpression/knockdown of exosomes from HSC-6/SCC-25 cells	miR-24–3p	HSC-6; SCC-25	PER1	Overexpression of miR-24–3p increases the proliferation of OSCC cells
10	Chen et al., /2021	Serum derived exosomes from patients with OSCC; Exosomes derived from primary OSCC cells; Exosomes produced by SCC4 cells	miR-155 miR-21 miR-126	FaDu cells	PTEN; Bcl-6; EGFL7	Overexpression of miR-155 and miR-21 can promote the proliferation and invasion of receptor FaDu cells; Overexpression of miR-126 inhibits the proliferation and invasion of receptor FaDu cells
11	Pang et al., /2021	CAL-27	CMTM6	Macrophage	ERK1/2 signal pathway	Exosomes derived from donor CAL-27 cells carry CMTM6 to act on recipient macrophages and promote M2 polarization of macrophages
12	Xiao et al., /2018	SCC-25; CAL-27	THBS1	THP-1 and PBMCs derived macrophages	P38, Akt and SAPK/JNK signaling pathway	The transfer of exosome THBS1 to recipient macrophages can promote its M1 polarization
13	Wu et al., /2022	Stem cells derived from CAL-27	LncRNA UCA1	Macrophages; CAL-27	LAMC2	Promote M2 polarization of receptor macrophages
14	Cai et al., /2019	SCC-9;CAL-27	miR-29a-3p	Macrophages; CAL-27; SCC-9	SOCS1	The high expression of miR-29a-3p from donor cells promote the M2 polarization of recipient macrophages; And promote the proliferation and

(*continued on next page*)

Table 1 (*continued*)

	Author/ year	Donor cells/body fluids/tissues	Exosome carrier molecule	Receptor cell	Molecular/ signaling pathways in receptor cells	The function of exosomes acting on receptor cells
						invasion of receptor CAL-27 and SCC-9 cells
15	Yan et al., /2021	OECM1	miR-130b-3p	HUVECs	PTEN	Overexpression of miR-130b-3p from donor cells can promote the vascular viability of recipient HUVEC cells
16	Capik et al., /2023	FaDu cell model of hypoxia, SCC-9 cell model of hypoxia; FaDu and SCC-9 model of normoxia	miR-1825	HUVECs	miR-1825/ TSC2/mTOR	Hypoxia induces the secretion of miR-1825 from donor OSCC cells to act on HUVEC cells, which can promote angiogenesis
17	He et al., /2021	CAL-27	miR-221	HUVECs	PIK3R1	Overexpression of miR-221 by exosomes derived from donor cells can increase the migration and angiogenesis of HUVEC cells
18	Wang et al., /2020	CAL-27	miR-210–3p	HUVECs	EFNA3	It can up regulate the expression level of miR-210–3p in receptor HUVEC cells, and promote the proliferation, migration and tubulogenesis of HUVEC
19	Zhang et al., 2022	CAL-27 cells treated with phenformin	miR-1246; miR-205	HUVECs	_	The exosomes overexpressing miR-1246 and miR-205, acting on the receptor cells, can inhibit the angiogenesis of HUVECs
20	Li et al., /2022	MSCs (mesenchymal stem cells) derived from OSCC; OLK derived MSCs (mesenchymal stem cells)	MMP1	HUVECs	_	Knockdown of MMP1 can inhibit the migration, invasion and angiogenesis of receptor cells by exosomes extracted from OLK derived mesenchymal cells and OSCC derived mesenchymal cells
21	Morioka et al., /2016	Primary culture of highly metastatic OSCC cell line (SQUU-A); non-metastatic OSCC cell line (SQUU-B)	_	HUVECs HDLECs	_	The exosomes extracted from highly metastatic OSCC cell lines have stronger ability to promote lymphatic and vascular survival than those extracted from non metastatic OSCC cell lines

4.2. Exosomes extracted from OSCC cells enter macrophages and play an important role

Macrophages act as part of the innate immune system and are involved in the host defense against cancer progression. Two main subtypes of macrophages are: the classically activated M1 subtype can promote anti-tumor immunity in the inflammatory response, while the alternatively activated M2 subtype promotes tumorigenesis and tumor progression [64]. Macrophage infiltration and polarization may also have an important effect on the promotion of tumor progression. Pang et al. found that CMTM6 was highly expressed in OSCC cells; they extracted exosomes secreted by OSCC, and observed that the exosomal CMTM6 could enter macrophages, activate extracellular signal-regulated protein kinase 1/2 (ERK1/2) signaling, promote the polarization of M2-like macrophages, and induce migration and invasion by increasing PD-L1 expression [65]. Moreover, the exosomal THBS1 secreted from OSCC cells, was observed to be involved in the polarization of macrophages toward an M1-like phenotype. Subsequently, the exosome activated macrophages in the conditioned culture medium were co-incubated with OSCC cells, and it was observed that the migratory ability of OSCC cells was enhanced [66]. The OSCC stem cell-derived exosome lncRNA UCA1 mediates the activity of the phosphoinositide 3-kinase (PI3K)/AKT axis via LAMC2 and promotes M2 macrophage polarization [67]. Cai et al. found that the expression level of miR-29a-3p was upregulated in OSCC tissues and exosomes derived from OSCC. Exosome miR-29a-3p derived from OSCC cells, can act on downstream M2 macrophages; when the expression of miR-29a-3p was inhibited, the polarization ability of M2 macrophages weakened. Overexpression of suppressor of cytokine signaling 1 (SOCS1), which is a downstream target of miR-29a-3p, reversed this effect [68]. Exosomes released by tumor cells have the potential to promote tumor development through the control of macrophage polarization. Macrophages are involved in tumor-related angiogenesis, tissue inflammation, and immune remodeling processes due to their ability to stimulate auxiliary signaling pathways [124]. They also activate cancer-associated fibroblasts and regulate pro-angiogenic and metastasis factors. Additionally, they participate in the formation of TME [125]. Therefore, exosomes play a crucial role in facilitating cell-cell contact and fostering cancer progression between OSCC cells and macrophages.

4.3. Mechanism of action of exosomes secreted by OSCC cells in human umbilical vein endothelial cells (HUVECs)

Angiogenesis mainly occurs during development and reproduction, and tumor angiogenesis is necessary for tumor invasion and metastasis, which is crucial for controlling the course of the disease. Yan et al. found that the expression level of miR-130b-3p was elevated in OSCC cells; miR-130b-3p could directly target and bind PTEN, and the exosomal miR-130b-3p extracted from the OSCC cell line OECM1 was enhanced in the angiogenesis of HUVECs [69]. In hypoxia-induced OSCC-derived exosomes and OSCC cells, Capik

et al. observed that the expression of miR-1825 was upregulated, and hypoxia-induced OSCC-derived exosomal miR-1825 stimulated angiogenesis via the TSC2/mTOR axis [70]. Meanwhile, CAL27 cell-derived exosomal miR-221 also promotes HUVEC migration and angiogenesis and negatively regulates PIK3R1 [71]. Wang et al. found that the expression level of miR-210–3p in OSCC tissues was higher than that in para-cancerous tissues, and exosomes extracted from CAL27 cell-conditioned medium carried miR-210–3p to HUVECs to target the downstream molecule ephrin-A3 (EFNA3) and alter angiogenesis [72]. Phenformin was used to treat OSCC cells, and the expression levels of miR-1246 and miR-205 in exosomes extracted from OSCC cells after the treatment were determined. After HUVECs were treated with the exosomes, it was observed that in the HUVECs, overexpression of miR-1246 and miR-205 inhibited angiogenesis via downregulation of vascular endothelial growth factor A (VEGFA) expression [73]. Oral leukoplakia- and OSCC mesenchymal stem cell-generated exosomes (OLK-Exo and Ca-Exo, respectively) increase the expression levels of CD31/VEGFA in HUVECs and promote the angiogenic ability of HUVECs compared to the effect of exosomes (N-EXO) secreted by normal mucosal mesenchymal stem cells. Additionally, both OLK-Exo and Ca-Exo show enhanced levels of matrix metalloproteinase 1 (MMP1); however, suppressing MMP1 production can counteract the stimulatory effects of OLK-Exo and Ca-Exo on HUVECs [74]. Morioka et al. studied two OSCC cell lines established from locally recurrent tongue cancer and found that exosomes derived from highly metastatic OSCC cell lines (SQUU-B cells) had a greater ability to promote vascular growth and lymphangiogenesis than exosomes derived from non-metastatic OSCC cell lines (SQUU-A cells) [75]. Tumor cells secrete substances that promote the growth of new blood vessels, thereby bringing oxygen to support tumor growth and altering their adhesive properties to promote migration and invasion of the newly formed vasculature [76]. Table 1 summarizes the role of exosomes secreted by OSCC cells in transmitting them to other cells.

5. Exosomes secreted by non-OSCC cells enter OSCC cells and play an important role in the progression of the disease

5.1. The regulatory mechanism of exosomes secreted by carcinoma-associated fibroblasts (CAFs) on OSCC cells

CAFs contribute to cancer development by releasing growth factors, cytokines, and exosomes. The TME is rich in CAFs, which are crucial for cell-cell communication and tumor development. Li et al. found that the expression level of miR-34a-5p was downregulated in exosomes extracted from CAFs, and after exosomal miR-34a-5p molecules were transferred to OSCC cells, the expression of miR-34a-5p was downregulated. Moreover, targeted binding with the downstream molecule AXL regulates the AKT/glycogen synthase kinase 3β (GSK-3β)/β-catenin/Snail signaling axis, the EMT and increases the metastatic ability of OSCC cells [77]. Other studies have also shown that the expression level of miR-382–5p in CAFs is higher than that in the fibroblasts of normal tissues. Analysis of exosomes extracted from CAFs revealed that those carrying miR-382–5p could enter OSCC cells and increase the migratory and invasive abilities of OSCC cells [78]. He et al. discovered that miR-146b-5p from CAFs-derived exosomes directly binds to the downstream homeodomain-interacting protein kinase 3 (HIKP3) molecules, thereby altering cell growth and metastatic abilities of OSSC cells [79]. Similarly, overexpression of lncRNA TIRY in CAFs activates Wnt/β-catenin signaling; miR-14 is carried to the recipient OSCC cells by CAFs-derived exosomes that overexpress TIRY, Overexpression of miR-146b-5p can enhance the growth and metastasis of OSSC cells [80]. Principle et al. established a primary culture of CAFs and normal fibroblasts, and also cultured SCC25 cells, either in a medium containing exosomes secreted by fibroblasts or in a medium without exosomes. The proliferation and migration of SCC25 cells were distinctly obvious when the SCC25 cells were co-incubated in the exosome-containing medium [81]. In addition, Wang et al. discovered that exosomes derived from CAFs might enhance OSCC cells proliferative capacity and participate in the immunological control of tumors after co-incubation with OSCC cells [82]. CAFs-derived exosomes can serve as transport vehicles for proteins, nucleic acids, metabolites, and other substances to the TME. They provide raw materials for cancer cells, participate in cancer cell proliferation, migration, and invasion, and induce metabolic reprogramming. Additionally, intake of CAFs-derived exosomes by cancer cells enhances their ability to evade immune cell attacks [126]. Thus, during OSCC development, CAFs maintain bidirectional crosstalk with cancer cells by secreting exosomes, thereby creating a supportive niche.

5.2. The regulatory mechanism of exosomes secreted by macrophages on OSCC cells

Macrophages in the OSCC tumor environment are closely associated with OSCC progression. Tumor-associated macrophages can promote tumor progression by stimulating tumor proliferation, angiogenesis, and metastasis and providing an antitumor immune barrier [83]. According to the finding of AI et al., co-incubation of OSCC cells in a culture medium containing exosomes derived from macrophages overexpressing the recombination signal binding protein for immunoglobulin kappa J region (RBPJ) may reduce the ability of OSCC cells to proliferate and invade; when RBPJ-overexpressing macrophage-derived exosomes deliver LBX1-AS1 to the recipient OSCC cells, overexpression of LBX1-AS1 can inhibit tumor growth through the miR-182–5p/FOXO3 axis [84]. When M2 macrophage-derived exosomes (M2-exos) carrying miR-31–5p are taken up by OSCC cells, these exosomes promote OSCC growth and block the Hippo signaling pathway and large tumor suppressor kinase 2 (LATS2) gene expression [85]. Four years after the publication of this report, You et al. reported that the expression level of interleukin-6 (IL-6) was significantly increased in M1 macrophages treated with exosomes derived from OSCC cells; they extracted the conditioned medium (CM) from exosome-activated M1-like tumor-associated macrophages (TAMs) and observed that the expression of membrane metalloendopeptidase and matrix metalloproteinase 14 (MMP14) was upregulated in OSCC cells treated with the CM extracted from M1-like TAMs; moreover, M1-like TAMs promoted the EMT of OSCC cells, enhanced the cancer stem cell (CSC) phenotype via the IL-6/Janus tyrosine kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling pathway, and promoted the expression of THBS1 in OSCC cells [86].

5.3. Regulation mechanism of exosomes secreted by mesenchymal stem cells and other cells on OSCC cells

Exosomes secreted by mesenchymal stem cells (MSCs) may influence the tumor microenvironment [87], and stem cell-derived exosomes can transport a variety of non-coding RNAs (including microRNAs and lncRNAs) and proteins to promote cell proliferation and survival [88]. Exosomes produced by MSCs are useful for delivering drugs and treating inflammation. MSC-derived exosomes can exist stably for a long time after their generation in the plasma, which can be stored at −20 °C, and thus, MSCs have certain advantages over other cell types. Qiu et al. found that transfection of MSC-derived exosomes (MSC-Exos) and treatment with cabazitaxel (CTX) induced apoptosis in OSCC cells (range, 10:1–5:1) [89]. Exosomes secreted by human bone marrow-MSCs can transfer miR-101–3p to OSCC cells, downregulate COL10A1, and inhibit OSCC growth [90]. Rosenberger et al. used hamster buccal pouch carcinoma as an animal model, which shows a pattern of abnormal gene expression similar to that observed in human OSCC cells and found that stem cell-derived exosomes inhibited angiogenesis and tumor growth in OSCC cells [91]. Liu et al. established xenografted tumor mouse models and found that exosomes derived from the stem cells of human deciduous exfoliated teeth (SHED-Exos) inhibited the formation of microvessels in OSCC tumors, suggesting that these exosomes exhibited an antitumor activity [92]. Furthermore, in addition to receiving signals from the tumor, MSCs can pass information horizontally to neighboring cells, transforming the cellular

Table 2
Exosomes secreted by non-OSCC cells reach OSCC cells.

	Author/ year	Donor cells/body fluids/tissues	Exosome carrier molecule	Receptor cell	Molecular/ signaling pathways in receptor cells	The function of exosomes acting on receptor cells
1	Li et al., /2018	Carcinoma-associated fibroblasts (CAFs)	miR-34a-5p	CAL-27; SCC-15	AXL; Akt/GSK-3β/ β-catenin/Snail	Exosomes overexpressing miR-34a-5p from donor cells act on recipient OSCC cells, reducing their proliferation, invasion and migration ability
2	Sun et al., /2019	Fibroblasts around primary cultured OSCC tissue; Fibroblasts isolated from primary cultured normal tissues	miR-382–5p	miR-382–5p	_	The exosomes overexpressing miR-382–5p from CAFs donor cells act on the recipient OSCC cells and promote their migration and invasion
3	He et al., /2023	Primary cultured CAFs	miR-146b-5p	CAL-33; HSC-6	HIPK3	After knockdown of exosome miR-146b-5p from CAFs donor cells, it acts on recipient OSCC cells and inhibits their migration and invasion
4	Jin et al., /2020	CAFs overexpressing TRIY	miR-14	Tca8113	EMT	When the exosomes carry miR-14 and act on the receptor Tca8113 cell, the invasion and migration ability of Tca8113 cell with exosomes is lower than that of Tca8113 cell without exosomes
5	Principle et al., /2018	Primary cultured CAFs	_	SCC-25	_	Exosomes secreted by CAFs can increase the proliferation and migration of recipient OSCC cells
6	Wang et al., /2023	CAFs	_	CAL-27	_	Exosomes derived from donor CAFs can promote the proliferation of recipient OSCC cells, which is related to immune infiltration
7	AI, etc./ 2021	Macrophages overexpressing RBPJ; and macrophages not expressing RBPJ	LncRNA LBX1-AS1	SCC-4; CAL-27	LncRNA LBX1-AS1/miR-182–5p/ FOXO3	Knockdown of LBX1-AS1 can eliminate the inhibitory effect of RBPJ overexpressed macrophage derived exosomes on receptor OSCC cells
8	Yuan et al., /2021	M2 macrophage	miR-31–5p	OSCC cells	LATS2; Hippo signaling pathway	Exosome mir-31–5p promotes OSCC progression when acting on OSCC cells
9	Qiu et al., /2020	The exosomes derived from mesenchymal stem cells expressing TRAIL were transfected and co-incubated with docetaxel CTX (MSCT-exo/CTX)	_	SCC-25	_	MSCT-exo/CTX can induce apoptosis of SCC-25 cells
10	Xie et al., /2019	HBMSCs (human bone marrow mesenchymal stem cells)	miR-31–5p	Tca8113	COL10A1	The exosome miR-101–3p can inhibit the proliferation, migration and invasion of OSCC cells
11	Liu et al., /2019	SHED-Exos (stem cells of human decidous exfoliated teeth)	miR-100–5p miR-1246	HUVECs	miR-100–5p/ mTOR/HIF-1α; miR-1246/ACE; VEGFA	SHED-exos inhibits angiogenesis in vivo
12	Deng et al., /2022	HEK293T	miR-34a	HN6	_	After co-incubation with the receptor hn6 cells, miR-34a inhibited the proliferation, migration and invasion of HN6 cells
13	Chen et al., /2018	HIV infected T cells	_	HSC-3	_	Exosomes secreted by HIV infected T cells can promote the proliferation, migration and invasion of HSC-3 cells

environment into one that supports tumor survival [93].

Meanwhile, Deng et al. found that transferring cholesterol-modified miR-34a into exosomes secreted by HEK293T cells, followed by transferring exosome miR-34a into HN6 receptor cells, affected the proliferation and metastatic ability of HN6 cells [94]. In another study, exosomes released by HIV-infected T cells upregulated proto-oncogenes in HSC-3 cancer cells, promoting cell proliferation [95]. Overall, exosomes serve as "messengers" for cell-cell communication, carrying their contents to target OSCC cells and influencing the proliferation, migration, invasion, and vascularization of OSCC cells. Owing to the close association of OSCC cells with exosomes, exosomes have emerged as key markers for the treatment of OSCC. Table 2 summarizes the role of exosomes secreted by other cells in delivering them to OSCC cells.

6. Relationship between OSCC-derived exosomes and clinical prognosis

OSCC patients have poor overall survival rates. The TME promotes tumor proliferation, local invasion, distant metastasis, and other factors. Exosomes are important factors in the crosstalk between cancer cells and various components [96]; thus, they have important research significance, because they are relatively easy to isolate from body fluids and they can deliver a variety of indicators with varying degrees of specificity. In addition, the number of exosomes detected in body fluids can serve as a marker for detecting or predicting tumors and distinguishing patients with cancer from healthy individuals [97]. For OSCC diagnosis, in addition to analysis of cell-derived exosomes, exosomes can be extracted from body fluids such as plasma, serum, and saliva. Exosomes secreted by these components may also serve as potential disease biomarkers.

6.1. Relationship between exosomes extracted from plasma of patients with OSCC and prognosis

One week after surgery, in the plasma of OSCC patients, the expression level of exosomal CD63 was decreased, and that of exosomal CAV-1 increased, which may have been related to the immediate postoperative inflammatory response. Statistical analysis has shown that when the expression levels of CD63 and CAV-1 in exosomes are low, the mean survival time after OSCC surgery is relatively high [98]. He et al. found that the expression level of miR-130a in exosomes extracted from the plasma of patients with OSCC before surgery was higher than that in exosomes extracted from the plasma of healthy people; furthermore, the expression level of miR-130a in tumor tissues was higher than that in non-cancerous tissues. Moreover, high expression levels of exosomal miR-130a were significantly associated with poor patient survival [99]. These findings indicate that exosomes isolated from the plasma can be used as biomarkers for prognostic prediction and diagnosis of patients with OSCC.

6.2. Relationship between exosomes extracted from serum of patients with OSCC and prognosis

Li et al. divided patients with OSCC into two groups based on the presence or absence of lymph node metastasis and compared these patients with those in the control group. Proteomic analysis was performed on the serum exosomes in these patients, and it was found that PF4V1, CXCL7, F13A1, and AP0A1 in the exosomes may serve as markers for the diagnosis of lymph node metastasis in OSCC [100]. Furthermore, when exosomal Circ-047733 is highly expressed, the patients are at a low risk of lymph node metastasis [101]. In another study, exosomes were extracted from the serum of patients with OSCC and healthy controls, and it was observed that the expression level of exosomal Circ-0000199 in the OSCC group was significantly higher than that in the healthy control group; prognostic analysis revealed that the survival rate in patients with high expression levels of exosomal Circ-0000199 was lower than that in patients with its low expression levels [102].

6.3. Relationship between exosomes extracted from salivary of patients with OSCC and prognosis

Apart from the exosomes extracted from the plasma and serum, salivary exosomes can also be used as biomarkers [103]. Nakamichi et al. analyzed exosomes in the serum and saliva of patients with OSCC and healthy controls and found that the expression levels of ALIX in serum- and saliva-derived exosomes in the OSCC group were higher than those in the control group [104]. Furthermore, miR-1307–5p was reported to be highly expressed in the salivary exosomes of patients with OSCC, suggesting that it may be related to poor prognosis [105].

7. Relationship between exosomes and OSCC treatment

7.1. Relationship between exosomes and resistance to treatment in OSCC

Resistance to chemotherapy is one of the main causes of OSCC recurrence, hindering its treatment and management. The main causes of chemotherapy resistance include EMT, drug efflux, DNA damage repair, cell death inhibition, changes in drug targets, drug inactivation, and epigenetics [106]. In one study, miR-155 mimics were added to cisplatin-resistant OSCC cells, exosomes were extracted and transferred to cisplatin-sensitive OSCC cells. The expression of miR-155 was upregulated in cisplatin-sensitive OSCC cells, drug resistance of cisplatin-sensitive OSCC cells was enhanced with FOXO3a as a binding target [107]. One year later, the authors conducted further experiments to verify these findings using three-dimensional tumor sphere and mouse models and demonstrated that exosomes containing miR-155 inhibitors induced mesenchymal-to-epithelial transformation in cisplatin-resistant models and improved cisplatin resistance in OSCC cells [108]. Treatment with recombinant epidermal growth factor (EGF) promotes the entry of

OSCC cell-derived exosomes into OSCC cells, and this process can be blocked by EGF receptor (EGFR) inhibitors (erlotinib and cetuximab). However, EGFR inhibitors not only inhibited the proliferation and metastasis induced by exosomes in OSCC cells, but also inhibited the chemical resistance of OSCC cells induced by exosomes [109]. By triggering the AKT/GSK-3 signaling pathway, macrophage-derived exosomes may reduce the susceptibility of OSCC cells to 5-FU and cisplatin (CDDP) [110]. Gui et al. reported that in comparison to that observed in HSC-3 and docetaxel (DTX)-resistant HSC-3 (HSC-3DR) cells, normal tongue epithelial cells (NTECs) show a higher expression level of miR-200c. When exosomes are extracted from NTECs and transferred to HSC-3DR cells, the exosomal miR-200c boosts the sensitivity of DTX-resistant HSC-3 cells to DTX by targeting tubulin, beta 3 class III (TUBB3) and protein phosphatase 2 scaffold subunit Abeta (PPP2R1B) [111].

7.2. Exosomes as a drug delivery system for the treatment of OSCC

Exosomes are thought to serve as intercellular drug delivery systems because of their capacity to deliver materials to recipient cells. Exosomes, as exogenous or endogenous drug delivery vehicles, can increase target sensitivity [112]. Compared with liposomes and synthetic nanoparticles, exosomes show higher antitumor efficacy [113] and lower cytotoxic effects upon delivery [114]. Zhang et al. used milk-derived exosomes to establish a pH/light-sensitive milk exosome-based drug system for OSCC therapy. The advantages of this novel milk exosome-based drug delivery system include controlled drug release, biocompatibility, and safety [115]. In another study, Kase et al. constructed a specific OSCC-targeted engineered exosome that could stably transfer siLCP1 to recipient OSCC cells, thereby significantly inhibiting the proliferation and migration of OSCC cells [116]. Exosomes secreted from gingival MSCs (GMSCs) or a combination of GMSCs and small intestinal submucosal extracellular matrix (SIS-ECM) can promote recovery of tongue papillae and taste bud regeneration [117]. However, the isolation of high-purity exosomes is a long and challenging process; the number of exosomes extracted is usually relatively low, and some patients may experience adverse immune reactions after exosome delivery [118]. Although previous studies have suggested that engineered exosomes, including those combined with other nanomaterials, can lead to enhanced or synergistic therapeutic effects [127], their clinical translation is still facing challenges. These challenges include standardizing the extraction, quantification, and analysis of exosomes from blood and tissues, as well as selecting the appropriate exosomes for different tumor types. It is important to address these issues. Owing to the burgeoning significance of exosomes in the identification and management of OSCC, the investigation of exosomes for abating drug resistance and devising personalized therapeutic medications represents one of the current research hotspots.

8. Discussion

Exosomes are excellent biomarkers for the detection of OSCC; however, many aspects, including their production, secretion, cargo transport, and fusion with target membranes, which are worthy of in-depth study, remain unknown. Exosomes have not been consistently detected or isolated using the existing methods. We will be able to better comprehend the disease mechanism and offer recommendations for the diagnosis and therapy of OSCC if we have a thorough understanding of the intricacies of exosomes [19]. The safety of use of exosomes requires further investigation. Further studies involving large animal models are required to establish the effectiveness of exosomes in therapeutic settings. In this paper, we have summarized the known information on the biogenesis of exosomes and the transport of exosomes between OSCC and normal cells. As universal and important intercellular linkers, the exploration of exosomes' function provides an important direction for the treatment of OSCC. OSCC-derived exosomes promote tumor growth, angiogenesis, invasion, and pre-metastatic niche formation, enhance the treatment-resistant behavior of tumor cells, and affect the functioning of macrophages and other cells [119]. The mRNAs, miRNAs, lncRNAs, and circRNAs can be delivered to OSCC cells via cell-derived exosomes, which may affect OSCC cell proliferation, migration, and invasion. Exosomes are non-cytotoxic, long-lasting, and can be used as drug delivery systems [19]; however, clinical investigations using natural exosomes are still in the early stages. Artificial exosomes have the commercial advantage of large-scale production, and their combination with anti-cancer drugs may be the key to cancer treatment. The first steps toward exosome-targeted treatment for OSCC have been taken. Exosomes can be modified to bind and encapsulate relevant DNA, RNA, or protein molecules, interact with different receptor cells in the body, and target and inhibit the spread of OSCC. Exosomes have the potential for treating cancer, and this has been proven in other areas of cancer treatment [120]. Safety concerns associated with OSCC-derived exosomes need to be explored further because they may impede the antitumor response and promote metastasis [1]. Exosomes produced by OSCC cells may have heterogeneous effects and varying impacts, which may be the main direction of future research. Further basic and clinical studies are needed to confirm the efficacy of the current exosome-based vaccines for OSCC prevention before these can be applied clinically. In the future, we will fully exploit the advantages of exosomes as natural carriers and overcome their shortcomings to provide a new and effective treatment strategy for patients with cancer.

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CRediT authorship contribution statement

Xingyue Ma: Writing – review & editing, Software, Resources, Methodology. **Ruisi Yang:** Writing – original draft, Validation, Resources. **Haiyang Li:** Investigation, Data curation. **Xiaoyan Zhang:** Validation, Conceptualization. **Xiao Zhang:** Resources, Data curation. **Xiangjun Li:** Writing – review & editing, Validation, Supervision.

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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