

# Progress of Tumor-Derived Exosomes in Head and Neck Squamous Cell Carcinoma

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**Abstract:** Exosomes are extracellular vesicles 40 to 160 nm in diameter that mainly mediate information transmission and substance exchange between cells, and increasing evidence suggests that exosomes are involved in the development of tumors and have great potential in cancer diagnosis and treatment. Squamous cell carcinoma of head and neck is one of the common malignant tumors in the whole body. Although various treatments continue to develop, the 5-year survival rate remains only 50%, which may be related to its characteristics such as easy lymphatic metastasis, chemotherapy resistance and poor radiotherapy sensitivity. Researchers are paying more and more attention to TDE, and studies connected to it have significantly improved our understanding of the causes, development, diagnosis, and prognosis of HNSCC. Head and neck squamous cell carcinoma-derived exosomes involve tumor initiation, progression, immune regulation, diagnosis and treatment application, and are anticipated to serve as therapeutic targets and biomarkers for early tumor diagnosis, and new ideas for improving the survival rate and prognosis of patients with head and neck squamous cell carcinoma are provided by their related studies. Here, in order to bring our knowledge of exosomes derived from head and neck squamous cell carcinoma up to date, we examine the development of research on tumor-derived exosomes in the disease.

**Keywords:** Head and Neck Squamous Cell Carcinoma, Tumor-Derived Exosomes, miRNAs, Proteins

## 1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the most widely recognized head and neck danger and creates from the mucosal epithelium of the oral cavity and throat, chiefly including oral disease, nasopharyngeal malignant growth, oropharyngeal disease, hypopharyngeal malignant growth, and laryngeal malignant growth. HNSCC has the sixth highest incidence of all cancers worldwide, additionally, the incidence is rising annually, with factors like smoking and drinking alcohol, exposure to environmental pollutants and viral infections, namely human papilloma virus (HPV) and Epstein-Barr virus (EBV). The five-year survival rate of HNSCC is only 50%, and the main current treatments include surgical treatment, chemoradiotherapy, and immunotherapy, but the results are unsatisfactory, and most patients have a

poor prognosis and a lower standard of living [1, 2]. Therefore, it is crucial to investigate the biomarkers and development mechanism of HNSCC and further explore new treatments for head and neck squamous cell carcinoma to improve the prognosis of patients.

Exosomes are extracellular vesicles that can be released by a variety of cell types and have a diameter of 40 to 160 nm, such as immune cells, endothelial cells, blood cells, smooth muscle cells, etc., and mainly contain proteins, DNA, mRNA, miRNAs, lipids and other substances [3]. Exosomes are naturally found in blood, saliva, urine, cerebrospinal fluid, milk, and other body fluids, and mediate information transmission and substance exchange between cells [4].

In addition to their general properties, tumor-derived exosomes (TDE) are involved in the onset and progression of various cancer processes and mediate tumorigenesis in a significant way, microenvironment of a tumor remodeling,

immune tolerance, promoting metastasis, and therapeutic resistance [5]. TDE may be a tumor diagnostic marker and therapeutic target, according to increasing evidence. Therefore, this article examines the role that TDE played in the formation of HNSCC from the perspective of different contents of exosomes, as well as its application in tumor diagnosis and treatment, generating fresh concepts for the appropriate medical diagnosis and treatment.

## 2. Exosomes and HNSCC Diagnosis

Tumor-associated exosomes are continuously secreted into various body fluids and are expected to be important liquid biopsy markers for tumor diagnosis [6]. Hofmann et al. [7] demonstrated that compared to TDE, total exosomes from HNSCC patients' plasma contained higher levels of CD16, and total exosome CD16 surface levels were correlated with tumor clinicopathological parameters. CD16 + exosomes have the potential to serve as biomarkers for the aggressiveness and stage of HNSCC tumors. Theodoraki et al. [8] found that CD44v3 relative fluorescence intensity values on serum CD3-exosomes correlated with UICC stage and lymph node metastasis and were higher in HNSCC patients than in healthy controls. In addition, CD44v3 + exosomes exhibited more immunosuppressive proteins in the body (PD-L1, FasL, TGF- $\beta$ 1) compared to CD44v3 - exosomes in HNSCC patients, and the relative fluorescence intensity of these markers was also linked to a more advanced disease stage and lymph node metastasis.

Exosomes contain abundant contents, of which proteins are one of the potential tumor diagnostic markers. Sanada [9] et al. found that by comparing serum samples from HNSCC patients and healthy controls, elevated levels of exosomal LOXL2 (lysine oxidase 2) were found in early but not advanced tumor stages. Nakamichi et al. [10] found that exosome Alix (apoptosis-junction gene-2-interacting protein X) levels in saliva and serum were significantly higher in OSCC patients than in healthy controls. Exosome Alix was thought to be a potential OSCC diagnostic biomarker. Li et al. [11] used proteomics and bioinformatics to look at the content of serum exosomal protein in 30 patients with oral squamous cell carcinoma (OSCC) who had lymph node metastasis, patients without lymph node metastasis, and healthy controls. They found that the PF4V1, CXCL7, F13A1, and ApoA1 proteins from serum exosomes may have something to do with OSCC's metastasis and help diagnose OSCC patients. Similarly, proteomics analysis was performed, and Qu et al. [12] found 43 unique dysregulated extracellular vesicle-associated proteins by comparing serum extracellular vesicle-associated protein content between non-cancer controls and oral tongue squamous cell carcinoma (OTSCC) patients with or without lymph node metastasis, which could serve as differentiating biomarkers between OTSCC with and without lymph node metastasis and controls who are not cancerous.

Serum exosomes containing miRNAs play a crucial part in both physiological and pathological conditions, and therefore

also have the potential to be tumor diagnostic markers. Wang et al. [13] found that the expression of exosomal miR-21 and HOTAIR was significantly higher in patients with laryngeal squamous cell carcinoma (LSCC) than in patients with vocal cord polyps. This difference was correlated with the clinical stage of LSCC as well as the presence or absence of lymph node metastasis. It's possible that HOTAIR expression analysis and serum exosomal miR-21 expression analysis can help diagnose LSCC. 16 miRNAs were found to be differentially expressed between paired tumor tissues and benign tissues in OTSCC patients' plasma and benign and malignant tongue tissues, of which 9 were up-regulated and 7 were down-regulated in tumor tissues [14]. Fifteen of the 16 miRNAs were expressed in circulating exosomes, and the number was more than that directly detected in plasma, suggesting that detecting miRNAs expressed in exosomes may be a more dependable strategy to survey coursing miRNA articulation in cancers. Similarly comparing exosomal miRNA expression differences, Langevin et al. [15] compared miRNA content in exosomes derived from Oral epithelial control cells and lineages of HNSCC cells and miR-486-5p, miR-486-3p, and miR-10b-5p were found to be useful non-invasive HNSCC biomarkers after being validated in salivary exosomes from HNSCC patients and healthy controls. In addition, it has been shown that miR-365 concentration in exosomes secreted by OSCC cells is increased, and the detection of exosomal miR-365 content in saliva or blood of OSCC patients is expected to be one of the important methods for tumor diagnosis [16].

## 3. TDE Contents and Tumor Development

Tumor-derived exosomes are secreted by tumor cells and transmit molecular and genetic information from tumors to nearby or distant normal or abnormal cells. The mechanism of tumor-derived exosomes serving tumor development is one of the hotspots in cancer research.

### 3.1. Proteins

Proteins in TDE have the ability to alter normal immune cell function and can reflect the presence and activity of disease. Theodoraki et al. [17] found that by PD-1 and PD-L1 staining of exosomes in plasma, PD-L1 levels carried by exosomes were correlated with disease activity, UICC stage, and lymph node metastasis in forty HNSCC patients. In contrast, sPD-L1 levels or exosomal PD-1 levels in plasma were not associated with any clinicopathological parameter. In addition, co-incubation of exosomes with high PD-L1 expression with activated human CD69 + CD8 + T cells suppressed CD69 expression levels, indicating that immunosuppression in HNSCC was reduced by inhibiting signaling from PD-1+ T cells to exosomes containing PD-L1. Also in tumor-related immunosuppression, Theodoraki et al. [18] found that both CD3 + and CD3 - exosomes carry anti-inflammatory proteins and inhibit the human immune

system's function. HPV is one of the most crucial factors influencing the prevalence of HNSCC, and HPV (+) patients respond well to treatment, possibly because there are more powerful immune responses against tumors. Exosomes from HPV (+) and HPV (-) HNSCC cell lines were compared to see which ones had more CD47 and CD276 antigens, which are associated with immune effector cells, in their proteomes [19], and only exosomes from HPV (-) cell lines contained the MUC-1 and HLA-DA antigens that promote tumor growth, and differences in protein content in exosomes from the above two cell lines may contribute to differences in HPV (+) and HPV (-) HNSCC immune responses.

Macrophages polarize into M1/M2 macrophages in the microenvironment, express corresponding specific genes, and exercise different functions, and polarization typing of macrophages is widespread in most tissues such as tumors and fats. It has been shown that exosomal CMTM6 (chemokine-like factor superfamily member 6) secreted by OSCC cells induces M2 macrophage polarization through the signaling pathway ERK1/2 (extracellular signal-regulated kinase 1/2) and promotes tumor malignant progression, which demonstrates a novel method of tumor and immune cell interaction in the OSCC microenvironment [20]. Xiao et al. [21] showed that THBS1 (thrombospondin) from exosomes of OSCC cells is necessary for macrophage polarization to the M1 phenotype and further induces M1 tumor-associated macrophages, significantly promoting migration of OSCC cells.

A sufficient supply of blood is necessary for the growth of solid tumors, and Ludwig et al. [22] found that through functional reprogramming and phenotypic regulation of endothelial cells, TDE in HNSCC effectively induced angiogenesis in vitro and in vivo, which may be related to angiogenic proteins carried by TDE.

In addition, tissue hypoxia is one of the characteristics of HNSCC, which is thought to accelerate tumor progression and increase anti-tumor therapy resistance. KT33B, DYSF, STON2, MLX, LIPA3, NEK5, and P12L1 were the seven hypoxia-related proteins found in tumor-derived extracellular vesicles released under hypoxic conditions, while pro-angiogenic proteins were abundant in extracellular vesicles released under normoxic conditions [23]. A biomarker for underlying hypoxic conditions, the protein profile of HNSCC-derived extracellular vesicles reflects the degree of tumor hypoxia.

### 3.2. miRNAs

MiRNA (microRNA) is an endogenous non-coding RNA, mostly composed of 19 to 22 nucleotides, and miRNAs in TDE are mostly abnormally expressed in tumors and are potential tumor biomarkers, which have a lot to do with how tumors grow in different situations. Zhao et al. [24] discovered that serum exosomes from LSCC patients showed upregulation of 34 miRNAs and downregulation of 41 miRNAs compared with healthy controls, with miR-941 significantly upregulated and the same pattern in LSCC cells and tissues. Serum exosomal miR-941 may be a promising

oncogenic biomarker and important therapeutic target for the diagnosis of LSCC, as studies have further demonstrated that miR-941 overexpression encourages tumor cell proliferation and invasion. Yan et al. [25] demonstrated that OSCC cell-derived exosomes mediated miR-130b-3p promoted progression and angiogenesis in vivo and in vitro, providing new perspectives for exploring effective therapeutic strategies against OSCC. Also against exosomal miRNAs derived from OSCC cells, He et al. [26] found that PIK3R1 (phosphatidylinositol-3-kinase regulatory subunit 1) could be targeted by miR-221 and negatively regulated, thereby promoting vascular endothelial cell migration and angiogenesis. Chen et al. [27] found that both exosomal miR-155 and miR-21 inhibited tumor progression by downregulating the expression of PTEN and Bcl-6, and exosomal miR-126 also downregulated target gene EGFL7 as a tumor suppressor in OSCC. Both miR-155 and miR-21 were significantly upregulated in the primary cells and serum of OSCC patients. In addition, this study suggests that biomarkers for OSCC diagnosis and prognosis may be serum exosomal miRNAs.

### 3.3. lncRNAs, circRNAs and Purine Metabolites

In addition to the main exosome contents mentioned above, increasing studies have shown that tumor-derived exosomes also contain other types of substances, such as lncRNAs, circRNAs, purine metabolites, which can also act as a mediator between tumor cells and the microenvironment in which they live.

Zhou et al. [28] observed that lncRNA ADAMTS9-AS2 was down-managed in OSCC tissues contrasted and oral submucosal fibrosis (one of the precancerous sores of oral squamous cell carcinoma) tissues and ordinary mucosal tissues, and utilitarian examinations showed that lncRNA ADAMTS9-AS2 in cancer cell-determined exosomes restrained the development, movement and attack of OSCC cells, and these outcomes uncovered that lncRNA ADAMTS9-AS2 assumes a critical part in the carcinogenesis of oral mucosal tissues.

The tumor recurrence rate and mortality rate of patients with high exosome circ0000199 expression are higher than those of patients with low exosome circ0000199 expression, and studies have demonstrated that the level of circ0000199 in the serum exosomes of patients with OSCC is significantly correlated with areca nut chewing, tumor size, lymphatic metastasis, and TNM stage. Additionally, OSCC cell growth was slowed down when circ0000199 was knocked out, whereas OSCC cell growth was accelerated when circ0000199 was overexpressed. This proof proposes that upregulation of circ0000199 in serum exosomes from patients with OSCC is decidedly connected with more terrible endurance results, and serum exosome circ000019 can be utilized as a biomarker and likely helpful objective for OSCC [29].

Ludwig et al.[30] found that compared with healthy controls, the levels of purine metabolites in exosomes isolated from the plasma of HNSCC patients were higher, the levels of adenosine in exosomes of patients with early tumor

stage and without lymph node metastasis were significantly increased, and the levels of adenosine in exosomes of patients with advanced tumor stage and lymph node metastasis were decreased. This suggests that changes in the content and levels of purine metabolites in circulating exosomes reflect disease progression in HNSCC patients.

#### 4. Exosomes and HNSCC Treatment

Exosomes, as endogenous nanocarriers of various molecules, are expected to be used to treat tumors by delivering chemotherapeutic drugs and siRNA (small interfering RNA), and in addition, exosomes have applications in improving tumor chemoradiotherapy sensitivity and evaluating treatment prognosis.

Li et al. [31] demonstrated that the miR-1224-5p/NSD2 (oncogene nuclear receptor binding SET domain protein 2) axis induced 5-fluorouracil resistance in OSCC through tumor-derived exosome-mediated transfer of the lncRNA APCDD1L-AS1. This provided a new target for enhancing OSCC's chemoresistance. Sayyed and co. [32] demonstrated the therapeutic potential of exosomes loaded with miR-155 inhibitors to improve cisplatin sensitivity in cisplatin-resistant OSCC 3D tumor spheroids and xenograft mouse models by demonstrating the role of exosomal miRNA-155 in OSCC cisplatin resistance by downregulating the target gene FOXO3a and inducing epithelial to mesenchymal cell transformation. Tong et al. [33] demonstrated that in HPV (+) HNSCC, miR-9-rich exosomes can polarize macrophages into the M1 phenotype and raise radiosensitivity. As a result, new strategies for increasing the radiosensitivity of tumors can be developed using exosomal miR-9 in the treatment of HNSCC. CircCUX1 has been viewed as upregulated in hypopharyngeal squamous cell carcinoma (HPSCC) patients with low radiosensitivity and predicts unfortunate endurance results, and knockdown of circCUX1 improves radiosensitivity of HPSCC cells. In addition, circCUX1-promoted radioresistance in HPSCC cells is dependent on the caspase 1 (cysteine protease 1) pathway. According to the evidence, circCUX1 may be a potential therapeutic target for HPSCC patients suffering from radiotherapy tolerance [34]. The epithelial mesenchymal transition (EMT), which can lead to a decrease in epithelial characteristics and an increase in mesenchymal characteristics in tumor cells, is crucial to the growth of malignant tumors. The anti-EGFR therapeutic antibody cetuximab inhibits this carcinogenesis by inhibiting epidermal growth factor receptor (EGFR) conversion of normal epithelial cells into a mesenchymal phenotype in extracellular vesicles derived from OSCC [35].

Engineered exosomes are one of the research hotspots of exosomes in cancer therapy in recent years. They are artificially prepared exosomes loaded with specific bioactive substances by nuclear drug loading and membrane modification, or changing the donor cell culture environment to achieve specific purposes. After finding that LCP1 (lymphocyte cytoplasmic protein 1) promoted OSCC

progression, Kase et al. [36] combined RNA interference technology with exosomes to prepare exosomes loaded with siLCP1 and demonstrated that it produced significant OSCC inhibition both in vivo and in vitro, and the findings of this study provided a useful new treatment idea.

Circulating exosomes have the role of real-time monitoring of tumor treatment efficacy and evaluating treatment prognosis, and have good clinical application prospects in the precise treatment of tumors. Theodoraki et al. [37] enrolled 18 HNSCC patients in a phase I clinical trial. All of the patients received a combination of cetuximab, ipilimumab, and radiotherapy, and the plasma of the patients was continuously checked for TDE and T cell-derived exosomes. In patients with tumor recurrence (N = 5) within two years, the results demonstrated that total exosomal protein, TED to total exosome ratio, total CD3 +, CD3 - PD-L1 +, and CD3 + 15s + exosomes increased from baseline; In patients without recurrence (N = 13), total exosomal protein and TED decreased, and CD3 + and CD3 + CD15s + exosomes remained stable for two years. CD3 + CTLA4 + exosomes decreased. This result reveals the possibility that exosomes instead of immune cells are used to monitor patient response to cancer therapy.

#### 5. Conclusion

Multivesicular bodies (MVBs), which are fused to the cell membrane, secrete exosomes into the extracellular space. Exosomes mediate communication between cells by sending a lot of contents that control how the recipient cells work [3]. TDE has received increasing attention from researchers, and its related research has made great progress in the HNSCC diagnosis, progression, treatment, and outlook. However, HNSCC has not been clinically diagnosed or treated with TED, which requires further exploration of the TDE release mechanism and its content action principles under conditions closer to physiologically relevant conditions. At the same time, engineered exosomes carrying specific bioactive molecules have also shown great promise in cancer therapy.

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