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Pivotal role of Exosomes in the diagnosis and treatment of Esophageal cancer: Entering a new Era of precision medicine

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Abstract

In this editorial we comment on the article published by Xing-Yu Ning *et al*, "Role of exosomes in metastasis and therapeutic resistance in esophageal cancer". Esophageal cancer (EC) represents a significant global health concern, being the seventh most common and sixth in terms of mortality worldwide. Despite the advances in therapeutic modalities, the management of patients with EC remains challenging with only 25% 5-year survival rate and a limited eligibility for curative surgery due to its late diagnosis. Conventional screening methods are impractical for the early detection of EC, given their either invasive or insensitive nature. The advent of liquid biopsy, with a focus on circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes, heralds a non-invasive avenue for cancer detection. Exosomes, small vesicles involved in intercellular communication, are highlighted as potential biomarkers for EC diagnosis and prognosis. Along with a diverse cargo encompassing various types of RNA, DNA molecules, proteins, and metabolites, exosomes emerge as key players in tumorigenesis, tumor development, and metastasis. Their significance extends to carrying distinctive biomarkers, including micro-RNAs (miRNAs), Long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), underscoring their potential diagnostic and prognostic value. Furthermore, exosomes may be utilized for therapeutic purposes in the context of EC treatment, serving as efficient delivery vehicles for therapeutic agents such as

chemotherapeutic medicines, miRNAs, *etc.* In this Editorial we delve into the applications of exosomes for the early detection and treatment of EC, as well as the future prospectives.

INTRODUCTION

Esophageal cancer represents a prevalent malignancy within the digestive system, ranking seventh globally in incidence and sixth in mortality, accounting for over 604,000 new cases and more than 544,000 deaths worldwide in 2020 [1-5]. This malignancy predominantly manifests in two histological subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). EAC typically arises in the lower part of the esophagus and is often associated with chronic gastroesophageal reflux disease (GERD). It is characterized by changes in the lining of the esophagus, known as Barrett's esophagus. On the other hand, ESCC typically originates in the upper or middle part of the esophagus and is closely linked to factors such as tobacco and alcohol consumption [1,4]. ESCC primarily affects East and Central Asia, while EAC is presented more in Western Europe and North America. Notably, China with its high prevalence, contributes to over 50% of newly diagnosed EC cases worldwide [1-3].

Despite advancements in surgical and systemic drug therapies, EC poses considerable challenges, with nearly half of patients experiencing distant metastasis or therapeutic resistance post-treatment. The 5-year survival rate for patients remains below 25%, with a median survival time ranging from 13.6 to 19.3 months. Surgery stands as the cornerstone treatment, yet only around 30% of newly diagnosed patients are eligible for curative resection [1-3,5]. Presently, there is a scarcity of effective biomarkers for early-stage ESCC detection. Moreover, a significant percentage of patients experience loco-regional recurrence following surgical resection aimed at cure. While adjuvant radiotherapy and chemotherapy hold importance for ESCC, their clinical efficacy remains a subject of debate, emphasizing the critical need for earlier diagnosis [1,3,5].

Endoscopic examination with biopsy or imaging studies, while being two of the main screening methods for EC they are invasive or insensitive, respectively. Emerging minimally invasive technologies like cytosponge or transnasal endoscopy face barriers related to cost and discomfort, limiting their widespread acceptance as screening methods for ESCC [5].

Liquid biopsy, which focuses on circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and extracellular vesicles (EVs), particularly exosomes, is a potential early detection method [2,5]. Exosomes, microvesicles (MVs), and apoptotic bodies are three types of EVs with exosomes having dimensions ranging from 30 to 150 nm playing an important role in intercellular communication. Exosomes carry a diverse cargo of RNA types (miRNAs, regulatory mRNAs, piwi-interacting RNA (piRNA), small nucleolar RNA (snRNA), tRNA-derived small RNAs (tsRNAs), long noncoding RNAs (lncRNAs), and unidentified small RNAs), DNA sequences, proteins, lipids, glycoconjugates, and metabolites, while they are present in multiple biological fluids, such as blood, saliva, urine, malignant ascites and cerebrospinal fluid, offering a non-invasive avenue for cancer detection compared to methods requiring phlebotomy, like ctDNA and CTCs [1–6]. Recent studies underscore the significant role of exosomes in tumorigenesis, development, and metastasis, participating in processes such as angiogenesis, extracellular matrix remodeling, and miRNA transfer [1,3]. Furthermore, exosomes harbor lncRNAs, pivotal in intercellular material exchange, signal transduction, and regulation of crucial oncological behaviors. The dysregulation of exosomal lncRNAs shows promise as diagnostic and prognostic biomarkers across various cancers [3].

In-depth comprehension of esophageal cancer epidemiology, subtypes, and associated biomarkers, with a particular focus on the role of exosomes, presents invaluable insights for advancing early detection, prognostication, and therapeutic strategies, aiming for enhanced outcomes among EC patients.

DIAGNOSIS AND EXOSOMES

Exosomes play pivotal roles in various stages of the tumor development cascade, encompassing tumor proliferation, angiogenesis, epithelial–mesenchymal transition (EMT), migration, microenvironment remodeling, and therapeutic resistance [1,2,7,8]. The early diagnosis and accurate prediction of therapy outcomes using exosomes have the potential to significantly enhance the prognosis of patients with esophageal squamous cell carcinoma (ESCC).

Exosomes emerge as potent cancer biomarkers due to their ease of extraction from most biofluids, exceptional stability, and capacity to convey dynamic information regarding the tumor state [1,2]. Zhao *et al* observed a notable upregulation in the levels of circulating exosomes (CEs) from ESCC patients, demonstrating a sensitivity of 75% and specificity of 85% in distinguishing ESCC patients from healthy individuals. The elevated level of CEs independently serves as a prognostic marker for ESCC patients [3].

Exosomal miRNAs, including miR-652-5p, miRNA-21, miR-766-3p, and miR-182, exhibit potential as diagnostic and prognostic biomarkers for ESCC. Particularly, miR-182 depletion in the postoperative period renders it a promising biomarker post-surgery. The serum miR-25/miR-203 ratio is significantly higher in ESCC, presenting potential for monitoring the effect of tumor resection and recurrence (sensitivity = 71.9%, specificity = 96.6%). Following surgery, the expression level of miR-25/miR-203 significantly decreases, as indicated by the ROC curve (sensitivity = 97.4%, specificity = 65.8%) [2,5,9–11].

Exosomal Dicer assumes a significant role in miRNA synthesis; thus, monitoring exosomal Dicer may prove more efficient than miRNA for diagnosing esophageal cancer [2]. Small RNAs derived from tRNA (tsRNAs), such as tRNA-GlyGCC-5 and sRESE in exosomes, display potential as pre-operative biomarkers for ESCC, predicting prognosis and response to adjuvant therapy. The combined sensitivity of tRNA-GlyGCC-5 and sRESE reaches 90.5%, with a specificity of 94.2% [5].

LncRNAs are extensively investigated as crucial biomarkers in various cancer types. Exosomal Related-lncRNAs (ER-lncRNAs), including AC082651.3, AP000487.1, PLA2G4E-AS1, C8orf49, and AL356056.2, are identified as potential markers for ESCC,

diminishing after surgery. ER-lncRNA pairs exhibit superior predictive value compared to traditional clinical indicators for median survival time [3].

ER-lncRNAs, such as PCAT1, UCA1, POU3F3, ESCCAL-1, and PEG10, are promising biomarkers for ESCC diagnosis and prognosis. Specifically, lncRNA UCA1 serves as a potent diagnostic marker with a sensitivity and specificity of 86.7% and 70.2%, respectively. These lncRNAs, as a diagnostic panel, provide an accurate diagnosis of early esophageal cancer [12]. Candidate lncRNAs, including AC098818.2, RASSF8-AS1, LINC00958, GMDS-DT, and AL591721.1, are significantly overexpressed in ESCC blood serum samples and cancerous tissues compared to healthy donors or other cancer types, indicating increased specificity for screening [13]. The expression levels of lncRNAs NR_039819, NR_036133, NR_003353, ENST00000442416.1, and ENST00000416100.1 increase in patients with ESCC and decrease after surgery. Serum lncRNA RASSF8-AS1 is identified as the most reliable diagnostic marker for ESCC [14].

CircRNAs also exhibit potential as diagnostic biomarkers. Has-circ-0001946 and has-circ-0043603, secreted by ESCC cells, may serve as diagnostic biomarkers for ESCC, with combined detection showing improved accuracy compared to single detection. Serum exosomal has-circ-0026611 emerges as a novel predictor of ESCC prognosis [15].

Exosomes, as carriers of various types of non-coding RNAs (nc-RNAs) and a multitude of molecules, present a comprehensive landscape for potential biomarkers. Zhu *et al* investigated four exosomal metabolites in ESCC patients, revealing a marker panel, including 3'-UMP, palmitoleic acid, palmitaldehyde, and isobutyl decanoate, with excellent diagnostic performance (AUC = 0.98) for predicting ESCC recurrence. Among these, 3'-UMP is identified as the most crucial for diagnosis [4]. Rao *et al*, observed that Intercellular adhesion molecule-1 (CD54) is upregulated in cancer tissues as well as the exosomal CD54, thus making it a great option for diagnostic biomarker. Utilizing exosomal CD54 as biomarker, they observed a sensitivity and specificity of 66.13%, and 71.31% respectively [16]. Exosomes exhibit advantages over other cancer biomarkers, such as circulating tumor cells and circulating tumor DNA, owing to their ample quantity, robust stability, and ease of accessibility.

UTILITY OF EXOSOMES IN THE TREATMENT

Exosomes serve as delivery tools, transporting miRNAs, mRNAs, lncRNAs, and proteins selectively to target cells. They possess unique natural advantages including immune-escape, easy penetration of cell membranes and specific recognition by receptor cells. Their low immunogenicity, high biocompatibility, long circulating half-life, less toxicity, and the ability to cross biological barriers, rendering them potent vectors for therapeutic agents [1,6,12].

Exosomes encapsulate various therapeutic agents, such as chemotherapeutic medicines, proteins, siRNAs, lncRNAs and miRNAs. Exosome-derived miR-154-5p attenuates the invasion of EC cells and inhibits their angiogenic capability in vitro, curbing the malignant progression of ESCC. Exosomal lncRNA UCA1 is observed to inhibit EC progression, and miR-339-5p transferred *via* exosomes induces radiosensitivity in ESCC cells. Certain exosomal miRNAs, like miR-339-5p, promote sensitivity to radiation therapy, downregulating Cdc25A. Thus, high levels of miR-339-5p in tumor tissues and serum indicate a good prognosis. Exosomal derived miR-375 promotes apoptosis and suppresses proliferation, invasion and migration of tumor cells, explaining its potential [1,17,18]. Exosomal miR-19b-3p transferred to cells reverses the inhibitory effect of PTEN overexpression on cell invasion. PTEN overexpression down-regulates MMP-2 and vimentin, and up-regulates E-cadherin. Thus, PTEN upregulation through exosomal miRNA seems promising [12,19]. Exosomes play a significant role in gene therapy, and exosomal ECRG4 mRNA is a potential target for EC gene therapy, suppressing cell proliferation *in vitro* and inhibiting tumor growth in vivo. Moreover, exosomes can exert antitumor effects from immune cells by displaying specific surface antigens, activating T cells vital for tumor immunity [2]. Specifically, engineered M1 macrophage-derived exosomes inhibit tumor growth and transform M2-type TAMs into M1-like macrophages [1]. Exosomes are also superior drug delivery systems compared to liposomes, polymers, *etc.*, due to their biocompatibility, biodegradability, and better target specificity. Adriamycin- and paclitaxel-loaded exosomes exhibit low

immunogenicity and toxicity, improving efficacy in treating multidrug-resistant cancer cells [1,12]. Engineered exosomes, with specific molecules attached, enhance targeting, increase production, and offer various lipid and protein compositions. The utilization of exosomes in immunotherapy is an important aspect. Dendritic cell-derived exosomes loaded with tumor antigens induce anti-tumor immune responses, showing potential in cancer therapy. Exosomes may play a role in inducing senescence, representing a promising strategy for ESCC treatment.

CONCLUSION

EC is a major worldwide health issue, with high incidence and mortality. At the present, the only definitive therapy is surgery, but by the time the tumor is diagnosed, it is at an advanced stage. Early identification and diagnosis may be the key to a better prognosis, and exosomal miRNAs, lncRNAs, and circRNAs show promise as diagnostic and prognostic indicators for ESCC. Exosomes are an appealing option for enhancing the accuracy of early diagnosis and prognosis prediction due to their ease extraction, stability, and ability to communicate dynamic information about the tumor status. Furthermore, the utilization of exosomes in the therapy of EC as a therapeutic drug delivery method, is under investigation. Their unique natural advantages, including immune-escape and specific recognition by receptor cells, rendering them as potent vectors for therapeutic interventions. In summary the potential of exosomes in early diagnosis and as carriers of therapeutic agents opens new avenues for precision medicine in the management of esophageal cancer.

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