Dichotomy of exosomes in oral squamous cell carcinoma: Prey or play!

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Abstract

Exosomes are nano-sized particles which belong to the family of extracellular vesicles (EVs) that are produced in the endosomal compartment of those cells which mediate intercellular communication. These particles can be found abundantly in the biological body fluids such as urine, blood, saliva, cerebrospinal fluid and breast milk. These vesicles can transfer genetic materials such as the microRNAs, noncoding RNAs, DNA and lipids by means of direct or indirect cell-to-cell interaction. Consequently, there has been lot of growing interest related to cancer exosomes as biomarkers and as potential therapeutics. There are studies done which demonstrate the exosomes in relation to cancer, by targeting specific cells and also promote the tumor progression. The other part of the spectrum has stressed the importance of exosomes stability and its potential role in targeting cancer cells through drug delivery system of anticancer molecules. The dichotomy allied with exosomes and their role in oral squamous cell carcinoma biomarkers or as therapy enhancement will be highlighted.

Keywords: Biomarkers, drug delivery, exosomes, oral squamous cell carcinoma

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common cause for death and is the tenth most common cancer types occurring worldwide.[1] Despite the progress happening in the field of diagnosis and treatment, the survival rate for OSCC is accounted to be only 50%.[2] Surgical resection, radiotherapy and chemotherapy have been the common treatments for OSCC.[3] However, not all tumors respond to these treatments due to their therapy resistance and recurrence which pose a challenge since their mechanism is not well known. Hence, a better knowledge on the initial genetic mutations occurring in OSCC is necessary for the primary detection and early intervention of the disease.

Genetic biomarkers-based diagnosis would be essential for the detection of early molecular changes and better prognosis.[4] Apart from early detection of OSCC, the discovery of drug-related targeted therapies has been advanced in cancer treatment which has increased the overall patient survival rate.[5,6] These therapies mainly focus on proliferation and survival of cancer cells, angiogenesis and metastasis.[7] It is proven that cancer cells can communicate with cell-to-cell or within their microenvironment to proliferate and metastasize through

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cell junctions and cytokine interactions.[8,9] Recently, focus has been shifted on extracellular vesicles (EVs) which act as important players for intercellular crosstalk with adjacent or distant cells and their microenvironment.[10] Earlier, EVs were thought to be cellular junk and were later established that it had a pivot role in maintaining homeostasis, immunomodulation and physiological regulation of functions, blood coagulation and various stages of cancer progression.[11-13] There are different variants of EVs described based on their origin including apoptotic bodies, microvesicles and exosomes, but exosomes are commonly studied subtype in cancer-related research. Clinically, exosomes are used as diagnostic biomarkers, therapeutic targets or as anticancer drug delivery vehicles, and have all been emphasized as a result of their unique biological and pathophysiological characteristics. Here, we provide a comprehensive overview of exosomes in cell biology and their role as cancer biomarkers. In addition, we summarize the role of exosomes in clinical applications in relation to their molecular and biological characteristics.

EXOSOMES

Exosomes, nano-sized EVs, were discovered three decades ago measuring about 40–100 nm in size.[14] They were initially noticed as Microvesicles (MVs) reticulocyte culture media containing proteins and later in the extracellular environment.[15] They are secreted by all types of cells including epithelial, endothelial, neuronal, fibroblasts, immune cells and tumor cells.[16] These are endosomal in origin and are released through the fusion of the plasma membrane with cytosolic multivesicular bodies. The composition varies according to the origin of site and the parent cell type reflecting their physiologic or pathologic conditions.[17] The membranes of exosomes are composed of a cholesterol-enriched bilayer of lipids, sphingomyelin, gangliosides and ceramide, which provide them high stability.[18] Exosomal genetic cargo is enriched with extensive range of proteins along with bioactive molecules of mRNAs, long noncoding RNAs and miRNAs.[19] B lymphocyte-derived exosomes showed antigen-presenting properties, which suggested their role in immune response, aiding the initiation of T-cell and dendritic cell response.[20,21]

EXOSOMES AS CANCER BIOMARKERS

Exosome-mediated cellular crosstalk is not limited to tumor cells, but inside the tumor microenvironment locally and distantly also.[22] They have the ability to deliver specific bioactive molecules at different stages of cancer progression, which suggest their potential role as a diagnostic biomarker. Once the exosomes are being detached from its parental cells, the exosomal carriers resemble the intracellular structure of the original secreted cell. Thus, finding the changes within exosomal molecules might provide information for the fundamental requirement of accuracy medicine in terms of diagnosis, prognosis and disease monitoring.[23] Currently, cancer diagnostics rely mostly based on tissue biopsies. The latent use of exosomes has the benefit of being a highly sensitive and noninvasive method. These cancer exosomes allow the early detection of cancer including oral, breast, prostate and ovarian cancer, melanoma and many more.[24] These are noninvasive testing procedures causing less discomfort to the patient. Several functional studies have reported the increased level of exosomes in different types of cancer origins. These cancer exosomes provide an enhanced source of biomarkers since they contain bioactive molecules suggesting the pathological condition of host cells.[25]

Tumor-specific markers such as proteins, mRNA and miRNAs and long-coding RNA have been found in circulating exosome and have gained attention as proficient biomarkers. Precise marker molecules were found on the surface of exosomes, such as CD9, CD81 and CD63.[26] Recently, pilot studies have shown that miRNA, salivary exosome protein and amniotic fluids are useful markers for the detection of many diseases. miRNA content can be useful to detect more than one condition which provides a potential prenatal diagnostic tool.[27-29] Zlotogorski-Hurvitz *et al.* in their study demonstrated that the molecular and morphological characteristics of exosomes vary between healthy and oral cancer patients, which could aid as an early diagnostic tool to detect any malignant changes in patients with high risks.[30] Furthermore, Li *et al.* found that exosomes secreted by hypoxic OSCC cells enhanced the migration and invasion of OSCC cells.[31]

EXOSOMES AS THERAPEUTIC TARGETS

Exosomes, being a nano-level intercellular carrier, are known as potential therapeutics since they can produce effective cellular responses *in vitro*/*in vivo* and improve the efficiency during chemotherapies.[32,33] Currently, experimental trials are ongoing to validate this mode of therapeutic approach; but still, the production, isolation and packing them into nano-sized vesicles are challenging their use for drug delivery. The ability of exosomes to cross blood–brain barrier and cytoplasmic membranes makes it the most advantageous property as a therapeutic target molecules.[34,35] They have a property of natural material carrier and transportation, long-term internal circulatory capability and excellent biocompatibility suitable for drug

delivery including variety of chemicals, nucleic acids, genetic and protein therapeutic mediators.[36] Experimental studies have found that the process of angiogenesis, cellular immunity and regenerative effects in cell-based therapy which is mediated through mesenchymal stem cells (MSCs) and other cells are executed by the exosomes released by these cells. Hence, exosomal-based cell therapy is proved to be a great potential in the field on oncology to regenerative medicine,[37,38] which provides the possibility of "cell-free cell therapy."

Currently, the application of exosomes in clinical treatment can alienate into the subsequent areas. Direct aiming of exosomal therapy directly inhibits the synthesis and secretion of tumor-associated EVs by preventing absorption. EV-based immunization preparations, relating the separation and purification of autoimmune cell-derived EVs from patients with tumor and modification of antigen for delivering to the patient, can trigger the capability of the immune system to destroy tumor cells.[39] Sometimes, patients may develop side effects with the use of aggressive measure, and thus, further clinical trials in larger number before exosomal cell-based therapy on patients in the future are required.

It is beneficial to use exosomes relating to cell-based procedures. This is because the exosomes are of nano size and can easily pass through capillaries when compared with MSCs which are large to pass through capillaries.[40] The usage of exosomes evades complications associated with damaged or mutated DNA within the cells[41] Exosomes attain high dose than transplanted MSCs where their levels decrease after transplant. Exosomes may also be useful to confront toxicity and immunogenicity complications resulting from biomaterial therapies as nanoparticles.[42] All these characteristics make them suitable for theranostic approach.

CONCLUSION

OSCC is the most prevalent oral cancer, which poses a challenge during diagnosis and treatment. Exosomes being a microvesicle, plays a significant role in cancer development, progression to different stages and as biomarkers in OSCC. Research related to these studies are going on. On the other hand, the ability of exosomes in drug delivery anticancer molecules for cancer treatment is also focused. This "all-in-one theranostic approach" has a huge potential in personalized medicine, as it permits the recognition and monitoring of a disease in early stages of individual patients, along with targeted drug delivery molecules at the site of the disease. Although the study of exosome application has made great advancement, many challenges still remain unanswered and need further investigation.

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Conflicts of interest

There are no conflicts of interest.

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