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Letter to the editor

Mitochondrial DNA in circulating exosomes: A novel biomarker and potential therapeutic target for oral cancer

To the editor,

Cancer is a primary cause of death and a major impediment to improving life expectancy in every country across the globe. The oral-related cancers are considered to be a great threat to the male population, especially in South-Central Asia. The incidence rate of oral cancer is also high in Eastern and Western European countries, and Australia. Particularly, consumption of alcohol, tobacco usage, HPV infection, and radiation are linked to this type of cancer. In the last two decades, the number of new cases in cancer of lips and oral cavity were rising rapidly. According to GLOBOCAN prediction, in 2040 the number of cancers will increase by 47% than now including cancers of the oral cavity. Failure in detecting cancer at an early stage is the major drawback in the management of cancer [1].

Currently, histological examination plays a very important role in diagnosis of oral cancer, but this invasive procedure poses limitations on oral cancer diagnosis. In addition, oral cancers are mostly asymptomatic in the early stages, which starts with lesions, termed as oral premalignant lesions such as leukoplakia and erythroplakia. In a low social-economic country, the assessment of premalignant lesions by the healthcare agencies, fear of surgery/biopsy among patients delays the early screening process. From the professional side, incorrect biopsy site selection, improper intraoral, and extraoral examination cause false-negative results [2]. Advancements in cancer research has helped to find out early biomarkers for cancers, but most of them are under development. An efficient screening marker is needed to detect oral-related cancer at an early stage. Recently exosomal DNA, mitochondrial DNA (mtDNA), mRNA, and micro-RNA were discovered as a biomarker for various cancers. The mitochondria possess a major role in cancer metabolism. Mitochondria have been observed migrating to nearby cells via tunneling nanotubes, bringing mtDNA with them [3].

Mitochondria are essential organelles in the eukaryotic cells that act as a central metabolic hub. Mitochondria holds a small 16 kb DNA (mtDNA) that encodes tRNAs, rRNAs, and protein-coding mRNAs which is essential for respiration. Mitochondria regulate various cellular functions, including cellular energy production to the activation of apoptosis and cellular differentiation. Mitochondrial dysfunction has major implications for both cells and organisms which are exacerbated by damaged mitochondria's production of harmful reactive oxygen species (ROS). Damaged mitochondria, as well as the release of N-formyl peptides and mtDNA from them, can act as damage-associated molecular patterns (DAMPs) that trigger the innate immune system [4].

A study discovered that cancer cells have considerably higher glycolysis rates than differentiated cell counterparts. They termed these phenomena as "aerobic glycolysis" because cancer cells rely on glycolysis even under hypoxic conditions, a circumstance known as the "Warburg effect." Warburg theorized at the time that the shift to aerobic glycolysis was caused by defective mitochondria and that this metabolic shift was a cause of cancer [5]. However, it was eventually discovered that having functional mitochondria was necessary for several types of cancer, leading to the hunt for alternative theories. In addition, cancer cells have consumed a large amount of glucose via glycolysis, a significant amount of their ATP is produced via oxidative phosphorylation (OXPHOS) which suggests that the mitochondria play an essential role in cancer [6]. Interestingly, mtDNA has been discovered to migrate from one cell to another as an exosome carrier in a paracrine form.

For the role of mitochondria in cancer development, there is no single canon. Rather, mitochondrial functions in cancer differ based on tumor genetic, environmental, and tissue-of-origin variations. Because many classic cancer hallmarks result in altered mitochondrial function, it is obvious that the biology of mitochondria in cancer is critical to our understanding of cancer biology.

Recent research provides evidence that mtDNA from exosomes is identified as a potential biomarker for renal cell carcinoma (RCC). By ultracentrifugation of whole blood samples from RCC patients and control, the exosomes were fractionated into different phases (named from B to F). Especially the exosome F phase contains a large number of mtDNA contents in RCC patients, which is considered as a potential biomarker for susceptibility to RCC [7]. Singel et al, previously reported that extracellular mtDNA in the tumor microenvironment activates neutrophils and is related to poor outcomes in individuals with advanced epithelial ovarian cancer. In ascites, mitochondrial and other damage-associated molecular patterns (DAMPs) may activate neutrophil and platelet responses, facilitating metastasis and obstructing anti-tumor immunity [8]. These results indicate that the mtDNA from exosomes can act as a potential biomarker and prognostic marker for cancers that include oral cancers.

The mtDNA defects and dysfunctional mitochondria have been reported in various cancers including oral cancer [9]. Several studies reported that exosomes directly promote the oral cancer progression through transportation of exosomal components between cells and the tumor microenvironment. Although exosomes are regulating the immune system, they cause metabolic dysfunction and chemoresistance [10]. The biogenesis of exosomes started as an early endosome in the cytoplasm, whose release is regulated by several complexes. The endosomes carry nucleic acid contents from the nucleus and mitochondria along with several non-coding RNAs and proteins. Finally, these endosomes are released into the extracellular environment as exosomes that interact with nearby cells. They gain entry into the body fluids such as saliva, cerebrospinal fluid, breast milk and urine, (Fig. 1). In oral cancer, exosomes contain protein that promotes tumorigenesis, regulates stromal cells around cancer tissues, and induces cancer cell proliferation [10]. Circulating tumor (ct) DNA in the plasma is highly researched as a

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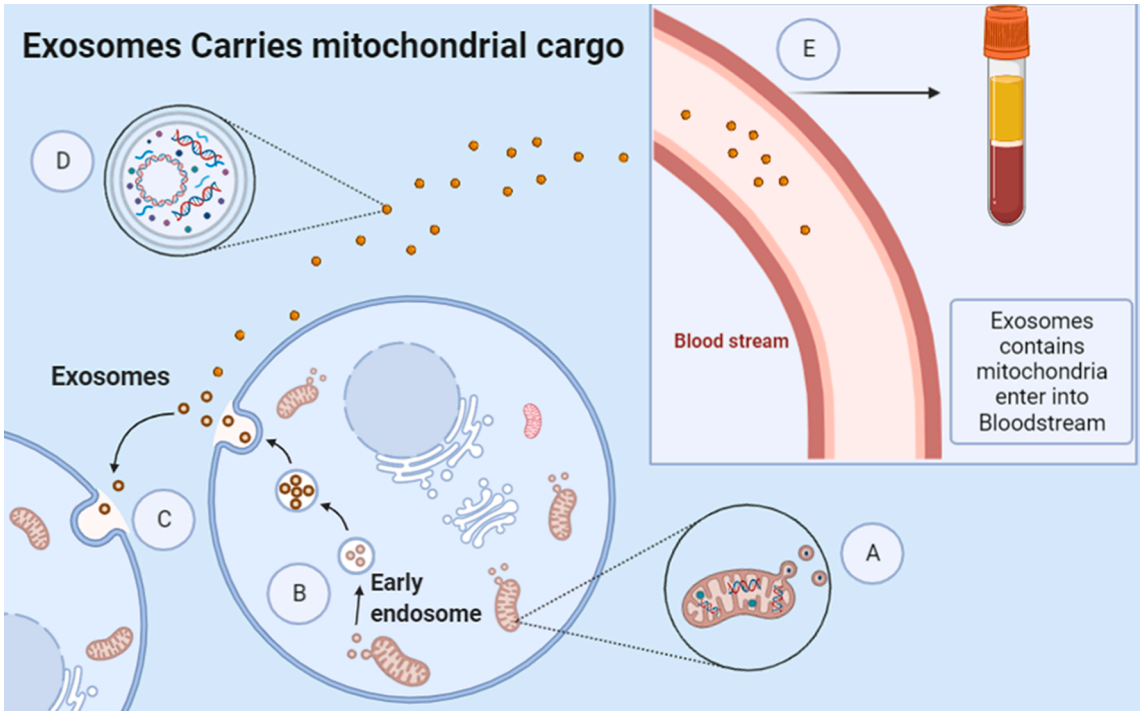

Fig. 1. Role of exosome mitochondria in Oral related cancer. (A) Mitochondria release their contents such as defective mitochondrial DNA (mtDNA), damaged DNA fragments and proteins into their cargo. (B) Mitochondrial cargo enters into early endosomes and is released in the outer cell wall (cancer cell) as an exosome. (C) Exosomes carrying mitochondria enter into nearby cells. (D) Exosomes carry mitochondrial defected circular DNA, damaged DNA fragments and mitochondrial proteins. (E) These exosomes enter the bloodstream. So we could use exosome mtDNA as a novel biomarker for oral cancer (Figure was made using Biorender.com).

liquid biomarker in head and neck cancer, and it has shown considerable response in monitoring of disease recurrence [11]. But currently, researchers are concentrating on exosomal mitochondrial DNA since exosomal mitochondria have a higher copy number of DNA than the nuclear DNA. Hence, mtDNA could be an efficient target and biomarker for various tumors including oral cancer.

The defective mtDNA and mitochondrial protein carried by exosomes to another cell might promote metastasis and cancer progression. So, targeting the release of exosome and the functional molecules associated with mitochondria would be a great therapeutic strategy for the treatment of oral cancer. Further studies on the role of exosome-containing mtDNA in oral cancer can help in understanding the potential role of these biomolecules in the initiation, progression and metastatic abilities of transformed tumor cells.

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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Kannan Balachander[a], Anitha Roy[b], Jayaseelan Vijayashree Priyadharsini[a], Senthil Murugan[c], Arumugam Paramasivam[a,*]

[a] *Centre for Cellular and Molecular Research, Saveetha Dental College & Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, India*

[b] *Department of Pharmacology, Saveetha Dental College & Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, India*

[c] *Department of Oral Surgery, Saveetha Dental College & Hospital, Saveetha Institute of Medical and Technical Sciences [SIMATS], Saveetha University, Chennai, India*

[*] Corresponding author at: Centre for Cellular and Molecular Research, Saveetha Dental College & Hospital, Saveetha Institute of Medical and

Technical Sciences [SIMATS], Saveetha University, Chennai 600077, India.

E-mail address: paramasivama.sdc@saveetha.com (A. Paramasivam).