International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 03 (E); March 2019; Page No.17898-17903
DOI: http://dx.doi.org/10.24327/ijcar.2019.17903.3411

Research Article

SALIVARY EXOSOMES IN HEALTH AND DISEASE- A CRITICAL REVIEW

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A R T I C L E I N F O

Article History:
Received 12th December, 2018
Received in revised form 23rd January, 2019
Accepted 7th February, 2019
Published online 28th March, 2019

Key words:
exosomes, saliva, cancer

A B S T R A C T

Exosomes are nanometer- sized membranous vesicles, containing varied compositions of proteins, lipids and enzymes which are released from different types of cells. They have a significant physiological role in intercellular communication, signal transduction and immune regulation. Exosomes are isolated from various body fluids like blood, urine, plasma, amniotic fluid, breast milk, hydro thoracic fluid, saliva and ascitic fluid. Exosomes isolated from saliva are similar in composition to other body fluid exosomes except for IgA, chemokines, CD26 and few others. Exosomes also have a pivotal role in autoimmune diseases, transmission of viral infectious agents and neoplastic conditions by promoting tumor growth, progression, angiogenesis and metastasis. Demonstration of salivary exosomes revealed the presence of mRNA transcripts which are believed to have a role in intercellular communication and alteration of genes in the target cells. The present review focuses on the exosomes in general and their role in tumor biology. This article also highlights the importance of salivary exosomes and its recent findings on physiological and pathological conditions like in head and neck cancers, viral diseases and autoimmune diseases.

INTRODUCTION

Exosomes are small, lipid bilayer membrane vesicles of endocytic origin with a diameter of 40-100nm that are secreted by many cell types intothe extracellular milieu (Mathivanan *et al*. 2010). They were first described by Pan and Johnstone (1983) in mammalian reticulocytes in the "shedding" process of transferring receptor during maturation. They were initially thought to be as "garbage bags" to dispose of the unwanted cargo of the cells, but recent molecular techniques proved that they have an important role in cell to cell communication and cell to extracellular matrix communication (Lin *et al*. 2015; Schorey *et al*. 2008).

Multivesicular Bodies (MVBs) and Their Fate

Endosomes are the membranous organelles which have an active sorting mechanism to distribute their contents (neo-synthesised and endocytic proteins) to particular destinations mediated by transport vesicles (Schorey *et al*. 2008; Fevrier *et al*. 2004; Stoorvogel *et al*. 2002; Lakkaraju *et al*. 2008). Multivesicular bodies (MVBs) are commonly called as Multivesicular endosomes, are defined compartments formed by inward budding of the endosomal membrane in a process that sequesters particular proteins and lipids (Schorey *et al*. multi-protein complexes called ESCRT-0, I, II, III (endosomal sorting complexes required for transport), Tsg101(tumour suppressor gene 101), Vps proteins and Alix/ AIP **(**Fig 1) (Mathivanan *et al*. 2010; Lakkaraju *et al*. 2008; Keller *et al*. 2006). The type of cargo present in the exosomes is of particular significance in both physiological and pathological conditions, most importantly in tumorigenesis, because exosomes excreted from one cell interacts and fuses with the surrounding cells and help in initiating the signaling responses (Tickner *et al*. 2014).

Exosomes

Exosomes are defined as vesicles formed by "inward/reverse budding" of the limiting membrane of the MVBs in the late endocytic compartment and released upon the fusion of MVB with the plasma membrane (Stoorvogel *et al*. 2002). They are of size 40-100nm, density of 1.13-1.19 g/ml in sucrose gradient. They exhibit "cup" or "saucer" or "disk shape" in transmission electron microscopy (Yang *et al*. 2011). Studies revealed that exosomes are present in almost all biological fluids such as blood, urine, plasma, amniotic fluid, breast milk, hydrothoracic fluid, saliva and ascitic fluid. They are released from many cells like dendritic cells, lymphocytes, platelets, mast cells, epithelial cells, neurons and endothelial cells (Michael *et al*. 2010). In neoplastic conditions, tumour cells secrete exosomes in substantially higher concentrations than that in physiologic conditions (Yang *et al*. 2011).

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Composition

By using various molecular techniques, the lipid and protein composition of exosomes has been analyzed and composition varies in exosomes of different origins of cell, and may also vary based on the various physiological and pathological conditions (Zhang *et al*. 2015). Most of the exosomes has definite number of common proteins **(**Table 1) (Schorey *et al*. 2008; Stoorvogel *et al*. 2002).The Exocarta database which deals about the exosomal content released in May 2012, identified that 13,333 proteins, 194 lipids, 2375 mRNAs and 764 miRNAs are been present in exosomes of various microorganisms (Lin *et al*. 2015).

Very limited data is available about the lipid composition of exosomes. As similar to proteins, composition of lipids also varies based on the cell of the origin and they play a pivotal role in the biogenesis of exosomes as confirmed by the lipid analysis done on different cell lines which includes dendritic cells, mast cells, reticulocytes, B lymphocytes (Schorey *et al*. 2008; Stoorvogel *et al*. 2002). Exosomes presents a typical lipid composition of lysophosphatidylcholine, phosphatidylethanolamine, sphingomyelin, phosphatidylcholine, phosphatidylserine, cholesterol and diglyceride and the ratios of these lipids may vary depending on the cell type (Schorey *et al*. 2008). Lipid composition analysis done on internal vesicles of late endosomes and exosomes of Epstein-Barr virus(EBV)-transformed B lymphocytes demonstrated that these cells are highly rich in cholesterol and sphingomyelin which are responsible for the formation of lipid rafts (Thery *et al*. 2002). Lipids in exosomes also have a potential role in tumourigenesis. In the hypoxic tumor microenvironment, it is believed that the lipid bilayer of exosomal membrane changes its composition, fuses with neighbouring cells and increases its rigidity which is attributed to the decreasing pH seen in hypoxic microenvironment (Tickner *et al*. 2014).

Various enzymes are demonstrated in exosomes which would promote the biogenesis of exosomes like GAPDH (glyceraldehyde-3-phosphate dehydrogenase), pyruvate kinase, enolase,phosphoglycerate kinase, myeloperoxidase (catalytic activity),Peroxiredoxin (antioxidant activity) (Mathivanan *et al*. 2010; Ogawa *et al*. 2011).

Biological Functions

Exosomes which were once thought to be required for the disposal of cellular waste and toxins, are now considered for a wide range of its functions, firstly because of their ability to merge with and release their contents into recipient cells and secondly, by bearing a combinations of ligands that would engage different cell-surface receptors simultaneously (Tickner *et al*. 2014).

Intercellular Communication

Exosomes are considered as important mediators of cell- cell communication and in active signaling mechanisms, as these vesicles interact and regulate the function of target cells by a sequence of interactions, i.e. Binding to target cells through exosomal adhesion molecules, phosphatidylcholine and cellular receptors, leading to direct fusion of the vesicles with the plasma membrane and are internalized into endocytic compartments through endocytosis (receptor mediated) (Yang *et al*. 2011). These intercellular interactions also play a vital role in tumour progression and invasiveness (Mathivanan *et al*. 2010).

Immune Response and Antigen Presentation

Exosomes have important immunomodulatory activities in both physiological and pathological conditions. In vitro demonstration of exosomes derived from B-cells carrying peptide-loaded MHC class II shown to stimulate CD4 + T cells. Studies done both invitro and invivo on bone marrow derived mast cells demonstrated MHC II exosomes which are released in response to crosslinking of cell surface IgE (Stoorvogel *et al*. 2002; Raposo *et al*. 1997). Dendritic cells (DCs) normally have the function of antigen presentation and initiation of immune response by stimulating the inactive T cells. Immature DCs has insufficient MHC restricted stimulation as MHC is stored intracellularly in the MVBs. Upon stimulation by a particular antigen, DCs become mature by release of these exosomal MVBs containing MHC I and II to the surface of the cell and presents the antigen to T cells (Meehan *et al*. 2016; Kleijmeer *et al*. 2001). They also have the potential to stimulate and amplify the expression of other antigen presenting cells to achieve a blown immune response (Schorey *et al*. 2008; Fevrier *et al*. 2004).

Nucleic acid Trafficking

Exosomes contain large amount of RNAs (mRNAs, miRNAs) which are transferred between cells. Studies by Hadi Valadi *et al* (2007) showed the presence of nucleic acids (RNA) and miRNA in exosomes derived from mast cell line (MC), bone marrow derived mast cells (BMMC) and human mast cell line (HMC-1) cells to prove the potential mechanism by which exosomes may mediate cell–cell communication and transport RNA to neighbouring cells. These transferred RNA are termed as "exosomal shuttle RNA" (Valadi *et al*. 2007). miRNAs are a group of small RNAs involved in regulation of cell development, differentiation, proliferation and survival and more stable compared to that of mRNAs (Yang *et al*. 2011; Liu *et al*. 2015).

Salivary Exosomes

Saliva is an important body fluid which reflects both oral and systemic diseases, as it has large number of proteins which helps in the protection of oral tissues. Exosomes are usually identified in body fluids and they are shown to participate in intercellular communication and immune regulatory functions. Isolation of exosomes from saliva is non-invasive, painless, stress free, and relatively simple when compared with blood sampling (Ishikawa *et al*. 2014; Zlotogorski *et al*. 2014).

The salivary exosomal structural characterisation was first time published by Palanisamy *et al* (2010) reported that salivary exosomes are taken up by the oral keratinocytes which play a role in intercellular communication and alteration of genes in the target cells and the probable reason is the presence of mRNA transcripts which help in transfer to the target cells (Palanisamy *et al*. 2010; Zhang *et al*. 2015). In a study conducted by Kapsogeorgou *et al*, on salivary gland epithelial cell exosomes (SGECE), where Salivary gland epithelial cells constitutively secretes exosomes which contains sjogrens syndrome (SS) antigens, which acts as intracellular autoantigens presented to immune system with an immunogenic outcome (Kapsogeorgou *et al*. 2005).

The first proteomic profiling done by Gonzalez-Begne *et al*. presented 491 proteins in the exosomes of human parotid saliva using the shotgun approach where 43% percent of 491 proteins were of cytosolic origin, 26% were integral plasma membrane proteins, and 13% were associated/peripheral plasma membrane proteins. Integral plasma membrane proteins were annotated according to their function: pumps (2%); channel protein (5%); and solute carriers (14%) (Gongalez *et al*. 2009). Proteomic analysis of human whole saliva done by Yuko Ogawa *et al* (2011) demonstrated that there are two types of exosomes (Exosome I and Exosome II) present in whole saliva that differed in their size and composition. This analysis proved that salivary exosomes contain lipid and protein complexes similar to that of other body fluid derived exosomes(Alix, Tsg101 and Hsp70, all exosomal markers) in addition to IgA and dipeptidyl peptidase IV(CD26) and metabolically active chemokines (CXCL11 and CXCL12). These results showed that human salivary exosomes might participate in the catabolism of bioactive peptides and play a regulatory role in local immune defense in the oral cavity (Ogawa *et al*. 2011).

Exosomes in Diseases

Cancer

As discussed, intercellular communication plays a vital role in the physiological and pathological processes. During the development and progression of cancer, the exosomes transfer oncogenic proteins that affect the cellular composition of the tumor microenvironment, which further influences the activity of the tumor cell to recruit and educate host stromal cells into tumor supportive cells. These effects provides access to the tumour growth, progression, metatstatic niche formation, regulation of tumour immune responses (Yang *et al*. 2011; Tickner *et al*. 2014). Tumour -derived exosomes (TDE) re-semble those of DC origin in both biophysical and biochemical aspects. Specific cell type differences like expression of tumour-associated antigens and certain immunosuppressive proteins like FasL ligand, TRAIL, and TGF- β are observed with TDE (Clayton *et al*. 2009).

Table 1 Cytosolic and membranous protein composition of exosomes. (MHC- Major histocompatibility complex), ICAM-intercellular adhesion molecule.

Cytosolic and membrane proteins	Function
Rabs (small GTPases)	Promote exosome docking and the membrane fusion events
Annexins (I, II, IV, V, VI, VII &XI)	Regulate membrane cytoskeleton dynamics and membrane fusion events
Adhesion molecules (ICAM-1)	Signal transduction
Cytoskeletal proteins (actin, coffilin, moesin and tublin)	Cell structure, motility and signal transduction
Tetraspanins(CD9, CD63, CD81, CD82)	Help in cell adhesion by trafficking and biosynthesis of associated integrins, interact with MHC molecules and aids in oraganisation of large molecular complexes.
Heat shock proteins (Hsp70, Hsp84/90)	Facilitate peptide loading onto MHC I and II
LBPA(lysobisphosphatidic acid), Alix, Gag, Tsg101 and Clathrin	Participate in multivesicular bodies formation and trafficking
Protein kinases	Signal transduction
MHC I, MHC II and CD 86	Antigen presentation
Thioredoxin peroxidase II, Galectin3 &9	Apoptosis

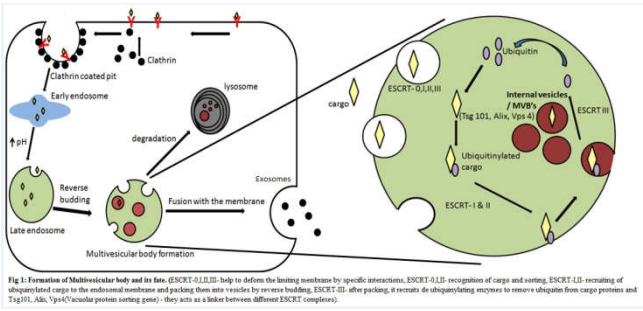

Fig 1 Formation of Multivesicular body and its fate.

(ESCRT-0,I,II,III- help to deform the limiting membrane by specific interactions, ESCRT-0,I,II- recognition of cargo and sorting, ESCRT-I,II- recruiting of ubiquinylated cargo to the endosomal membrane and packing them into vesicles by reverse budding, ESCRT-III- after packing, it recruits the ubiquinylating enzymes to remove ubiquitin from cargo proteins and Tsg101, Alix, Vps4(Vacuolar protein sorting gene) - they acts as a linker between different ESCRT complexes).

Role of miRNA in Cancer

Exosomal miRNAs have a potential role in cancer. miRNAs present in immature form in the cell nucleus gets matured in exosomes and carry the necessary information from cancer cells to the target cells which will phenotypically change them in a fashion that shapes and alters microenvironments favoring cancer cell growth and invasion. The TDE showed higher concentration of mature miRNAs compared to miRNA of exosomes derived from healthy cells (Melo *et al*. 2014).

Tumour Growth and neo-Angiogenesis

Studies proved that many tumour cell-lines (melanoma-derived, glioblastoma derived exosomes on human umbilical cord endothelial cells *in vitro*) derived exosomes are capable of promoting the tumour angiogenesis, stimulation of proliferation of endothelial cells and the sprouting of endothelial cells (Meehan *et al*. 2016; Miller *et al*. 2015; Filipazzi *et al*. 2012).

Tetraspanins, enriched proteins in TDE also promote the growth of the tumour by increased support in tumour neo-angiogenesis. Studies conducted by Nazarenko *et al* (2010) on cell surface tetraspanin8 (Tspan8/D6.1A) showed that the Tspan8 enriched TDE had a role in selective recruitment of oncogenic proteins, mRNA, CD106, CD49d which helps in inducing endothelial cell activation and also many angiogenesis related genes like von willebrand factor, VEGF, chemokine CXCL5 (Nazarenko *et al*. 2010).

TDE actively delivers the angiogenic factors into the endothelial cells and also modulates the action of endothelial cells by exosomal miRNAs. Tumour growth also seems to be induced by uptake of exosomes with apoptosis inhibitory proteins like survivin into cancer cells which would protect them from genotoxic stress induced cell death which will enhance their replicative, proliferative and metastatic potential (Khan *et al*. 2011).

Formation of Metastatic Niche

Metastasis involves the spread of tumour cells from the primary site to other areas of the body. Before the formation of the metastatic niche at a secondary site, the tumor cells prepare

this distant site which is called as "pre-metastatic niche". Studies suggest that the exosomes released by the primary tumour cells modulate the bone marrow derived cells to be recruited to the pre-metastatic niche into the cells that supports the incoming tumour cells by release of various cytokines and growth factors.

The cells which are usually affected by the influence of TDE in microenvironment mostly include fibroblasts and immune cells (Zhang *et al*. 2015; Miller *et al*. 2015; Filipazzi *et al*. 2012). The key events in the formation of the pre- metastatic niche is conversion of the fibroblast to exosome associated myofibroblast phenotype and are known to support tumor growth, vascularization and metastasis. These cancer associated fibroblasts (CAF) are seen in great quantities in the tumour microenvironment of many solid cancers (Tickner *et al*. 2014;Filipazzi *et al*. 2012). Studies conducted showed that CAF can make the microenvironment favourable for the promotion of tumour growth. Exosomes of CAF can reprogram the metabolism of cancer cells as it is evident from proteomic analysis, that they contain intact metabolites, which includes amino acids, lipids, and TCA- cycle intermediates that are avidly utilized by cancer cells for carbon metabolism and promoting tumor growth under nutrient deprivation or nutrient stressed conditions (Zhao *et al*. 2016).

As the metastatic niche is formed, tumour cells leave the primary site and are trapped by the extracellular matrix containing collagen, laminin, fibronectin and elastin. It is followed by the degradation of extracellular matrix by various metalloproteinases (Matrix metalloproteinases) that are secreted by TDEs (An *et al*. 2015)**.**

Tumour Immunity Regulation

TDEs can even modulate the important components of immune system. Exosomes possess the ability to directly suppress the activity of the apoptosis induction in cytotoxic T-cells (Whiteside *et al*. 2013). Studies demonstrated that TDE induces differentiation of T-helper cells to regulatory T-cells (Treg cells), which evades immune surveillance. TGF-*β*-dependent mechanism guides TDE to selectively impair the IL-2 response to cytotoxic effector cells while supporting Treg cell activities to induce, expand, and upregulate the suppressor functions of Treg cells and enhance their resistance to apoptosis via a TGF-*β*- and IL-10-dependent mechanism (Yang *et al*. 2011; Zhang *et al*. 2015; Clayton *et al*. 2007).

TDEs help in tumor evasion by suppressing the activation of natural killer cells (NK) by blocking interleukin 2 which usually mediates the activation of NK cells. Studies also demonstrated that exosomes derived from tumor cells had direct inhibitory effect on NK cells and suppressing the action of same by decreasing the expression of NKG2D ligand (Yang *et al*. 2011; Zhang *et al*. 2015; Filipazzi *et al*. 2012).
This explains the hypothesis that TDE have an important role in evasion of host immunity by various mechanisms in different levels of immune system.

Head and Neck Cancer

Head and neck cancer collectively comprises a variety of anatomical subsites, which includes the tumours of nasal cavity, oral cavity, paranasal sinuses, nasopharynx and oropharynx. Squamous cell carcinomas of oral cavity and oropharynx are common malignancies of the head and neck region. Human papilloma virus (HPV) which has different serotypes is implicated to causation of nasopharyngeal and oropharyngeal carcinoma. Studies done on pathogenic HPV strains to demonstrate the miRNA profile of exosomes have shown to exhibit enriched miRNA in HPV affected cells that control cell proliferation and apoptosis (Anderson *et al*. 2016). Various studies conducted on salivary exosomes demonstrated that exosomes isolated from saliva of oral cancer patients differed in size but not in their numbers compared to the exosomes isolated from normal saliva, probably due to the modifications related to their role in intercellular interactions throughout the cancerous process (Zlotogorski *et al*. 2015).

Autoimmune Diseases

Immune reaction to self-antigens and production of autoantibodies plays a very important role in the pathogenesis of autoimmune diseases. Studies conducted by Kapsogeorgou *et al*, proved that salivary gland epithelial cells constitutively secrete exosomes that contain the major autoantigens (E3 ubiquitin protein ligase TRIM21, Ro(SS-A), La(SS-B) and the Smith antigen (Sm)) which are involved in Sjogren's syndrome (SS) and Systemic lupus erythematosus. These intracellular autoantigens are presented to the immune system with an immunogenic or tolerogenic outcome (Kapsogeorgou *et al*. 2005).

Studies also demonstrated successful isolation and characterization of miRNAs from exosomes of human saliva, proposed that these exosomal miRNAs from the salivary gland holds good as a diagnostic tool to detect pathologies that directly or indirectly affect the salivary glands and also used to detect SS conditions (Michael *et al*. 2010).

Viral Diseases

In viral diseases, exosomes have been involved in multiple mechanisms, depending on the type of virus, its life cycle, and the type of infected cell (De Toro *et al*. 2015).

Herpes Simplex Virus1

Herpes simplex virus1 interacts with the ESCRT complex through viral tegument proteins and glycoproteins, gets incorporated into exosomes and are released outside from the infected cells, so for this reason, exosomes are composed only of virus envelope and tegument proteins but lack viral genome and capsid proteins which are together called as L- particles (Anderson *et al*. 2016). These L- particles as such are non-infectious, but on increased secretion and infectivity into non-infected cells of the host might induce increased susceptibility in non- infected cells (Mclauchlan *et al*. 1992).

HIV (Human Immunodefieciency Virus)

Exosomal mediated transfer of HIV virus by transfer of genetic material (RNA, miRNA) from infected cell to non-infected cell modulates the host immune response. Studies are done to demonstrate the exosome mediated transfer of viral proteins like Gag, Nef, and p17 to recipient cells in HIV-1 infected macrophages (Kadiu *et al*. 2012). Another study was done to demonstrate that the Nef protein of HIV virus, was found in released exosomes and showed that increased uptake of this Nef protein led to increased susceptibility of the naïve T cells to HIV infection and exosomal Nef has also shown a contributory role in AIDS pathogenesis by increasing the apoptosis of T cells and in turn in the depletion of CD4 T cell count (Anderson *et al*. 2016).

EBV and Kaposi's Sarcoma Herpes Virus (KSHV)

As mentioned in HSV 1 virus, EBV and KSHV also interacts with ESCRT complex and are released out by incorporating the viral proteins into exosomes. Exosomes play a very important role in the propagation of EBV and KSHV-associated cancers, including nasopharyngeal sarcomas and Kaposi's sarcoma, respectively. In KSHV, tumor cell derived exosomes increases cell migration and IL-6 production in recipient endothelial cells (Anderson *et al*. 2016).In EBV, various signal transduction proteins like latent membrane protein 1 (LMP1), which are found in exosomes are said to inhibit NK cell activity and increased activation and proliferation of T-cell (Meckes *et al*. 2011). Galectin-9, found in exosomes released from EBV+ cells induces the apoptosis of EBV-specific T cells, by which the virus goes undetected by the host's immune system (Schorey *et al*. 2015). These are the mechanisms by which EBV cancers alter the microenvironment to increase propagation and survival of transformed cells.

CONCLUSION

Exosomes are the nanoparticles which can mediate the intercellular communication and immune regulation. Various studies conducted showed that they have a pivotal role in tumor progression and metastasis. The researches on exosome functions and its significant applications are increasing progressively. Salivary exosomes are also demonstrated to have a role in head and neck cancers, but very limited studies are available to put forward substantial evidence. So, the utilization of salivary exosomes needs to be expanded to use them as potential biomarkers in diagnostic and prognostic purposes.

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How to cite this article:

Deepthi G., Pavan G Kulkarni and Nandan S.R.K (2019) 'Salivary Exosomes in Health and Disease- A Critical Review', *International Journal of Current Advanced Research,* 08(03), pp. 17898-17903.
DOI: http://dx.doi.org/10.24327/ijcar.2019.17903.3411

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