

## Exosomes-An Imperative Miniature: A Review

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**Abstract:** Exosomes are secreted membrane vesicles formed inside intracellular multivesicular compartments. They are released extracellularly when these compartments fuse with the plasma membrane. They were known as trash bins carrying unwanted waste products and cellular debris. But later they were known to play a vital role in immunity as they had Major Histocompatibility Complex (MHC) dimers. Proteomics and genomic studies concluded that they have miRNA, mRNA and some proteins. They transfer genetic information to distant sites and play a significant role in intercellular communication. A review on literature, their structure, their function in our body and their role in treating diseases has been attempted.

**Key words:** Exosomes • Vesicles • miRNA

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### INTRODUCTION

Exosomes are secreted membrane vesicles formed inside intracellular multivesicular compartments. They are released extracellularly when these compartments fuse with the plasma membrane [1]. They were discovered about 30 years before. Initially they were considered as trash carrying unwanted waste products and cellular debris. In the last decade they were found to contain miRNA, mRNA and some proteins. They had significant role in intercellular communication by transfer of their genetic material. This property is used presently to try them in treating many diseases [1].

**Glance on Literature:** For several decades in substances such blood “microparticles” were known to exist [2]. They were considered as unwanted materials and cellular wastes. Later they were thought to have role on intercellular communication. Nearly 25 years ago Philip Stahl *et al* [3] using electron microscopy and pulse-chase explained that in reticulocytes that were maturing to red blood cells multivesicular late endosomes may possibly fuse with the plasma membrane but not with lysosomes. The contents were thus released extracellularly. The term Exosomes was proposed in 1987 to define these vesicles that were released extracellularly [4].

After 10 years in 1996 it was noted that Epstein-Barr virus (EBV)-transformed B-lymphocytes secreted exosomes that had major histocompatibility class (MHC) II dimers [5].

This suggested that they may perhaps have a significant role in adaptive immune responses. On viewing this it was considered that exosomes might play a role in intercellular communication atleast in the immune system. This encouraged them to try them as a new form of anticancer remedy in humans. At present a phase II trial is ongoing at the Gustave Roussy Institute in France [6].

Proteomic analyses of exosomes secreted by dendritic cells [7, 8] and other cells [9] showed that they have a definite set of a few protein varieties, principally from the cytosol, the plasma membrane and endocytic pathway. But they had very few proteins from other intracellular compartments like nucleus, Golgi apparatus. This confirmed their intra-endosomal origin and differentiated them from membrane vesicles released by apoptotic cells.

Revolution in this field emanated in 2007, when Jan Lötvald described the presence of mRNA and micro RNA (miRNA) inside exosomes [10]. They also showed some mRNA existing in exosomes might be translated into proteins in target cells. This suggested that exosomes could transfer genetic information.

This discovery popped the current exponential increase in the sum of papers on exosomes. International Workshop on Exosomes (IWE) 2011 [1] exposed ongoing researches straddling cell biology and immunology. Their role in tumor and other fields are also extensively studied.

#### Formation and Structure:

- Through clathrin-or non-clathrin-mediated endocytosis endocytic vesicles are formed at the plasma membrane. They are then transported to early endosomes.
- By acidification and some protein content changes late endosomes develop from early Endosomes. They have propensity to fuse with other membranes or vesicles.
- Endosomes then bud interiorly and form smaller vesicles within them, thus becoming Multiple Vesicular Bodies (MVB).
- Microvesicles enclose mRNAs, miRNAs and proteins that were obtained from the cytoplasm.
- MVB can proceed in two paths:
- They can fuse with lysosomes. Their contents are then degraded.
- They may fuse with cell membrane and release internal vesicles. They are then called exosomes [1, 11].
- Exosomes reach their destinations and by binding of specific ligands on their surfaces they get attached to cells.
- Exosomes may go into target cells in either of the two ways:
- They may enter through endocytic action of target cells.
- They could fuse with the cell membrane of the target cells and releasing the contents into the cytoplasm directly.
- Other membrane-derived vesicles called microvesicles, shed vesicles, or ectosomes can also be formed by direct budding from the plasma membrane of the cell. They should not be confused with exosomes. Extensive informations about their effects on distant tissues are not available.
- Exosomes were released by many cell types. Some known ones were B-and T-lymphocytes, hematopoietic cells, dendritic cells, mast cells, astrocytes, reticulocytes, platelets, neurons, intestinal epithelial cells and tumor cells.

- They are named depending on the cell from which it arises nowadays.
- But previously dendritic cell-derived exosomes were called dexosomes and T-cell derived ones were called texosomes.

**Structure:** Exosomes, the secreted membrane vesicles measures about 100nm in diameter similar in size to internal vesicles [1]. They are membrane coated structures enclosing mRNA, miRNA and proteins [1].

#### Proposed Role of Exosomes

**In Infection:** On interaction with recipient cell exosomes induce physiological changes in them. Exosomes secreted by mature dendritic cells have MHC-peptide complexes or antigen and through that it induced antigen-specific immune responses of other dendritic cells [6]. Mycobacteria infected macrophages release exosomes that accept antigens and promote immune responses if the strain is nonpathogenic. If it is a pathogenic strain exosomes inhibit macrophage activation and cytokine secretion, thus diminishing immune response [10]. Thus, they act as double edged sword in immunity.

**In Tumor:** Exosomes secreted by tumor cells have following roles:

- They have antigen which can be recognized by dendritic cells.
- They also have immunosuppressive components that will inactivate T lymphocytes or other immune cells or cells that suppress immune response like myeloid cells [1].
- It was also thought that these simply represent tumor expansion but have no role in tumor progression.

**Others:** Exosomes present in bronchoalveolar fluid of mice bear tolerance to allergen. Conversely in asthmatic patients airway epithelial cells showed increased proinflammatory cytokine secretion. Thus, they are thought to contribute to host tolerance by reducing immune response or on contrary contribute to host's pathologic inflammatory reactions. Placenta-derived vesicles have ligands for natural killer lymphocytes and were found in blood circulation of pregnant women. Extensive studies on the components of these vesicles are done. It was thought that they have role in mothers tolerance to the fetus.

Exosomes help in communication in the nervous system. Exosomes from neurons and others help in that role [12, 13]. Exosomes from cardiac tissue contribute to tissue repair. They from lung tissue modify stem cells to help differentiation of the lung tissue into lung epithelial cells [14, 15]. Exosomes are help in the formation and transfer of pathogenic proteins like amyloid materials and prions [16, 17]. Many others roles are yet to be identified in future.

#### Proposed Therapeutic Uses

**In Auto-immune Diseases:** Exosomes secreted by dendritic cells when subjected to immunosuppressive treatments, or altered to express immunosuppressive cytokines, could promote tolerogenic immune responses thus helping in treating autoimmune diseases [1].

**As Vectors in Gene Therapy:** A proper understanding on the role of exosomes in intercellular communication can help us to deliver therapeutic RNA through reverse engineering. They can be used as drug delivery vehicles. This help in treating many diseases mainly cancer and immunological diseases [18]. Exosomes isolation is a difficult process. They can be isolated from bodily fluids or conditioned cell culture media by liquid chromatography paired with centrifugation, polymer-based precipitation differential centrifugation, filtration paired with centrifugation, high-performance adsorption to antibody-coated beads [19, 20].

**In Cancer Treatment:** In vitro studies were conducted on treating melanoma, prostate cancer and some more fields which had given promising results [11]. Thus, in future it can be used in treating cancer mainly oral cancer which is our field of interest.

#### CONCLUSION

Exosomes which are membrane bound vesicles of 100nm diameter were once considered to be garbage. But after the advent of its contents through electron microscopy they have revolutionized many fields. As they have capacity to transfer genetic material to different sites they are now tried as vectors in gene therapy and cancer treatment. They also can be used as bio-markers. Thus, they are really an imperative miniature.

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