

## Microvesicles: Transporter of Proteins in *Mycobacterium tuberculosis* Pathogenesis

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### Introduction

In current scenario tuberculosis (TB) is a crucial problem of mortality and morbidity which is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) [1]. Recent WHO report of 2015 declared TB as deadly as HIV in accordance with global death rate [2]. *M. tuberculosis* is an effective intracellular pathogen of alveolar macrophages of lungs where it resides within phagosomes [3]. *M. tuberculosis* has the capacity to inhibit fusion between phagosome and lysosome due to these bacilli is responsible for dampening the acidification of phagosome which ensures its longevity [4]. The foremost step during bacterial infection is host pathogen interaction which initiate by various antigenic proteins of *M. tuberculosis* [5]. During infection bacilli releases various mycobacterial antigenic components from phagosome in small membranous vesicles [6]. These vesicles are behaving as transporter or carrier of various virulent proteins which modulate host immune system in its favour [7]. The Microvesicles (MVs) (also can be seen in other literature as the name of ectosomes, shedding bodies, microparticles, oncosomes, etc.) are the heterogeneous membrane bound nanovesicles which contains proteins, phospholipids and LPS and also contains some virulence factor like adhesins, toxins and immunomodulatory compounds that are vital for the pathogenesis [8]. Also the composition of MVs depends upon the cell type from which they are originated. MVs are produced by the process of budding and fission of membrane vesicles from the plasma membrane [9]. MVs are produced by most of the cells and are involved in the various intercellular communications by acting as nanovectors and transferring proteins, mRNA, microRNAs and also have significant role in immune modulation [10]. One of the most important features of MVs is that it is involved in the transfer of genetic information, in gene therapy to treat various genetic disorders and also in the stem cell plasticity [11]. MVs are regulated by several GTPases, including the members of ARF (ARF6 and ARF1), Rab, Rho (Rac1 and RhoA) families. Rab proteins are involved in the endosome trafficking and have crucial role in the pathogenesis of *M. tuberculosis* [12]. It is also seen that MVs which are released from circulatory cells have functional role in immunity and coagulation [13]. Environmental condition is also an important factor in the production of these vesicles and it had been seen

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that *M. tuberculosis* MVs production increases under the iron limitation and restriction. MVs that are released at such condition contain mycobactin which helps in the replication of iron starved mycobacteria [14]. MVs, along with the pathogenesis of *M. tuberculosis* are also involved in other disease like osteoarthritis, pulmonary hypertension and thrombosis, cancer, etc. [15].

MVs infected from the bacilli stimulate both innate and adaptive immune receptors and contributes to the genesis of CD4+ T-cell response [16]. Certain MVs are also released by the neutrophils and it is seen that innate immune response is accompanied when these neutrophils migrate at the site of infection and the infected neutrophils has the ability to influence the survival of *M. tuberculosis* within macrophage [17]. Although neutrophils are not able to kill the virulent *M. tuberculosis* but they are important in granuloma formation and suppression of infection. *M. tuberculosis* infection causes rise in the neutrophil apoptosis and which elicits proinflammatory response in macrophages [18].

Due to the incessant study, MVs can be used as biomarkers in disease, therapeutic targets, drug delivery etc. One major advantage of using MVs as biomarker is that it can be easily accessible in the biological fluids [19].

It has been known that apoptosis is involved in the development of autoimmune disease and the apoptotic MVs can hasten autoimmune response in the specific tissue or organs [20]. Apoptotic MVs are said to be the combination of apoptotic bodies and microparticles (MVs) which are mainly released by the infected macrophages and these carries several mycobacterial antigens that stimulate the CD8+ T-cells response and provide protection from *M. tuberculosis* [21].

The impact of MVs can be studied by measuring the production of human and murine macrophages in mice during mycobacterium infection. MVs, released from the infected alveolar macrophages contribute to the disruption of epithelial cells which later on facilitate formation of granuloma, which in turn stimulate the production of TNF (Tumor Necrosis Factor) and enhance the transfer of antigens to APCs (Antigen Presenting Cells). Also there are certain proinflammatory cytokines and chemokines are released from the infected macrophages [21]. Further research in the field of microvesicles need to be done for the future research and development work as we know that microvesicles have easy accessibility in the biological fluids. On the basis of this research area may be best possible way in the drug discovery

## Summary

Tuberculosis is global threat to human health due to its indocile nature of bacilli has drawn profound interest of many researchers.

Bacilli contain several antigenic proteins which involve in pathogenicity which actively participate in host pathogen interaction. Bacilli uses host membranous trafficking mechanism to transport its virulent proteins which modulate host immune system. During mycobacterial infection various MVs are released which have distinct function in the transfer of cargo from donor to recipient cells through intercellular communication. MVs that are released by infected macrophages stimulate CD8+ T-cell immune response which helps in the protection. MVs serve variety of function as they contain the type of cellular proteins from which they are originated. MVs which are apoptotic in nature can function to accelerate the autoimmune response in specific tissue and organs.

So, while performing the key role in modulation of host immune system MVs can also be used as biomarker. Due to their easy accessibility in biological fluids, they can be targeted in research purpose to provide hassle free environment to bring out the best possible way in the drug discovery.

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