Exosomes and Shedding Microvesicles are Mediators of Intercellular Communication: How do they Communicate with the Target Cells?

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Intercellular interactions are pivotal for basic cellular activities and errors in either receiving or transmitting these signals are shown to cause pathological conditions. Whilst, such intercellular communications were once thought to be regulated by membrane surface molecules and/or soluble secreted proteins by stimulating the target cells through receptor mediated activation, increasing evidences suggest that extracellular microvesicles (EMVs) can also trigger such signaling events in the target cells. Exosomes and shedding microvesicles (SMVs) are classes of EMVs that are membrane enclosed organelles released by cells under physiological and pathological conditions [1-6]. Among the EMVs, exosomes are small (40-100 nm diameter) intracellular vesicles of endocytic origin while SMVs (also referred to as ectosomes) are large membranous vesicles (50-1000 nm diameter) that are shed directly from the plasma membrane (PM) [7]. Recent studies have shown that these EMVs mediate intercellular communication [8-10] and are shown to harbour mRNA, microRNA, proteins and lipids [8,11-14] based on the host cell [13].

While many of such recent observations have proven the role of EMVs in cell-cell communication, the exact mechanism in which these EMVs communicate with the target cells still remains elusive. Excluding the study by Rana et al. that showed the role of tetraspansins in target selection [15], the factors that influence target cell selection are poorly understood. Possible mechanisms of EMVs communication with target cells are shown in Figure 1 (exosomes as an example). EMVs harbor membrane proteins that can interact with the target cells in a juxtacrine manner, thereby activating the target cell (Figure 1B). Alternatively, exosomes can fuse with the target cell resulting in the non-selective transfer of exosomal proteins and RNA (Figure 1C) to the target cell. In addition to proteins and lipids, exosomes also contain mRNA and microRNAs that can be transferred to the target cell, conferring new functional properties to the recipient cell after the acquisition of the exosomal genetic material. Such fusion might change the membrane features of the target cell (e.g., arachidonic acid transfer from platelets-derived shedding microvesicles to leukocytes and endothelial cells [16]) including varied lipid concentrations and the transfer of exosomal membrane proteins on the target cell surface (e.g., CD41 antigen from platelets-derived shedding microvesicles to tumor and endothelial cell surface [17,18]). Proteins that are present in the soluble secretome are not only a result of protein secretion, cell death and cell surface membrane ectodomain shedding but also due to ectodomain shedding of exosomal membrane proteins [19,20]. Exosomal membrane proteins can be cleaved by proteases and the resulting fragment may act as ligands for cell surface receptor in the target cell (Figure 1D). In addition to juxtacrine, ectodomain cleavage-based signaling and membrane fusion, exosomes can be engulfed by antigen presenting cells and phagocytosized [21] (Figure 1E). The antigen presenting cells can later process the molecular information and trigger the cellular signaling cascades [21].

Whilst these are the possible mechanisms of intercellular communication by EMVs, the precise mechanism need to be clearly understood to manipulate these bioactive vesicles as efficient drug delivery vehicles.

References


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**Figure 1**

[Diagram showing the interaction between host cell and target cell through exosomes.]