

In pleural effusion, cancer, and cardiovascular disease, metabolites act as extracellular vesicle cargo

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ABSTRACT

Extracellular Vesicles (EVs) are a broad class of membrane-bound nanoscale entities that are released into the extracellular environment by various cell types. By delivering their cargo, which includes proteins, RNA, DNA, lipids, metabolites, and tiny molecules to destination cells, they perform crucial roles in cell

signalling. Recent research has indicated that EVs may control carcinogenesis by transporting cargo to recipient cells. Recent study has also shown that variations in plasma-derived EV levels and cargo in patients with metabolic illnesses have been noted by numerous researchers, indicating that EVs may be a promising source of disease biomarkers. Metabolites are one of the EV cargos that have recently garnered the most interest.

Key Words: *Gene therapy; Pleural disease; Interventional pulmonology; lung injury*

INTRODUCTION

According to recent research, cells going through apoptosis or death release vesicles into the extracellular space. But it's becoming more and clearer that healthy cells can even release vesicles while they go about their daily business. Any of the several vesicles created by healthy cells, such as micro particles, endosomes, exosomes, microvesicles, and exosomes, are referred to as "Extracellular Vehicles (EVs)". EVs are tiny, double membrane-enclosed vesicles that cells secrete. They are involved in cell signaling and carry a cargo of lipids, proteins, metabolites, small molecules, DNA, microRNAs (miRNAs), mRNAs, and Long Non-Coding RNAs (lncRNAs). EVs have a lipid bilayer and are spherical structures. Microvesicles, apoptotic bodies, nuclear material, organelles, and nanometer-sized exosomes are a few of these structures. Exosomes are tiny vesicles that cells secrete; they can move through the bloodstream and end up in bodily fluids such as saliva, bile, lymph, amniotic fluid, breast milk, cerebrospinal fluid, urine, and blood. Once there, they have the ability to interact directly with the receptor-ligand of a target cell, fuse or incorporate with the target cell membrane to release their materials further into the cytoplasm, and therefore affect the biological processes or pathophysiology of the recipient cell. Exosomes contain special substances that are either contained within or bound to the membranes of these vesicles as their payload. Recent research has shown that the outcome of many pathological illnesses,

including cancer, autoimmune diseases, and infectious diseases, is significantly influenced by EVs and their cargo. For instance, EVs may promote carcinogenesis, alter the tumor microenvironment, encourage metastasis, and let tumor cells bypass the immune system. Specific cargo molecules, like proteins and miRNAs, are frequently linked to these actions. Additionally, EVs and their payload may be used as biomarkers for both diagnosis and treatment. For instance, it has been demonstrated that the patterns of lncRNA and miRNA isolated from the circulating exosomes of patients with non-small cell lung cancer are consistent with those found in primary tumors. Exosomal proteins and RNA molecules are the present subjects of the majority of studies. Despite being part of the exosomal cargo, metabolites have received little attention. Since metabolites represent the beginning and finish of all biological activities, they may serve as a phenotypic activity of an organism's state. Monitoring metabolic changes in the patient's biological fluids, such as urine, synovial fluid, saliva, blood, cerebrospinal fluid, and semen, thus, may provide useful diagnostic information regarding the condition of the patient's disease and the effectiveness of treatment. Exosome metabolomics has received a lot of attention since studies to identify lipids in the membrane of exosomes from many cell types have been conducted. Demonstrated that exosomal metabolites are important in the development of tumors. Although exosomal components are similar to those of donor cells, they contain more of a few particular lipids,

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such as cholesterol, phosphatidylinositol, and phosphatidylcholine, which serve as lipid facilitators in intercellular transit. EVs of Human Mesenchymal Stem Cells (hMSCs) include glutamate and lactate, according to a metabolomics investigation. Lactate may aid tumor cells in surviving in low-oxygen and low-nutrition environments, whereas glutamate may be used via carbon and nitrogen trafficking to provide precursors for the major macromolecular categories. molecular pathways. Exogenous or endogenous functional genes are transfected into target cells or tissues during gene therapy in order to express the appropriate proteins and carry out their tasks. To uncover biomarkers in this area, metabolomics, a relatively new "omic" research technique, may be helpful. The full collection of low molecular weight metabolites, known as the metabolome, is discovered and determined using a procedure known as metabolomics depending on the tissue and in accordance with the physiological, developmental, or pathological state of a cell, tissue, or organism. EVs have also been the subject of numerous investigations to determine whether or not they could serve as disease-specific medication carriers. There are large gaps in this field, but they must be remedied in the upcoming years. The limitations include a lack of detailed identification of the cellular source of EVs, poor nomenclature, considerable technological difficulties in EV characterization and quantification, and others. The most recent research on the function of metabolites as EV cargos in the pathophysiology of illnesses like cancer, pleural effusion (PE), and cardiovascular disease is presented in this paper (CVD). The relevance of metabolites as EV payloads of bacteria and their function in host-microbe interaction were also covered. This paper also presents the most recent research on metabolites as EV cargoes and biomarkers for disease diagnosis and therapy. The distinct biosynthesis and discharge methods of exosomes, microvesicles, apoptotic bodies, and endosomes allow them to be classified as subclasses of EVs [26]. Although the mechanism underlying EV generation and secretion are not fully understood, the biosynthetic mechanism of EVs is renowned for being challenging to understand. Exosome synthesis is a challenging endocytic procedure. A cup-like morphology is created as a result of the plasma membrane invagination process. Proteins on the cell surface and soluble proteins associated with the early-stage endosome are what create early endosomes (ESE). The Golgi apparatus and the endoplasmic reticulum are both involved in building at this point in the process. Eventually, the growing ESE becomes a Multivesicular Body or a Late Endosome (LSE) (MVBs). In contrast to other MVBs that fuse with lysosomes and are destroyed prior to fusing with the cytoplasmic membrane, newly formed MVBs are influenced by MVB vesicles and intracellular organelles to fuse with the plasma membrane and deliver their Intraluminal Vesicle (ILV) cargo to the extracellular environment. The pathway of MVB biosynthesis which has been studied in more depth is the ESCRT complex which is crucial for filtering ubiquitinated proteins into ILVs. Following the limiting membrane's involution caused by ESCRT-I/II through the MVB lumen, ESCRT-III forms a spiral-shaped construct that inhibits the budding neck and the ATPase VPS4 (Vacuolar Protein Sorting 4), leading to membrane separation. In order to release exosomes, MVBs can either combine with the plasma membrane, or they can combine with lysosomes, which will destroy their cargo. The soluble-ethyl maleimide Sensitive-Factor Attachment Protein Receptor (SNARE)

membrane fusion complex is where secreted MVBs connect after being transported to and bound to the plasma membrane. Small Gases, such as RAL-1, have been shown to have a role in exosome release by engaging SNAREs that are bound to the MVB, according to research by Hyenne and colleagues. Exosomes are released into the extracellular milieu when MVBs fuse with the plasma membrane. Here, they may interact with the extracellular matrix, have an impact on cells in the microenvironment, and enter through the lymphatic or blood circulatory systems. Exosomes have been found to stick to the cell membrane in some types of cells, where they may function as signaling molecules for juxtacrine interactions. Readers are directed to publish works by others for more information on EV biogenesis. One of the physiological functions of EVs is to participate in coagulation. They are also essential for preserving homeostasis. One of the traits of bigger EVs is their pro-coagulant effects, which have also been found in healthy persons' saliva and urine. EVs of the innate immune system may function as paracrine transporters and transmit pro-inflammatory substances during sepsis, chronic illnesses, and infections, including rheumatoid arthritis. The possibility that EVs contain complement molecules and contribute to complement activation has been demonstrated. However, EVs may also contribute to the harmful modulation of the inflammatory response by causing the creation of Transforming Growth Factor beta (TGF- β). For instance, antimicrobial proteins in urine may aid EVs in killing bacteria and preventing their growth. Seminal fluid EVs play a part in fertilization as well as in controlling sperm development, motility, and defense in the female reproductive system. During pregnancy, Syncytiotrophoblast (STB)-derived vesicles interact with nearby cells to control coagulation, development, revascularization, inflammatory responses, and mother-to-child immunological transmission. These EVs may move between neurons, microglia, and oligodendrocytes, among other nervous system cell types from which they are released. EVs support neuronal survival, neurite outgrowth, and myelination. EVs may include some harmful proteins, such as prions or beta-amyloid peptides, which contribute to neurological disorders. These secretory vesicles aid in the spread of illness once they penetrate recipient cells. Stem cells produce Extracellular Vehicles (EVs), which may aid in tissue regeneration. Because they replicate the function of these cells, they might be useful in regenerative medicine. The composition of EVs has received a lot of attention as a potential biomarker for a number of illnesses or due to the interest in its functional consequences. In EVs, cargo such as proteins, miRNAs, metabolites, nucleic acids, and lipids can be loaded and delivered. Different types of EVs may carry different substances, depending on the parent cell and the packing techniques employed. Drugs, pathological circumstances, and other stimuli may all have varied effects on a given cell type, resulting in differential enrichment of various cargo molecules. The exosome lumen contains cytosol-derived proteins like annexin II, heat shock proteins, and the heterogenic G protein Gi2. Exosome metabolomics is a novel approach, as the knowledge of metabolites in EVs has only just been available. Several research on the general profile of metabolites in blood or urine has been evaluated with encouraging results. The majority of pertinent research has been on exosomes (small EVs) obtained from cell culture media, whereas studies studying vesicles isolated from bodily fluids have been underrepresented. In addition to lipids, cyclic alcohols, minerals, nucleosides, sugars, and their conjugates, organic acids,

vitamins, aromatic compounds, carnitines, and amino acids have all been identified in certain studies as potential EV payloads. Consequently, tracking metabolic changes in a patient's bio-fluids, such as whole blood, serum, plasma, urine, and other bodily fluids, may offer vital clinical information regarding the stage of the disease as well as the treatment's effectiveness. Exosome metabolomics research that aims to identify the lipids in the membrane of exosomes produced by various cells has received a lot of attention. Exosomes extracted from blood and urine were afterward subjected to metabolomics methods, which revealed a variety of components. Despite the fact that exosomes are crucial for therapeutic purposes, little is known about their metabolome, especially when they are separated from biological fluids. This article makes an effort to give a quick overview of the metabolite that is carried by EVs in diseases such as cancer, CVD, nervous system disorders, and the serum levels of metabolites connected to the glycolytic pathway, primarily glucose, ribose, and fructose, on the other hand, increased. Wojakowska and colleagues performed a pilot study comparing the metabolite patterns of total serum and serum-derived exosomes between healthy controls and head and neck cancer patients who received radiotherapy in order to better understand the effects of radiotherapy on these patients. They found that exosomes made from sera showed a metabolite profile that is probably less complex and composed of fewer elements than the total serum. Importantly, these researchers showed that samples from head and neck cancer patients and control subjects had different ratios of metabolites related to the Warburg effect energy production processes, TCA gluconeogenesis cycle, glycolysis, pyruvate metabolism, and mitochondrial electron transport chain discovered that exosomes produced by CAFs unexpectedly influenced the metabolism of tumors in the prostate and pancreatic cancers. Their research suggests that exosomes produced from CAFs of cancer patients may change the metabolism of cancer cells by blocking mitochondrial oxidative metabolism and providing brand-new "off-the-shelf" compounds. Exosomes produced from CAFs have been demonstrated to reduce mitochondrial oxidative phosphorylation, resulting in a parallel rise in glycolysis. Exosomes generated from CAF that blocked the electron transport chain dramatically increased reduced glutamine carboxylation for generation in tumors cells.