Review Article

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EMERGING FUNCTIONS OF EXOSOMES IN CARCINOGENESIS AND CHEMOTHERAPY RESISTANCE

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ABSTRACT

Globally, cancer and related disorders are major health issues. The scientific community has many obstacles in tackling this problem and creating a streamlined therapy and drug administration plan. Chemotherapy is necessary for cancer treatment, however many individuals acquire drug resistance due to recurrent medication delivery. Chemotherapy resistance hinders cancer treatment. Exosomes are vesicles their size range from 40 to 160 nm (the average being 100 nm). Exosomes can include DNA, RNA, fatty acid, metabolites as well cytosol, and cell surface proteins. Since exosome formation's physiological purpose is unknown, more research is needed. Exosomes regulate intercellular communication and help cancer cells develop chemoresistance. Exosomes can reveal physiological and pathological information about their parent cells. Liquid biopsies assess cancer chemosensitivity using exosomes. Because exosomes are stable and sensitive. This review covers exosome-mediated cancer chemoresistance. We also studied tumor-related processes, exosome biogenesis, and their current and potential roles in cancer diagnosis and treatment, drug delivery systems, and chemoresistance.

KEYWORDS: Exosomes, Exosome Biogenesis Cancer, Chemoresistance, mi-RNA.

INTRODUCTION

Cancer continues to be a prevalent ailment that poses a significant threat to the well-being of individuals worldwide. Cardiovascular disease aside, it ranks as the second most prevalent cause of mortality on a global scale. The unique characteristics of cancer cells encompass their ability to swiftly proliferate, metastasize, and transition between diverse molecular pathways to attain resistance to therapeutic drugs (1,2). In recent times, novel therapeutic interventions have been devised to specifically recognize cancer cells and their progression by leveraging these inherent properties. In addition, novel methodologies, such as the implementation of nanoparticles, have been employed for the accurate and correct delivery of therapeutic agents to cancerous cells (3). Chemotherapy plays an vital role in the remedy and treatment of cancer. The phenomenon of drug resistance is commonly observed in a significant proportion of cancer patients who undergo repeated treatment with chemotherapeutic agents. This resistance typically develops sequentially, starting with resistance to one agent and subsequently extending to other agents (4).

The development of chemoresistance poses a significant obstacle to the efficacy of anticancer treatment. The involvement of exosomes derived from cancer in chemoresistance has been suggested as they facilitate the transfer of DNA, RNA, and proteins to cancer cells (5). The present review has placed significant emphasis on the role of extracellular vehicles (EVs)also known as exosomes as a new structural entity in the cancer context, and play a significant role in chemo resistance (5-6).

Exosomes are small extracellular vesicles found in eukaryotic cells, they play a very important role in cell to cell communication and trafficking. The common average size of an exosome is 100 nanometers, but its diameter can range anywhere from 40 to 160 nanometers. Even after they were discovered in the late 1980s, exosomes were at first merely categorized as a type of waste product produced by cells. Exosomes transport protein, mRNA, and DNAs , these are main cellular material which is basically responsible for the transfer of information between donor cells and recipient cells in tumor microenvironments, which may be responsible for drug resistance (7,8). Exosomes have been linked to a wide variety of biological processes, including the immunological response, viral pathogenesis, pregnancy, cardiovascular illness, neurological disorders, and cancer development. Exosomes can effectively influence the

biological response of recipient cells by delivering proteins, metabolites, and nucleic acids. Disease progression or suppression may result from exosome-mediated responses. Exosomes' inherent properties in controlling intricate intracellular pathways have raised their therapeutic promise for a wide range of ailments, including neurological disorders and cancer. Exosomes have the ability to carry various therapeutic payloads such as small interfering RNAs (siRNAs), chemotherapeutic drugs (chemo), and immunological modulators. These payloads can be modified and incorporated into exosomes for therapeutic purposes.Exosomes' natural contents, including their lipid and protein makeup, may contribute to increased bioavailability and reduced adverse effects. Exosomes can be used not only as a therapeutic tool but also in the diagnostic process. Exosomes have been found in every known body fluid, and it is simple to obtain their complicated payload by sampling bodily fluids (liquid biopsies).

This review highlights and explains the examination and pathway of exosomes mediating chemoresistance in cancer. Additionally, it explores the potential use of exosomes as a means to counteract chemoresistance and reverse its effects.

The process of biogenesis of exosome and isolation

The endocytic pathway is a multi-step process that ultimately results in the production of exosomes. Cell membrane invagination are primarily responsible for the formation of early secretory endosomes during this stage. Intraluminal vesicles (ILVs) surrounded by endosomes are formed during MVB biogenesis via inward sprouting. Intraluminal vesicles (ILVs) fuse with the cell membrane and then release exosomes as the last stage (6,9). Multivesicular bodies (MVBs) possess a size range of 250-100 nm, allowing for the formation of numerous intraluminal vesicles (ILVs) with a approximately 30 to 150 nm which combined to form the MVBs, as reported by a study. Several proteins participate in the generation of intraluminal vesicles (ILVs) and multivesicular bodies (MVBs), as well as in the process of selecting cargo for inclusion.

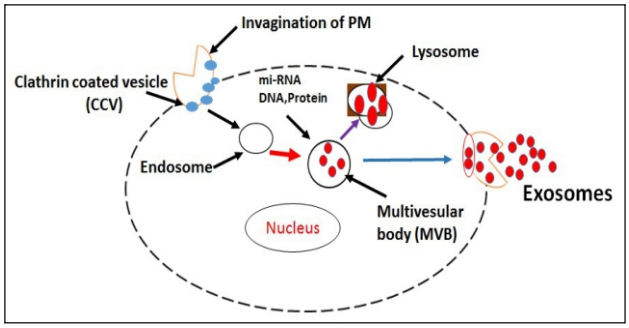

Fig. 1: General outline for the Biogenesis of Exosomes

It is generally agreed upon that the endosomal sorting complexes necessary for transport, abbreviated as ESCRT, are the most prominent proteins contributing to the formation of exosomes. ESCRT-0, -I, -II, and -III are the four individual components that come together to form this complex. The primary functions of these components, which alternate between assisting in the creation of membranes and sorting cargo, are described below. Within the cell, the process of linking ubiquitylated contents with microdomainsof fats /lipids is carried out bytransport protein such as ESCRT-0 and ESCRT-I. These two proteins are responsible for carrying out this process (10). The processes of membrane invagination and the formation of Multivesicular Bodies (MVBs) and the formation of Intraluminal Vesicles (ILVs) involve both ESCRT-II and ESCRT-III. PDCD6IP, VTA1, VPS4, and TSG101 are proteins that assist the ESCRT machinery in the process of exosome biogenesis. Furthermore, alternative mechanisms that are not reliant on ESCRTs have been discovered to impact the generation of exosomes. These include pathways that are dependent on neutral sphingomyelinase 2, heterogeneous nuclear ribonucleoproteins, post-transcriptional modification of miRNA 3′ends, and pathways related to the RNA-induced silencing complex (7,11).

Exosomes and tumor angiogenesis

The formation of new vessels is primarily attributed to angiogenesis and vasculogenesis, which are widely regarded as the two most significant mechanisms (12). Nevertheless, significant distinctions exist between angiogenesis and vasculogenesis. The process of vasculogenesis plays a crucial role in the embryonic development of the cardiovascular system by facilitating the formation of complete vessels. The process involves the release of VEGF by the endoderm, which subsequently triggers the expression of VEGF receptor 2 on mesodermal cells through paracrine signaling (13). Then, cells in the peripheral regions of blood islands, known as angioblasts or endothelial progenitor cells, undergo a mesodermal-derived transformation. The merging of these cells results in the emergence of rudimentary capillary networks. Vasculogenesis pertains to the genesis of novel vessels, while angiogenesis denotes the mechanism of vessel formation from preexisting vessels.

In recent times, there has been a notable emphasis on the significance of angiogenesis in the context of cancer. The induction of angiogenesis by tumor cells is imperative for their sustenance, proliferation, and metastasis to various anatomical locations. According to reports, the growth of cancer cells is limited to a size range of 1-2 mm in the absence of angiogenesis. Hence, the inhibition of angiogenesis could be a potential strategy in the treatment of cancer (13,14).

Exosomes have been identified as key players in cancer chemoresistance

Researchers have discovered that exosomes are important participants in the development of chemoresistance in cancer.In recent years, exosome research has become an increasingly exciting area of study, particularly within the context of the study of cancer. Many researchers are interested in these compounds because of the potential applications they have in the treatment of cancer, cancer metastasis, and chemoresistance. How the cytoplasmic content of exosomes an important player in the process of promoting cell-to-cell contact, the transfer of cargo, and the epigenetic control of genes. (15). Exosomes are now commonly believed to play the role of mediators in a diverse range of biological and pathological processes. In particular, research has demonstrated that they are important for influencing carcinogenesis, metastasis, angiogenesis, and treatment resistance in cancer. In addition, the research showed that the exosomes in question encouraged the growth of tumor cells. (6). The value of exosomes in the serum of patients with esophageal squamous cell carcinoma (ESCC), compared to the value of exosomes in the serum of healthy volunteers, was shown to be significantly higher according to the findings of this study (16). Exosomes have been shown to play a crucial role in the progression and growth of hepatocellular malignancy, according to research that was carried out by a group of researchers that worked together. Learn how to harness the power of angiogenesis by controlling your energy metabolism, inflammation, and the microenvironment. Recent discoveries made in the field of study have shown that non-tumor cells that are present in the tumor microenvironment (TME) play an important part in the development of treatment resistance. (8,17). Even when chemotherapy is present, these cells are known to emit signals or chemical messengers that encourage the growth and survival of cancer cells. This occurs even while chemotherapy is present.

The fundamental mechanism behind chemoresistant behavior, which is mediated by exosomes

The phenomena known as chemoresistant disease can be broken down into two distinct categories: 10 drug resistance and multiple drug resistance (also known as MDR). According to the researcher (18), the term "former" is used to describe cancer cells that have the potential to be resistant to drugs that are induced, whereas the term "latter" is used to describe cancer cells that acquire resistance to induced drugs and other chemotherapeutic agents through a variety of structures, topologies, and mechanisms, even in the absence of having been previously exposed to said agents. In addition, cancer cells that exhibit resistance to medications that have been created are referred to as "former" cells in this context. Researchers (19,20) assert that there are a number of different pathways that are responsible for the resistance of cancer cells to chemotherapy. These strategies include increased expression of MDR proteins, better DNA repair, decreased apoptosis, altered drug targets, and rapid drug efflux. Both the regulation of signal transmission and the expression of genes requires the presence of exosome proteins and nucleic acids as key components. Because they are able to activate signal transduction pathways and connect with cell surface receptors, they play an essential part in the activities that are taking place (21). This topic is about the role that proteins and nucleic acids play in exosomes, specifically with regard to their ability to mediate chemoresistance.

Chemoresistant mechanisms controlled by exosomal proteins

Exosomal proteins are a cluster of proteins that are discovered in exosomes, which are small extracellular vesicles (Evs), that are released by cells. Exosomes are the source of the proteins that make up exosomal proteins. Because these proteins are engaged in a wide variety of cellular functions, substantial research has been conducted on them in recent years due to the possibility that they have a role in the diagnosis or treatment of disease (22). Because they are a component of EVs exosomes play a part in both normal and aberrant biological processes. This is accomplished by the transmission of a wide variety of signaling molecules, some of which include, but are not limited to, messenger RNAs, nucleic acids, lipids, and proteins. The process of ubiquitination, which is unique to exosomal proteins and helps ESCRT-0 recognize them, is one of the distinguishing characteristics of exosomal proteins. The step of deubiquitination is an essential one in the process of sorting these proteins into intraluminal vesicles (ILVs), as shown in reference number 23. It is not entirely clear whether or not ubiquitination is required in order to facilitate the transport of proteins into exosomes; this issue is currently under discussion. Exosomal proteins include a wide array of membrane transport and fusion-related proteins, such as annexin, Rab-GTPase (Ras-related protein GTPase Rab), and heat shock proteins (HSPs), which include Hsp60, Hsp70, and Hsp90. Exosomes are organelles that are found in the exosome. Facilitating the process of angiogenesis is the responsibility of the cytokine known as vascular endothelial growth factor (VEGF), which plays a significant role in the progression of cancer. The formation of new blood vessels, known as angiogenesis, is a process that occurs in tumors. By

interacting with receptors, in particular VEGFR1 and VEGFR2, the Vascular Endothelial Growth Factor (VEGF) is able to have an effect on the process of neovascularization. The VEGFR1 and VEGFR2 receptors are the ones responsible for mediating this link. Additionally, it is essential to keep in mind that the Vascular Endothelial Growth Factor, also known as VEGF, has a propensity to bind to cofactors, most especially Neuropilin-1 (NRP-1) and NRP-2. This is something that needs to be taken into account, so keep that in mind. The Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is largely produced by endothelial cells, whereas the VEGFR1 receptor is present in macrophages, cancer cells, and fibroblasts. Endothelial cells are principally responsible for its synthesis. Recent research (9,24) demonstrates that monoclonal antibodies are a promising method for blocking VEGF or VEGFR and lowering angiogenesis. This is proven by the fact that monoclonal antibodies have been found. Exosomes, which are secreted by tumor cells, play a role in the mechanism that serves to commence the progression of cancer by the activation of angiogenesis. This process is made easier by the fact that tumor cells secrete exosomes. Numerous investigations, both preclinical and clinical, have shown that activation of STAT3 is linked with patient survival and is present in a wide variety of cancers (25). These studies have shown that this association is important.

According to earlier study publications, data demonstrates that exosomal proteins are implicated in the induction of chemoresistance in exposed or diseased cells via many methods (15). These processes include the transmission of chemoresistance features as well as the lowering of intracellular drug concentrations. It is essential to take into consideration the fact that these proteins have the potential to for the monitoring of chemosensitivity.

Chemoresistant mechanisms that are mediated by exosomal noncoding RNAs

Exosomal noncoding RNAs, also known as exosomal ncRNAs, are a specific kind of RNA molecule that is carried about by exosomes, which are small extracellular vesicles. It has been demonstrated that these noncoding RNAs play critical roles in the communication between cells and can have major influence on the processes that occur within cells (5).

The length of microRNAs, also known as miRNAs, ranges anywhere from 20 to 22 nucleotides and is considered to be a substantial fraction of short noncoding RNAs. In a wide variety of physiological and pathological processes, microRNAs have been the focus of a significant amount of research. During the early phases of cancer development, exosomes that contain miRNAs have the potential to function as biomarkers for cancer prognosis and/or grading (26).

Exosomal micro-RNAs such as micro-RNA-451a, micro-RNA-21, and micro-RNA-4257 have been found to be overexpressed in patients with non-small cell lung cancer. This overexpression has been found to be substantially connected with the progression of the tumor, its recurrence, and a poor prognosis. The study of plasma extracellular vesicle (EV) samples taken from people diagnosed with prostate cancer revealed that the expression of let-7a-5p in plasma EVs was significantly lower in patients with high Gleason scores (GS) in contrast to those with low GS. This was discovered through the research of plasma EV samples obtained from prostate cancer patients. It has been demonstrated that a combined analysis of exosomal micro RNA-1290 and 375 has the ability to predict the overall survival of patients who suffer from castration-resistant prostate cancer (27).

In addition to the non-coding RNAs known as microRNAs, it has been discovered that exosomes may also include long non-coding RNAs known as lncRNAs. These lncRNAs are involved in the regulation of angiogenesis. Certain circular RNAs, known as circRNAs, have been shown to be capable endogenous molecules that can compete with miRNAs, and as a result, they have the potential to play a role in the regulation of genes involved in the development of cancer (28).

To summarize, a large number of preclinical and clinical studies have pointed to the critical role that nucleic acids contained within exosomes play in the promotion of chemoresistance, which has generated heightened enthusiasm for the discovery of miRNA. It has been discovered that the modification of the expression of nucleic acids has the ability to counteract the adverse effects of chemotherapy. Monitoring levels of nucleic acid, on the other hand, is an effective method for reducing the risk of developing chemoresistance and increasing overall survival rates.

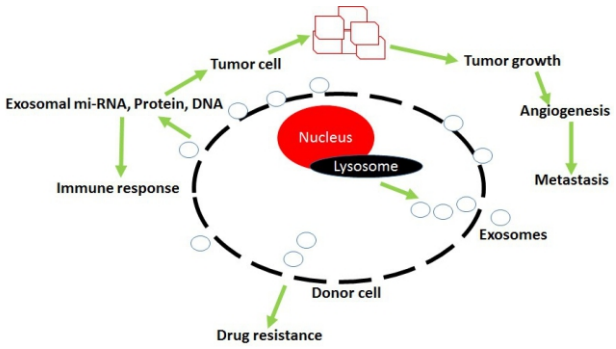

Fig. 2: Shows role exosomal mi-RNA and protein in and cancer metastasis and drug resistance

Approaches to Address Exosome-Mediated Chemoresistance

The phenomena of chemoresistance that are connected with exosomes must be thwarted to achieve the maximum therapeutic benefit from chemotherapy. Two potential avenues can be pursued to accomplish this goal: (i) the suppression of exosome production, and (ii) the exploitation of exosomes as carriers for the sake of delivery.

Exosomes have been reported to produce chemoresistance in malignant cells; thus, some studies have proposed that chemoresistance can be overcome by decreasing the process of exosome formation. This is because exosomes can cause chemoresistance in cancer cells, inhibiting the creation of multivesicular bodies (MVBs), which is the most important for preventing the synthesis of exosomes, is one of the most important strategies (29,30). The drug GW4869, which is a hydrochloride hydrate, is frequently utilized to impede the creation of exosomes, it was observed that this drug obstructs the sprouting of multivesicular bodies (MVBs) that are facilitated by ceramide, consequently preventing the discharge of exosomes from MVBs (6). The other study also shows a significant reduction in the levels of exosomal proteolipid protein (PLP) and CD63 in the administration of GW4869 treatment to cells (31). According to Richards et al. (2017), the administration of gemcitabine to cancer-associated fibroblasts (CAFs) resulted in an elevation in the secretion of exosomes that promote chemoresistance (32). This finding highlights the crucial function of GW4869 in reversing chemoresistance. In addition, the compound Manumycin-A, which is a naturally occurring microbial metabolite, has been discovered to act as a suppressor of exosome biogenesis and secretion in castration-resistant prostate cancer (CRPC), while not impacting cellular proliferation.

The presence of exosome proteins and nucleic acids plays a crucial role in controlling signal transduction, cellular communication, and gene expression. They can initiate signal transduction pathways and cellular communication via engaging with cell surface receptors, which is crucial for these mechanisms. This discussion pertains to the mediation of chemoresistance by proteins and nucleic acids that are present in exosomes. The inhibition of exosome biogenesis as a means of reversing chemoresistance shows promise, albeit with significant challenges.

In a recent study (33), it was observed that the administration of sulfisoxazole to cancer cells did not result in a decrease in exosome count. The observed differences between the two studies could potentially be attributed to variances in experimental conditions, such as the utilization of distinct cell lines at varying passages or the employment of dissimilar equipment. In general, research on drug incubation has indicated the potential for either hindering or facilitating the process of exosome release in surrounding medium. This technique is currently in its early stages and necessitates further comprehensive experimental, clinical, and human trails validations in the future.

Exosomes as Therapeutic Carrier Particles

The study of exosomes has advanced rapidly in the past few years. Liposomes, nanosponges, and self-assembling peptides are just a few examples of nanoparticles (NPs) that have been the focus of extensive research for nanomedicine over the past few decades, particularly in the context of targeted cancer therapy (3). Multiple studies have shown that the use of exogenous nanomaterials for drug delivery to target cancer cells faces many obstacles due to the diversity of these cells and the differences between human and animal models in terms of biological barriers and immune systems. Creating naturally occurring carriers is one way to overcome the limitations of manufactured nanoparticles (3,34). Numerous studies have shown that exosomes can enter and exit cells through lipid bilayer membranes because of their lack of immunogenicity, high biocompatibility, efficient distribution, and sturdy stability in circulation (35,36). Because of this quality, exosomes may one day be used to transport pharmaceuticals or genetic material.

Exosomes as Chemosensitivity Biomarkers

Exosomes are useful in both preclinical and clinical investigations as indicators for predicting chemosensitivity in cancer patients undergoing liquid biopsy. It was shown that exosomes played a significant part in the process of upregulating ADM resistance by acting as a facilitator in the movement and the transportation of Glutathione S-transferase P1 from breast cancer cells that exhibit resistance to ADM to cells that are susceptible to the drug. (37). So, GSTP1 could be a useful biomarker for determining which breast cancer patients would respond to anthracycline and taxane-based chemotherapy.In research including patients with advanced, chemoresistant colorectal cancer. The activation of stem cell subsets and epithelial-mesenchymal transition by the exosomes was discovered to increase the metastatic potential and chemoresistance of colorectal cancer cells (38).

Exosomes isolated from different physiological fluids are used as biomarkers in the detection of chemoresistance.

Urine and blood exosomal biomarkers have become increasingly prominent as diagnostic tools in recent years. It is common practice to use exosomes found in urine as emerging biomarkers for diagnosing malignancies of the prostate, bladder, and kidneys (38). The lipid composition of urine exosomes was examined between prostate cancer patients and healthy controls. Based on their findings, these lipids have a great affinity and open a new path as biomarkers for the diagnosis, detection, and follow-up of prostate cancer (39). Multiple myeloma patients develop resistance to protease inhibitors due to the presence of exosomes containing lncPSMA3 and PSMA3-AS1, which encode proteasome subunit a7, according to a study by Xu et al (40). Their research suggests that the exosomal signaling pathway PSMA3/PSMA3-AS1 may be useful as a diagnostic for diagnosing chemoresistance and as a therapeutic target for overcoming resistance to protease inhibitors. Finding low-level biomarkers might be difficult due to the large number of proteins found in the blood.

Exosomes and their possible applications in Oncology and Chemoresistance

Exosomes have a very wide range of possible uses in the field of chemoresistance, from their use as novel biomarkers in liquid biopsy (urine) to track chemoresistance's development to the discovery of its underlying mechanisms and the creation of novel strategies to overcome it.

Traditional tissue biopsies are invasive and upsetting for patients, and they prevent continuous monitoring by requiring frequent sampling. New strategies for reducing cancer treatment resistance could be developed through research into the underlying mechanism of chemoresistance. The nucleic acids and proteins contained in exosomes have been linked to their ability to activate intracellular signaling pathways and mediate the transmission of signals across cells. This happens when they fuse or interact with target cells, such as cancer cells. Scholars can get down to the bare bones by using this strategy and getting rid of the fluff (24). The expression of some micro-RNA128-3p was found to be the lower expression in oxaliplatin-treated CRC cells compared to their parent control cells. Combining exosomes and liposomes has led to the creation of hybrid therapeutic nanovesicles (20,26). Current research demonstrated the promise of hybrid nanovesicles by combining the best qualities of exosomes and thermosensitive liposomes for blocking CD47 immunological checkpoints during drug administration for cancer therapy. Therefore, despite exosomes' intriguing potential as nanocarriers, their use is still in its early stages and requires more research before it can be implemented clinically (41).

Despite their importance in carcinogenesis and development, exosomal lipids have received less study funding than nucleic acids and proteins. The study found that exosomes with a high concentration of prostaglandin were implicated in cancer's immune evasion and helped tumors spread. As a result of its uptake by cells, prostaglandin stimulates phospholipid metabolism, and increased phospholipids play a significant role in the fatty acid oxidation status of the target cells, hence easing the migration of malignant cells (42). The lipids in exosomes have the potential to be both indicators and mediators of chemoresistance. Exosomes may have a role in chemoresistance modulation via lipids; however, this mechanism needs to be studied in more depth.

CONCLUSION

One of the biggest obstacles in cancer treatment is the emergence of resistance to chemotherapy. Scientists are increasingly investigating exosomes' role in cancer progression and spread. Exosomes promote chemoresistance traits and reduce drug entry into cells. The synthesis of nucleic acids, RNA,mi-RNA, and proteins in exosomes can provide insight into the physiological, intracellular, and pathological conditions and homeostasis of cells. Exosomes have potential applications in monitoring chemoresistance in cancer cells and as a possible anti-chemotherapy agent.

However, the present knowledge and experimental data to understand the role of exosomes in the emergence of chemotherapy resistance in cancer is limited. There are also substantial challenges to studying exosomes. Therefore, consistent efforts from medical researchers, new research projects, and clinical trials are required to successfully incorporate exosome research into clinical practice.

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