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Review Article

Exosomes and Tumor Progression: Our Current Knowledge

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Abstract

Exosomes are tiny vesicles that cells secrete into the extracellular environment. They are crucial in cellular communication and have wide-ranging physiological and pathological ramifications. Cargo sorting, MVB development and maturation, MVB transport, and MVB fusion with the plasma membrane are the four essential steps in exosome biogenesis. The high heterogeneity of exosomes is due to the fact that each process is modulated by the competition or coordination of multiple mechanisms, resulting in the sorting of diverse compositions of molecular cargos into different subpopulations of exosomes. In cancer, exosomes have been shown to play a crucial role in tumor growth, metastasis, and pre-metastatic niche formation. In this mini-review, we briefly compile what we know about exosomes at present, including how they are made, what they carry, and how they promote tumor growth. Exosomes' potential as diagnostic and prognostic biomarkers is discussed. We also take a look at the research that hasn't been done and the challenges that have been overlooked.

Keywords: Exosome; Cancer; Tumor Progression; Extracellular Vesicles; Cancer Biomarkers

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Indroduction

Cancer is the world's second leading cause of death, and it has become a major public health issue. Previous research has primarily focused on cytokines and chemokines in the tumor microenvironment(1). There is little known about how the tumor microenvironment influences tumor progression and metastasis(2). It is becoming clear that exosomes are an essential component of the tumor microenvironment, playing a role in both local and long-distance cell-cell communication in cancer(1). Exosomes are extracellular vesicles (EVs) that are produced by all cells and found in all bodily fluids. Cells release a variety of EVs that vary in size **(Figure 1)**(3). Exosomes, which are rich in bioactive molecules such as nucleic acids, proteins, lipids, and metabolites, have the ability to relay signals between cells. Bile, blood, breast

milk, urine, cerebrospinal fluid, and saliva are just some of the bodily fluids that have been found to contain exosomes, implying that exosomes play multiple roles in regulating physiological responses. Exosomes' pathophysiological effects on diseases, particularly cancers, have recently been discovered. Tumor-derived exosomes are thought to play a role in cancer development by promoting cancer proliferation(4). Exosomes have been linked to a number of tumor-promoting processes, such as anti-apoptosis, metastasis, angiogenesis, immune evasion, and chemoresistance(5). These roles have been extensively discussed from numerous vantage points, such as donor cell type and content category. Due to their diverse roles as intercellular messengers, their ability to alter recipient cell bioactivities, and their therapeutic potential in disease diagnostics and targeted drug delivery, exosome research has gained traction in recent years(6). Here, we discuss how intercellular communications regulate cancer progression and provide a comprehensive overview of exosomes in cell biology. In addition, we summarize the role of exosomes in cancer prognosis and diagnosis and discuss the research challenges in the field.

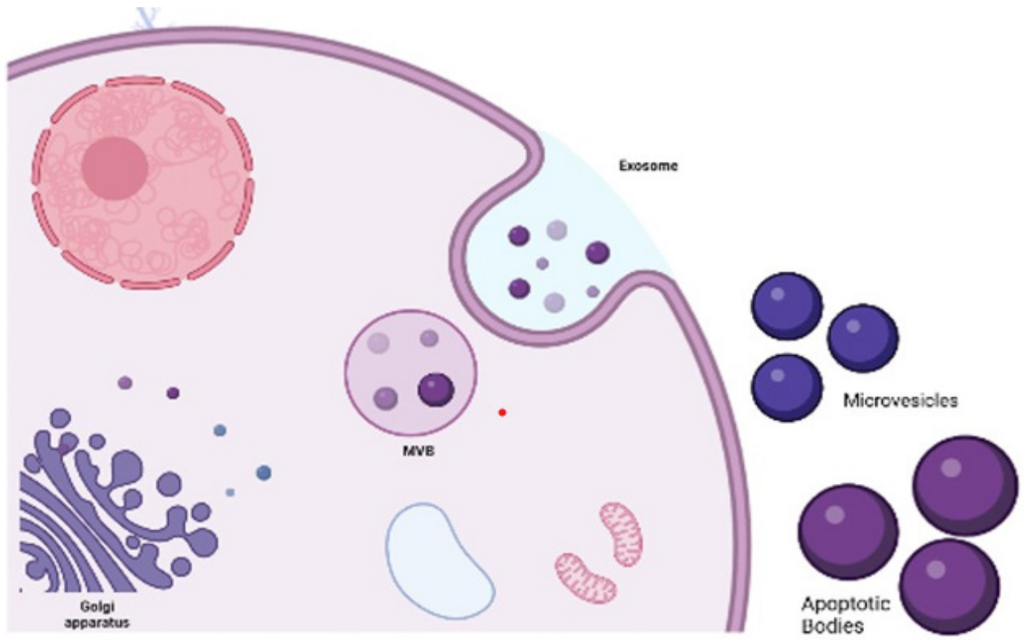

Figure1. Exosomes are extracellular vesicles (EVs) that are produced by all cells and found in all bodily fluids. Cells release a variety of EVs that vary in size. Other types of extracellular vesicles include apoptotic bodies and microvesicles.

Biogenesis of exosomes

Extracellular vehicles (EVs) produced from various non-cancer and cancer cells have been the subject of increasing research in recent years(7). At least three distinct lipid-bilayer EV types exist: exosomes, microvesicles, and apoptotic bodies, each with its unique size, biogenesis, and physicochemical properties(8). As shuttling vesicles, these vesicles transport many biomolecules to target cells, including microRNAs (miRNAs), messenger RNAs (mRNAs), long noncoding RNAs, DNA, proteins, and lipids. Exosomes were first described nearly three decades ago (in the 1980s) by Johnstone et al., who noted that reticulocytes release vesicles during maturation, which were later dubbed exosomes. Despite exosomes' initial reputation as a disposal, interest in exosomes has increased in the last decade due to their critical functions in physiological and pathological situations. When MVBs are generated, they can go one of three ways:

By the exosomal pathway, MVBs can exchange information with neighboring cells by fusing with the plasma membrane and releasing exosomes into the extracellular matrix. Bio-Exosomes can travel through various bodily fluids, including

blood, breast milk, cerebrospinal fluid, urine, amniotic fluid, ascites fluid, saliva, and bile. More and more research points to three mechanisms by which exosomes can affect their targets in the body. Direct fusion occurs when an exosome fuses with the plasma membrane of a recipient cell, allowing the exosomal payload to enter the recipient cell's cytoplasm. Receptors on the exosome membrane, like intercellular adhesion molecule 1, interact with molecules on the plasma membrane of recipient cells, like lymphocyte function-associated antigen 1 receptor, to stimulate or inhibit downstream molecular events within the recipient cells. This process is known as surface molecular interaction(7). The cargo of exosomes may affect trans-arrangements of regulation in target cells via all routes of absorption. These modifications may involve genomic instability, reprogramming, differentiation, and the control of genes in recipient cells, all of which can lead to pathological circumstances like the creation of tumor cell phenotypes and resistance to specific therapies(9).

Biogenesis of exosomes in cancer progression

Cancer progression is a dynamic and multistep process in which several Known signaling events play a role in orchestrating the malignant progression of cancer(4). Exosome release is a commonly occurring event, but cancer cells release exosomes at a heightened rate, and their cargos are particularly well-suited to cancer progression(6). Tumor-derived exosomes have been shown to actively regulate cancer progression through autocrine/paracrine oncogenesis, stromal cell reprogramming, immune system modulation, and angiogenesis. Oncosomes are vehicles for the spread of cancer, specifically for the transfer of oncogenic molecules from primary tumors. This causes morphological transformation as well as an increase in anchorage-independent growth in recipient cancer cells. Similarly, tumor-derived exosomes promote cancer proliferation by exerting antiapoptotic effects of TGF-ß1 signaling in an autocrine manner(4). Physiological context and the parent cell type both play a role in determining the precise molecular composition of exosomes beyond the signature set of membrane markers. Importantly, the composition of an exosome is not simply a reflection of the donor cell, and it has been demonstrated that the profiles of exosomal cargo can differ significantly from the originating cell, indicating the presence of a highly controlled sorting process. The tumor's ability to communicate with its microenvironment is critical for tumor growth, metastasis, and chemoresistance. Exosomes are an innovative means of sending data locally and long distances. Cells in the microenvironment release exosomes that can affect neighboring cells and tumor cells. Meanwhile, tumor cells secrete exosomes that reprogram their surroundings to be tumor-friendly, if not tumor-promoting(10). Exosomes have been shown to play an important role in cancer cell communication on a regional and global scale. Particularly, exosomes produced by malignant tumors may aid in the recruitment and remodeling of the tumor microenvironment. Epithelial tumor cells have been found to secrete exosomes containing EpCAM. Human epidermal receptor (HER) family proteins have been detected in cancer exosomes from breast, gastric, and pancreatic tumors. In addition, it is well established that tumor progression is facilitated by proinflammatory environments, which increase the adhesion of exosomes to target cells by upregulating the expression of membrane receptor proteins like ICAM-1(11).

Exosomes as prognostic and diagnostic biomarkers in cancer

The unmet need for sensitive and precise biomarkers is crucial because early detection of cancer increases the likelihood of a positive therapeutic outcome and the likelihood of survival(4). Biomarkers in the bloodstream may one day serve as non-invasive tools for monitoring treatment outcomes, helping doctors decide whether to continue with chemotherapy or try a different approach(12). The use of exosomes, their contents, and surface proteins may allow for earlier detection of cancers, potentially improving prognosis and survival(6). The advantages of identifying tumor markers in liquid biopsies are that they are less invasive, easier to obtain, and faster and less expensive than tissue biopsies. Furthermore, the vast amount of dynamic information

that can be extracted from a patient is useful in identifying early-detection biomarkers in cancer patients(4). Exosomes, according to emerging evidence, can carry specific cargoes such as proteins and nucleic acids that reflect tumor status. Exosomes are thus being used as diagnostic and prognostic biomarkers for a variety of cancers. Blood profiling from cancer patients appears to be useful in determining tumor status. Many serum cancer biomarkers have been widely used in clinical settings since Gold's 1965 demonstration of the role of glycoprotein antigen in detecting human colon cancer. With the added benefits of being abundant in blood, frozen serum, or plasma samples, highly stable, and amenable to analysis in low volumes, exosomes hold molecules that strongly reflect the parental property and could be used as a new source of biomarkers for personalized diagnosis and prognosis(13). Melo et al. (2015) found that the percentage of glypican-1 GPC1+ exosomes is significantly higher in people with pancreatic cancer (100%) compared to the general population (2.3%). They found that this marker was 100% sensitive and specific for detecting pancreatic cancer in its earliest stages(14). Overall, there may be significant diagnostic and prognostic value in focusing on exosomal cargos(13). Compared to healthy people, breast cancer patients' exosomes in the blood had much more of a specific protein (HER2), according to a 2018 study published in the Journal of Clinical Oncology. This provides supporting evidence for the potential utility of HER2-positive exosomes as a biomarker for breast cancer diagnosis(15). Furthermore, in 2017 Sueta. et al. indicated that the levels of specific microRNAs in breast cancer exosomes were linked to the development of the disease and the likelihood of survival(16). Shimada et al. demonstrated in a study on patients with non-small cell lung cancer that measuring serum exosomal PD-L1 as a quantitative complementary factor in conjunction with tumor PD-L1 status could help predict anti-PD-1 response and assess clinical outcomes in patients with NSCLC. In light of these findings, PD-L1-positive exosomes have the potential as a biomarker for the diagnosis and prognosis of lung cancer(17). However, more work is needed to identify biomarkers that are both sensitive and specific for use in the early detection of various cancers(12).

Challenges and obstacles

Although EV analyses have advanced significantly in recent decades, the precise mechanisms of biogenesis remain unknown. Improvements in exosome isolation and purification methods, on the other hand, are required to study cargo contents and functions, which would shed light on biogenesis. Despite rapid advancements in exosome research, isolation and purification techniques remain underdeveloped and unstandardized. Some components of raw biological fluids, such as lipoprotein, chylomicrons, and microvesicles, have size overlaps with exosomes, making exosome isolation challenging (30–150 nm). Isolation from conditioned cell culture media is less complicated; however, due to size overlap and a lack of specific biomarkers, other types of EVs are frequently co-isolated(6). Exosomal research in cancer is still in its early stages. Cancer-related exosomes, like other new biomarkers, have drawbacks. Since its discovery, ultracentrifugation has remained the most widely used method for isolating exosomes. This is a disadvantage because some protein fragments become encased in urine or serum during the isolation process, potentially interfering with the results(13). Body fluid-derived exosome studies are difficult because the isolated exosomes are derived from a variety of cell types and contain body fluid components ("contaminants") that must be removed during exosome isolation. The majority of what we know about exosomes today comes from studies of cell lines propagated in long-term cultures. However, despite recent technological advances, there is still no consensus on whether or not exosome isolation is beneficial. In this area, picking and re-creating various isolation methods is challenging. Furthermore, approaches to data acquisition/analysis differ greatly. The International Society for Extracellular Vesicles (ISEV) guidelines are vague, leaving extracellular vesicle (EV) isolation to the discretion of investigators. This state of affairs is a reflection of the relative youth of the rapidly expanding EV field, and ISEV recommendations are developed as a community of leading EV researchers. There will be no way to verify the promising results for exosomes reported by multiple researchers until a standardized methodology for their isolation and characterization is in place. While novel technologies are being introduced and evaluated to address this major challenge, the results of studies with EVs, including exosomes, remain open to criticism(18).

Conclusion

To conclude, extracellular vehicles (EVs), particularly exosomes, have become an area of increasing research interest in recent years due to their role in transporting biomolecules, including microRNAs, messenger RNAs, proteins, and lipids to target cells. Exosomes are critical in both physiological and pathological situations, including cancer progression, where they are involved in oncogenesis, stromal cell reprogramming, immune system modulation, angiogenesis, and tumor-friendly or tumor-promoting communication within the tumor microenvironment. Exosomes are a promising diagnostic and prognostic biomarker for various cancers, and their cargo can reflect tumor status, providing early detection and a personalized approach to cancer diagnosis and treatment. Exosomes represent a novel method of transferring information locally and remotely, and their potential for the development of cancer treatments warrants further research in the field.

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