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REVIEW ARTICLE

Exosomes: The Messengers of Health and Disease

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Abstract: Exosomes are small vesicles comprised of a lipid bilayer containing various proteins, RNAs and bioactive lipids. They act as intercellular messengers that give the ability to communicate between both cells of the same type and other cell types. They are released by healthy cells, both constitutively and upon cell activation and play an important role in immune system function. Exosomes are essential for healthy physiological conditions, however under pathological circumstances, they act to potentiate cellular stress and damage. This review explores the characteristics, biogenesis, role(s) in the pathogenesis of diseases and role(s) in progression of cancer of these nano-sized messages-in-a-vesicle: exosomes.

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Keywords: Cancer exosomes, exosome pathology, exosome physiology, exosomes.

INTRODUCTION

Cell to cell communication is an essential process in multicellular organisms. Methods of cellular communications are evolutionarily conserved processes. They involve signaling molecules being released into the extracellular space and interacting with membrane receptors on the surfaces of the recipient cell [1]. Cells are also able to directly interact by exchanging macromolecules through either gap junctions or tunneling nanotubes, making electrical and metabolic synchronizing among groups of cells possible [2, 3]. One of the most fascinating methods of cell-to-cell communications is by way of vesicles formed from membrane structures and released into the extracellular space [4]; these vesicles are called exosomes.

History

Exosomes were first described by Stahl and Johnstone in the 1980s. They were described as nano-sized vesicles discovered during reticulocyte maturation [5, 6]. It was hypothesized that these vesicles functioned to eliminate unwanted cellular proteins from the cytoplasm of the cell [7]. They were further classified as a way to eliminate unnecessary components, more specifically, receptors, from the plasma membrane during reticulocyte maturation. Within the last few years, the complexity of exosome functions began to unravel and appreciate including immune response induction [5, 8-10] plus many additional other functions [4, 11, 12].

The importance of intercellular communication by way of exosomes was evident by the evolutionary conserved process in the formation of these vesicles. Exosomes have been shown to be involved in the cellular communication across many different types of living organisms: from prokaryotes to eukaryotes. These vesicles are secreted by protists [13, 14], fungi [15], plants [16], invertebrate [17-19] and vertebrate animals [12].

Exosomes have been shown to be both produced and released by many different healthy cell types, including epithelial cells [20-30], adipocytes and fibroblasts [31], nervous system cells including Schwann cells [31], astrocytes [20, 32] and neurons [20, 32]. They were first detected to secrete by hematopoietic cells, more specifically reticulocytes [20, 33, 34], subsequently other hematopoietic cells including B lymphocytes, T cells [10, 20, 21, 35-37], platelets [20, 21, 35-39], mast cells [10, 20, 21, 35-38, 40], dendritic cells [10, 20, 35, 36, 38], and macrophages [40, 41]. In addition, these nanovesicles are present in many different types of biological fluids, such as blood, breast milk, urine, sperm, amniotic fluid, saliva, bronchoalveolar lavage, cerebrospinal fluid, synovial fluid, pleura effusions, and ascites [8, 31, 42, 43].

Exosomes are among multiple types of vesicles within a cell, including microvesicles, apoptotic bodies, etc., all of which vary by the size and characteristic proteins they contain and the method of biogenesis. The discrimination between the vesicle types is typically based on size;

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Apoptotic bodies are in the 50-500nm diameter range and microvesicles are in the 100-1000nm range [11]. For exosomes, various sizes were reported in the literature ranging from 10-140nm [5, 11, 36]. Other distinct characteristics of exosomes are their lipid bilayer structure and density (1.13-1.21 g/ml flotation on a sucrose gradient) [44], which is utilized in the specific isolation of these vesicles from cell culture media and biological fluids. There is a division between two different types of exosomes; one is involved in the presentation of antigens and are immunologically active, and the second group is involved in the communication between cells specifically utilizing RNA [45].

Biogenesis

Exosomes are actively secreted from cells *via* an exocytosis pathway for both receptor removal and crosstalk between cells [44, 46, 47]. This pathway is initiated by activation of a growth factor receptor located on the plasma membrane surface. Stimulation of this receptor initiates target protein activation as well as endocytosis of the ligand-receptor complex. Endocytosis begins as inward budding of the membrane with the involvement of particular proteins such as clathrin [30]; this inward budding forms an early endosome [46]. Early endosomes mature into late endosomes, the latter of which has been found to contain smaller vesicles, and thus being referred to as a Multivesicular Body (MVB). The process of vesiculation giving rise to these smaller internal vesicles (exosomes) inside the MVB is distinctive because of the direction of the membrane budding; opposite the cytoplasmic matrix. This type of vesiculation is poorly understood but is likely to involve processes of sorting, packaging and rearrangement of the endosome membrane to allow the exosomes to detach. The process involved in the formation of MVBs and exosomes was first reported in 1983 by Harding *et al*. [5], later confirmed in 1985 by Pan *et al*. [6]. Using immunoelectron microscopy, they visualized the transfer of a transferrin receptor in reticulocytes from the cell surface to an early endosome, to a multivesicular endosomes, localized at the surface of the internal vesicles, then finally fusion of these multivesicular compartments with the plasma membrane and the smaller vesicles bearing transferrin receptors were released into the extracellular environment [5, 6]. Once these exosomes are formed and released, the uptake by other cells dependent on the proteins contained on the surface of the vesicle [48]. Specifically, tetraspanin-integrin complexes contribute to the targeting and enabling of binding of the exosomes to target cells [49, 50]. In an environment that is pro-inflammatory the expression of particular membrane receptor molecules may increase, which promotes the adhesion to the membranes of the target cells [51].

Exosomes are composed of and contain a various composition of macromolecules including proteins, lipids, mRNAs and microRNAs. The discovery and analysis of the proteins that are contained within exosomes indicate that the origin of these vesicles is from living cells, as opposed to apoptotic or necrotic cells [8]. The exosomal protein composition is highly dependent on the cell that formed the exosomes; they contain similar proteins to the cell they originated from [35]. Studies of exosomes from immature dendritic cells (DCs) [52, 53], B lymphocytes [10, 54], intestinal epithelial cells [30] and other cell types show that there are common, as well as cell-type specific proteins within exosomes. Common proteins among exosomes are the Ras superfamily of monomeric G proteins (Rab), which could act to aid in exosome docking and their ability to fuse with membranes of other cells [22, 55]. Annexins I, II, V and VI are also common proteins that could be involved in the cytoskeleton dynamics and membrane fusion [22, 56]. Adhesion molecules [22, 53, 55], apoptosis proteins, heat shock proteins (Hsc73 and Hsc90), tetraspanins (CD9, CD63, CD81 and CD82 [8, 30, 52, 53]), GTPases, and cytoskeletal proteins (actin, synenin, moesin, albumin) [57] are classically found within exosomes of various origins.

In addition to shared proteins within exosomes from various cell types, there are cell origin specific proteins such as MHCII and CD86 [22] from antigen presenting cells and MFG-E8/lactadherin [58] from immature DCs. Cardiomyocyte exosomes characteristically contain HP60 [59], von Willebrand factor [39], perforin and granzymes [60] were found in platelet and cytotoxic T cell exosomes, respectively.

In addition to proteins, an important macromolecule composing exsosomes are lipids: particularly cholesterol, diglycerides, sphingolipids (sphingomyelin, ceramide), phospholipids and glycerophospholipids. Increased ratios of lipids are found in exosomes when compared to the parental cell: up to four times greater, which may account for the increased rigidity of the membrane of the exosome [20, 22, 37]. In addition to these lipids, specific bioactive lipids are found within exosomes, specifically, protstaglandin, leukotrienes, activated enzymes of lipid metabolism (that may generate these lipids) [42, 61].

Another class of macromolecule found in exosomes that is of particular interest is nucleotides, or more specifically, RNAs (mRNA, miRNA) [8, 62-66]. The RNAs found encapsulated within exosomes are mostly involved in cell cycle progression, angiogenesis, migration, or histone modification [49, 64, 67, 68]. Exosomal miRNA generally involve modulation of gene expression related to stem cell differentiation, organogenesis, hematopoiesis, tumorigenesis and metastasis [69-71].

ROLE OF EXOSOMES IN NORMAL PHYSIOLOGY

The Immune System

The cells of the immune system release exosomes [10]. It is well known that exosomes are involved in communication within the immune system and act to mediate immune modulation: both immunosuppressive and immune-activating effects. The activation of T helper cells and the initiation of adaptive immunity are regulated by antigen presenting cells such as Dendritic Cells (DCs). Mature DCs release exosomes with MHC membrane molecules that directly bind to T cell receptors and cause T cell activation, inducing the adaptive immune response. In the case of infection, DCs take up antigens, resulting in the release of

MHC complexes, which activate T helper cells. The T helper cells then activate B cells and lead to an increase in exosome production and release, which also contain MHC complexes. The B cell derived exosomes stimulate $CD4^+$ T cells, suggesting that B cell exosomes play a role in modulating the immune response. In addition to activating T cells, the exosomes that are released by DCs also act to transfer antigens between other DCs. (Reviewed by Corrado *et al*. [69]).

Immature or suppressive DCs release exosomes involved in reducing the adaptive immune response as well. These exosomes induce T cell apoptosis, promoting a tolerogenic immune response. These exosomes may also balance both the pro-inflammatory and anti-inflammatory effector T cells by inducing T helper cells to differentiate into regulatory T cells (Reviewed by Corrado *et al* [69]).

The Brain

Exosomes play an important role in the brain. Neuronal exosomes are essential for the communication with other cell types within brain tissue; this includes cells that function to support axon integrity and myelination, microglia. This relationship between these cells is becoming more apparent in both the developing and the adult nervous system. Communication between neurons and oligodendrocytes (also cells involved in myelinating axons and supporting axon integrity) is also highly dependent on exosome release. This secretion is triggered by the neurotransmitter, glutamate, through activation of glial ionotropic glutamate receptors; the exosomes are then internalized by the neuron and the cargo is then available within the neuronal cell. These oligodendrocyte exosomes support axonal integrity by comprising enzymes that are enzymatically functional to resist oxidative stress: catalase and superoxide dismutase-1. It has been shown that neurons under oxidative stress conditions survived better in the presence of oligodendrolglial exosomes, which suggests that release of these exosomes has a protective function by increasing the stress tolerance of the neuron [72, 73]. It has also been shown that a number of signaling pathways such as AKT and ERK are expressed at higher levels, and activated, in neurons that received exosomes [72].

The Heart

The cardiovascular system also highly relies on exosomes for normal function. Exosomes are released from cardiomyocytes (CMs) constitutively. Under hypoxic conditions, however, the release of these vesicles triples in response [59], and the content changes as well. TNF-α is a component of these exosomes released due to hypoxia [74]. TNF-α is not normally produced within the heart, but CMs have the ability to produce it under stress and transfer it to neighboring healthy cells to induce apoptosis [74]. This suggests that the release of exosomes is a mechanism in which stressed cells have the ability to propagate an inflammatory response. In addition, it has been shown that DNA and RNA can be transferred between different cell types to induce gene expression changes within the recipient cells, specifically CMs to fibroblasts [75], indicating that the exosomes are not necessarily a cell-type specific method of communication within the heart (Reviewed by [76]).

Stem Cells

It was reported that stem cells transplanted into the heart survive and have a more beneficial effect than surviving engrafted donor cells. It was hypothesized that not only direct differentiation of the engrafted donor stem cells to the terminal lineage, but paracrine factors released by these stem cells also contribute to the improvements in functions of the heart [77, 78]. This had been confirmed by studies that conditioned media from stem cells can enhance CM survival after hypoxic injury [79], induce angiogenesis in infarcted myocardium [80] and reduce infarct size in both mouse [81, 82] and porcine [80, 83] models of myocardial ischemia reperfusion injury. Many of the factors responsible for these improvements are normally packaged within vesicles. In fact, a reduced infarct size and improved cardiac remodeling in a pig model of myocardial ischemia/reperfusion is a direct result of vesicle exposure [80].

ROLE OF EXOSOMES IN DISEASE PATHOLOGY

In addition to their normal function, exosomes are involved in the pathological development and progression of numerous diseases. It has been shown that pathogens have the ability to take advantage of exosome release to infect host cells, by manipulating host derived exosomes to evade the immune system responses [84]. Other diseases involving exosomes include neurodegenerative diseases [85], liver disease [86], heart failure [87] and cancer [42].

Alzheimer's Disease (AD) is a neurodegenerative disease characterized to by amyloid plaque formation in the brain [88]. Evidence shows the involvement of exosomes in the spread of these amyloid β (Aβ) molecules to other neuronal cells within the brain of the patient. These molecules have been shown to be physically associated with exosomes, further supporting this evidence. Furthermore, Alix (an exosomal marker) had been shown to be enriched in brain sections of AD patients, when compared to healthy control patients where Alix is virtually absent [89]. Parkinson's Disease is another neurodegenerative patogenesis that has been linked to exosomes. This disease progression has been associated with an increase in aggregation of α-synuclein. In the presence of neuroblastoma exosomes, the aggregation lag time is reduced. Exosomes provide a catalytic environment for α-synuclein aggregation, which is catalyzed by lipids present on the exosomes [90].

Exosomes were also shown to be involved in the pathogenesis of liver diseases; including hepatocellular carcinoma, viral hepatitis and liver inflammation. A human hepatoma cell line releases exosomes that, when taken up by hepatocellular carcinoma cells, results in ablation of a protein, TAK1. Loss of TAK1 has been implicated in hepatocarcinogenesis. In viral hepatitis, exosomes are required for the release of Hepatitis C Virus (HCV) from infected cells, HCV envelope proteins are found within exosomes, and viral RNA associated with exosomes can be found in viral hepatitis patients. In the case of liver inflammation, exosomes isolated from mice fed high-fat

diets were injected into mice fed a regular diet. This led to the accumulation of activated immature myeloid cells in the liver, causing chronic liver inflammation and promoted obesity-related disorders such as fatty liver disease. (Reviewed by Masyuk *et al*. [86]).

Peripartum cardiomyopathy (PPCM) is a life-threatening disease characterized by sudden onset of heart failure in pregnant women in the last month of pregnancy or the first months after child birth [91]. Exosomes were shown to play a role in the pathogenesis of PPCM. A prolactin fragment induces the expression of a specific microRNA in endothelial cells, which functions in preventing angiogenesis in these cells. Additionally, the prolactin fragment induces the release of exosomes, which contains this specific microRNA. These exosomes are subsequently absorbed by cardiomyocytes, resulting in decreased metabolic activity and alterations in gene expression, characteristic of PPCM phenotype [87].

ROLE OF EXOSOMES IN CANCER PROGRESSION

Exosomes may play multiple roles in the progression of cancer. They have the ability to manipulate both the local tumor environment, and the systemic environment to support tumor cell growth, dissemination and early events in metastasis [92, 93]. Exosomes are more frequently released by tumor cells and may facilitate communication within the local microenvironment and the primary tumor [94].

Within the tumor microenvironment, tumor cells have the ability to exchange oncogenically active proteins between one another *via* exosomes. Mutant epidermal growth factor receptors were shown to transport from cells expressing this receptor on the membrane, to cells lacking the mutant receptors. Consequences of such movements include activation of anti-apoptotic gene expression and increased anchorage independent cell growth [95]. Another example is the release of the mutant form of KRAS within exosomes by colon cancer cells and internalized by colon cancer cells harbor the wild type KRAS, resulting in enhanced cell growth and tumorigenicity [96]. In addition to exchanging macromolecules between each other, tumor cells have the ability to manipulate the cells that surround them that alter the microenvironment in which the tumor cells grow, advance, and create an atmosphere conducive for angiogenesis. Myofibroblasts are a source of matrix remodeling proteins for the tumor microenvironment and participate in angiogenesis [97], and recruitment of this type of cells could support tumor progression. Exosomes from prostate cancer cells and mesothelioma cells contain TGF-β1 protein, which is biologically active and can be transferred to recipient cells. *In vitro* cultured cell studies demonstrated the transfer of TGF-β1 to fibroblasts resulting in differentiation into myofibroblasts [98]. In addition, breast cancer cell exosomes have the ability to promote mesenchymal stem cell (derived from adipose tissue) differentiation into myofibroblasts through a SMAD-mediated pathway [99]. In addition to the manipulation of the tumor microenvironment by the tumor exosomes, the surrounding stroma has an impact on the tumor cells as well. It has been shown that fibroblasts that express CD81 tetraspanin protein secrete exosomes that contain CD81. The exosomes are then taken up by breast cancer cells, and CD81 participates in the formation of an autocrine Wnt-signalling pathway within the cells, which is associated with increased protrusive activity, motility, invasion and lung metastasis in a mouse model of breast cancer [100] (also reviewed by [101]).

Although the cells from the primary tumor are what make metastasis a threat, the cells from the surrounding tumor microenvironment play critical roles in prompting metastatic ability. Circulating tumor cells can be found in the blood supply of various organs, however, these cells may not become a secondary tumor, while other specific organs are sites of common metastasis [102]. Cancer patients have been shown to harbor primary tumors that preferentially hone to particular organs, for example, melanoma selectively metastasizes to the lung and brain [103]. Successful metastatic growth is dependent on a microenvironment that is receptive of that particular cancer cell [103]. Normal cell types such as fibroblasts, endothelial cells and bone marrow derived cells [104] all are recruited to, and involved in, the formation of the future site of secondary tumor formation, or the pre-metastatic niche [105, 106], to which the tumor cells metastasize. Using rat pancreatic adenocarcinoma cell exosomes the involvement of exosomes in the preparation of the premetastatic niche has been implicated. Injections of exosomes produced by a highly metastatic pancreatic cancer cell line into rats allowed the metastasis of the pancreatic cancer to lymph nodes and lung [107].

To support the notion that exosomes help remodel tissue to form the premetastatic niche, renal cell carcinoma cells secrete exosomes that have the ability to induce endothelial cells to form capillary-like structures in matrigel *in vitro*, and contribute to the establishment of a premetastatic niche in the lung of immunodeficient SCID mice. This was accomplished by upregulation of matrix metalloproteinases and VEGFR expression [108]. This concept was further supported by a report by Peinedo and colleagues, in which they described the involvement of melanoma exosomes in tumor progression and the preparation of the pre-metastatic niche of future secondary tumor sites [109] (also reviewed by [101]).

Cancer cells have the ability to recruit immune cells to enhance the ability for tumor invasion, angiogenesis and dissemination [105]. Furthermore, melanoma exosomes have the ability to "educate" bone progenitor cells to be receptive of and support tumor cell growth and metastasis [109]. Communication between tumor cells and the immune system mediated by exosomes is involved in the recruitment of pro-tumorigenic immune cells. Blockade of exosome secretion by a murine breast cancer cell line is associated with a decreased mobilization of neutrophils, which results in decreased primary tumor growth and lung metastasis [110]. MicroRNAs in exosomes released from lung cancer cells have the ability to silence the transcripts associated with Toll-like receptor (TLR) family in macrophages, which stimulates macrophages to secrete proinflammatory cytokines, supporting tumor dissemination [111].

Another important role exosomes play in tumor progression is the inhibition of the anti-tumor abilities of the immune system. It has been shown that exosomes have the

capacity to activate myeloid-derived suppressor cells, which have immunosuppressive functions that suppress the T cell response [112]. These exosomes also induce IL-6 production, which results in an autocrine Stat3 phosphorylation, promoting immunosuppression [112]. Exosomes have multiple roles in immune modulation including the ability to induce immunosuppression, which in turn supports the growth and metastasis of the tumor. In addition to evading immune response, tumors spontaneously acquire resistance against chemotherapy used to treat the cancer, or acquire chemoresistance. Preliminary results suggest the ability of exosomes to transfer proteins such as drug transporters to one another, spreading the ability to become chemoresistant. These data suggest that when non-resistant prostate cancer cells were exposed to exosomes from docetaxel-resistant prostate cancer cells, a drug transporter, Multi-drug Resistance Protein (MDR-1) is transferred to the non-resistant cells, resulting in their ability to acquire resistance [113].

Taken together, these studies highlight the importance of exosomes in the two-way communication between the healthy stroma, immune system and the tumor. In addition, exosomes also participate in the manipulation of both the tumor microenvironment and distant sites of future metastasis to enhance the progression of tumor.

CONCLUSION

Exosomes are a ubiquitous, evolutionarily conserved mechanism of cellular communication. They play important roles in healthy physiological functions, and in their absence, normal function would be abolished. However, despite their necessity as part of normal cell, they also participate in the pathogenesis of diseases that plague various organ systems within us, one of these diseases being cancer. Tumor derived exosomes have pro-tumorigenic functions; promote proliferation, migration, invasion, microenvironment modulation, pre-metastatic niche remodeling, angiogenesis, immune manipulation and chemoresistance. Understanding the mechanisms of action of exosomes have the potential for rational design of a new target for the treatment of numerous diseases, including cancer.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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