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Review / Derleme

An Overview of Association Between Exosomes and Lung Cancer

Eksozomlar ve Akciğer Kanseri Arasındaki İlişkiye Genel Bakış

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Abstract: Exosomes; are bioactive receptors which is indirectly originating from the cell membrane. The dimensions vary between 50-140 nm. The most important features distinguishing exosomes from other extracellular vesicles (microvesicles and apoptotic bodies) are their unique biogenesis pathways, lipid compositions, and RNA cargos (mRNA, miRNA, lncRNA) they carry. Exosomes that play a role in cell-cell interaction by virtue of their RNA content can alter the transcriptome and function of the cell with the RNA strands they carry when transferred to the recipient cell. It has also been identified that they carry nucleic acids (DNA, RNA), proteins, nucleoproteins and various enzymes for use in signal transduction. Exosomes are also secreted by cancer cells and tumor-associated stromal cells as they are secreted from healthy cells under physiological conditions. Through the exosomes, autocrine, paracrine and endocrine communication is established between cancer cells. Although exosomal secretion is a normal process, the increase in rate and exosomal mediated transfer of different cargos (oncogenic signals) may mediate oncogenic progression and metastasis. The increase in exosomal quantities and altered cargo expression can be considered as a powerful biomarker for altering normal physiological conditions and can be used to diagnose cancer and many other diseases. Exosomes can be obtained by ultracentrifugation from body fluids such as blood, plasma, cerebrospinal fluid, bile, breast milk, amniotic fluid, saliva, urine and can be evaluated for molecular components such as DNA, RNA, miRNA, and proteins. In addition, as they are derived from the plasma membrane, they are inherently liposomal and nano-sized and can easily move through the blood-brain barrier, due to their protein-lipid content in their membranes. Although exosomes are associated with many types of cancer, they are also important in lung cancer. It has been showed that exosomes are increasing lung endothelial permeability and lung metastasis, and also plays an important role in angiogenesis in lung cancer. As a result, exosomes are smart munchkins carrying cargo between cells and have the ability to convert healthy cells to carcinoma according to the cargo that they carry. They can also be obtained from whole-body fluids and can be used for targeted treatment with their ability to enter the cells easily and to carry them in circulation.
Key Words: Exosome, cancer, metastasis, angiogenesis.

Özet: Eksozomlar; hücre zarından indirekt olarak köken alan biyoaktif reseptörlerdir. Boyutlar 50-140 nm arasında değişmektedir. Eksozomları diğer hücre dışı veziküllerden (mikro-veziküller ve apoptotik cisimler) ayırt eden en önemli özellikler, kendilerine özgü biyolojik oluşum yolakları, lipit bileşimleri ve taşıdıkları RNA yükleridir (mRNA, miRNA, lncRNA). RNA içerikleri sayesinde hücre-hücre etkileşmesinde rol oynayan ekzomlar, alıcı hücreye aktarıldıklarında taşıdıkları RNA iplikleriyle hücrenin transkriptomunu ve işlevini değiştirebilir. Ayrıca, sinyal iletiminde kullanım için nükleik asitleri (DNA, RNA), proteinleri, nükleoproteinleri ve çeşitli enzimleri taşıdıkları bilinmektedir. Eksozomlar fizyolojik koşullar altında sağlıklı hücrelerden salgılanmakla birlikte kanser hücreleri ve tümörle ilişkili stromal hücreler tarafından da salgılanır. Eksozomlar sayesinde kanser hücreleri arasında otokrin, parakrin ve endokrin iletişim kurulur. Eksozomal salınım normal bir süreç olsa da, farklı kargoların (onkojenik sinyaller) hız ve ekzomal aracılı transferindeki artış onkojenik ilerlemeye ve metastaza neden olabilir. Eksozom miktarlardaki artış ve kargo ifadesinin değişmesi normal fizyolojik koşulları değiştirmek için güçlü bir biyobelirteç olarak kabul edilebilir ve kanseri ve diğer birçok hastalığı teşhis etmek için kullanılabilir. Eksozomlar, kan, plazma, beyin omurilik sıvısı, safra, anne sütü, amniyon sıvısı, tükürük, idrar gibi vücut sıvılarından ultrasantrifüj yoluyla elde edilebilir ve DNA, RNA, miRNA ve proteinler gibi moleküler bileşenler için değerlendirilebilir. Ek olarak, bunlar plazma zarından köken aldığı için, doğal olarak lipozomal ve nano boyuttadırlar ve böylelikle zarlarındaki protein-lipid içeriğinden dolayı kan beyin bariyeri boyunca kolayca hareket edebilirler. Eksozomlar birçok kanser türüyle ilişkilendirilse de, akciğer kanserinde de önemlidir. Eksozomların akciğerdeendotel geçirgenliğini ve akciğer metastazını arttırdığı ve ayrıca akciğer kanserinde anjiyogenezde önemli bir rol oynadığı gösterilmiştir. Sonuç olarak, eksozomlar hücreler arasında kargo taşıyan akıllı moleküllerdir ve taşıdıkları yüke göre sağlıklı hücreleri karser hücresine dönüştürme kabiliyetine sahiptir. Ayrıca tüm vücut sıvılarından da elde edilebilirler ve hücrelere kolayca girme ve dolaşımda taşıma yetenekleriyle hedeflenen tedavi için kullanılabilirler.
Anahtar Sözcükler: Eksozom, kanser, metastaz, anjiogenez.

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1. Introduction

Actually, these important and nanoscale molecules were found almost 40 years ago at the same time by two different research groups (Stahl et al. and Johnstone et al.) when investigating the transferrin receptors in reticulocytes.These small molecules, which have been ignored as cellular waste for years, have been recognized to have scientific importance beyond time; the societies were established (International Society for Extracellular Vesicles and The American Society for Exosomes and Microvesicles), the dedicated journal was published (Journal of Extracellular Vesicles) [1-3]. So much so that, there is a database named Exo Carta and even they have been included in the Nobel Physiology and Medicine Award in 2013.

Exosomes: Smart Biomolecules

Exosomes are simply defined as extracellular vesicles (EVs) released from cells. They are lipid-encapsulated and transmit molecular markers such as proteins and nucleic acids between the cells to alter the phenotype of the recipient cells [1, 4]. The term exosome was first reported in 1981 by Trams et al. and used to identify exfoliated microvesicles derived from the membrane with 5'-nucleotidase activity [5, 6].

In fact, EVs are divided into four classes according to the formation and size of the cells. These are microvesicles released directly from the cell membrane to the outside of the cell, apoptosomes resulting from apoptosis, retrovirus-like vesicles, and exosomes that occur indirectly through the cell membrane [7].

Exosomes have been studied in many investigations and are called as;

- vexosome (microvesicles/exosomes that are associated with adeno-associated virus vectors) [8],
- oncosomes (tumor-derived microvesicles that transfer oncogenic signals and protein complexes across cell boundaries) [9],
- prostasomes (exosomes originating from the epithelial cells of theprostate and prostatic fluid) [10],
- dexosomes (exosomes derived from dendritic cells) [11],
- cardiosome (microvesicles/exosomes from cardiomyocytes) [8],
- texosomes(exosomes derived from tumors) [12],
- epididymosome (found in the intraluminal epididymal compartment) [13],
- argozome (exosome-like bodies in drosophila) [14],
- archeosome (liposome from polar lipids of Archaea)[15]according to the cell type they originate from[7, 16].

Exosome function varies depending on the type of cell they are derived from and the composition of the exosomes[17]. Initial investigations suggested that exosomes were only involved in removing waste from the cell. But recent studies have shown that vesicular content of exosomes also includes distinct molecular and genetic components such as nucleic acids, proteins, miRNAs, mRNAs, nucleoproteins, mitochondrial DNA, single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), soluble factors and various enzymes [18, 19].

Exosomes are found in vivo in many biological fluids including blood, urine, saliva, epididymal fluid, amniotic liquid, bronchoalveolar lavage, synovial fluid, and breast milk [20-23].

Biological functions of exosomes can be listed as follows;

- Exosomes can regulate the bioactivity of recipient cells by transporting lipids, proteins, and nucleic acids while circulating in the extracellular space [21].
- Exosomes play an important role in immune response, tumor progression and neurodegenerative disorders also increase angiogenesis [24-26].
- Exosomes are involved in communication within the immune

system and mediate immune modulation as immunosuppressive and immunogenic effects [2].

- Exosomes are also very important for the brain. Neuronal exosomes are necessary for communication with other cells in the brain tissue. This includes axon integrity and cells that function to support myelination, microglia [2].
- Exosomes are also released from cardiomyocytes and are required for normal functioning of the cardiovascular system [2].

The Role of Exosomes in Cancer

Exosomes affect tumor progression, metastasis and therapeutic efficacy due to cell-cell communication [27]. Therefore exosomes in cancer have often been described as promoters of tumor progression. But it is conceivable that the exosomes also have antitumor functions and may act to limit disease progression [28].

Exosomes are also secreted by cancer cells and tumor-associated stromal cells but they are adapted in cancer processes and serve as a pathway for neoplastic cells to communicate with each other (autocrine) and non-neoplastic cells (paracrine and endocrine) [29].

Exosomes have an important role in many malignant processes such as cancer progression, metastasis and drug resistance in cancer;

- Malignant cells secrete about 10 times more exosomes than normal cells [30].
- They can inhibit the immune response by transferring their genetic information to the recipient cells [30].
- They cause invasion and metastasis by carrying cargo contents into cells in the tumor microenvironment [31].
- They promote metastasis by promoting epithelial-mesenchymal transformation [32].
- They stimulate cell proliferation by transmitting mitogenic signals to the tumor environment.
- They suppress the immune system cells (macrophages, natural killer cells) or deliver apoptotic signals to these cells.
- In addition, they cause drug resistance and resistance to chemotherapy by activating multidrug-resistant proteins.

Exosomes in Metastasis

Exosomes are known mobile elements that function as escape routes for proteins and miRNAs (some of these miRNAs may be promoters of metastatic pathways) from distant locations in a cell. As expected, the role of exosome-mediated signaling in cancer metastasis is also evident. For example, Grange and colleagues have shown that exosomes released from kidney cells develop angiogenesis in lung cancer assays [33].

Cancer cells can metastasize through blood circulation or lymphatic pathways. For metastasis, cells must invade systemic circulation or lymphatic circulation by invading the extracellular matrix. Metastasis is a very active process, involving cancer cells as well as the microenvironment, cytokines, stromal cells, and immunocyte cells. Epithelial-mesenchymal transformation is necessary for cells to acquire metastatic properties [32].

EMT (epithelial-mesenchymal transition) is defined as losing epithelial properties of cells and acquiring mesenchymal properties and directed by a complex network of interactions. At this point, the cells gain the ability to invasion and migration and considered to be one of the distinguishing features of aggressive tumors. EMT-passing cells have improved plasticity and tendency to migrate from the origin zone, which causes tumor spread. EMT type cells secrete factors that act on neighboring cells and tissues and contribute to resistance by protecting the tumoral microenvironment. The role of exosomes in EMT has recently been determined [6, 34].

In addition, exosomes can promote the invasion and metastasis by directly targeting tight and adherens junctions. For instance, the

increased vascular permeability, lung and brain metastases were observed when the expression of the tight junction protein ZO-1 downregulated by exosomal miR-105 in endothelial monolayer cells [35].

Exosomes and Angiogenesis

The process of angiogenesis is the occurrence of new vessel formation from the existing vessels. This process is controlled by multiple growth factors, signaling pathways pro-angiogenic and antiangiogenic factors. In addition, recent studies have shown that angiogenesis can also be regulated by cell-derived microparticles such as micro-vesicles and exosomes [36].

The growth of new vessels at the beginning of tumor development is related to the exosome levels produced by the tumor. For example, glioblastomas produce tumor-derived exosomes that affect the proliferation of endothelial cells and are highly vascularized compared to other solid tumors. Extracellular vesicles secreted by glioblastomas contain angiogenic proteins and have pro-angiogenic properties in vitro and in vivo [37].

The rapid proliferation of solid tumors causes hypoxic and necrotic areas in tissues. Endothelial proliferation and angiogenesis are induced by pro-angiogenic factors in the tumor stroma, as more oxygen, nutrition, and removal of cellular waste products are needed, in the case of hypoxia. Studies have shown that exosomal secretion increases in hypoxic conditions in multiple myeloma and breast cancer cells [38].

Exosomes in Lung Cancer

Lung cancer is the leading cause of cancer-related death between men and women, and approximately 70% of patients with lung cancer are found with symptoms that are locally advanced or cause metastatic disease, which is not appropriate for treatment [39].

The exosomes are the components contributing to metastasis as mentioned earlier. Studies have been conducted on the role of exosomes in a cancer type in which metastasis is common, such as lung cancer [24, 40, 41]. These studies also show that exosomal miRNAs can be used as diagnostic markers for lung cancer [41].

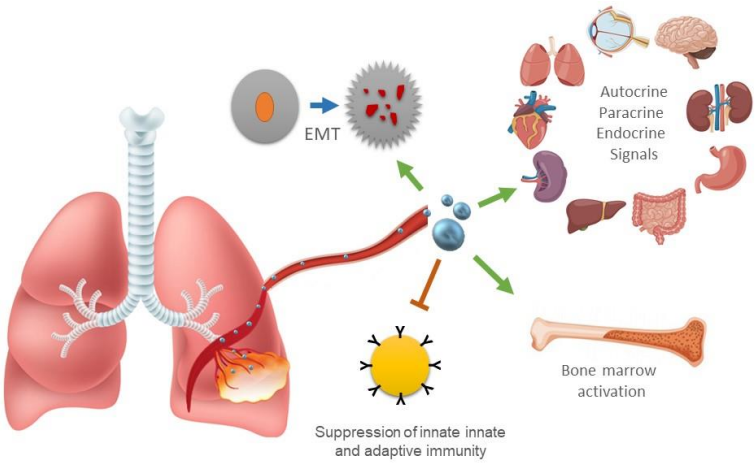

Figure 1. Exosome-mediated metastasis in the lung. *Exosomes are small secondary structures that are also released by tumor cells and present signs of various autocrine, paracrine and endocrine signals that result in metastasis in the secondary regions. Initiation of metastasis; Tumor-derived exosomes (TED) induce EMT (Epithelial-Mesenchymal Transition) by increasing the invasiveness and mobility of neoplastic cells and eliminating the natural barriers to metastasis. Premetastatic Niche Formation/ Preparation: Bone marrow-derived cells (BMDC), myofibroblast activation, remodeling of extracellular matrix and initiation of angiogenic procedures. The escape of tumor cells from immuno-surveillance: Suppression of natural and adaptive Immunity in recipient tissue [35]. (Figure was adapted and redraw from reference).*

Tumor-derived exosomes were initially demonstrated in the peripheral circulation of cancer patients in 1979 [42]. Tumor-derived exosomes overexpose a number of common tumor proteins, as well as a number of tumor antigens that reflect tumor cells. These exosomes also mediate tumor growth, metastasis, drug resistance, and facilitating immunosuppression. Although exosomal release can be demonstrated in many proliferating cell types, their proliferation increases in tumor cells, as evidenced by their increased presence in the plasma and pleural effusions of cancer patients [43, 44].

Tumor-derived exosomes mediate tumorigenesis by facilitating tumor growth, metastasis, drug resistance, and immunosuppression. Peinado et al. showed that melanoma-derived exosomes increased endothelial permeability in mice and increased lung metastases [45].

Very few studies in lung cancer have characterized exosomes and their role in lung cancer progression. Recent experimental studies have emphasized that exosomes can activate target cells by ligand-receptor interaction and fusion of recipient cells with the plasma membrane [45-49]. Furthermore, endocytosis of exomes and subsequent transfer of molecules directly to the cytosol of the recipient cell can functionally suppress target genes in recipient cells [50]. Vimentin, as a part of exosomal content, has been shown to induce epithelial-mesenchymal transit (EMT) in the recipient cells. All of these mechanisms may contribute to EMT in normal bronchial epithelial cells [51].

In a study of exosomes in lung cancer cell lines (A549, CRL 2066, CRL 2062, HTB 183, HTB 177) exosomes (PMV: platelet-derived microvesicles) were found to contribute to metastatic spread. It has also been suggested that PMV may play an important role in angiogenesis in lung cancer [24].

It was possible to produce DEX vaccine in phase I study to test the safety, feasibility and efficacy of autologous dendritic cell (DC) - based exosomes (DEX) loaded with MAGE tumor antigens in non-small cell lung cancer (NSCLC) patients and DEX treatment in patients with advanced NSCLC well-tolerated. In some patients, long-term disease stability and activation of immunologic effects have been observed [52].

The significant difference between total exosomal and exosomal miRNA levels between lung cancer and control individuals and the similarity between circulating exosomal miRNA and tumor-induced miRNA patterns suggests that exosome miRNA may be useful as a screening test for lung adenocarcinoma. The miRNAs in the exosome content are parallel to the miRNA expression profiles of the tumor cells [53].

2. Conclusions

Success in the treatment of complex diseases such as cancer can be achieved by a good understanding of the interactions between different components within the tumor. Exosomes are components with large functions relative to their small size and play a major role in intracellular communication. Although exosomes were first described in the 1980s, studies on exosomes have been remarkably increased over the last five years, especially after the discovery of functional mRNAs and miRNAs in exosomes. The exosomes are almost smart biomolecules with the cargo contents they carry (mRNA, miRNA, protein, etc.).

Exosomes are components that have the potency to use in the diagnosis and treatment of many diseases not only in cancer. They characteristically carry the membrane and cytoplasmic properties of the cells they release. In addition, the availability of ultracentrifugation and isolation kits from all the fluid in the body can facilitate diagnosis for many diseases.

In addition, exosomes are an intensive research area with miRNA contents, and targeted inactivation of miRNAs does not only target tumor cells but may also be a new strategy to target the microenvironment.

Due to the interesting and unusual features of exosomes, research studies on diagnosis and treatment are ongoing. Their origins differ

from cell types and are obtainable from all the body fluids, an advantage for cancer-related studies. Exosomes will be an important component not only for the formation, progression, diagnosis, and treatment of cancer but also for the formation mechanism and recognition of many diseases.

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