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A Review of Exosome-Mediated Immunotherapy in Iran

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ABSTRACT

For decades, chemotherapy and radiotherapy have been considered the two main pillars of cancer treatment, but with the advent of immunotherapy, the focus has shifted towards this treatment method. The main goal of immunotherapy is to strengthen or support the patient's immune system in destroying malignant cells. From the first immunotherapy in 1981 to 2013, when immunotherapy was introduced as the "Scientific Achievement of the Year," various immunotherapy methods have been used to treat patients. Since using the cells in treatment has always been associated with problems, the introduction of exosomes as nanoparticles that could easily reach the target tissue could greatly overcome the challenges of immunotherapy. In this review, we aimed to review studies on exosome-mediated immunotherapy. Although the studies have shown favorable outcomes, it would be valuable to conduct research in this field that could help to better advance and solve the challenges of exosome-mediated immunotherapy.

Keywords:

Immunotherapy, tumor-derived exosome, Immune cell-derived exosomes.

INTRODUCTION

For many years, cancer treatment has primarily relied on surgery, chemotherapy, and radiotherapy. In recent years, cell therapy and immunotherapy have emerged as promising alternatives in cancer treatment as a leading area of research. Today, the main focus in cancer treatment is to bolster the patient's immune system in response to the tumor (1, 2).

Tumor cells must overcome the immune system in order to proliferate within the body. These cells use various strategies, such as recurrent mutations in malignant cells, to delay, alter, or even halt immune responses against the tumor, ultimately resulting in the evasion of malignant cells from the immune response. These strategies are referred to as "immune escape mechanisms" and lead to the inability to control tumor growth. Therefore, blocking immune escape mechanisms could be a new approach to enhance the immune response against tumors. Immunotherapy unlike previous treatments such as chemotherapy or radiotherapy, which kill cancer through cytotoxic properties, aims to strengthen or support the patient's immune system in destroying malignant cells (1, 3). Oncolytic vaccines (vaccines based on tumor antigens), monoclonal antibodies, antibody-like molecules, BiTEs/BiKEs (Bispecific T cell engagers/Bispecific Killer cell Engagers), checkpoint blockade or checkpoint inhibitors (ICB), cytokines, and oncolytic viruses are the old immunotherapy methods, and CAR-T (Chimeric Antigen Receptor) and CAR-NK technologies are the emerging immunotherapy methods against tumors.

Each of these methods has been associated with obstacles. One of the most important challenges is the failure of the designed CAR to reach the tumor tissue (which is less common in leukemias). Other problems include the lack of influence of inhibitory factors secreted from the tumor microenvironment, the occurrence of GVHD (Graft Versus Host Disease), and the instability of the CAR. Today, with the introduction of exosome into immunotherapy, we

would hope to overcome these challenges to a large extent (3-5). In recent years, there has been a surge of interest in exosome-mediated immunotherapy, both within and outside of Iran. This approach has been utilized to treat a wide range of diseases, including hematological malignancies, as well as cancers such as colon and breast cancers, and even asthma and allergies. As a result, a comprehensive review of the existing literature on this topic can serve as a valuable resource for researchers and clinicians seeking to explore new avenues in this field.

Extracellular vesicles

Extracellular vesicles, or EVs, are nanoparticles with a phospholipid bilayer membrane that are secreted by most cells into the extracellular space, such as blood, lymph, saliva, urine, semen, bile, milk, cerebrospinal fluid, and ascites fluid. EVs are produced under conditions like hypoxia, oxidative stress, inflammation, aging, and apoptosis. EVs are produced under conditions like hypoxia, oxidative stress, inflammation, aging, and apoptosis.In general, EVs are divided into three general categories-based on size, biogenesis, and cellular origin-including exosomes, microvesicles, and apoptotic vesicles (6). In 1946, experiments by Chargaff and West demonstrated that removing clotted plasma after high-speed centrifugation inhibited plasma clotting (7). Later, Peter Wolf discovered that suppressive clots were 20-50 nm vesicles derived from platelets. In 1983, transferrin receptors on the surface of reticulocytes were shown to interact with 50 nm activated vesicles derived from mature reticulocytes and secreted into the extracellular environment. And finally, these vesicles were named exosomes by Rose Johnstone in 1986 (8).

Exosomes

Exosomes are nano-sized lipid vesicles secreted from living cells, such as immune cells. These vesicles contain lipids, proteins, and nucleic acids, and have different functions depending on their contents. Due to their nano-size, exosomes have good stability and are able to penetrate the tumor site easily. They are more resistant to the immunosuppressive effects of the tumor microenvironment compared to cells. The low risk of GVHD and cytokine storm are considered the positive points of using exosomes in immunotherapy (9).

Exosome biogenesis

The classical (endosomal) and non-classical (ESCORT-independent) pathways are the two main pathways for exosome secretion. In the classical pathway, early exosomes are first formed by the plasma membrane retraction into the cell and then released as a vesicle, which is called an early sorting exosome. Then, with the help of the endoplasmic reticulum and the Golgi apparatus, they are transformed into late sorting exosome. The membrane of late sorting exosome buds inward and small vesicles are released into them, which are called MVB (Multi vesicular Body or Multi Vesicle Endosome) and the tiny vesicles inside them are called ILV (Intra Luminal Vesicle). In the next step, MVB fuses with the plasma membrane and secretes ILVs as exosomes. In the non-classical pathway, microdomains based on Raft (Klc) play a role in the separation of the vesicle from the endosome membrane (6, 10).

The role of exosomes in cellular communication

Exosomes could have a role in cell-to-cell communication due to their lipid, protein, and nucleic acid content. Success of exosomes in various biomedical and scientific applications relies greatly on their ability to safely deliver genetic material. Efficient transfer of genetic materials is feasible through certain biological pathways, involving the receptor-ligand interaction, direct fusion between exosomal and recipient cell membrane, or endocytosis.

A closer examination of these events elucidates several plausible mechanisms which potentially illustrate the intercellular communication facilitated by exosomes, these mechanisms include: (a) the presence of a preexisting receptor on the recipient tissue to bind with and trigger signals from exosomal content, (b) the transferal of active receptors to recipient cells via intercepting exosome delivery, and (c) triggering epigenic alterations in targeted recipient cells through the activity of proteins, lipids, and nucleotides enclosed within these nanosized vesicles (6).

The role of exosomes in the immune system

The role of exosomes has been demonstrated in antigen presentation, regulation, activation, suppression, and immune tolerance. For example, exosomes derived from TCD4+ and TCD8+ cells

could bind to dendritic cells and induce apoptosis of these cells, resulting in T cell ignorance to some antigens. Or conversely, in the presence of tumor cells, dendritic cell-derived exosomes lead to the activation of T cells to destroy tumor cells. Exosomes derived from Treg cells could help these cells function effectively in maintaining immune tolerance and suppressing immune responses (6).

Exosomes in cancer

Studies on exosomes suggest that these vesicles could influence neoplasia, tumor growth, metastasis, and even resistance to treatment, but the extent of their involvement in malignancy progression depends on the specific treatment, genetic makeup, and stage of cancer. Studies have also focused on the interaction of exosomes with stromal cells within the tumor microenvironment, which include fibroblasts and endothelial among others. Exosome-derived microRNAs have the ability to affect the behavior of tumors in the body, adding to the complexity of exosomes role in cancer (10, 11).

Exosome-mediated immunotherapy

Exosomes have good stability and can easily penetrate the tumor site due to their small size and more resistant to the immunosuppressive effects of the tumor microenvironment compared to cells. Exosomes play a significant role in immunotherapy. Many studies have confirmed that tumor-derived exosomes influence on apoptosis, angiogenesis, chemotherapy resistance and immune evasion, pathogenesis and development of leukemia through bone marrow microenvironment modulation. These nanoparticles can serve as biomarkers to monitor leukemia progression and also have potential as drug carriers. Consequently, exosomes hold potential value in leukemia diagnosis and treatment and monitoring disease progression (12).

Immune cell-derived exosomes (IEXO) hold significant potential in cancer therapy due to their anti-tumor function and ability to deliver therapeutic cargoes efficiently. Only a limited number of clinical trials have been used these exosomes in cancer therapy. This is due to some of the problems while using exosomes in immunotherapy. However, their use in clinical immunotherapy is limited owing to several challenges, such as the difficulty of producing exosomes in large quantities, issues surrounding exosome storage and freeze-thaw cycles, and variations in the size, function, and composition of exosomes extracted from different cell sources. Among the various IEXOs, DEXOs (dendritic cell-derived exosomes) from cancer patients appear safe for use in clinical immunotherapy trials (13).

The results of studies have demonstrated that MSCs (Mesenchymal Stem Cell) are regulated by their secreted exosomes. These exosomes are key elements in the carcinogenesis process through cell communication, cell growth and cell migration and have been shown to increase the growth of glioblastoma tumor cells (14). These exosomes have been implicated in cell proliferation and migration in breast cancer cells by inducing the Wnt signaling pathway (15).

In addition, reduced expression of mir15a in MSC-derived exosomes from multiple myeloma patients have been found to be associated with reduced tumor growth (16). Therefore, exosomes serve as key components of intercellular communication, with the ability to manipulate the extracellular and systemic tumor microenvironment (17).

Several cell type are involved in asthmatic inflammation including epithelial cells, eosinophils, lymphocytes, macrophages, and dendritic cell (DCs). Exosomes are released from these cells and have been found to play a role in the pathobiology of asthma. Co-stimulatory molecules in DC-derived exosomes, increased in eosinophil-derived exosomes and alter in miRNA content are some examples in this field. Exosomes can regulate homeostasis by modulating inflammatory responses in the lung microenvironment. These findings make exosomes attractive candidates for designing new treatment strategies for asthma (18, 19). Additionally, immunotherapy for non-small-cell lung cancer (NSCLC) using exosome is currentlty undergoing clinical trials (20).

Based on the recent review of the literature, exosomes have the potential to remodel the tumor microenvironment and regulate tumor progression through several key mechanisms. Colorectal-derived exosomes can promote macrophages differentiation into the M2 phenotype, enhance MDSC (myeloid-derived suppressor cells)-mediated immune suppression, activate the tumor phenotype of neutrophils,

regulate B cell activities, and inhibit T cell function. As a result, exosome identification holds significant potential for use as early diagnostic, companion, and predictive biomarkers in cases involving distant metastasis and drug resistance (21).

In a therapeutic cancer model, tumor-derived exosomes (TEXs or Texasome) could potentially be used as an immunotherapeutic cancer vaccine. In this study, tumor derived exosomes were extracted from a breast cancer cell line and loaded with CpG ODN and p (I:C). The results indicated that an exosome based therapeutic vaccine promoted strong cellular and humoral anti-tumor immunity, leading to tumor regression(22).

Exosome-mediated immunotherapy in IRAN

Texasome, derived from tumor cell, is not only capable of stimulating antitumor immune responses by containing tumor-associated antigens, but they also act as natural carriers of microRNAs. In vivo investigations have demonstrated that incorporating miRNAs derived from texasomes into treatment could yield more potent antitumor responses than texasomes alone. Significant inhibition of tumor growth and increased median survival time, enhanced cytotoxicity and proliferation of spleen cells, and reduction in CD4/CD8 and Treg/CD8 ratios in tumor tissue are some beneficial effects of treatment involving miRNA-124 derived from tumor-derived taxasomes(12). Mir-34a, a major tumor suppressor, is also secreted by exosomes derived from tumor cells, including colorectal cancer. Administration of TEX-mir-34a leads to a reduction in tumor size and prolongs survival, while also reducing the expression of genes involved in invasion, angiogenesis, and immune evasion. T-cells differentiation towards cytotoxic T lymphocyte(CTL), depletion of lymph nodes and spleen cells are also some observed effects of this type of Mir(23).

Cancer stem cells(CSCs) are responsible for resistance to treatment and relapse in colorectal cancer. A review of the literature have revealed that CSC-derived exosomes from colorectal cancer patients have had a higher IL-12/IL-10 ratio in dendritic cells. Dendritic cells loading with these exosomes have led to an increase T-cell proliferation(24). In a study, the effect of TNBC(Triple-Negative Breast Cancer)-derived exosomes (this type of breast cancer shows a lower survival rate compared to other subtypes) on the maturation and function of monocyte-derived dendritic cells(moDC monocyte-derived DCs) has been investigated. TNBC-derived exosomes induce immunogenicity by increasing the maturation and function of dendritic cells. These exosomes then lead to Th1 differentiation following co-culture with T cells. Such results could provide the basis for the design of dendritic vaccines(25).

Results from studies have shown that DEXOs(Dendritic Cell-Derived Exosomes) play a central role in tumor immunogenicity and could be a novel and useful tool for the diagnosis and treatment of malignancies. These exosomes have the ability to activate CD8+ cytotoxic T lymphocytes and induce antitumor responses in vivo. However, in the tumor microenvironment, tumor cells produce exosomes(so-called oncosomes) that may act in favor of tumor progression(26). Mir-155 play an important role in DC(dendritic cell) maturation and IL-12 production. In a study, DC immunotherapy with miR-155-enriched exosomes have been evaluated in mice with colorectal cancer. These engineered dendritic cells have been shown to increase IL-12p70 and IFN-γ significantly, and accelerate differentiation, proliferation, and cytotoxicity on Th cells and CTLs. This type of treatment also increased the infiltration of Th and CTL cells into the tumor microenvironment while reducing the number of Tregs. This situation could control tumor growth and improves survival(27).

A study in mice with colorectal cancer has shown that subcutaneous injection of exosomes purified from colorectal cancer could inhibit tumor progression by reducing the number of Treg cells and increasing the expression of the IFN-γ gene. These exosomes could be used as vaccines in cancer immunotherapy(28). M2 macrophages are the main cell population in the tumor microenvironment, and their differentiation into M1 macrophages could be used as an immunotherapy method in cancer. In this study, following the use of rapamycin-texosome combination to differentiate M2 macrophages into M1, the expression of M1 markers(Irf5, Nos2, and CD86) have been increased and that of M2 markers(Arg, Ym1, and CD206) have been decreased. In addition, the levels of M1-specific cytokines(TNF-α and IL-1β) have been increased, while the levels of M2-specific cytokines

including IL-10 and TGF-β have been decreased(29). In another study conducted with the same goal, a different method has been used to differentiate M2 macrophages into M1. In this study, they have used the juxtaposition of M1 macrophages with exosomes extracted from cells transfected with PEDF(Pigment Epithelium-Derived Factor)(30).

In a study conducted by Najaflou et.al, it was observed that photothermal-derived exosomes exhibited more damaging effects on breast cancer cells than hyperthermia-mediated exosomes. Following the immune stimulation via these methods, the efficiency of exosomes on the breast cancer cells was determined. The results highlighted the potential of photothermal-derived exosomes as a potent therapeutic tool in the treatment of breast cancer (31).

Given the importance of hypoxia in tumors, a study has been evaluated the antitumor effects of co-administering hydrogen peroxide with tumor-derived exosomes. The aim of co-administration of hydrogen peroxide and tumor exosomes have been to reduce hypoxia and induce an effective immune response against tumor antigens, respectively. The study revealed that the simultaneous use of oxygen delivery in the form of hydrogen peroxide and tumor-derived exosomes resulted in an enhanced efficacy of the exosomes, which led to a reduced tumor size, reduced hypoxia, lessened angiogenesis, and minimized metastasis within the tumor microenvironment but enhance the effective immune response against the tumor systemically. This therapeutic approach could represent a novel approach to the development cancer vaccines (32).

Recent studies suggest that umbilical cord blood stem cell(CBSC)-derived exosomes may play a significant role in suppressing cancer progression. In lymphocytes from melanoma patients, these exosomes may serve as an effective anticancer treatment option (33).

Recently, the importance of microRNA in exosomes has been considered as a biomarker in plasma-derived exosomes for diagnostics related to asthma. In a study, patients with moderate and severe asthma compared to healthy subjects, miR-223 and miR-21 have been selected as biomarkers for targeting immunotherapy in asthma management(34). Increasing the efficacy of INIT(Allergen-Specific Intranasal Immunotherapy) has recently been the main goal of several studies as a safe delivery method via mucosal routes. In one study, the potential of INIT has been evaluated by using Exo-OVA in a mouse model of allergic asthma. In this study, INIT has significantly increased the secretion of IFN-γ and TGF-β, while decreasing the production of allergen-specific IgE and IL-4. In addition, the number of eosinophils and total cells in nasopharyngeal lavage fluid have decreased, and the inflammatory conditions and cell accumulation in the lung tissue have improved. Therefore, EXO-OVA treatment could potentially be an efficient immunomodulation approach (35). SLIT(Sublingual allergen-specific immunotherapy) is another needle-free treatment option. Experiments involving ovalbumin (OVA)-enriched mesenchymal stem cell (MSC)-derived exosomes show that incorporating OVA at an initial concentration of 500μg/ml and 6 hours of incubation yielded the greatest efficacy. Exosome injection led to reduced IgE and IL-4 levels while increasing IFN-γ and TGF-β secretion. Also, a decrease in total number of cells and eosinophils in the lavage fluid and lower levels of inflammation have observed in the lung tissue. OVA-exosome treatment has the potential to be a successful immunotherapy treatment for allergic asthma (36, 37).

NK (Natural Killer) cells are a crucial part of the innate immune cells and play a significant role in destroying tumor cells. Exosomes extracted from these cells are expected to have beneficial toxic effects on cancer cells. A study conducted on AML (Acute myeloblastic leukemia) cells demonstrated that exposing tumor cells to NK-exosomes led to a 34.56% increase in apoptosis after 48h.The expression of apoptotic genes such as caspase 3, p38, and cytochrome c were significantly increased. Therefore, NK-exosome could be an effective treatment option for leukemia (38). Similar finding have been observed in chronic myeloid leukemia cell lines (39).

Along with the use of exosomes in immunotherapy, this treatment has now taken a step forward and apopto-immunotherapy is emerging as a new breakthrough. Apopto-immunotherapy being able to induce apoptosis in addition to specific immune responses. A group for the first time designed a new construct that combined exosome and EXO/SEB

(staphylococcal enterotoxin B) as apopto-immunotherapy, and have been investigated its cytotoxic effect on breast cancer cell lines. EXO/SEB significantly has been reduced cell proliferation and increased apoptosis (40, 41). The effect of this structure on breast cancer has been also shown similar results (42). Other designed constructs include aptamer-exosome bioconjugates prepared in a mouse model have been potently suppressed the inflammatory response and also reduced the area of demyelination lesions in the CNS. Therefore, using exosome-based nano-medicine as a new approach for the management of MS (multiple sclerosis) could be hoped to improve the quality of life of these patients (43).

Psoriasis is a chronic inflammatory skin disease. Immunotherapy plays a significant role in managing these patients. In a study, injection of mesenchymal stem cells-derived exosome have been shown to reduce hyperplasia through an increase in TGF-β2 (44).

Additionally,HSP70 (Heat Shock Protein70)-enriched exosomes could be used as an effective immunoadjuvant in cancer immunotherapy. The use of HSP70-enriched exosomes has been shown to decrease the number of tumor cells and stimulate immune responses in animal models (45).

Daneshi et.al. have demonstrated that mixing S1b-RBD-expressing mesenchymal stem cell-derived exosomes with 47D11 antibody could lead to effective transferring of these targeted exosomes to the targeted microenvironment of coronavirus disease (46).

CONCLUSION

Immunotherapy, has emerged as a novel and promising treatment approach in the fight against cancer. There are various approaches in immunotherapy, and each of these approaches faces challenges and obstacles. One such approach involves utilizing exosomes, small nanoparticles known for their ability to effectively penetrate in tumor site. The use of exosomes in therapy is not without its challenges. Large-scale production of these exosomes and stability during storage are considered as major challenges in exosome therapy. Nonetheless, the potential applications of exosomes span a range of diseases, from the treatment of colorectal cancer to the alleviation of allergies. Newly apopto-immunotherapy is emerging as a new breakthrough. While the preliminary research outcomes are promising, continued investigation in the field is crucial to not only consolidate these gains but also to address and overcome the challenges associated with exosome-mediated immunotherapy.

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

ABBREVIATION TABLE

BiTEs/BiKEs	Bispecific T cell engagers/Bispecific Killer cell Engagers
CAR-T	Chimeric Antigen Receptor
GVHD	Graft Versus Host Disease
ESCORT	
MVB	Multi vesicular Body or Multi Vesicle Endosome
ILV	Intra Luminal Vesicle
IEXO	Immune cell-derived exosomes
DEXO	dendritic cell-derived exosomes
MSC	Mesenchymal Stem Cell
DC	dendritic cell
NSCLC	non-small-cell lung cancer
TME	Tumor Microenviroment
MDSC	myeloid-derived suppressor cells
TEXs or Texasome	Tumor-Derived Exosomes
CSCs	Cancer stem cells
TNBC	Triple-Negative Breast Cancer
DEXO	Dendritic Cell-Derived Exosomes
PEDF	Pigment Epithelium-Derived Factor
CBSC	Umbilical cord blood stem cell
INIT	Allergen-Specific Intranasal Immunotherapy
SLIT	Sublingual allergen-specific immunotherapy
OVA	Ovalbumin
AML	Acute meloblastic leukemia
SEB	staphylococcal enterotoxin B
MS	multiple schlorosis
HSP70	Heat Shok Protein70
CTL	Cytotoxic T Lymphocyte

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