Review Article

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Exosomes: Novel Bio-Inspired Nanocarriers for Efficient Targeting of Glioblastoma Tumor Cells

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ABSTRACT

BACKGROUND AND OBJECTIVE: Glioblastoma is a highly malignant brain tumor that is characterized by poor prognosis and high recurrence rate in patients. Surgery, chemotherapy and radiotherapy are considered as standard methods of glioblastoma treatment. However, these methods have not been able to completely kill cancer cells. One of the most important barriers to the treatment of glioblastoma is the blood-brain barrier, which prevents drugs from reaching the brain tissue. The aim of this study was to investigate the possibility of using exosomes as drug carriers in the treatment of glioblastoma tumor.

METHODS: In this review article, we searched Google Scholar and Pub Med databases using the keyword “exosomes”, “glioblastomas”, and “drug delivery systems” to provide an overview of exosomes as an opportunity for the delivery of drug into the central nervous system through the blood-brain barrier.

FINDINGS: In the initial search, 14400 articles were found, and after an initial review and removal of unrelated studies, 40 articles were finally reviewed. Exosomes are natural nanoparticles that are secreted from different cells. Using exosomes in drug delivery systems is an efficient approach for transferring various contents to cancer cells. These particles are also able to transfer biological and drug molecules from the blood-brain barrier to brain cells. These natural nanoparticles are stable with long circulations that do not cause immune rejection responses.

CONCLUSION: According to the results of this study, as a potential carrier with very interesting and attractive advantages in drug delivery and transfer of drug agents, exosome-based nanocarriers can be used to treat brain tumors such as glioblastoma multiforme.

KEY WORDS: *Exosome, Nanocarrier, Glioblastoma.*

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Introduction

Glioblastoma multiforme (GBM) is a stage 4 glioma that is one of the most common primary brain tumors, and each year, 13,000 people die from this disease. Brain tumors range from benign astrocitoma pilocitico to very malignant and progressive glioblastoma multiforme. Compared to metastatic brain tumors that arise from other organs and tissues, primary brain tumors, such as gliomas, originate primarily from brain cells (1, 2). The most common site of glioblastoma tumor is inside the brain tissue and is one of the most malignant brain cancers due to the high migration capacity of these cells. This tumor has the worst prognosis and clinical results, and despite the combination of different treatment strategies, including surgery, radiotherapy and chemotherapy, the average life expectancy of patients is about 12 to 14 months (3, 4).

The treatment of this disease faces many challenges and despite the existing treatment methods, the neurotoxicity of these methods is itself a major challenge in the treatment of this disease (5, 6). The development of new methods of drug delivery to prevent systemic toxicity of these drugs as well as targeted drug delivery to the tumor site are among the new approaches that are currently being considered by researchers. The use of stem cells as carriers in the treatment of cancers is one of these treatments. However, the use of these cells due to their low acceptance at the transplant site, ethical problems in their preparation and isolation, immunological barriers, transplant rejection, as well as the risks and concerns about tumor formation by these cells, opens a new chapter in cell therapy research using stem cell products including exosomes (7, 8).

The interesting point about cell transplant is that about 48 to 72 hours after the time of transplantation, these cells are removed from the transplant site and on the other hand a very large percentage of cells are trapped into the lungs during systemic injection (9). Therefore, in recent years, the paracrine effects of stem cells and especially the exosomes secreted from mesenchymal stem cells have been considered and have been used in many diseases including acute liver failure, acute renal failure, myocardial infarction, wound healing and diseases related to immune system such as rheumatoid arthritis (10-13). Exosomes are particles approximately 30 to 100 nm in size that are secreted from different cell types into the extracellular environment. The nature of these vesicles is based on lipid membrane and can integrate with cell membranes. These vesicles are rich in tetraspanins, CD63, CD9, CD81, ceramide lipids, and sphingomyelin. They are involved in cellular communication, regulation of immune function, tumor migration, and modulation of drug responses. Today, exosomes are used for several therapeutic and functional purposes that are still under research. For example, exosomes secreted by Antigen - Presenting Cell (APC) can be used in cancer immunotherapy (14).

Since exosomes can carry signals from their secretory cells, they can also be used to carry drugs, RNA, or proteins as a drug delivery system. Various cells, including mesenchymal stem cells, are able to secrete exosomes (15, 16). Due to their internal origin and specific surface markers of exosomes, these lipid vesicles are more stable than synthetic polymers and liposomes and can remain in the body longer, hence being an alternative strategy for targeted drug delivery (17, 18). These nanometer-scale and bubble-shaped particles can be used to transfer proteins, microRNAs, siRNAs, small and biological drugs, as their wide dispersion and long cycle will definitely provide higher efficiency for drug delivery and can also pass through physiological barriers and can be used to target specific tissues through their surface proteins (11, 19).

In most studies, exosomes have been used to transmit siRNA, and fewer studies have examined the potential of exosomes to be loaded by other therapeutic agents (20). Therefore, the aim of this study was to investigate the possibility of using exosomes as drug carriers in the treatment of glioblastoma tumor.

Methods

This review article was approved by the ethics committee of Semnan University of Medical Sciences with the code IR.SEMUMS.REC.1399.048. We searched Google Scholar and PubMed databases using the keywords “exosome”, “glioblastoma” and “drug delivery systems”. There was no time limit for starting the search and any article that met the inclusion criteria was included in the study until July 2020. Only articles in English and Persian were used in this study. After screening the articles based on the title and abstract of the article, duplicate cases, articles that did not fit the purpose of the study, non-English articles and articles that only had abstract were removed. The results of some of the researches and articles that we have published are also mentioned in this study.

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Results

In the initial search, 14400 articles were obtained, and after an initial review and removal of unrelated studies, 40 articles were finally reviewed.

Exosome as a drug delivery system: Exosomes can carry a variety of contents, including small molecules, miRNA, siRNA, DNA, proteins, and chemotherapeutic drugs, and have been considered in targeting certain diseases such as brain cancers, central nervous system diseases and other neurodegenerative diseases. Exosome-based drug delivery system has certain advantages such as specificity, safety and stability. Moreover, the biological function of exosomes causes the cargo to be transferred to targets at long distances (21, 22). On the other hand, since exosomes are small in size and are derived from the body itself, these factors prevent their phagocytosis as well as attachment to cell membranes and prevent their absorption by lysosomes (23).

Another fact that increases the benefits of exosomes is that exosomes are a natural product of the body and thus decrease immune responses. Exosomes are highly stable in the bloodstream, allowing them to travel long distances in physiological and pathological conditions. In addition, they have a hydrophilic center, which is a good option for loading hydrophilic drugs (24). To date, chemotherapeutic drugs such as doxorubicin, paclitaxel, celastrol, and curcumin have been injected into exosomes. Several studies have shown that loading the drugs increases the effects of these drugs efficiently. The capacity of exosomes to target cancer cells is about 10 times greater than that of liposomes of the same size, and often target cancer cells more strongly due to ligand/acceptor interactions on the recipient cell (25-27).

The antitumor effects of curcumin have been shown in various in vitro studies, but its poor solubility has been considered a major barrier to its appropriate clinical effects. After encapsulation of curcumin into the exosomes, the bioavailability of the drug increased and its antitumor effects improved. Phase I clinical trials are underway to evaluate the pharmacokinetics and pharmacodynamics of curcumin-loaded exosomes under the code NCT01294072 (28). Exosomes with special ligands can also be engineered and produced to be used in various in vitro experiments to target cancer cells. For example, the iRGD peptide, which is specific to αv integrin, was used to deliver doxorubicin to breast cancer cells. The results showed that in an in vivo study, exosomes loaded with doxorubicin improved the anticancer effects in breast cancer cells, which had a positive expression of integrin protein compared to the group receiving free drugs (29). Increasing the targeting and lethality of drug-loaded exosomes has opened a new chapter in cancer studies. For example, Kim et al. loaded paclitaxel into macrophage-derived exosomes to use it for the treatment of cancers resistant to multiple drugs. These drug nanoparticles were 50 times more potent than free drugs in killing multidrug resistant cancer cells. In addition, after intranasal injection in a mouse model of pulmonary metastases and after examination of the location of exosomes loaded with doxorubicin by confocal microscope, it was found that doxorubicin-loaded exosomes were positioned near cancer cells.

These results suggest that doxorubicin-loaded exosomes have a high inhibitory power for the growth of tumors resistant to multiple drug therapies as well as pulmonary metastases, possibly due to the presence of specific proteins on the surface of the exosomes. Their ability to overcome drug resistance can be due to entry through endocytosis, which in turn prevents the release of therapeutic agents by P-Glycoprotein. Such studies well demonstrate the ability of exosomes to deliver chemotherapeutic drugs to cancer cells, cancer cells resistant to multiple drug therapies, and on the other hand, show the increased ability of loaded drugs to kill cancer cells compared to free drugs (30).

The use of exosomes as suitable carriers in the treatment of central nervous system diseases: Diseases of the central nervous system such as neurodegenerative diseases, brain tumors and cerebrovascular diseases are among the global health problems. Most drugs and therapeutic agents cannot enter the brain through the blood-brain barrier, and therefore the treatment of central nervous system diseases faces this great challenge (31). Brain capillary endothelial cells are tightly connected, and only molecules smaller than 500 kDa and highly lipophilic molecules can pass through the blood-brain barrier. Therefore, drug delivery systems using nanocarriers to deliver therapeutic agents to the brain have been welcomed by researchers (32).

An ideal system for delivering drugs to the brain should have properties such as biodegradability and non-toxicity. In addition, it should not damage the blood-brain barrier and must selectively pass drugs through the blood-brain barrier after systemic injection and deliver a sufficient amount of the drug to the target tissue at the appropriate therapeutic concentration (32, 33). The systems most commonly used to deliver drugs to the brain, such as liposomes, solid lipid nanoparticles

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(SLNs), and lipid-polymeric micelles, are lipid-based, though their low biocompatibility as well as rapid clearance by phagocytic system has limited their use. On the other hand, in order to reduce clearance, PEGylation of these compounds has reduced their biological distribution in brain tissue (34). In recent years, due to low immunogenicity, exosomes have received a lot of attention, and the small size of exosomes facilitates their penetration into the blood-brain barrier. In their study, Yuan et al. showed that macrophage-derived exosomes can increase the penetration of exosomes into the brain tissue by interacting with intercellular adhesion molecule-1 (ICAM-1) on cerebrovascular endothelial cells that create a blood-brain barrier and improve its therapeutic effects in inflammatory conditions, because in inflammatory conditions, a higher level of expression of this molecule is observed (35).

Based on the innate desire of the exosomes, the researchers loaded brain-derived neurotrophic factor into macrophage-derived exosomes to target diseases of the central nervous system. In an in vivo study, the exosomes were able to enter the brain 3 times faster and accumulate 5.8 times more in brain tissue in inflammatory conditions than in healthy conditions. These results indicate that exosomes are promising and suitable nanocarriers for targeting brain diseases (36). In another study, Haney et al. used catalase-loaded exosomes to target and treat Parkinson's disease. In the end, it was found that the exosomes were able to maintain the catalase activity of the drug, and the drug was released slowly from the exosomes, while the drug-loaded exosomes remained in the bloodstream for a long time. After using catalase-loaded exosomes in the in vivo study and through intranasal administration, they showed significant effects on neuroprotection. These results clearly indicate that exosomes isolated from peripheral blood monocytes and loaded with drug agents can be used to treat inflammatory and neurodegenerative diseases of the brain (37).

Qu et al. also isolated peripheral blood exosomes from mice and used them to transfer dopamine to treat Parkinson's disease. After intravenous injection of dopamine-loaded exosomes, the distribution of dopamine in brain tissue was 15 times higher than that of free drug, and drug-loaded exosomes showed higher therapeutic efficacy in the mouse model of Parkinson's disease. Examining the amount of exosome entering the cells, the researchers found that the presence of transferrin dimers on blood exosomes caused a higher accumulation of drug exosomes in the brain, followed by a specific interaction between transferrin and transferrin receptor (38). Therefore, exosomes can be used without any modifications and with the inherent ability to target for the treatment of central nervous system disorders.

Overall, all these researches have shown that exosomes have an innate ability to cross the blood-brain barrier. In their study, Taghdiri Nooshabadi et al. used endosomes derived from endometrial stem cells to transfer atorvastatin to three-dimensional culture of the human glioblastoma tumor cell line U87. This drug delivery method increased the entry of drug with effective concentration into tumor cells and subsequently increased apoptosis in these cells (39). Therefore, it seems that exosomes can be considered as very suitable carriers for the transfer of drugs such as small molecules, biomolecules, and chemotherapeutic agents to treat diseases and brain tumors.

Discussion

Nanocarriers as a drug delivery system have seen significant growth over the past few years. One of the most important barriers to the entry of these nanoparticles is inadequate safety and poor and inefficient transfer. In recent decades, exosomes, as natural nanoparticles, have shown great potential for delivering a variety of drugs and overcoming the limitations of synthetic nanoparticles, leading to a gap between scientific research and clinical treatment. Exosomes provide an opportunity for scientists to have nanostructures with higher compatibility, and stability, and longer circulation time.

The advantages of exosomes over other synthetic carriers lie in their small size, low toxicity, natural targeting ability, encapsulation of various biologically active endogenous molecules, and ability to cross many physical barriers. Therefore, exosome-based nanocarriers may have a bright future as a new generation of drug delivery systems. However, there are several challenges and obstacles to building a commercial exosome delivery system. The exact mechanisms of interaction between exosomes and target cells need further explanation. To produce exosomes on a large scale, we need standard and repeatable methods for mass and pure production of exosomes so that we can produce suitable and very pure nanocarriers for use in drug delivery systems. In addition, innovative approaches should be developed to optimize the loading

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efficiency of exosomes, to evaluate the stability of the loaded agent, to modify the properties of the exosome, and to exploit the full potential of the exosomes for drug delivery. In addition, the development of synthetic exosomes with higher safety and more desirable properties has led to the further development of exosome-based drug delivery strategies and their advancement towards clinical applications. It can be concluded that exosome-based nanocarriers have shown significant potential as delivery vehicles for drug, DNA, oligonucleotides, proteins, peptides, etc. Due to these issues and limitations, exosome-based nanoparticles lead to the development of effective drug delivery systems. They can be used as a potential carrier with very interesting and attractive advantages in drug delivery and transfer of drug agents for the treatment of brain tumors, including glioblastoma multiforme.

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