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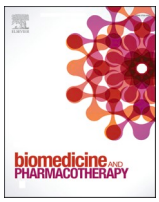

Exosomes as nature's nano carriers: Promising drug delivery tools and targeted therapy for glioma

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ABSTRACT

Exosomes, minute vesicles originating from diverse cell types, exhibit considerable potential as carriers for drug delivery in glioma therapy. These naturally occurring nanocarriers facilitate the transfer of proteins, RNAs, and lipids between cells, offering advantages such as biocompatibility, efficient cellular absorption, and the capability to traverse the blood-brain barrier (BBB). In the realm of cancer, particularly gliomas, exosomes play pivotal roles in modulating tumor growth, regulating immunity, and combating drug resistance. Moreover, exosomes serve as valuable biomarkers for diagnosing diseases and assessing prognosis. This review aims to elucidate the therapeutic and diagnostic promise of exosomes in glioma treatment, highlighting the innovative advances in exosome engineering that enable precise drug loading and targeting. By circumventing challenges associated with current glioma treatments, exosome-mediated drug delivery strategies can enhance the efficacy of chemotherapy drugs like temozolomide and overcome drug resistance mechanisms. This review underscores the multifaceted roles of exosomes in glioma pathogenesis and therapy, underscoring their potential as natural nanocarriers for targeted therapy and heralding a new era of hope for glioma treatment.

1. Introduction

A brain tumor is an unusual mass of cells that forms either inside or near the brain. These growths can be categorized as cancerous (malignant) or non-cancerous (benign) [1–3]. Brain tumors come in over 150 different types. They can be classified based on the type of cells they originate from, how invasive they are, and their histological features, which means how they look under a microscope [4,5]. The primary types of brain tumors frequently encountered are gliomas, meningiomas, and medulloblastomas [6].

Gliomas, the most common primary tumors in the brain and spinal cord [7,8]. Constituting 81 % of malignant central nervous system (CNS) tumors, gliomas arise from glial cells and evolve into various subtypes including astrocytoma, ependymoma, oligodendroglioma, or oligoastrocytoma [9]. Glioma is classified into different grades based on histological and genetic features, ranging from localized type I to diffusely infiltrating type II-IV, following WHO criteria (2021) [10]. Among all grades of glioma, Glioblastoma multiforme (GBM), a grade IV glioma, stands out as the most persistent and fatal subtype [11,12]. According to the World Health Organization (WHO), Among the different grades of glioma grades 1 and 2 indicate low-grade gliomas (LGG), while grades 3 and 4 signify high-grade gliomas (HGG) [13–15]. Reportedly, individuals diagnosed with low-grade gliomas (LGG) demonstrate a 5-year survival rate ranging between 70 % and 97 %, with a 10-year survival rate falling within the range of 49–76 % [16–18]. Recurrence occurs in about 52–62 % of cases within a 5-year timeframe [19,20]. Among recurrent cases, a portion maintains LGG status, while 17–32 % progress to high-grade gliomas (HGGs) [21–23]. For high-grade gliomas (HGG), patients diagnosed with grade 3 gliomas typically have a median overall survival (OS) of about 3 years. In contrast, grade 4 gliomas show a significantly poorer median OS time, lasting approximately 15 months [13,24,25].

The clinical presentations of gliomas are contingent upon the dimensions and positioning of the neoplasm. Main common symptoms, range from early signs such as headaches, nausea, vomiting, and seizures to more advanced indications like weakness or altered mental status. This complexity extends to cognitive issues, motor deficits, visual disturbances, speech impairments, personality changes, and fatigue. Timely recognition of these symptoms is critical for prompt intervention, significantly impacting treatment outcomes in glioma patients

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[26]. Glioma treatment typically involves surgery, radiotherapy, and chemotherapy. Surgery aims to remove the tumor, while radiotherapy and chemotherapy target the remaining cancer cells [27]. Despite the use of multiple therapies, the 5-year survival rate for glioblastoma is only 3–5 % due to resistance mechanisms and difficulties in delivering treatments past the blood-brain barrier (BBB) and blood-brain tumor barrier (BBTB) [28]. To improve outcomes, there's a critical need for new drug delivery methods that can efficiently overcome these barriers and deliver chemotherapy to the glioblastoma [29]. The blood-brain barrier (BBB) is a selectively permeable membrane that delineates the bloodstream from the interstitial fluid of the brain. This barrier facilitates the regulation by cerebral blood vessels of the transport of molecules and ions between the blood circulation and the brain parenchyma. Beyond its role in maintaining homeostasis for neuronal functions, the BBB acts as a defence mechanism against toxic substances, regulates communication between the central nervous system (CNS) and the periphery, and facilitates the supply of essential nutrients to the brain [30,31].

In case of the gliomas, the blood-brain barrier (BBB) plays a crucial role, posing a challenge to effective chemotherapy delivery due to its tight structure. Gliomas can interact with and compromise the BBB. To address this, researchers are exploring innovative drug delivery methods and therapies to improve therapeutic agent penetration through the BBB, enhancing glioma treatment. Overcoming BBB limitations is vital for advancing targeted therapies in glioma patients [32–34].

In recent research, exosomes have emerged as promising candidates for overcoming this challenge. Exosomes are small vesicles released by cells that can carry therapeutic cargo such as drugs or genetic material. Their potential lies in their capacity to traverse the BBB and deliver payloads to the brain. This capability opens up new avenues for targeted drug delivery to the brain, holding significant implications for the development of innovative treatments for neurological conditions [35].

Our review aims to assess the potential of exosome modulations as advanced tools for drug delivery in glioma treatment. By summarizing existing literature, we seek to uncover insights into how these exosomes can be optimized to serve as effective carriers for therapeutic medications, offering a new ray of hope for targeted therapy in glioma treatment.

2. Exosomes: Nature's nano carriers

Exosomes, the smallest subset of extracellular vesicles (EVs), have a size ranging from 30 to 100 nm. Discovered in the 1980s by researchers Pan, Stahl, and Johnstone, these microvesicles originate from endosomes. Their presence was noted during the study of reticulocyte maturation to erythrocytes, where exosomes released transferrin receptors into the extracellular space. Structurally, exosomes are double-layered, with a lipid bilayer mirroring that of their parent cells. Initially considered cellular waste in the context of maintaining cellular balance, exosomes were not thought to have significant effects on neighbouring cells and tissues [36].

In the last decade, there's a widespread acknowledgment that exosomes, once thought of as cellular debris, now serve as functional carriers. These tiny vesicles transport a diverse cargo of lipids, proteins, DNA, mRNA, and miRNAs, facilitating communication between nearby and distant cells and tissues [37,38]. Initially observed in blood cells, exosome release is now recognized in nearly all cells within the body, including immune cells (like dendritic cells, T-cells, B-cells, and astrocytes), tumor cells, and various vascular and epithelial cells [37–42].

Importantly, the cargo within exosomes varies depending on the cell source. This diversity makes exosomes and their contents valuable for understanding cell communication and offering insights into various diseases such as cancer, neurodegenerative conditions, chronic inflammation, and renal and cardiovascular diseases (CVD) [42–48].

2.1. Exosome biogenesis: Unravelling the intricacies

Exosomes are generated within the endosomal system as part of their biogenesis process. Exosomes form as a regular process from late endosomes. These endosomes are created when the membrane of a special compartment, the multivesicular body (MVB), folds inwards. Small vesicles, called intraluminal vesicles (ILVs), are formed as the endosomal membrane invades the larger MVBs. During this, the inner contents of the cell are taken in and enclosed within these ILVs, and specific proteins are incorporated into the folding membrane [49]. Afterward, most of these ILVs, now called "exosomes," are released into outer space when they merge with the cell's outer membrane [50,51].

The biogenesis of intraluminal vesicles (ILVs) initiates with the engagement of the endosomal sorting complex required for transport (ESCRT). This protein machinery, composed of four ESCRT complexes (ESCRT 0 through III), synergistically participates in vesicle budding, the formation of multivesicular bodies (MVBs), and the sorting of protein cargo [52]. The process starts when parts of ESCRT-0 bind to ubiquitinated proteins, tagging certain spots on the endosomal membrane to kick-start ESCRT. The full complex joins with ESCRT-III, a protein group aiding budding, following interactions with ESCRT-I and -II. ESCRT-III then breaks away from the MVB membrane, helped by the sorting protein Vps4, leading to the formation of ILVs [53]. Exosomes from various cell types contain ESCRT components and ubiquitinated proteins, although debates persist on whether exosome release is regulated by ESCRT. Notably, the protein Alix, a typical exosomal protein linked to ESCRT proteins, plays a role in cargo selection, membrane budding, and abscission through interaction with syndecan [54]. Recent research suggests an alternative mechanism that relies on raft-based microdomains for cargo segregation inside the endosomal membrane. This process sorts exosomal cargo into MVBs without the involvement of ESCRT. In addition to exosomes, cells can produce apoptotic bodies and plasma membrane-budded microvesicles (MVs). MVs, ranging from 100 to 1000 nm, are diverse vesicles formed by outward budding of the plasma membrane. They exhibit various shapes and are mainly identified as originating from red blood cells, platelets, and endothelial cells (ECs) based on composition [54] [Fig. 1]. Exosome release is a complex and controlled process that involves the movement of multivesicular bodies (MVBs) to the plasma membrane, where they fuse and release their contents. The cytoskeleton, including microtubules and actin filaments, aids in this process, moving MVBs to the cell's edge. Motor proteins like dyneins and kinesins are essential in this intracellular transport [50,51].

Exosomes and their molecular markers can be influenced by the cellular environment and characteristics. They comprise a mixture of membrane proteins, cytosolic and nuclear proteins, extracellular matrix proteins, metabolites, and various nucleic acids including DNA, non-coding RNA, and mRNA [55,56]. Studies reveal that exosomes from different cell types contain approximately 4400 proteins, 194 lipids, 1639 mRNAs, and 764 miRNAs, underscoring their intricate composition and potential functional versatility [57]. Tetraspanins (such as CD9, CD63, CD81, and CD82) are implicated in cellular processes such as penetration, invasion, and fusion. Heat shock proteins (such as HSP70 and HSP90) are involved in the cellular stress response and contribute to antigen binding and presentation [58].

3. Decoding exosome biogenesis in cancer: Implications for tumor growth

Exosome secretion has gained attention as a potential therapeutic target due to its various roles in promoting tumor growth. It has been studied in different contexts, with a focus on how exosomes contribute to communication between primary tumor cells and distant sites. In breast cancer cells, exosome release is crucial for the formation of invadopodia and enhances invasive activity, aiding these cells in moving away from the main tumor site [59]. Exosome formation can happen

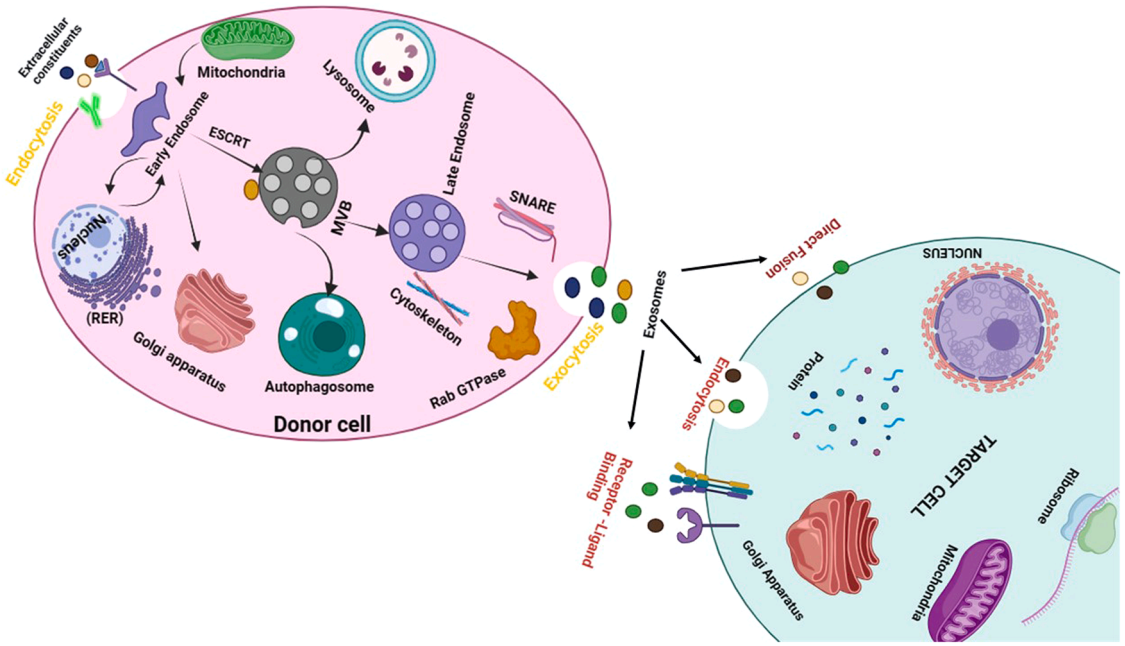

Fig. 1. Diagram of biogenesis of Exosome.

through two pathways: one involving ESCRT proteins and another independent of ESCRT. Early studies on exosome release identified ceramide as a key driver. Ceramide, produced by neutral sphingomyelinase, plays a role in the inward budding of endosomes, leading to the creation of multivesicular bodies (MVBs) that house exosomes [60]. Several investigations have linked ceramide production to exosome secretion in cancer cells [61–66]. However, there is some uncertainty as one study suggested that ceramide might not be essential for exosome release [67]. Therefore, it remains unclear if this pathway universally regulates exosome secretion in all types of cancer.

The microenvironment surrounding a tumor plays a crucial role in modulating the release of exosomes. Tumor cells encounter various challenges within this environment, such as restricted nutrient and oxygen availability, prompting the development of adaptive survival mechanisms. Exosome secretion has been suggested as a mechanism through which tumor cells adapt to and endure stressful conditions within their environment [68,69]. In conditions of hypoxia, characterized by low oxygen levels within the microenvironment, there is an augmentation in exosome secretion attributable to the development of a secretory lysosome phenotype. Exosomes discharged under hypoxic conditions are enriched with elevated levels of STAT3 and FAS, among other factors. These exosomes can transfer these molecules to neighboring tumor cells, thereby fostering their proliferation and dissemination [70]. Glioblastoma cells cultivated under hypoxic conditions secrete exosomes that stimulate angiogenesis and advance tumor progression, possibly by transferring hypoxia-associated RNAs and proteins [71].

PKM2 expression plays a role in modulating exosome release, suggesting a connection between cellular metabolic processes and the secretion of exosomes. This regulation occurs through the phosphorylation of synaptosome-associated protein 23 (SNAP-23) by PKM2 [72]. Cancer-associated fibroblasts (CAFs) transport exosomes that impact cancer cell metabolism, promoting glycolysis and potentially influencing exosome secretion [73]. Tumors often exhibit increased glycolysis and lactate accumulation in the acidic microenvironment resulting from hypoxia. The intracellular pH also affects exosome biogenesis, with acidic pH (pH = 6.0) enhancing exosome secretion, while alkaline pH reduces it [74,75]. Additionally, an acidic extracellular pH influences integrin activation, crucial for exosome uptake, suggesting that the microenvironment's pH may affect exosome entry into recipient cells [76]. All these findings indicate that hypoxia in the tumor microenvironment stimulates the production of exosomes from tumor cells, influencing cellular activity in that specific setting.

Research indicates that individuals with tumors have elevated levels of circulating exosomes compared to healthy individuals, suggesting a correlation between carcinogenesis and heightened exosome release [77]. When non-tumorous epithelial cells express oncogenic RAS or glioma cells overexpress oncogenic EGFRvIII, there is an increase in exosome secretion. These exosomes can then be transmitted to nearby cells, facilitating the transfer of oncogenic activity [78,79].

4. Exosomes: Nature's cellular messengers in medicine

Exosomes, derived from both healthy and diseased cells, are versatile tools for medication delivery, immune modulation, and more [80–82]. Serving as messengers between cells, exosomes facilitate the transfer of, mRNAs, microRNAs (miRNAs), proteins, and lipids from donor to recipient cells, allowing for drug delivery using these naturally endowed nanocarriers [83]. Exosomes derived from the patient's cells demonstrate enhanced biocompatibility and reduced toxicity when compared to synthetic carriers [84]. Exosomes exhibit advantages over nanoparticles, such as heightened biocompatibility and enhanced cellular uptake, attributed to the presence of membrane proteins like tetraspanin and fibronectin [57,85]. Resembling liposomes in shape and function, exosomes are durable in body fluids, in contrast to liposomes easily eliminated by macrophages or reticuloendothelial cells [86]. Their potential to enter tissues, circulate, and breach the blood-brain barrier (BBB) is a promising feature [87]. Exosomes also evade the immune system, extending circulation time [88–90]. Furthermore, exosomes are amenable to genetic modification, enabling surface protein engineering that imparts selectivity for specific cells and tissues. This characteristic has garnered growing interest among researchers who are investigating exosomes as effective vehicles for drug delivery **[**Fig. 2**]**.

Exosomes are integral players in cancer progression, immune responses, viral pathogenesis, pregnancy, cardiovascular diseases, and disorders of the central nervous system. Their inherent capacity to modulate intricate intracellular pathways has elevated their therapeutic promise across a wide array of conditions, encompassing cancer and

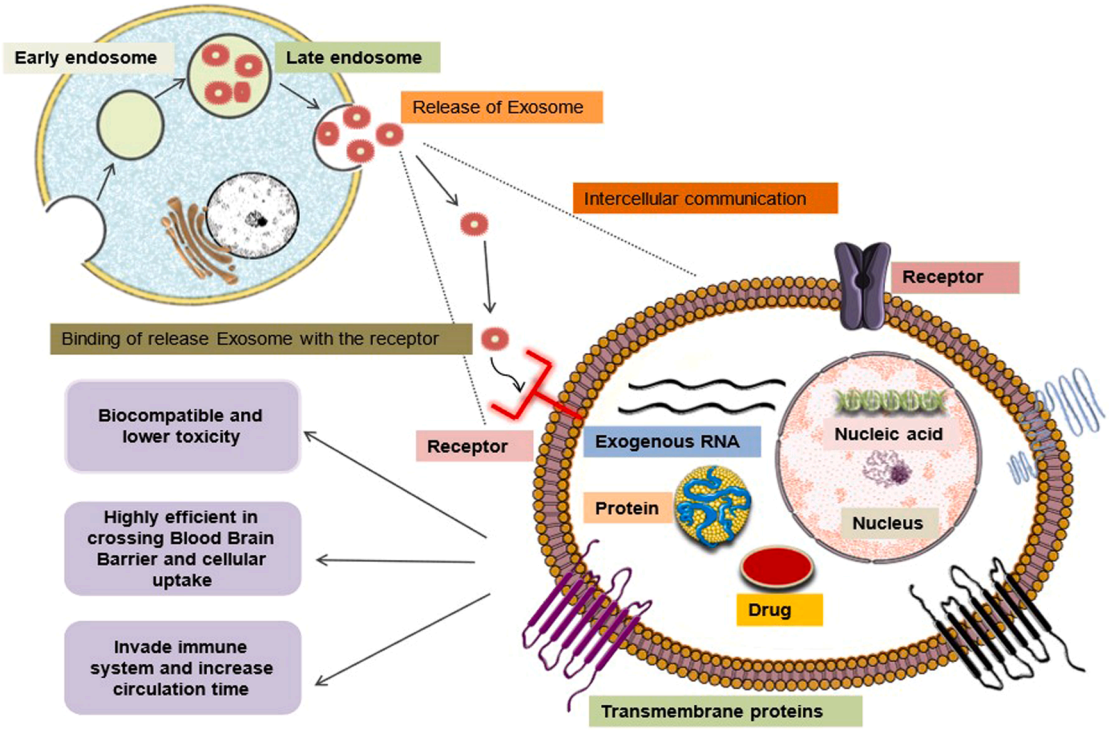

Fig. 2. Exosomes - Potent Drug Delivery Vehicles for Glioma Therapy.

neurological ailments. Beyond their therapeutic applications, exosomes serve as valuable tools for disease diagnosis. Present in all bodily fluids, exosomes can be easily analyzed through biological fluid sampling, offering insights into their intricate cargo composition, especially for liquid biopsies. The application of exosome-based liquid biopsy shows potential for diagnosing and prognosticating cancer and various other diseases. A thorough investigation of exosomes within multifaceted studies could aid in elucidating disease advancement and improving therapeutic approaches [44,91].

Exosomes exhibit a wide array of characteristics, including involvement in gene regulation at the levels of transcription and translation, modulation of immune responses within both central and peripheral immunity, mediation of communication between receptors and ligands, roles in cellular immunology, and maintenance of immune response balance, contributions to differentiation and neoplastic processes, facilitation of cellular migration and regulation of metastatic diseases, regulation of apoptosis, control of metabolic alterations, involvement in reproduction and development, participation in angiogenesis and wound healing processes, and influence on host-microbiome interactions and viral immunity [92,93].

Exosomes' involvement in immune responses is well-documented [94,95]. Notably, animals repeatedly administered a very low exosome dosage over an extended period showed no severe immune reactions [96,97], suggesting a potential context- and dose-dependent relationship between exogenous administration and endogenous exosomal secretion with immunological responses, requiring further clarification. Recent research using synthetic exosomes indicates a role for exosomes in both adaptive and innate immune responses, suggesting their potential coordination in immune responses to cancer or infectious pathogens [91,98,99]. Exosomes are believed to influence the immune system through antigenic peptide transfer and presentation, gene expression modification via exosomal miRNA, and activation of various signaling pathways by surface ligands [100–102].

Exosomal DNA plays a crucial role in immune responses and cancer development. Exosomes can induce adaptive immune responses, activating dendritic cells through the absorption of exosomal genomic DNA from breast cancer cells, leading to cGAS-STING signaling and an anti-tumor response in mice [103]. Through the transfer of miRNAs, exosomes can modify gene expression and signaling pathways in recipient cells, influencing the immunological response. Exosome-mediated communication also impacts dendritic cell development by exchanging exosomal miRNAs across cells, suppressing gene expression [104]. In various biological fluids like blood, breast milk, amniotic fluid, and sperm, exosomes play potential roles, including preventing placental infection by delivering exosomal miRNA from placental trophoblasts to promote autophagy and the body's defence against viral infections [105]. Additionally, exosomes influence cardiovascular health and metabolic disorders by transporting metabolites and promoting intercellular communication across different tissues [106]. The connection between exosomes and neurodegenerative diseases is highlighted by their involvement in synthesizing secretory vesicles in neuronal cells, potentially affecting the accumulation of misfolded proteins in the brain [107,108].

Research on exosome biology in disease is continually evolving, with a growing focus on its potential for diagnosing and treating various disorders. Some studies suggest that exosomes contain small amounts of DNA, which could be valuable for identifying cancer-related mutations in serum exosomes. This ongoing exploration holds promise for advancing our understanding and applications in the field of disease diagnosis and treatment.

5. Exosomes in gliomas: Impact on tumor growth and neurological dynamics

Brain exosomes are vital for the regeneration and activation of neurons, impacting their developmental processes. Moreover, they play a role in the initiation and advancement of diverse neurological conditions. Within the nervous system, extracellular vesicles (EVs) are emerging as a novel mechanism for material exchange. These vesicles, released by astrocytes, harbor neuroactive substances including neurotransmitters and other factors that influence neurons as well as other glial cells.

Exosomes constitute a noteworthy component in the intricate array of substances produced by tumor cells, encompassing growth factors, metabolites, cytokines, and ions [109]. Within glioma cells, exosomes have demonstrated the capability to transport various molecules such as histones, oncogenic species like EGFRvIII, non-coding RNA (miRNA), and tumor suppressors like PTEN [79,110–112]. Exosomes originating from glioma cells are small vesicles that play a crucial role in the tumor microenvironment. They carry RNA molecules that can affect different processes within the tumor. These exosomes essentially help in transmitting important genetic information, contributing to various activities within the tumor surroundings [113]. Exosomes from glioblastomas (GBMs) can change how the immune system behaves in the tumor environment. They do this by altering immune cells' ability to engulf foreign substances, changing the proteins on their surfaces, and controlling the production of signaling molecules called cytokines. [114,115]. The strong tendency of glioblastoma (GBM) to spread widely into surrounding brain tissue, leading to its frequent recurrence after surgery, has sparked extensive research into understanding the intricate molecular mechanisms responsible for this pronounced invasiveness. [116]. In recent years, scientists have discovered that certain tumor cells, with a tendency for tumor growth or spreading to other parts of the body, can create invadopodia structures [117–120]. Recent research has emphasized the significance of exosomes throughout different phases of the invadopodia lifecycle, including their initiation, durability, and secretion of protein-degrading enzymes [59] [Fig. 3].

Exosomes also contribute to remodeling the microenvironment by modulating the characteristics of nearby supportive cells, thereby promoting conditions conducive to tumor growth and invasion. When cells are exposed to exosomes released by mesenchymal cells, tumor growth can be facilitated. These exosomes not only negatively impact normal support cells like astrocytes but also induce abnormal traits in various molecular subtypes of GBM. Moreover, angiogenesis, a critical process in glioma development, is promoted by GBM-derived exosomes containing multiple angiogenic factors [121–123]. Tetraspanins play a specific role in transporting proteins and mRNA to exosomes. This helps in sharing information between exosomes and vascular endothelial cells, which in turn stimulates the formation of new blood vessels, a process known as angiogenesis [124]. Gliomas release many factors that promote the growth of new blood vessels, with a notable one being the epidermal growth factor receptor variant III (EGFRvIII). Through a process relying on phosphatidylserine, EGFRvIII can move between glioma cells using exosomes, aiding in communication between these cells [79,125].

Exosomes control the proliferation and invasion of glioma cells, essential for their survival and recurrence [126]. These extracellular vesicles, capable of exporting drugs from tumor cells, significantly contribute to the resistance of gliomas to therapy [127]. Exosomes induce fibroblastic responses, acting as a hindrance to anticancer drugs by stimulating fibroblast production. On the contrary, exosomes employ biomolecules such as miRNA to induce the conversion of drug-sensitive tumor cells into drug-resistant phenotypes [128,129].

Exosomes are pivotal in mediating how tumor cells respond to low oxygen levels (hypoxia), a condition intricately linked with processes such as angiogenesis, tumor proliferation, and metastasis. Hypoxia is a defining feature of the glioblastoma (GBM) microenvironment, exerting influence on the genetic and protein profiles of tumor cells [125]. The changes in the composition of exosomes originating from GBM cells, driven by hypoxic conditions, substantially alter the functions of nearby or distant cells in both qualitative and quantitative manners. The protein payload carried by exosomes exerts diverse effects on the expression of various genes, reflecting the hypoxic status of glioma cells [68]. In reaction to hypoxia, cancer cells escalate their exosome release, bolstering their resilience and invasiveness, particularly within normoxic regions [130,131]. Changes in exosomal miRNA caused by low oxygen levels drive the enhancement of cell signaling and movement, particularly under low oxygen conditions. These processes are crucial for aiding the growth of blood vessels within tumors, ensuring adequate coverage by support cells called pericytes, and promoting the expansion of glioblastoma (GBM) cells [68,132,133].

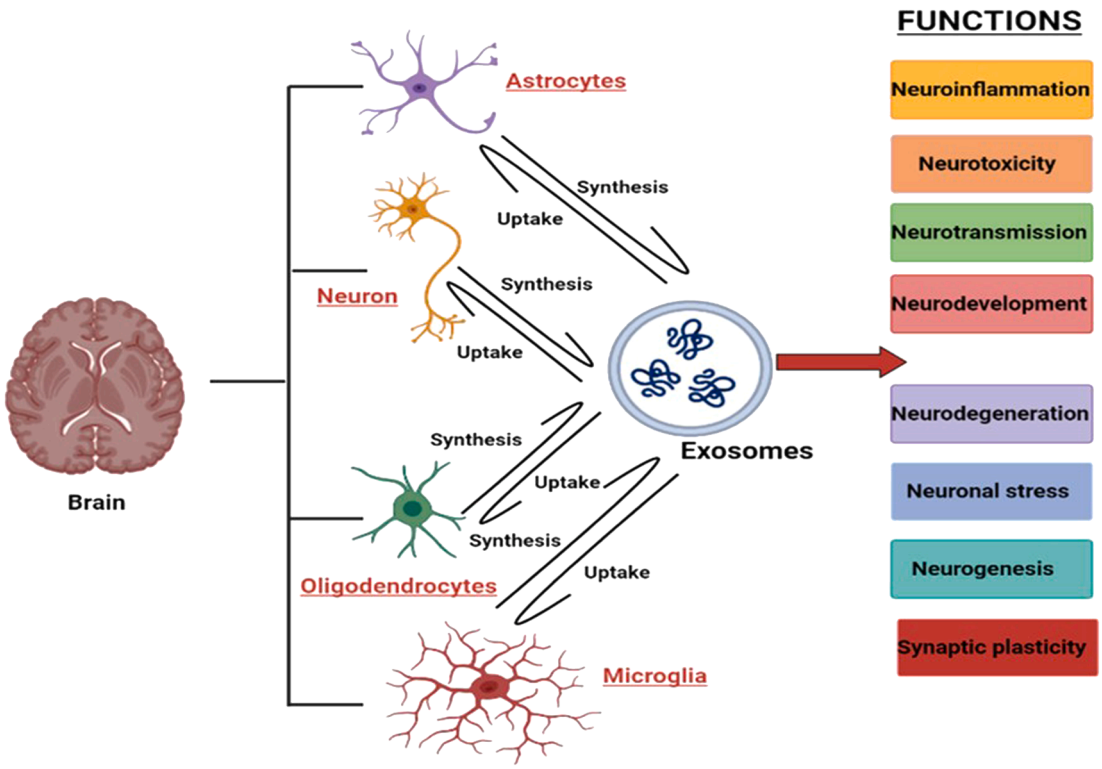

Fig. 3. Exosome-Mediated Cell Communication in the Brain: Insights and Mechanisms.

6. Exosomes: Crossing the blood-brain barrier for targeted drug release

Despite considerable progress in drug delivery, effectively treating central nervous system (CNS) diseases, including cancer, remains difficult due to the blood-brain barrier (BBB). The BBB comprises various components such as neurons, astrocytes, pericytes, the endothelial basement membrane, and microvascular endothelial cells. Tight junctions and adherens junctions in the endothelial cells of the brain play a vital role in controlling the movement of substances between cells, known as paracellular permeability [134]. These junctions act as barriers that stop most molecules from passing through, illustrating how the BBB works. However, it does allow essential substances needed for maintaining balance, such as nutrients and hormonal signals, to pass through, highlighting the BBB's selective permeability [135]. The BBB presents a major obstacle to delivering drugs accurately to the brain tissue, restricting the movement of drugs from the blood [136].

The BBB presents a formidable challenge due to its tight connections that significantly reduce the absorption of ions and other hydrophilic substances through the intercellular space, creating a "physical barrier." Additionally, the "transport barrier" facilitates the removal of metabolic wastes and foreign chemicals from the brain parenchyma, directing them to circulation. The brain's enzymatic activity, involving extracellular and intracellular enzymes, acts as an "enzymatic barrier" eliminating hazardous chemicals [137]. With their small size and inherent features, exosomes offer significant advantages in bypassing the BBB. Recent findings suggest that exosomes can effectively traverse the BBB, whether or not they undergo surface modifications, both in vivo and in vitro [138].

Natural exosomes come in various shapes and can stick to or be taken in by different types of cells. Their ability to target specific cells is closely linked to what they're made of and the condition of the cells they're targeting. Recent research suggests that certain kinds of natural exosomes could cross the blood-brain barrier in certain situations. Studies have shown that cancer cell exosomes are taken up and affect cells through receptors on their surfaces, like HSPGs [139]. The main suggested way for exosomes to get through the blood-brain barrier (BBB) involves the connection between certain molecules on the surface of exosomes and receptors found on cells lining the brain's blood vessels. Additionally, exosomes could enter the brain by passing through the choroid plexus, which is part of the cerebrospinal fluid-brain barrier. This suggests possible routes for exosomes to cross the BBB [140].

In addition to natural exosomes, engineered exosomes can also pass through the blood-brain barrier (BBB) using a process called Receptor-Mediated Transcytosis. This is a built-in mechanism that helps exosomes penetrate the BBB [138,141,142]. In a study, a scientist combined methotrexate with engineered exosomes designed for therapy. These exosomes were tailored to target the low-density lipoprotein receptor, a crucial receptor in the blood-brain barrier (BBB). This approach aimed to create a treatment for glioblastoma multiforme. By adding the LDL peptide, the exosomes were able to pass through the BBB and gather the drug at the glioma sites, as detailed in the study [143].

Injecting precursor cells with a combined gene containing a brain-targeted peptide, along with a gene that encodes a protein found in exosomes, results in exosomes containing higher levels of the combined protein. These exosomes can then cross the blood-brain barrier [144]. Given the unclear understanding of the transportation mechanisms of extracellular vesicles (EVs), the influence of EVs on endothelial cells (ECs) remains poorly elucidated. To classify the interaction between exosomes (EXOs) and recipient cells, five hypothetical pathways have been proposed, with a focus on EXOs [145–147].

I) Engagement with a G-coupled receptor on the cell surface, setting off a series of signaling events.
II) Exosomes (EXOs) attach to the cell surface, fuse with it, and then release their contents into the cell's interior, where they trigger different activities, like cell signaling.
III) Macropinocytosis is a way cells gulp down different stuff from the outside without picking and choosing specific items.
IV) Exosomes enter the cell through endocytosis and are stored in multivesicular bodies (MVB) using receptor-mediated transcytosis.
V) Nonspecific or lipid raft pathways.

7. Exosome modulation and drug delivery: Advancements and challenges

Exosomes can undergo modification through two main methods: **Genetic engineering** and **Chemical alterations**. Each approach has its limitations.

- **Genetic engineering** combines the gene sequence of a guiding protein with that of a particular exosomal membrane protein, but it's only effective for targeting genetically coded signals [148].
- **Chemical modification** enables the presentation of various natural and synthetic ligands on the exosome surface through crosslinking or lipid assembly. On the other hand, genetic engineering is proficient in displaying peptides and proteins on the surface [148]. Crosslinking through chemical modification can permanently alter exosomal surface proteins. However, its effectiveness is constrained by the complexity of the exosome surface. Moreover, it lacks precise control over specific sites and might disrupt the normal functions of the exosome [148,149].

Genetic engineering provides an easy way to give exosomes new abilities. First, ligands or homing peptides are linked to transmembrane proteins found on exosome surfaces. Cells that have been transfected with plasmids containing these fusion proteins then create modified exosomes with targeting ligands on their surfaces. Moreover, exosomes can be equipped with a pH-sensitive fusogenic peptide and a positively charged lipid for distributing inside cells. [150,151].

Furthermore, engineering exosomes with PEG and AA can enhance their ability for lung metastasis and medication delivery [152,153]. Another avenue involves the use of metal-organic frameworks (MOFs), which have gained popularity in academic circles for their unique structures, high crystallinity, exceptional porosity, and versatility for various applications [154] **[**Table 1**]**

8. Exosomes as therapeutic agents: Understanding uptake mechanisms and clinical implications

Exosome uptake is a multifaceted process comprising three key steps: **Receptor contact, Membrane Fusion, and Endocytosis/Phagocytosis**. This intricate mechanism facilitates the delivery of exosome-derived signals to the recipient cell. Research indicates that internalization, predominantly influenced by the recipient cell type and the exosomal surface proteins, stands as the primary mode of exosome uptake [169,170]

Many studies have consistently suggested that the interaction between particular surface receptors on recipient cells and exosomes controls how exosomes target and attach to them. [148]. This phenomenon contributes to the cell-specific nature of exosome absorption. The intricate interplay between cell surface receptors and exosomes underlines the importance of understanding the molecular interactions that regulate exosome uptake, shedding light on the nuanced processes involved in intercellular communication [171].

In recent years, nanoscale drug delivery methods have gained significant popularity. Chemical and biomolecular medications have experienced enhanced therapeutic efficacy through various nano-based formulations. The exploration of exosomes as biological messengers for

Table 1
Engineering Exosomes for Targeted Drug Release in Cancer Treatment.

S. No.	Cargo	Target Ligand	Target Cells	Therapeutic Function	Reference
1.	5-Fluorouracil anti-miRNA−21	HER affibody	Colorectal Cancer (HCT−116)	Improving chemotherapy success and overcoming resistance.	[155]
2.	Curcumin-SPION	Neuropilin−1-targeted peptide	Glioma (U251)	Diagnosing and treating glioma simultaneously.	[156]
3.	DOX	iRGD peptide	Breast Cancer	Directing doxorubicin specifically to breast cancer cells.	[157]
4.	Imatinib, BCR-ABL siRNA	IL−3	Chronic Myelogenous Leukemia Cells (LAMA84, K562, K562R)	Stopping cancer cells from multiplying and growing.	[158]
5.	KRAS siRNA	iRGD peptide	Adenocarcinoma (A549) Cell Line	Targeting oncogenic KRAS expression to inhibit tumor growth	[159]
6.	Mannosamine	RGD	αvβ3 Overexpressing Cells (HUVEC)	Promoting blood vessel formation with targeted imaging	[160]
7.	Methotrexate, KLA (Lys-Leu-Ala)	ApoA−1 mimetic peptide	Glioma	Targeted treatment for brain tumors	[143]
8.	PTX	AA	Murine Lung Cancer (3LL-M27)	Enhancing drug flow and preventing lung metastasis.	[154]
9.	PTX, Tirapazamine	D-CGKRK	B16F10	Targeted therapy with hybrid membrane vesicles	[161]
10.	SOX2 siRNA	Tlyp−1	Non-small Cell Lung Cancer (A549 stem cells)	Delivery of SOX2 siRNA for cancer therapy	[162]
11.	Smart-exos	αCD3/αEGFR	T-cells (Jurkat), Breast Cancer Cells (MDA-MB−468)	Using exosomes for cancer immunotherapy without needing whole cells.	[163]
12.	Tpd50 siRNA	DARPin	HER2-Positive Cells (SKBR3)	Directing treatment toward cancer cells that have HER2 receptors.	[164]
13.	aSIRPα, aCD47 antibodies	Antibodies	Macrophages and Tumor Cells	Enhancing cancer cell engulfment by macrophages	[165]
14.	miRNA−26a	ApoA−1	Hepatocellular Carcinoma (HepG2)	Preventing the spread and growth of tumor cells.	[166]
15.	miRNA-let7, VEGF siRNA	AS1411 aptamer	Nucleolin-Positive Cancer Cells (MDA-MB−231)	Delivering RNA specifically to tumor cells.	[167]
16.	miRNA-let7a	GE11 peptide	Breast Cancer (HCC70)	Directing treatment towards tumors that express EGFR	[168]

delivering payloads to target cells has garnered substantial research attention [172–175].

To achieve effective delivery into the cell's interior, exosomes can be modified to interact with a pH-sensitive fusogenic peptide and a cationic lipid. One such peptide is GALA, which is recognized for its sensitivity to pH because of its composition of repeating Glu-Ala-Leu-Ala sequences and its amphiphilic structure. Under acidic conditions within the endosome, the negative charge of Glu residues decreases, leading to a change from a random to a helical structure. GALA is often used to boost the efficiency of transfection [151,176,177]. In 2014, Nakase and Futaki utilized a combination of GALA, cationic lipids, and exosomes to deliver substances into the cell's interior. This combination was chosen because the high concentration of exosomes in physiological fluids makes cellular uptake challenging through endocytosis alone, limiting the efficiency of exosomal vehicles for treatment. The team utilized the GALA peptide along with cationic lipids to successfully deliver proteins and peptides to the cytoplasm. The design of the GALA peptide was influenced by sequences found in viral fusion proteins, making it better at interacting with cell membranes and aiding in the release of genetic material from acidic endosomes.

Exosomes, tiny extracellular vesicles released by cells, exhibit unique biochemical properties depending on their origin [178,179]. They can be derived from various cell types such as human embryonic kidney (HEK) cells, cancer cells, immune cells, and stem cells. HEK293T-derived exosomes, for example, share similarities with membranes found in different human organs, making them versatile for drug delivery [180,181]. These exosomes have desirable characteristics like easy growth, low maintenance requirements, and high transfection efficiency, which are advantageous for biopharmaceutical production.

Research has indicated that exosomes derived from HEK293T cells, containing therapeutic membrane proteins, can improve tumor penetration and enhance the effectiveness of anticancer treatments. Particularly, exosomes expressing PH20 hyaluronidase from HEK293T cells have been observed to hinder tumor growth by breaking down hyaluronan in the tumor microenvironment. When combined with drugs such as doxorubicin (Dox), these exosomes notably enhance the anticancer effects compared to using Dox alone [182,183]. Investigating the distinct properties of exosomes from different sources is crucial for understanding their potential in drug delivery. HEK-derived exosomes, with their organ-mimicking membranes and therapeutic capabilities, hold promise for diverse biomedical applications.

Cancer cells produce abundant exosomes due to the overexpression of Rab27a and Rab27b proteins involved in their release [183]. While these cancer-derived exosomes show potential as drug delivery vehicles, there are significant hurdles to their use in cancer treatment. Firstly, exosomes produced by cancer cells have suboptimal pharmacokinetic profiles. Secondly, research indicates that cancer exosomes may promote tumor spread, indicating potential drawbacks to their use for drug delivery in cancer therapy [184,185].

On the other hand, mesenchymal stem cells (MSCs) are regarded as a highly suitable source for producing exosomes intended for therapeutic applications. These MSCs can be harvested from diverse human tissues and possess a remarkable capacity for rapid proliferation in laboratory conditions. Such characteristics render MSCs ideal for generating exosomes, thus positioning them as a promising candidate for the development of exosome-based therapies targeting cancer and various other diseases [186,187].

While cancer-derived exosomes hold promise, their limitations and potential risks need to be carefully addressed. Meanwhile, MSCs offer a reliable and versatile source for generating exosomes with therapeutic potential. **[**Table 2**]**.

9. Exosome-mediated drug delivery: A promising approach for GBM treatment

The blood-brain barrier (BBB) presents a major hurdle for delivering chemotherapy drugs to treat central nervous system (CNS) tumors. However, exosomes show promising potential for overcoming this barrier, especially in the treatment of glioblastoma multiforme (GBM). Exosome-based combination therapies show the potential to address the limitations of current GBM treatments [161,195]. Prior research has shown that exosomes can transfer both lipophilic and hydrophilic drugs,

Table 2
Exploring Exosome Diversity in Cancer Treatment.

S. No.	Donor Source	Exosome Recipient	Exosome Vehicle	Outcome	Reference
1.	MSCs	male Fischer rats	miR−146b	The inhibition of EGFR expression leads to the halting of glioma growth.	[188]
2.	hBMSCs	Glioma cells (SHG44, C6, U87, and U251) and nude mice	miR−375	By suppressing SLC31A1, it encourages apoptosis and hinders the growth, migration, and infiltration of cells.	[189]
3.	GL26 cells	Microglial cells	Cucurbitacin	It promotes tumor cell death and reduces tumor cell proliferation by selectively reducing STAT3 activity and lowering the expression of IL−1b and IL−6.	[190]
4.	HEK-293T cells	U87-MG, C6 and rat model	miR−21 sponge construct	Reducing miR−21 levels and increasing the expression of miR−21 target genes (PDCD4 and RECK) leads to a decrease in tumor volume.	[191]
5.	DCs carried CRCLs with GL261 glioma cells	6-weekold female C57BL/6 mice	CRCLs	By modulating Cbl-b and c-Cbl signaling, it prolongs the survival of mice with tumors and slows down tumor progression.	[192]
6.	hBMSCs	U87 cells; T98G cells	Anti-miR−9	It reduces glioblastoma (GBM) cell resistance to TMZ by lowering miR9 levels and reducing the expression of drug transporters, including MDR1, in GBM cells.	[193]
7.	Human GBM cells	CTLs obtained from PBMCs	Tumour antigen	It kills autologous glioma cells by stimulating the generation of glioma-specific CD8 + cytotoxic T lymphocytes (CTLs).	[194]

such as curcumin and doxorubicin, without causing negative immune responses or activating the complement system. Prior research has shown that exosomes can transfer both lipophilic and hydrophilic drugs, such as curcumin and doxorubicin, without causing negative immune responses or activating the complement system [196,197].

Temozolomide (TMZ) is a commonly used chemotherapy drug for GBM, but resistance mechanisms, such as repair by O6 -alkylguanine-DNA alkyltransferase (AGT), limit its effectiveness [198–205]. Combining TMZ with O6 -benzylguanine (BG) can enhance its efficacy, but BG's side effects and poor BBB penetration restrict its clinical use [206,207]. To address these obstacles, dual-receptor-specific exosomes loaded with TMZ and BG (EXO-An2-AptTMZ and EXO-An2-Apt-BG) have been created to improve drug delivery to the brain for treating GBM [208].

Exosomes can be loaded with drugs using three techniques: incubation, electroporation, and sonication [209–211]. Research has demonstrated encouraging outcomes using exosome-mediated delivery of therapeutic agents like cucurbitacin I, a STAT3 inhibitor, which prolonged survival in mice with GBM [144]. Additionally, brain endothelial cell-derived exosomes have demonstrated efficacy in reducing tumor growth markers in zebrafish cancer models [196].

Exosomes loaded with chemotherapeutic drugs like doxorubicin (Dox) and paclitaxel (PTX) exhibit enhanced anticancer effectiveness [190,212–214]. Dox, despite its effectiveness, is limited by its adverse effects and poor biocompatibility [215]. Exosomes derived from mesenchymal stem cells have demonstrated the potential to improve the absorption and effectiveness of doxorubicin (Dox) in osteosarcoma patients [215]. PTX, another commonly used anti-cancer drug, faces challenges related to toxicity and BBB penetration [216–219]. However, Exosomes derived from cancer cells containing paclitaxel (PTX) may provide a promising strategy to target drug-resistant cancer stem cells and enhance the toxicity against cancer cells [220].

10. Challenges and advances in exosome production and characterization for clinical applications

The utilization of exosomes in clinical settings is still in its early stages, facing several challenges that impede their therapeutic application. The primary obstacle lies in the large-scale production of exosomes while ensuring high-quality and thorough characterization [221,222]. Exosomes obtained from biological fluids or cell cultures typically have low yields [222] However, advancements in production techniques, such as employing 3D scaffolds, bioreactors, and microfluidics, have shown promise in enhancing exosome yield, with bioreactors notably increasing yields by up to 10-fold compared to traditional methods [223]. Despite these improvements, current methods for isolating and purifying exosomes require further optimization to achieve efficient, cost-effective, and reproducible production suitable for clinical applications [224,225].

Additionally, there is a need to develop techniques capable of isolating exosomes from various biological sources using a single method, thereby streamlining the process. Current methods for characterizing and validating exosomes, such as transmission electron microscopy (TEM) and fluorescence-activated cell sorting (FACS), have limitations in independently analyzing the biochemical and biophysical features of exosomes. More sophisticated techniques are necessary to accurately characterize exosomes in clinical settings, addressing this gap in current methodologies [221,226].

11. Physicochemical characteristics of drugs and their loading efficiency into exosomes

Exosomes have gained significant attention in recent years due to their potential as drug-delivery vehicles. The ability of exosomes to encapsulate various types of cargo, including drugs, makes them an attractive option for targeted therapy. However, the loading efficiency of drugs into exosomes is highly dependent on the physicochemical characteristics of the drug molecules. One of the most important physicochemical characteristics that determine the loading efficiency of drugs into exosomes is the hydrophobicity of the drug molecule. Hydrophobic drugs tend to interact more favorably with the lipid bilayer of exosomes, leading to higher loading efficiency. In contrast, hydrophilic drugs may have difficulty crossing the lipid bilayer and achieving efficient encapsulation. For example, paclitaxel, a hydrophobic anticancer drug, has been successfully loaded into exosomes with high efficiency due to its favorable hydrophobic interactions with the lipid membrane

[227]. The size and shape of drug molecules also play a crucial role in determining their loading efficiency into exosomes. Small molecules with a size similar to that of the lipid bilayer of exosomes are more likely to be encapsulated efficiently. Additionally, drugs with a spherical shape may have better compatibility with the curvature of the exosome membrane, leading to higher loading efficiency. For instance, curcumin, a small, spherical molecule with anti-inflammatory properties, has been successfully loaded into exosomes with high efficiency [198]. Furthermore, the charge of drug molecules can significantly impact their loading efficiency into exosomes. Positively charged drugs may interact more strongly with the negatively charged phospholipids present in the exosome membrane, leading to higher encapsulation efficiency. Conversely, negatively charged drugs may have lower loading efficiency due to repulsive interactions with the membrane. For example, doxorubicin, a positively charged chemotherapeutic agent, has been effectively loaded into exosomes with high efficiency [210]. To enhance the loading efficiency of drugs into exosomes, various methods have been developed. One common approach is the use of membrane permeabilization techniques, such as sonication or extrusion, to facilitate the entry of drugs into exosomes. Additionally, chemical modification of drugs to increase their hydrophobicity or charge can improve their encapsulation efficiency. For example, the conjugation of hydrophobic moieties to hydrophilic drugs has been shown to enhance their loading into exosomes [190]. Understanding these characteristics and utilizing appropriate methods can help optimize the encapsulation of drugs into exosomes for targeted drug delivery. Further research in this field is essential to advance the development of exosome-based drug delivery systems and improve therapeutic outcomes for various diseases.

12. Future perspectives

Exosomes have shown immense potential as medication carriers, offering solutions to overcome existing limitations. Their inherent qualities, including their natural origin and ability to target specific tissues, make them promising tools for enhancing therapeutic delivery. Moreover, exosomes can be easily modified to improve drug loading and targeting efficiency. However, our understanding of exosome biology is still in its early stages, warranting further exploration in the future. Choosing the appropriate source of exosomes for therapeutic purposes is critical and demands careful thought. Developing strategies to identify and control exosomal components is vital for advancing exosome-based drug delivery in cancer treatment. Overcoming the hurdles presented by diverse exosome subpopulations will be crucial for unlocking their complete potential. Current cargo loading techniques for exosomes do not meet the efficiency required for clinical applications. Traditional methods like basic incubation are limited in cargo variety and efficiency, necessitating the development of new approaches.

Aside from transporting medications, exosomes are potential indicators for cancer detection and prognosis. Ongoing research aims to comprehend their various profiles and roles, facilitating their use in clinical settings. Exosomes mark a new era in drug delivery, boasting low immunogenicity and strong biocompatibility.

While obstacles persist in creating commercial exosome-based drug delivery systems, a better grasp of their biological mechanisms and additional clinical investigations will drive them toward becoming cutting-edge tools for cancer therapy. Continuous experiments examine exosomes as a drug delivery system to devise potent and durable treatments.

13. Conclusion

In recent times, the investigation into exosomes has intensified, revealing their crucial role in normal body functions and the development of diseases. With exosomes being found widely in bodily fluids and their ability to facilitate communication between cells, they present significant potential as diagnostic indicators and treatment options, especially in cancer therapy. Their ability to carry different molecules makes them excellent candidates for delivering drugs precisely to targeted areas, offering optimism for more efficient and accurate treatments.

While exosome-based therapeutics are still in their infancy, ongoing research aims to identify cost- and time-efficient nanotechnologies for large-scale manufacturing. Although much of the biology of exosomes has been elucidated in cell-culture systems, further studies using physiologically relevant experimental models are essential. Moreover, standardizing the separation, categorization, and purification of exosomes is crucial to ensure their clinical utility.

Derived exosomes, such as those from macrophages with enhanced BBB-crossing abilities, present promising avenues for brain tumor treatment. By leveraging exosomes' inherent targeting capabilities, derived exosomes can deliver payloads specifically to target cells, overcoming barriers like the BBB. Additionally, combining exosome-based drug delivery with complementary strategies, such as hyperosmotic agents and focused ultrasound, holds potential for improving treatment outcomes in glioblastoma and other challenging diseases.

In conclusion, exosomes stand out as highly effective and competitive nanocarriers for drug delivery. Their natural ability to mediate cell-cell communication, coupled with advances in customization and manufacturing, makes them promising candidates for personalized medicine. As research advances, further refinement of exosome-based therapeutics holds the key to addressing current medical challenges, offering new avenues for targeted therapy and precision medicine. Future research should explore diverse cell types for exosome production to identify the most efficient sources for drug delivery, develop advanced engineering techniques to enhance exosome specificity for glioma cells, and focus on scalable, cost-effective methods for large-scale production and purification. Additionally, extensive clinical trials are necessary to evaluate the safety, efficacy, and optimal delivery methods of exosome-based therapeutics in glioma patients. Investigating the potential of combining exosome-based drug delivery with existing treatments and performing long-term studies to assess stability, biodistribution, and long-term effects will also be critical for the successful translation of exosome-based therapies into clinical practice.

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No data was used for the research described in the article.

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