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Exosome-Based Drug Delivery in Alzheimer's Disease: Current Advances and Emerging Strategies

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Abstract

Alzheimer's disease (AD) is the most prevalent age-associated neurodegenerative disease and has become one of the most serious public health issues worldwide, given that currently available therapeutics against AD demonstrate only limited effectiveness, and drug delivery into the brain is highly problematic due to the existence of the blood-brain barrier (BBB). Exosomes, naturally secreted extracellular vesicles that act as mediators in cell-cell communications, have recently been attracting tremendous interest as a sort of brain-targeting nanocarrier system, benefiting from excellent biocompatibility, low immunogenicity, intrinsic BBB-transporting capability, and diverse cargo loading capacity. In this review, the up-to-date development in exosome-mediated drug delivery for AD with a focus on exosome biogenesis, BBB-transporting mechanism, and engineered exosome-based systems toward efficient BBB targeting is comprehensively summarized. The use of exosome-delivered small molecules, RNA-based therapeutics, proteins, or enzymes against amyloid deposition, tau pathology, neuroinflammation, oxidative stress, neuronal dysfunction, etc. are summarized in detail. Diverse strategies such as genetic, chemical, and hybrid modifications of exosomes are discussed with the aim of enhancing targeting accuracy and efficacy of exosome-delivered therapeutic agents. Limitations of exosome-based delivery systems, such as scale-up manufacturing, loading efficiency, heterogeneity, and quality control of exosomes, and approval and regulation, are further analyzed. It can be concluded that various research findings demonstrate great promising potential of exosome-based delivery systems for future therapeutics of AD, although much further mechanistic study and clinical investigation are required for their ultimate translation into the clinic.

Keywords: Alzheimer's disease; Exosomes; Drug delivery; Blood–brain barrier; Engineered exosomes; Nanomedicine; Neurodegenerative disorders

Introduction

Age, reflecting the progressive decline of physiological function, is the single largest risk factor for most noninfectious diseases such as Alzheimer's Disease (AD). As the global population ages and the health care burden of AD patients grows, research into AD is developing at an ever-increasing rate [1]. Dementia is what older people fear more than any other disease condition [2,3]. Clinically, AD is characterized by intracellular accumulation of tau protein aggregates and extracellular deposition of A plaques [4]. The success of trials targeting reduction of these aberrant protein deposits has, to date, only shown modest disease-modifying benefits [5,6] and there is still an unmet need for further treatments aimed at preventing, slowing, and treating AD.

However, most candidate therapeutic agents have difficulty crossing the BBB, and even when they do, they may not reach therapeutic levels in the brain [7]. In practical terms, this situation is part of the reason why there have been very few effective treatments for NDDs. With the advent of nanotechnology, various drug delivery methods have been developed. For instance, liposomes [8], solid lipid nanoparticles [9], and polymer nanoparticles [10], have been developed to allow intracranial drug delivery. Nevertheless, there remain significant drawbacks to these technologies, including issues related to scalability, rapid clearance by the body's mononuclear phagocyte system, and toxicity [11,12]. Consequently, there remains a pressing need for alternative delivery mechanisms, especially since natural nanovesicles, such as exosomes, seem to be much more promising as drug delivery vehicles.

As for exosomes, with diameters ranging between 40 and 160 nm, they are naturally occurring vesicles generated from the endosomal system that arise through invagination of the plasma membrane, thus generating early endosomes that mature to multivesicular bodies (MVBs), which fuse with the plasma membrane, releasing the exosomes into the extracellular space and hence becoming a vital component of intercellular communication [13-15]. Being as such because of the mechanism

of generation of exosomes and its inherent capability of delivering drugs, exosomes have proven to be an ideal drug delivery vehicle with various benefits over traditional drug delivery vehicles such as minimal immunogenicity, biocompatibility, lack of toxicity, and structural stability among others, especially for diseases requiring continuous drug delivery like NDDs, while production and targeting capability of exosomes have made them even more attractive for the purposes of CNS drug delivery [15-18].

Notably, beyond acting as carriers for delivering substances into target cells, exosomes have been modified to deliver various therapeutic molecules such as proteins, nucleic acid-based drugs, gene editing, adeno-associated viruses, and chemical drugs [15-19]. Importantly, exosomes take part in biological processes associated with physiology within the nervous system, where they are responsible for regulating the growth, development, and remolding of neurons. Furthermore, exosomes have been found to participate in mediating neuroinflammation and immune responses and play a part in maintaining vascular integrity and modulating BBB permeability, which is crucially important for neurodegenerative disorders, where dysfunction of the BBB is one of the biggest issues for therapeutic intervention [20-23]. In addition, by delivering biologically active compounds, exosomes can control gene expression and signal transduction pathways, and eventually affect the survival of neurons, as well as their structure and function [20].

In this review, our objective is to provide a comprehensive discussion of the current advances and approaches that can be taken in the use of exosomes for delivering drug molecules to treat AD. In this regard, our focus will be on the generation of exosomes, the biological nature of exosomes, the crossing ability of exosomes across different biological barriers like the BBB, and their use as nanocarriers for delivery of bioactive agents, including small molecules, nucleic acids, and proteins. More importantly, we will emphasize recent studies regarding the use of engineered exosomes as targeted nanocarriers that can deliver drugs directly into the brain to treat AD, along with the therapeutic benefits observed in the treatment of AD. We will also discuss existing challenges for clinical applications of exosomes, along with future perspectives.

Biology and Biogenesis of Exosomes

Among EVs, exosomes are the most intensely researched because of their distinctive biogenesis mechanism and significant involvement in cell-cell communications that influence their composition, content, and behavior inside recipient cells [24,25]. The biogenesis process of exosomes entails formation of early endosomes by plasma membrane invaginations and subsequent transformation of the latter into MVBs containing ILVs; the next step involves fusion of MVBs with lysosomes for their degradation or plasma membranes for their expulsion into the extracellular environment in the form of ILVs [26,27].

Exosome biogenesis can be controlled by ESCRT-dependent and ESCRT-independent mechanisms. The ESCRT complex (composed of ESCRT-0, ESCRT-I, and ESCRT-II complexes) regulates the processes of cargo selection, endosomal sorting, and membrane budding necessary for ILV formation and MVB maturation [26,28]. In parallel, the ESCRT-independent pathways use lipid-based mechanisms and interaction of membrane proteins like tetraspanins (CD9, CD63, and CD81) along with induction of membrane curvature by production of ceramide through neutral sphingomyelinase 2 (nSMase2) activity to induce ILV formation [29,30]. These complementary pathways ensure efficient vesicle biogenesis and cargo packaging under both physiological and stress conditions.

The molecular structure of exosomes reflects their cell source and consists of a cholesterol, sphingolipid, ceramide and phospholipid-rich lipid bilayer and various molecules in the contents, such as proteins, nucleic acids, and lipids. Frequently contained proteins include tetraspanins, heat shock proteins, and signaling proteins; contained nucleic acids such as mRNAs and miRNAs [31-33]. This complex cargo enables exosomes to control the gene expression and signaling pathways of receiving cells, which then leads to their function in physiological or pathological mechanisms and potential roles as a new diagnostic and therapeutic system [33].

Beyond understanding biogenesis and molecular composition, exosome isolation from a variety of biological fluids is paramount for experimental and clinical investigation as source dictates yield, accessibility and relevance to disease. Most common sources come from blood (plasma, serum) for convenience and relevance to system-wide pathologies [34]. Samples from blood cellular fractions (platelets, red blood cells and white blood cells) are readily available and relevant to normal physiology and immunity. Non-invasive sampling sources include urine (relevant to kidney/urinary track function) and, more specifically for nervous system diseases such as AD, Cerebrospinal fluid (CSF) [35,36]. Saliva, breast milk and conditioned media derived from cell cultures are also possible sources [37-39].

Compared to conventional synthetic nanocarriers such as liposomes, polymeric nanoparticles, micelles, solid lipid nanoparticles, and dendrimers, which are likely to suffer problems such as toxicity, immunogenicity, low biocompatibility, and low efficiency in tissue targeting, etc., exosomes possess some merits to overcome these weaknesses [40-44]. Exosomes, naturally occurring nanovesicles with strong biocompatibility, low immunogenicity, long circulation, and natural targeting capacity, can efficiently carry and deliver their cargo through enzymatic degradation and physiological clearance [43,45]. The composition of the membranes ensures uptake into target cells, as well as intercellular communications through the delivery of their proteins and nucleic acids, and they differ from most

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synthetic vectors in that they can also be immune-shielded and pass biological barriers such as the blood-brain barrier, thus being desirable for drug delivery to the CNS [46-48]. These characteristics have already established exosomes as one of the most promising candidates among next-generation nanocarriers for specific therapy.

Role in CNS and BBB Transport

Within the CNS, exosomes play a role in mediating cell-to-cell communication between different cells, such as neurons, astrocytes, microglia, and oligodendrocytes, and are able to mediate communication between neuronal homeostasis, synaptic plasticity, neuroinflammation, and cellular signaling pathways via the transfer of proteins, lipids, and nucleic acids. These characteristics of exosomes, including their capacity to cross the BBB, have received considerable attention in the development of therapeutic applications targeting the CNS.

The BBB is a highly selective barrier that controls the passage of molecules between the systemic circulation and the CNS. Molecules crossing the BBB could undergo passive diffusion or an active process; the nature and extent of the transfer depend on the physicochemical nature of molecules: molecular weight, lipophilicity, plasma protein binding, flow to the brain, and so on. Passive diffusion is mainly limited to lipophilic small molecules such as oxygen and carbon dioxide. Most drugs, however, require specialized mechanisms such as carrier-mediated transport, receptor-mediated transport, efflux pumps, and adsorptive transcytosis to cross the BBB [49-54].

One of the unique properties of exosomes is their capacity to cross the BBB both bidirectionally from circulation to the brain and vice versa. This characteristic makes exosomes very attractive candidates for CNS drug delivery [55]. Although the precise mechanisms by which exosomes cross the BBB remain an area of active investigation, current evidence strongly suggests that transcytosis is the primary route [34,55]. By transcytosis, the exosomes are taken into the cells, transferred across the intracellular space rather than passing through the paracellular space. After being taken into the cells, they are then transferred through the endothelial cell and released into the brain parenchyma, or alternatively, the exosomes stay in the endothelial cell and can then influence endothelial cell signaling and BBB function [34,55,56].

There are several reported mechanisms of how exosomes may communicate with the specific target cells in the brain. These include the process mediated via signaling of cell-surface receptors, membrane fusion, micropinocytosis, receptor-mediated endocytosis with movement through MVBs, and the pathways associated with lipid rafts, which control membrane functions and cell communication [35,36]. The exosomal cargo might then cause some intracellular signaling cascades to occur, to be degraded through the lysosomes, or be incorporated into the newly budding MVBs, thus controlling the recipient cell [35,36]

Numerous experimental investigations employing fluorescently labeled exosomes have significantly increased our understanding of how exosomes traverse the BBB and their subsequent distribution within the central nervous system [37,38]. These studies suggest that exosomes initially bind and fuse with brain endothelial cells and then are transported transcytotically through them [39,57]. Evidence also indicates that exosome transport capacity may be related to size and density, with lower-density exosome subpopulations having increased preferential accumulation in the luminal side of endothelial cells and high-density exosome subpopulations being present more prominently in the abluminal side after transcrossing the BBB [58,59]. All these findings confirm the unique nature of exosomes that are capable of overcoming the first hurdle of neurotherapeutics and open up more opportunities to utilize natural nanocarriers for drug delivery to the central nervous system.

Because BBB dysfunction, neuroinflammation, and subsequent neuronal loss are central to AD, exosomes — given their natural capacity for crossing the BBB and transferring therapeutic cargos to targeted brain cells — appear to be an ideal vehicle for targeted drug delivery and potential disease-modifying therapeutics.

Exosome-Based Drug Delivery Strategies in Alzheimer's Disease

Small molecules

Small-molecule AD drugs suffer from their poor bioavailability, long half-life for elimination and metabolism, and poor blood-brain barrier penetration. BBB represents one of the biggest barriers to the delivery of therapeutics to the central nervous system, greatly limiting clinical translation of neuroprotective agents that have promising neuroprotective effects. Among those natural nano-carriers that show potential to surmount those challenges, exosomes have proved to be outstanding with their unique BBB-crossing capability, biocompatibility, and low immunogenicity, as well as the ability to protect therapeutic payload from enzymes.

Indeed, increasing evidence suggests that exosomes improve the brain accumulation and therapeutic effects of small-molecule agents in AD models. Exosomes derived from plasma promote the brain accumulation of quercetin to inhibit cyclin-dependent kinase 5 (CDK5) phosphorylation of tau and decrease neurofibrillary tangle formation in an AD mouse model [60]. Meanwhile, the BBB permeability of curcumin-loaded exosomes from macrophages is increased via receptor-mediated transcytosis, and tau pathology is alleviated by activating the AKT/GSK-3 signaling pathway, thereby improving neuronal function [61]. In line with these results, bovine milk exosomes were found to highly increase brain accumulation of curcumin over usual delivery routes, thus corroborating the role of exosomes in enhancing the pharmacokinetic profiles of insoluble compounds [62].

Apart from the use of natural phytochemicals, exosomal delivery platforms have also been used for drugs or bioactive compounds that are relevant in clinical practice. Indeed, it has

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been demonstrated that donepezil-loaded plasma exosomes are superior in terms of brain targeting efficiency than the drug in free form [63], and adipose-derived mesenchymal stem cell exosomes loaded with coenzyme Q10 can help alleviate cognitive impairment as well as regulate neuroprotective mediators such as SOX2 and BDNF in experimental AD models [64]. Furthermore, exosomes isolated from human amniotic fluid with an entrapment of sulforaphane were found capable of Nrf2 activation, inhibition of IL-6 production, and protection of neurons from oxidative stress-induced injury [65].

Taken together, these findings illustrate that exosome delivery platforms not only increase stability and circulation time of small compounds but also dramatically increase the brain barrier permeability and effectiveness. Consequently, exosome-mediated small-molecule delivery appears to be a prospective nanotechnology approach for AD treatment.

RNA-based therapy (miRNA/siRNA)

In addition to other approaches targeting AD, RNA-based therapeutics are also exciting disease-modifying strategies since RNA is able to achieve precise regulation of genes that contribute to amyloid genesis, tau pathology, neuroinflammation, and neuronal dysfunction. As ideal vectors for delivery of RNA in the body, exosomes are favored due to their natural mechanism of nucleic acid transport, low immunogenicity, favorable biocompatibility, and intrinsic potential to permeate through the blood-brain barrier. The work of Alvarez-Erviti et al was influential in demonstrating the use of exosomes in delivering therapeutic RNA to the brain. They modified dendritic cell-derived exosomes to express rabies virus glycoprotein (RVG) peptide fused to Lamp2b, which allows exosomes to target neurons. Then they loaded BACE1-targeting siRNA into modified exosomes by electroporation and delivered the engineered exosomes to the brain of AD mouse model via intravenous administration, successfully knocking down the expression of BACE1 in neurons, microglia, and oligodendrocytes in the brain [66]. BACE1 is a major enzyme in processing amyloid. Therefore, this research is an important proof-of-concept to deliver therapeutic RNA to treat AD via exosomes.

In addition to siRNA, exosomes have been increasingly utilized as delivery systems for therapeutic microRNAs to inhibit multiple pathogenic pathways in parallel. Exosome-mediated delivery of miR-223 decreased microglial-neuronal interaction and accordingly inhibited neuroinflammation and neuronal damage in AD models [67], suggesting exosomal miRNA in regulating neuroimmune reactions. Targeting delivery of miR-29 increased miR-29 in the hippocampus, inhibited its downstream targets, reduced A-induced neurotoxicity, and ameliorated impairment of learning and memory functions [68]. Furthermore, an experimental report demonstrated that somatostatin-receptor-targeted, exosome-carrying miR-29b-2 and modified exosome can successfully enter the BBB, resulting in a decrease in presenilin-1 levels and subsequently reducing A-amyloid in brains [69].

Exosome-based RNA therapeutics have seen further development with new discoveries, wherein the overexpression of exosome loading with miR-124-3p mimics resulted in neuroprotection via modification of neuronal signaling pathways [70]. In addition, custom exosome-based platforms have been successfully designed to deliver CRISPR guide RNAs and cytosine base editor (CBE) mRNA, enabling site-specific genome editing associated with neurodegenerative diseases [71]. Taken together, these discoveries highlight the use of exosomal delivery of RNA species as an efficient and flexible approach to site-specific genetic manipulation, opening the door to disease-modifying therapies otherwise unachievable by standard pharmacology.

Protein/enzyme delivery

Biologics such as proteins and enzymes are promising therapeutic candidates in the treatment of AD because they are able to directly affect pathogenic pathways that are difficult to control by typical small molecules. The efficient delivery of such biologics can be achieved by using exosomes as the vehicles since exosomes provide protection for protein cargo, allow transport across the blood-brain barrier, and deliver the cargo to the specific location in the central nervous system.

One of the most promising cases for biologics delivery is via exosomes to deliver NEP, which is one of the important enzymes that degrade Aβ. Katsuda et al proved that there are naturally abundant enzyme-active NEP on adipose tissue-derived mesenchymal stem cells exosomes, and when co-cultured with neuronal cells, the uptake of exosomes lowered both intracellular and extracellular Aβ levels and upregulated NEP expression in neurons [72]. This study suggests that enzyme delivery using exosomes directly helps to ameliorate the intrinsic A degradation system.

Exosome-bound catalase has also attracted attention due to its potent antioxidant activity. Wharton's jelly mesenchymal stem cell-derived exosomes were reported to transfer catalase and reduce oxidative stress, and provide a neuroprotective effect in neurodegenerative disease [73]. In addition to specific enzymes, a variety of neurotrophic and regenerative proteins are delivered by exosomes. Neurotrophic factor-containing mesenchymal stem cell-derived exosomes were reported to reduce neuroinflammation and support neuron survival and enhance cognitive performance in an experimental AD model [74]. Treatment with exosomes has also been reported to restore synaptic plasticity, improve neurogenesis, regulate neuronal and astrocyte activity, and restore metabolic performance in AD brain [75-77].

In conclusion, these studies indicate that the targeted delivery of proteins and enzymes by exosomes offers a potential therapeutic strategy to address both the amyloid pathology, oxidative stress, and neuroinflammation, as well as neuronal dysfunction in AD simultaneously (Table 1).

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Table 1: Exosome-Based Therapeutic Strategies in AD: Cargo, Source, and Outcomes.

Cargo Type	Therapeutic Cargo	Exosome Source	Molecular Target	Main Therapeutic Effect	Experimental Model	Ref
Small molecule	Quercetin	Plasma-derived exosomes	CDK5/Tau pathway	Reduced tau phosphorylation and NFT formation	AD mice	[60]
	Curcumin	Macrophage-derived exosomes	AKT/GSK-3β pathway	Reduced tau pathology and improved cognition	AD mice	[61]
	Curcumin	Milk-derived exosomes	BBB delivery enhancement	Increased brain bioavailability	Animal model	[62]
	Donepezil	Plasma-derived exosomes	Cholinergic signaling	Enhanced brain delivery efficiency	Experimental model	[63]
	Coenzyme Q10	ADSC-derived exosomes	SOX2, BDNF	Neuroprotection and cognitive improvement	AD rats	[64]
	Sulforaphane	Amniotic fluid exosomes	Nrf2 signaling	Reduced oxidative stress and IL-6 expression	Cellular model	[65]
RNA	BACE1 siRNA	RVG-engineered dendritic exosomes	BACE1	Reduced Aβ production	Mouse model	[66]
	miR-223	Microglial exosomes	Neuroinflammatory pathways	Reduced neuronal injury and inflammation	AD model	[67]
	miR-29b	Engineered exosomes	Presenilin-1 and Aβ pathway	Reduced Aβ accumulation	AD rodents	[68,69]
	miR-124-3p	Engineered exosomes	Neuroprotective signaling	Enhanced neuronal survival	Triculture AD model	[70]
	CRISPR/CBE mRNA	Synthetic exosome platform	APOE4-related targets	Precision genome editing	Experimental model	[71]
Enzyme and Protein	Neprilysin	MSC-derived exosomes	Amyloid-β	Enhanced Aβ degradation	Cell model	[72]
	Catalase	WJ-MSC exosomes	Oxidative stress	Reduced ROS-mediated injury	Experimental model	[73]
	Neurotrophic factors	MSC-derived exosomes	Neuroinflammation and neurodegeneration	Improved cognition and neuronal survival	AD models	[74-77]
	Tom40	Engineered exosomes	Mitochondrial dysfunction	Neuroprotection	Cellular model	[78]

Engineered Exosomes for Targeted Therapy

As exosomes naturally possess biocompatibility and low immunogenicity, and the ability to permeate many biological barriers (e.g., the blood-brain barrier, BBB), they are regarded as ideal carriers for targeted therapy [79-82]. Some exosome surface engineering strategies have been designed to increase exosome therapeutic performance and target specific tissues by using a ligand-receptor-mediated recognition mechanism to make strong interactions with target cells (Table 2) [83-85].

Genetic engineering

Of the techniques mentioned, genetic engineering is the most intensively studied. By expressing targeting peptides/proteins on the membrane of exosomes using genetically engineered donor cells, engineered exosomes with better targetability can be manufactured [86,87]. A lot of experiments revealed that the technique can function; for example, T7 peptide-modified exosomes for glioma targeting, curcumin-loaded exosomes functionalized with retinol-binding protein, RNA-delivery vehicles engineered with a fusion protein of CD9-HuR, tLyp-1-functionalized exosomes, and multivalent antibody-retargeted exosomes (SMARTExos) showed superior cellular targeting and therapeutic efficacy in animal models [79,88-96].

Chemical engineering

Alternative methods for exosome functionalization via the chemical modification of the exosomal membrane with covalent or noncovalent peptides, proteins, lipids, polymers, or aptamers are also demonstrated with chemical engineering approaches [97].

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Common chemical conjugation strategies include click chemistry, receptor-ligand recognition, electrostatics, and hydrophobic interactions [97]. Successfully targeting-improved methods were presented by cyclic RGD peptide [98], magnetic nanocrystal cluster [99], cationic lipid [100], heart-homing peptide [101], as well as an engineered exosome-liposome hybrid system [94,97,102,103].

Table 2: Engineering Strategies for Enhancing Exosome-Based Brain Delivery.

Engineering Strategy	Modification Method	Representative Example	Major Advantage	Main Limitation	Ref
Genetic engineering	T7 peptide display	T7-decorated exosomes	Enhanced BBB penetration	Scalability challenges	[94]
Genetic engineering	CD9–HuR fusion	RNA-loading exosomes	Efficient RNA encapsulation and delivery	Technical complexity	[95]
Genetic engineering	tLyp-1 functionalization	Targeted gene-delivery exosomes	Improved cellular uptake	Limited validation in CNS disorders	[96]
Genetic engineering	Multivalent antibody retargeting	SMARTExos	High targeting specificity	Manufacturing complexity	[88-92]
Chemical engineering	Click chemistry	Surface ligand conjugation	Flexible modification	Possible membrane alteration	[97]
Chemical engineering	RGD peptide decoration	Integrin-targeted exosomes	Improved receptor-mediated uptake	Limited tissue selectivity	[98]
Chemical engineering	Magnetic nanocrystal incorporation	Magnetically guided exosomes	Imaging and targeting capability	Additional complexity	[99]
Chemical engineering	Cationic lipid coating	Fusogenic exosomes	Enhanced intracellular release	Potential toxicity	[100]
Chemical engineering	Exosome–liposome hybridization	Hybrid nanovesicles	Increased loading capacity	Structural heterogeneity	[102,103]
Physical engineering	SPION incorporation	SPION-loaded exosomes	Magnetic guidance and theranostics	Specialized equipment required	[104]

Physical engineering

Furthermore, a physical modification strategy has also been developed to refine targeting and imaging capacity. Magnetic guidance and the tissue-specific accumulating ability and theranostic effect have been demonstrated after engineering SPIONs in the exosomes, which can be applicable for treating glioblastoma and diabetes [98,104]. All the strategies aforementioned make great efforts on the improvements in target-specific accumulation of exosomes.

However, many limitations restrict the application of engineered exosomes in clinical practice. Modifications should be carefully adjusted so that the vesicles would not aggregate, damage the structure, or lose biological function [104]. On the other hand, mass production, purification of modified exosomes from unmodified ones, and standardization of manufacturing procedures are still required to overcome these limitations [105-108]. Exosomes derived from different sources, containing different cargo and administered by various routes, have shown a variety of therapeutic effects, so standard operating processes are needed to overcome the variations and make use of therapeutic effects fully [107,108].

Besides surface modification techniques, exosomes are also largely exploited as promising nanocarriers for drug loading and transport against AD. The therapeutic compounds of various forms-small molecules, natural compounds, proteins, and nucleic acids-have been loaded into engineered exosomes, which can cross the BBB and effectively target brain tissues [61,78,109-112]. Exosomes have been found to be capable of inhibiting tau phosphorylation, reducing Aβ aggregate formation, modulating microglia activation, and reducing neuroinflammation.

Brain targeting mechanisms (natural + receptor-based + hybrid)

In addition to specificity targeting the brain, diverse engineering approaches have been successfully used to improve the delivery efficiency for nervous diseases. Factors including lipid composition and cell-binding surface molecules of the exosomes can determine the targeted delivery efficiency. Exosomal

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integrins, tetraspanins, and certain types of lipid can interact with brain microvascular endothelial cells (BMECs) and improve the translocation across the blood-brain barrier (BBB) [113-118]. Macrophage-derived exosomes interact with the C-type lectin receptor via the LFA-1 protein to enhance BBB permeation and uptake by the endothelial cell [114,118]. On the other hand, endothelial internalization efficiency and transendothelial transport were influenced by exosomal lipid content [113].

In addition to their composition, the cellular source of exosomes significantly influences their biodistribution and brain tropism. Exosomes produced from NSCs, brain endothelial cells, or astrocytes were proven to be delivered to the CNS more efficiently than exosomes from non-neural origin [119-123]. Importantly, MSC-derived exosomes also exhibit homing properties towards inflammatory sites in the brain and towards neurons. It was shown that after intranasal administration in AD mouse models, MSC-derived exosomes accumulated in the hippocampus, the region where neuronal loss is significant in AD patients [124]. These phenomena suggest that exosomes can home in on disease-specific molecular information in the pathological brain environment, thereby enabling more targeted therapy.

Given these natural targeting properties, there have been significant efforts to modify exosome surfaces with brain-targeting ligands to enable receptor-mediated endocytosis and BBB transcytosis. Transferrin-, neural cell adhesion molecule-, rabies virus glycoprotein (RVG) peptide-, and other target molecule-modified exosomes have been shown to promote brain accumulation and neuronal transport *in vivo* [125,126]. More recently, an approach combining the advantages of exosomes and artificial nanomaterial has emerged. The exosome-gold nanoparticle constructs and exosome-liposome hybrid nanoplatforms were designed to enhance BBB traversal efficiency and therapeutic efficacy in diseases model [127,128].

In summary, these combined effects, resulting from intrinsic bio-tropism, surface engineering with a receptor-mediated approach, and a hybrid nanotechnology-based strategy, have greatly improved the efficiency and accuracy of exosomes-mediated brain delivery. Therefore, these strategies are complementary and applicable for the development of a novel generation of exosome-based drugs against AD to deal with BBB-associated limitations.

Challenges and Limitations

Exosome-based AD treatment has made great strides, but there are still a lot of obstacles to overcome before it can be used clinically. One critical issue is the absence of standardized methods for the isolation, purification, characterization, and loading of exosomes, which results in remarkable disparity among studies. Another issue is that the exosome population is highly heterogeneous, with diversity depending on the donor cell source, culture conditions, and isolation methods. Quality control and reproducibility are then impeded. Another significant challenge is the scale-up of manufacturing, since the quantity of exosomes prepared by existing methods is insufficient for clinical applications and is difficult to make batch-to-batch uniform.

Although modification of exosomes enhances brain targeting efficiency, controlled and precise delivery of exosomes in the complicated brain microenvironment is still challenging. Surface modification can achieve better targeting specificity, but it may affect their inherent biological activity, biodistribution, and stability. Besides, the long-term safety, immunogenicity, and pharmacokinetics of multiple doses are not fully understood. In addition, other concerns include off-target effects, non-specific loading and distribution of the cargo, and difficulty with in vivo tracking.

More research is needed on developing a scalable manufacturing platform, universal quality-control guidelines, and new engineering designs that enhance targeting efficiency while maintaining biological function. A new generation of experimental models, such as organoids and humanized models of AD, might help discover novel mechanisms and improve the translation of the findings into clinical treatments.

Conclusion and Future Perspectives

Designing effective treatments for AD is currently one of the largest issues in medicine. Even though many approaches have been taken to target Amyloid beta aggregation, tau pathogenesis, inflammation and oxidation, drugs and therapies are often limited due to the complex and multifactorial nature of AD as well as the lack of drugs penetrating to the brain; therefore, exosomes, which are biologically friendly, possess native intercellular communication mechanisms, and can pass through the BBB, is a novel drug delivery system overcoming a key limitation in the central nervous system therapeutics.

Numerous studies have reported the successful delivery of various therapeutic cargo substances using exosome-based systems: these range from small-molecule drugs and nucleic acids to proteins, enzymes, and relatively new tools like gene editing technologies. It is crucial that exosome-based platforms can achieve concurrent regulation of multiple disease mechanisms associated with AD, such as amyloid protein deposition, hyperphosphorylated tau and subsequent protein aggregates, inflammatory responses, mitochondrial abnormalities, and impaired synapse function. Engineering of exosomes in recent times has greatly enhanced targeting capability, drug loading efficiency, and therapeutic outcomes by moving exosome technology from a naturally occurring extracellular vesicle system to a custom-designed nanomedicine platform tailored for specific diseases.

Even though there is such promise demonstrated from the preclinical research study, the translation of these preclinical findings into a useful clinical therapy has not been a simple

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journey. Present data have predominantly come from cell culture and animal models, and this still needs to be applied to AD patients to support a reliable therapeutic application. Several barriers have continuously been shown to block the translational pathway, such as the heterogeneity of exosomes, lack of standardized protocols for exosome isolation and characterization, inefficiency in cargo loading, poor scalability and variability, and insufficient data on long-term biodistribution and safety profiles. Moreover, it has not yet been sufficiently established whether donor cell type, production settings, or administration routes could impact the therapeutic effects.

Looking forward, the success of exosome therapeutics could be attributed to advancements in nanotechnology, synthetic biology, artificial intelligence-enabled design processes, and precision medicine. With the incorporation of gene editing techniques such as CRISPR technology, disease-specific targeting ligands, and theranostics into engineered exosomes, an approach where simultaneous diagnosis, therapy, and monitoring are possible for AD can be developed. Moreover, induced pluripotent stem cell engineering, brain organoids, organ-on-a-chip techniques, and humanized disease models may serve as more accurate predictors for assessing the safety and efficacy of potential treatments.

Another future avenue that warrants investigation and differs from enhancing BBB penetration would be to acquire cell-specific targeting ability to deliver drugs specifically to neurons, microglia, or astrocytes, or to a certain pathological niche within the complex AD brain microenvironment. Specific targeting to any one cell type or pathological region can thus have a beneficial impact while limiting off-target effects. Future research should also encompass comparative studies of exosomes with well-established nanocarriers such as liposomes and polymeric nanoparticles.

In summary, exosome-based drug delivery technology has rapidly evolved into a very promising field in the AD therapeutics area. While many scientific and translational issues still exist, development in exosome engineering, cargo design, and manufacturing processes has enabled us to explore a wide array of possibilities. Exosomes, being a type of biological nanovesicles, can become a viable precision-delivery system for AD treatment through careful mechanistic study, standardization, and clinical validation.

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