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Biomimetic Cell Membrane Vehicles: Navigating the Blood-Brain Barrier for Enhanced CNS Drug Delivery

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ABSTRACT

Disorders of the CNS, such as brain tumors, ischemic strokes, Alzheimer's, and Parkinson's disease, pose a significant risk to human well-being. The presence of the BBB further complicates the transportation of medications and the development of targeted drug delivery methods. In recent decades, considerable attention has been directed towards biomimetic vehicles derived from cell membranes, driven by the emergence of targeted drug delivery systems and biomimetic nanotechnology. Cell membranes are recognized as inherent multifunctional biomaterials, holding promise for the design and adaptation of targeted delivery strategies. The current conjunction of cell membranes and nanoparticles gives rise to biomimetic vehicles, offering fresh insights into BBB recognition, transportation, and efficient therapy. These vehicles leverage the diverse biological functions and strong biocompatibility of cell membranes, presenting a promising avenue for enhanced treatments. This article offers a summary of the current obstacles in achieving targeted delivery within the CNS and highlights recent progress made in utilizing various types of biomimetic vehicles derived from cell membranes for efficient CNS targeting. The discussion includes an exploration of the mechanisms involved in BBB targeting, in addition to an examination of the challenges and potential for clinical application. Ultimately, novel perspectives for advancement and development are also presented.

Keywords: Cell-based target drug delivery system, Central nervous system diseases, Biomimetic vehicles

1 INTRODUCTION

Addressing acute and chronic disorders of the CN, for instance, ischemic stroke, brain tumors, PD, AD and, continues to pose significant challenges and areas of concern. The brain, as the central component of the CNS, possesses intricate complexity, making achieving precise and targeted delivery for brain-related ailments an enduring challenge that researchers have strived to conquer. The BBB controls the boundary that separates the peripheral bloodstream and the CNS, safeguarding the brain's equilibrium by preventing harmful substances and blood cells from entering [1]. The BBB is a highly intricate and ever-changing structure that acts as a vital divide between the CNS and the circulatory system. It holds significant importance in advancing our knowledge of CNS functioning and conducting pharmacokinetic research [2]. This barrier consists of various cell types, as illustrated in Fig1. Because of the BBB's highly discerning entry process, it limits the intended therapeutic and diagnostic outcomes due to limited penetration capabilities and non-targeted dispersion upon systemic application. This presents hurdles in designing efficient drug delivery systems [3].

To circumvent the hindrance posed by the BBB and achieve successful treatment, invasive methods like neurosurgery and osmotic/biochemical approaches can be employed to either bypass or induce the opening of the BBB, enabling direct treatment of lesions. Nevertheless, this approach hinges on the utilization of manipulation methods and

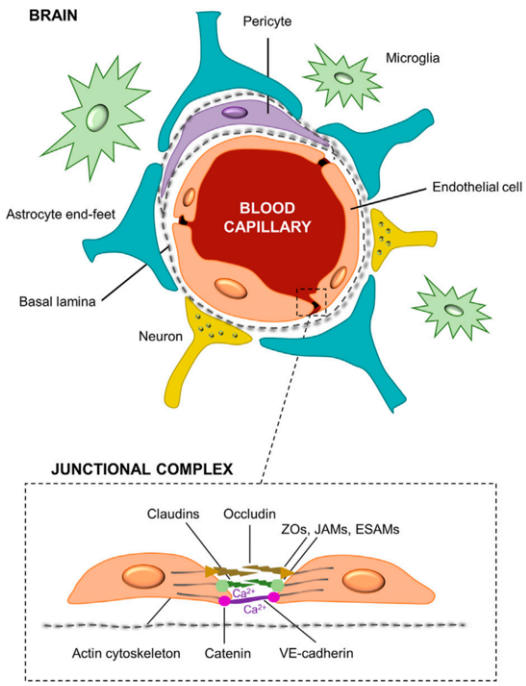

Fig. 1. A schematic representation of the blood-brain barrier (BBB) and its cellular components is provided. The BBB consists of capillary endothelial cells enclosed by a basement membrane, with astrocyte end-feet surrounding them. Additionally, it includes neurons, pericytes, and microglia cells. A close-up view of the interconnections between the brain endothelial cells, specifically the tight and adherens junctions known as the junctional complex, is depicted [4].

tools, which implies a potential reduction in therapeutic effectiveness and an elevated level of procedural risk for patients. Developing a targeted drug delivery system that is both non-invasive and effective could offer a solution to this issue [5]. In the prior studies, it was showcased the utilization of stem cells as carriers for delivering therapeutic agents aimed at treating CNS disorders. Stem cells possess the inherent ability to autonomously travel toward the vicinity of the ischemic stroke lesion and establish communication with damaged cells, thereby accomplishing precise targeting. Over time, cell membranes have come to be recognized as inherent and versatile biomaterials with multiple functions. As a result, a diverse range of cell membranes is utilized in the formulation of biomimetic vehicles. The vehicles based on cell membranes demonstrate effective targeting capabilities, underscoring their potential as carriers for drug delivery, which has become a focal point of research interest [6]. Biomimetic nanotechnology centered around cell membrane utilization capitalizes on the diverse biological functions of native cell membranes and engineered NPs. The advancements in biomimetic vehicles utilizing cell membranes herald a novel era in targeted drug delivery for the brain. Due to their homologous targeting ability after cell membrane integration, these biomimetic vehicles, based on cell membranes, enable improved interaction between foreign nanoparticles and the natural physiological environment. In earlier studies conducted by us, stem cell membranes were employed to create biomimetic vesicles based on stem cell membrane components [7]. Following the infusion of stem cell membranes, the bio-multifunctional element was integrated into biomimetic vesicles, leading to the successful targeting of inflamed brains and providing effective treatment in mice with ischemic models. By harnessing the inherent traits of cell membranes and advanced surface modification techniques, biomimetic vehicles based on cell membranes exhibit the desired capacity for brain targeting, exceptional specificity towards damaged cells, prolonged circulation within the body, reduced immune response, and enhanced biocompatibility. While natural cell membranes have already exhibited the capability for homologous targeting, there remains considerable potential for achieving more precise and exact targeting. Within this overview, we outlined the current obstacles related to targeting delivery to the CNS. Subsequently, we presented and contrasted various types of biomimetic vehicles based on cell membranes, designed to facilitate successful CNS targeting delivery. We also encapsulated the corresponding approaches to address the challenges inherent in achieving CNS target delivery using cell membrane-based biomimetic vehicles. Subsequently, a thorough examination was conducted regarding the benefits and the mechanism through which cell membrane-based vehicles target the BBB. Lastly, we provided a comprehensive survey of the progress made in CNS target delivery using these biomimetic vehicles based on cell membranes, along with

an outline of the forthcoming challenges and prospects in this field.

2 DELIVERY CHALLENGES FOR CNS TARGETING

2.1 *Identification of BBBs and intracellular transport*

The BBB functions as a concealed blockade, permitting only specific compounds to enter the brain. Generally, only molecules that are soluble in lipids and have a molecular weight ranging from 400 to 600 Da can traverse the TJ. Water-soluble compounds and larger macromolecules weighing more than 600 Da can access the brain via carrier-mediated transportation across the BBB . Consequently, the primary obstacle faced by delivery vehicles pertains to the constrained targeting precision and efficiency of transportation. The BBB contains BMECs, basement membranes, pericytes, and astrocyte end-feet. BMECs constitute the foundation of the BBB and hold a vital function in the establishment and upkeep of its structural integrity [8]. The inner part of the microvasculature contains BMECs. Consequently, the first stage in achieving BBB-targeted delivery upon systemic administration involves the recognition of BMECs. These cells stand apart from the peripheral microvascular endothelium due to their tight attachment, the formation of TJs, and minimal fenestrations and pinocytic vesicles. These characteristics pose challenges for the design of delivery vehicles [9]. Comprehending the attributes of the BBB, particularly the alterations and traits of BMECs, as well as understanding how the BBB functions and responds in different physical or pathological scenarios, can aid in identifying potential targets and facilitating the design of delivery systems. In order to enhance the effectiveness of BBB recognition and transportation, various strategies involving the transportation of molecules or proteins into the brain are employed for the design of BBB delivery systems. These strategies encompass carrier-mediated transport, receptor-mediated transport, and adsorptive-mediated transport. Although it has a low degree of selectivity, adsorption-mediated transport depends on electrostatic interactions between negatively charged BMECs and positively charged NPs. In contrast, receptor-mediated transport and carrier-mediated transport demonstrate improved identification capabilities through the incorporation of functional ligands [10]. Receptor-mediated transport within cells holds a crucial function in facilitating drug delivery across the BBB. Distinct receptors are necessary for enabling the passage of macromolecules sized between 200 and 500 nm through the BBB [11]. Following endocytosis, a vesicle for intracellular transport, bound by the cellular membrane, is formed. This process entails the invagination of the cellular membrane around the cluster of ligand-receptor complexes, leading to the encapsulation of this cluster. Subsequently, the cargo-laden vesicle traverses through the intracellular space, moving within the cytoplasm towards the opposing region of the BMECs membrane, where it ultimately merges with the membrane surface. Then, the ligand and receptor separate, allowing the receptor to be recycled to the apical membrane or the lysosome while simultaneously releasing the cargo into the brain parenchyma [3]. Contemporary investigations have suggested that receptor-mediated transport tends to preferentially route toward lysosomes, leading to an entrapment phenomenon within the BMECs. Developing strategies to avoid or reduce the trafficking of delivery vehicles to alternative locations, especially lysosomes, is essential for improving BBB transport efficiency [12].

2.2 *Diseased cell targeting and internalization*

A challenge in targeted drug delivery is the undefined spread of substances within the brain [13]. The brain, a complex organ with distinct segments, oversees diverse physiological functions through its various divisions. When dealing with drug delivery and managing CNS disorders, it's crucial to minimize the impact and undesirable outcomes of drugs on healthy brain areas. This underscores the importance of enhancing the accuracy of drug delivery in targeted approaches. Consequently, an optimal delivery system should not solely have the ability to traverse the BBB, but should also accomplish precise targeting of damaged or affected cells within the brain tissue. Over the course of many years, nano-sized delivery systems such as polymeric nanocarriers, liposomes, micelles, dendrimers, and other nanoparticles have showcased the utility of carrier-assisted transportation in facilitating drug conveyance to the brain [14]. To achieve precise targeting of damaged or affected cells, a range of functional ligands or components have been integrated into delivery vehicles. These include substances like low-density lipoprotein, insulin, and transferrin [15]. In order to attain a heightened level of specificity when directing these vehicles towards injured or diseased cells, a comprehensive understanding of the underlying pathological and pathogenic traits of various brain disorders is imperative, given that the targets may vary across different brain diseases. The internalization of injured or diseased cells follows a mechanism akin to the transport seen in BMECs. This process involves endocytosis, encompassing various pathways such as caveolae-mediated endocytosis, clathrin-mediated endocytosis, micropinocytosis, receptor-mediated endocytosis, and other endocytic routes unrelated to clathrin and caveolae [16]. In contrast to the transport in BMECs, the objective of internalizing injured or diseased cells is to enhance the delivery of therapeutic agents into these compromised cells. Therefore, gaining insight into the factors influencing the effectiveness of receptor-mediated endocytosis will play a pivotal role in refining the internalization of brain-targeted delivery vesicles into injured or diseased cells [3].

2.3 *Intracellular drug release*

Numerous medicines, including nucleic acids, proteins, and small molecular factors, need to be liberated as unbound pharmaceuticals within specific subcellular regions, typically the nucleus or cytoplasm of the afflicted cell, in order to elicit healing outcomes [17]. Even though delivery vehicles equipped with ligands can notably enhance the absorption of drugs by injured or diseased cells, insufficient drug concentrations can still arise due to several hurdles. These obstacles encompass challenges like inadequate drug liberation, a membrane-related mechanism fostering multidrug resistance, and impediments in delivering substances to subcellular sections [18].

3 BIOMIMETIC VEHICLES BASED ON CELL MEMBRANES

Cell membranes are the building blocks of cells and have innate, natural characteristics. The integration of cell membranes with synthetic nanoparticles has garnered significant interest, functioning as initial cells for transporting agents to specific targets [19]. Whether using individual cell membranes or combining hybrid cell membranes, it becomes possible to imbue biomimetic carriers with the versatile attributes of cell membranes. These cell membrane-based biomimetic delivery systems combine the beneficial physicochemical characteristics of artificial nanoparticles with the complex biological functions of cell membranes. The advancement of biomimetic delivery systems based on cell membranes could offer a promising solution to tackle the challenge of constrained brain-targeted delivery. This is due to their ability to provide distinct brain-targeting capabilities, improved penetration, and enhanced transcytosis potential. However, this modification approach also brings forth challenges related to production, low output, stability, and prolonged manufacturing duration. Consequently, these issues raise concerns about the costs and the duration of progress in this avenue [20].

3.1 *Various types of biomimetic vehicles based on cell membranes*

The advancement of biomimetic delivery systems based on cell membranes could offer a promising solution to tackle the challenge of constrained brain-targeted delivery. This is as a result of their specific capacity to target the brain, greater penetration, and improved transcytosis potential. However, this modification approach also brings forth challenges related to production, low output, stability, and prolonged manufacturing duration. Consequently, these issues raise concerns about the costs and the duration of progress in this avenue [20]. Based on the variations in synthetic nanoparticles, the biomimetic carriers originating from cell membranes can be categorized into distinct types, as illustrated in Fig.2. The initial category includes erythrocyte ghosts . While such unaltered or modified vesicles derived from cell membranes offer the benefits of their source cells, they do come with certain restrictions regarding drug loading and delivery. Zhang and colleagues were the first to employ erythrocyte membranes in combination with PLGA nanoparticles to create cell membrane-coated nanoparticles, which has since become the most prevalent variant of cell membrane-based biomimetic carriers [21]. With increased investments, the range of options for selecting cell membranes and synthetic cores has significantly broadened [22]. This approach is akin to assembling a puzzle, where the rearrangement of distinct components can create novel delivery systems. Various types of cell membranes, such as those from stem cells, cancer cells, immune cells, among others, have been combined with nano-sized delivery carriers like polymer nanoparticles, gold nanoparticles, iron nanoparticles, and more, in the formulation of biomimetic vehicles [23].

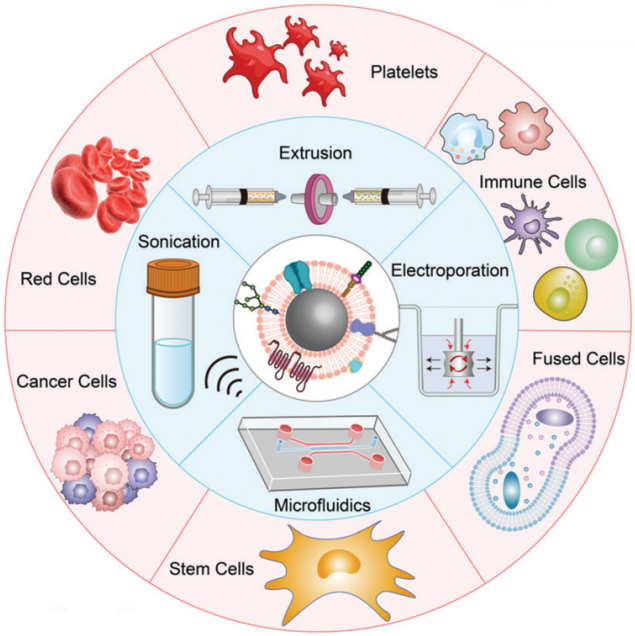

Fig. 2. Method for creating biomimetic vehicles using cell membranes: To create biomimetic vehicles, the first step involves obtaining isolated and purified cell membranes. This can be achieved through methods such as hypotonic treatment, repeated freezing and thawing, or ultrasonic cell disruption. Once the cell membranes are prepared, they are applied onto synthetic nanoparticles using various techniques like physical co-extrusion, sonication, or microfluidic electroporation [24].

Simultaneously, the integration of hybrid cell membranes imparts augmented capabilities to the biomimetic carriers [25]. Nevertheless, the technique of cell membrane coating is better suited for nanoparticles possessing robust mechanical properties. In the case of liposomes, which belong to nanoparticles with lower mechanical power, the recent studies have involved infusing them with stem cell membranes to produce biomimetic vesicles. Importantly,

exclusively negatively charged nanoparticles can undergo coating, as any other type would lead to the creation of a conglomerate of cross-linked material [6]. In contrast, positively charged liposomes possess the capability to encapsulate stem cell membranes, thereby circumventing the charge-related constraints associated with cell membrane coating technology. This approach empowers liposomes to undergo multifaceted biological modifications, enhancing their affinity for damaged cells and enabling greater flexibility in traversing biological barriers.

3.2 Methods to construct cell membrane-based biomimetic vehicles

There are two different methods for developing cell membrane-based biomimetic carriers. One approach capitalizes on the excretory capability of viable cells [17]. In this situation, living cells serve as "special aircraft carriers" [26]. Post nanoparticle incubation, extracellular vesicles containing nanoparticles are released. The membrane constituents coated through this process diverge from typical cell membrane components and instead closely resemble those of extracellular vesicle membranes. The alternative approach involves an artificial strategy and encompasses the development of three primary techniques [17]. Drawing inspiration from liposome formulation, the initial technique involves physical co-extrusion, which is a widely employed method. In order to create consistent and durable biomimetic carriers formed from cell membranes, cell membranes and nanoparticles are essentially suspended within the same dilution buffer and then subjected to reciprocal squeezing via a polycarbonate membrane. However, this method's practical application is restricted due to issues of low output and the labor-intensive nature of the process. At the laboratory level, the ultrasonic method gains popularity [27]. The process closely resembles the co-extrusion technique. Through ultrasonication treatment, strength is applied to disrupt the integrity of cell membranes, causing cell membrane chips to adhere onto NPs in a haphazard manner, or to become integrated with phospholipids. This method is simple to execute, demands minimal equipment, and utilizes fewer materials, resulting in lower costs [28]. In contrast to the co-extrusion approach, ultrasonication generates a more substantial force that can potentially cause structural harm to self-assembling nanoparticles or other nanoparticles possessing weaker mechanical attributes. Currently, particularly within the realm of cell membrane coating technology, the ultrasonic technique is better suited for nanoparticles exhibiting robust mechanical properties, exemplified by metallic NPs or PLGA NPs. The co-extrusion technique is utilized to modify nanoparticles possessing weaker mechanical attributes with biomimetic elements. A prior research indicated the advantages of both cell membrane infusion and phospholipid integration methods [7]. More recent endeavors highlight the utilization of microfluidic and electroporation techniques to enhance the coating of erythrocyte and exosome membranes [29]. However, the applicability of microfluidic-based coating technology is confined to specific laboratories, primarily due to the technical limitations associated with designing microfluidic chips and the demanding equipment requirements, making it challenging to be widely adopted.

4 VARIOUS CELL MEMBRANE-BASED BIOMIMETIC VEHICLES FOR CNS TARGETS

4.1 Biomimetic vehicles based on RBC membranes

Among the various cell types in the human body, RBCs are notably plentiful. Due to their ready availability and immunogenic properties, erythrocytes have developed into a robust field of biomedical study [30]. In comparison to other cell varieties, RBCs possess a relatively straightforward nature, and their membranes are also relatively uncomplicated. This simplicity offers prospects for functional adaptations. The utilization of RBC membrane-based biomimetic carriers has significantly advanced in the exploration of efficient CNS-targeted delivery and the modification of vehicle functions [31]. Erythrocytes lack inherent brain-targeting capabilities, thus utilizing erythrocyte membrane vehicles for CNS targeting necessitates the incorporation of targeting elements [32]. Through methods such as the incorporation of lipid molecules or the interaction of avidin and biotin, targeting moieties are introduced into the RBC membrane, thus equipping the RBC membrane with the skill to target the brain [33]. These targeted alterations primarily focus on BMECs with the intention of augmenting recognition, uptake, and transportation by impaired BMECs. Some studies have concentrated on creating actively targeted RBC membrane-based carriers that are adorned with specific targeting ligands or peptides [34]. The erythrocyte membranes have been embellished with various compounds, including transferrin, the CDX peptide, a virus polypeptide modified with 29 amino acids, the angiopep-2 peptide, ApoE, a specifically designed peptide for homing to stroke sites, and the c(RGDyK) peptide [14]. These additions confer heightened affinity for CNS disorder lesions such as glioblastoma, glioma, stroke, AD, and PD. The stroke-targeting peptide, specially designed for this purpose, altered the RBC membrane carriers by introducing lipids, thereby granting them the capability to target. In the presence of 1 mM H2O2, the release of NR2B9C was achieved through a ROS-responsive boronic ester, with a cumulative release of 50% [35].

4.2 Membrane-based biomimetic vehicles based on stem cells

Due to their propensity for differentiation, minimal immunogenicity, and capacity for self-renewal, stem cells occupy a special place within cell-based delivery systems. The ongoing endeavors have consistently highlighted the

positive therapeutic outcomes achieved through recombinant NSCs and MSCs, both administered systemically and implanted locally, in the context of ischemic stroke, glioma, and spinal cord injury [36]. The stem cells' propensity to home in on areas of inflammation is attributed to their homing ability, which hinges on the interplay between receptors on stem cells and the corresponding ligands expressed in ischemic regions, with a particular focus on the SDF-1/CXCR4 axis [37]. As the field of cell membrane-based biomimetic carriers progresses, the inclusion of MSC membrane and NSC membrane has been embraced in the formulation of stem cell membrane-derived biomimetic vehicles [38]. Following hypotonic treatment, fragments of the MSC membrane are extracted and integrated with empty liposomes, resulting in the creation of MSC-Lipo, designed for targeting the ischemic brain region. The biomimetic carriers derived from MSC membranes exhibited stronger attraction to activated microglia and induced a transformation of M1-type microglia to M2-type. Particularly, upon loading with curcumin and employing targeted delivery, a substantial improvement in the survival rate following middle cerebral artery occlusion was observed. Under acidic conditions, the MSC-Lipo formulation displayed an enhanced tendency to integrate, leading to a more rapid release of the drug. This suggests that its internalization into cells could potentially enable swift drug release within the acidic environment of lysosomes.

A similar outcome was noted with the neural stem cell-based biomimetic carriers. Upon integrating the NSC membrane, the VLA-4 molecule was introduced into the NSC membrane-derived biomimetic carriers (NSC-Lipo), equipping them with distinct identification capabilities for damaged BMECs through the interaction of VCAM-1/VLA-4. Additionally, the investigators observed that by upregulating CXCR4 expression on the NSC membrane, the capacity for targeting ischemic areas was concurrently enhanced. Consequently, Ma and colleagues encapsulated PLGA nanoparticles with NSC membranes featuring an overexpression of CXCR4, resulting in a notable therapeutic impact of glyburide in an ischemic mouse type [38]. Concurrently, the NSC membrane modified with the RVG peptide was employed to coat PLGA nanoparticles, facilitating targeted delivery in an AD model [39].

4.3 Biomimetic vehicles based on immune cell membranes

The innate immune response is triggered by immune system cells that autonomously move to areas of injury and cause inflammation, including neutrophils, macrophages, dendritic cells, and natural killer cells [40]. Therefore, due to the inherent propensity of immune cells to gravitate toward areas of inflammation through diverse interactions, recent investigations concerning brain tumors and inflammatory encephalopathies have underscored the substantial promise of immune cell membrane-derived biomimetic carriers for targeted drug delivery. Macrophages play a role in distinct stages of inflammation and are present in diverse CNS disorders [41].

Various chemokine receptors, such as CCL2 and CXCR4, are responsible for attracting macrophages to sites of damage [42]. Hence, derived from monocytes, macrophages have been employed for drug delivery targeting CNS diseases. Without impairing their intrinsic predisposition for inflammatory targeting, macrophage membranes and the related membrane proteins might be rebuilt into vesicles. Gao and colleagues formulated ROS-responsive biomimetic carriers by coating them with macrophage membranes, specifically designed for atherosclerosis therapy [43]. Research has showcased that the utilization of macrophage membranes can not only enhance the directed transport of nanoparticles and their cargo to the afflicted region but also serve as a means of scavenging proinflammatory agents. Long and colleagues, for instance, integrated naïve macrophage membranes onto baicalin-loaded liposomes. This modification led to macrophage membrane-coated liposomes exhibiting heightened capability for targeting the brain [44].

The amalgamation of macrophage membranes and chemodynamic therapy facilitated both T1-weighted MR imaging-guided traversal of the blood-brain barrier and precise targeting of gliomas. This approach demonstrated notable therapeutic efficacy in mouse glioma models. The synthetic core's disulfide link allowed the biomimetic macrophage membrane carriers to achieve pH- and redox-responsive drug release [45]. Apart from unmodified macrophage membranes, modified membranes featuring ligands are also incorporated in the formulation of cell membrane-based biomimetic carriers. Analogous to the approach used with RBC membranes, RVG29 and TPP peptides are introduced into macrophage membranes through lipid conjugation and insertion [46]. The adapted biomimetic carriers using modified macrophage membranes exhibit the ability to amass within the brain affected by AD. Moreover, macrophage membrane vesicles that have been pre-treated can redirect microglia towards either pro-inflammatory or anti-inflammatory phenotypes, holding potential as prospective delivery platforms for the treatment of strokes [47]. During instances of brain inflammation, activated neutrophils from the peripheral blood are mobilized to the vicinity of the lesion. They attach to damaged BMECs through interactions involving membrane-adherent proteins, enabling them to cross the BBB. This phenomenon is particularly pronounced in the context of ischemic stroke, where intense inflammation results in substantial alterations in the structure and expression of surface proteins on BMECs. Hence, employing neutrophil membranes to fabricate biomimetic delivery carriers allows for the utilization of adherent protein interactions to achieve precise targeting. Neutrophil-derived vesicles are utilized in loading Resolvin D2 for ischemic stroke therapy [48]. Notably, neutrophil-derived vesicles demonstrate the ability to dynamically adhere to inflamed brain vasculature. However, the underlying mechanism

governing this adhesion and targeting process remains a subject of investigation. By coating neutrophil membranes onto Prussian blue nanozyme, a potent anti-inflammatory effect is achieved, effectively steering activated microglia towards an M2 phenotype [49].

4.4 Platelet membrane-based biomimetic vehicles

Apart from their function in promoting hemostasis following vascular damage, platelets play pivotal roles in wound healing, inflammatory responses, and thrombosis. A particularly promising therapeutic approach for CNS disorders, particularly in ischemic stroke treatment, involves utilizing platelet membranes and platelet membrane-based biomimetic carriers. This is owing to the natural tendency of circulating platelets to be attracted to injured blood vessels. Leveraging the inherent capacity of platelets to adhere to injured vessels, Li and colleagues devised nanobubbles based on platelet membranes for acute ischemic stroke theragnostic purposes [50]. These nanobubbles have the ability to generate ultrasound-enhanced signals, facilitating the assessment of infarction size, location, and vascular distribution. Drawing inspiration from the functions of platelets in thrombus formation and the development of ischemic penumbra, Xu and co-workers devised biomimetic carriers based on platelet membranes. These carriers were engineered to encapsulate rtPA and the neuroprotective compound ZL006e, presenting a therapeutic strategy for ischemic stroke treatment. The biofabricated "nanoplatelet" accomplishes both targeted thrombolysis and concurrent neuroprotection. The cleavable peptide linker initiates the release of rtPA, and it was observed that this release was influenced by thrombin concentration, resulting in an accelerated release rate of up to 82.1%. The utilization of biomimetic carriers based on platelet membranes for stroke treatment offers advantages beyond improved circulation retention, stemming from its inherent biological activity [51].

4.5 Cancer cell membrane-based biomimetic vehicles

The approach of utilizing biomimetic carriers based on cancer cell membranes primarily capitalizes on the inherent resemblance of cancer cells, making it particularly suitable for treating malignant glioblastoma. Nanoparticles incorporating components from natural cancer cell membranes facilitate over-targeting of tumor cells through self-recognition of the cancer's origin, leading to selective internalization. This holds the potential to mitigate side effects on normal cells [52]. The capacity to establish homotypic bonds relies on a range of membrane proteins, such as tissue factor-antigen, galectin-3, and E-cadherin, which inherently collaborate. On a global scale, malignant glioblastoma multiforme stands as the most lethal primary cancer of the CNS in both adults and children [53]. As a result, the strategy of biomimetic delivery using cancer cell membranes primarily centers on the treatment of malignant glioblastoma. The interaction of cancer cell membrane-based biomimetic carriers with target cells is primarily contingent upon specific membrane proteins [54]. Han and collaborators, for instance, enveloped PEI25k/pDNA complexes with glioblastoma cell membranes, leading to heightened HSVtk expression and an increased anti-tumor effect in a rat model of glioblastoma [55]. Through the integration of nanosuspensions with C6 cancer cell membranes, these nanosuspensions acquired homologous adhesion capabilities and immune evasion properties [56]. In a similar vein, the adoption of C6 cell membranes served to camouflage the nanosuspension loaded with 10-hydroxycamptothecin, effectively leading to substantial accumulation at glioma sites [57]. In the broader context of targeting modification and employing cell membrane-based biomimetic carriers, targeting peptides for the BBB and BBTB are utilized to enhance the targeting and penetration ability of the BBB/BBTB. The Asn-Gly-Arg peptide, for instance, exhibits specific affinity for neovascular endothelial cells, facilitating the passage of cancer cell membrane-based biomimetic carriers through the BBTB [58]. Integrin-directed targeting aids in the traversal of the BBTB by the delivery carriers [59]. Duan and colleagues, for instance, engineered cancer cell membranes with cyclic RGD peptide. This achievement becomes feasible by incorporating nanomaterials into the intricate microenvironment of malignant glioblastoma [60].

4.6 Hybrid cell membrane-based biomimetic vehicles

While modifying ligands or peptides can introduce additional functionalities or enhance their original functions, certain challenges persist. These challenges encompass aspects like the effectiveness of the modification process, the alignment of ligands, and their distribution within the structure. To address these challenges, hybrid cell membranes have been developed. These membranes naturally combine two or three types of cell membranes, aiming to mitigate the aforementioned issues [61]. Through the fusion of distinct functional membranes from various cells, the amalgamation of inherent characteristics was enhanced, concurrently advancing the utilization of vehicles featuring complex surface modification chemistry. In contrast, the erythrocyte membrane is comparatively uncomplicated. Hence, the erythrocyte membrane serves as the foundational material for infusion with lipid membranes or other cellular membranes, encompassing both artificial lipid membranes and membranes from entities like cancer cells, neutrophils, and platelets [14]. Leveraging the enduring circulatory traits of red blood cells, the resulting hybrid membrane biomimetic delivery system gains fresh functionalities like immune activation and targeted inflammation response. Furthermore, variations such as

Table 1. Methods for extracting various types of cell membranes and their distinctive attributes and constraints.

Cell	Separation method	Properties	Limitations
Erythrocyte	Hypotonicity, Extrusion, freeze thaw, and ultrasound	Long circulatory lifespan (∼120 days in humans and ∼50 days in mice) and wide circulation range. Good biocompatibility, biodegradability, and non-immunogenicity. Uniform in size and shape, with a good surface area to volume ratio, without organelles and any DNA. Easy availability.	Poor targeting ability.
Leukocyte	Hypotonicity and extrusion	High loading capacity. Adhesion capacity. Migratory and chemotactic capacity in disease states.	Organization residency limitations.
Cancer cell	Dounce homogenizer and Extrusion	Strong homologous targeting ability.	Homologous tumor targeting.
Macrophage	Hypotonicity and extrusion	Innate immune evasion ability. Long circulation ability in vivo. Good targeting ability to AD lesions.	Organization residency limitations.
Platelet	Hypotonicity, extrusion, freeze thaw, and ultrasound	Lower immunogenicity. High targeting efficiency. Targeting to plaque. Controlled drug release. Long systemic circulation (around 7–10 days).	

the hybrid neutrophil-macrophage membrane, cancer cell-platelet membrane, platelet–leukocyte membrane, and cancer cell-bacterial outer membrane find application in the formulation and drug delivery of biomimetic vehicles [62]. Much like the cancer cell membrane, recent studies involving hybrid cell membranes designed for targeted delivery to the central nervous system have primarily focused on treating brain tumors. Jiao and colleagues, for instance, developed mesoporous silica nanoparticles camouflaged with a hybrid membrane derived from a combination of erythrocytes and cancer cells. This approach successfully led to the treatment of gliomas [63].

4.7 *Evaluation of diverse types of biomimetic carriers derived from cell membranes for targeted drug delivery to the CNS*

Across various CNS disorders, biomimetic vehicles based on cell membranes exhibit notable efficiency in targeting and delivering treatments. Owing to the distinct characteristics of these cell membranes, each biomimetic vehicle of this nature possesses specific strengths and downsides, as exemplified in Table 1. Platelet membranes are well-suited for targeting thrombi, while cancer membranes are utilized for targeting gliomas [63]. Although erythrocytes are abundant, they necessitate modifications to facilitate targeting, thereby augmenting the challenges in quality control during preparation and inflating the costs associated with their production and storage. The inherent inflammation-targeting ability of sourced cells is preserved in the membranes of stem cells and immune cells. These cell membranes possess innate capabilities for natural lesion targeting and traversing the BBB, making them appropriate for crafting biomimetic vehicles designed for CNS targeting [64]. When contrasted with immune cells, the reduced immunogenicity and the ability for significant in vitro expansion of stem cells establish a foundation for potential commercial manufacturing. Nevertheless, it's important not to overlook the challenges posed by costly in vitro cell cultivation and intricate cell membrane proteins, which introduce difficulties in storage and the scalability of production.

4.8 *Drug loading and release profile of cell membrane-based biomimetic vehicles*

Both the central components of nanoparticles and the structures resembling vesicles offer promise in drug delivery through biomimetic vehicles based on cell membranes. Presently, small-molecule chemical drugs represent the primary cargo. However, there is a scarcity of documented instances concerning the transportation of larger biomacromolecule drugs like nucleic acids for CNS therapy [55]. Simultaneously, nucleic acid-loaded polymers formed through self-assembly or structures devoid of vesicles are frequently opted for when considering the transport and release of nucleic acid drugs [65].

Facilitating drug release poses a significant hurdle in targeted drug delivery to the CNS. Currently, the release of drugs from biomimetic vehicles reliant on cell membranes hinges on the breakdown of the delivery structures. The integration of cell membranes can contribute to a certain degree of controlled drug release [25]. Achieving responsive drug release, such as in response to ROS or changes

in pH, continues to depend on various types of connectors [46]. In the context of nucleic acid release, the utilization of RNase H digestion aided in the release of miR155 from nanoparticulate carriers. The process of nucleic acid release through cell membranes remains enigmatic and could potentially involve the fusion and breakdown of cell membranes within acidic surroundings [7].

5 TARGET MECHANISM OF CELL MEMBRANE-BASED BIOMIMETIC VEHICLES

The integrity of the BBB can undergo rapid shifts, and its disruption is a dynamic procedure, particularly in acute conditions such as ischemic stroke and glioblastoma [66]. Yet, in the context of chronic encephalopathies like AD, Huntington's disease, and Parkinson's disease, alterations in BBB integrity unfold gradually and lack distinct targets showing notable fluctuations [67]. This scenario also presents challenges in the development of targeted delivery systems. Following injury or disruption of BBB integrity, cells—especially immune cells and stem cells—are activated and attracted to the site of the lesion. Upon systemic introduction, cells are mobilized toward the vicinity of the lesion by following the gradient of chemokine concentrations. These recruited cells subsequently undergo deformation to traverse the gaps between endothelial cells and access the brain tissue [68]. This process relies on several receptor-ligand interactions to accomplish the arrest phase and transition into a high-affinity conformation for improved deformation. Moreover, cells secrete matrix metalloproteinases that facilitate the breakdown of the basement membrane and extracellular matrix, culminating in the traversal of the BBB and penetration into the brain via compromised tight junction fenestration [69]. In contrast to cells, the mechanism by which cell membrane-based biomimetic vehicles reach the site of the lesion remains a puzzling enigma. Given that these vehicles lack the ability to perceive fluctuations in chemokine concentrations, their transportation and eventual arrival at lesions may largely involve a process of passive conveyance subsequent to systemic administration. The disruption of BBB integrity results in a marked increase in pinocytotic vesicles within BMECs. In BMECs that have sustained injury, the average count of pinocytotic vesicles rises to 25, and these vesicles range in size from 70 nm to 200 nm [70]. Concurrently, the ability of damaged BMECs to engage in phagocytosis and transcytosis is heightened. In this context, exogenous elements encompassing molecules and ions are more prone to infiltrate the brain by exploiting the fenestration and transcytosis of compromised BMECs, rather than relying on the compromised tight junctions for entry [71]. Recent studies have revealed that the predominant routes for cell membrane-based biomimetic vehicles to cross the BBB involve the endocytosis and transportation processes of compromised BMECs. Interestingly, it was noted that even when the BBB was temporarily made permeable through the application of hypertonic solutions, these vehicles still couldn't successfully traverse the barrier. Hence, the processes of recruitment, cell identification, intracellular conveyance, and BBB penetration might be governed by distinct mechanisms. Currently, investigations into the brain-targeting mechanisms of cell membrane-based biomimetic vehicles primarily center around BMECs recognition, transportation, and refined targeting of cells in altered or diseased states. While erythrocytes are commonly employed for crafting cell membrane-based biomimetic vehicles, they inherently lack brain-targeting capabilities. Therefore, achieving CNS targeting with erythrocyte membrane-based vehicles relies on the introduction of targeting components through modifications [32]. The targeting proficiency of various cell types, notably immune cells and stem cells, relies on their inherent systemic homing capability, a process involving tethering and rolling, activation, arrest, and transendothelial migration. By incorporating nanoparticles through coating or infusion, this homing capacity is transferred to cell membrane-based biomimetic vehicles. The CXCR4/ SDF1 signaling axis plays a pivotal role in guiding the trafficking and recruitment of both stem cells and leukocytes. Recent studies have indicated that when the expression of the CXCR4 protein on the surface of MSCs is heightened and subsequently integrated into cell membrane-based biomimetic vehicles, their capacity for brain targeting is also augmented in a mouse model of MCAO [72]. Once the CXCR4 and SDF1 molecules come into contact on the cellular membrane, cell movement hinges on intracellular signal transmission and protein synthesis. The CXCR4/SDF1 signaling axis is governed by the activation of G proteins, as well as the AKT, ERK, and JAK-STAT signaling pathways [73]. However, despite the overexpression of CXCR4 on cell membrane-based biomimetic vehicles, the internal cellular process remains incomplete. As a result, there is still a need for further exploration into the intricacies of its targeting mechanism. Divergent from cells, cell membrane-based biomimetic vehicles possess dimensions in the nanometer range. Unlike the mechanism governing the migration of endothelial cells across the BBB, the process through which cell membrane-based biomimetic vehicles traverse the BBB leans more toward endothelial cell transportation. Certain investigations have indicated that this progression relies on the recognition, internalization, and transportation by compromised BMECs [49]. Adhesive molecules such as ICAM-1 and VCAM-1 experience heightened expression on compromised BMECs, offering a prospective targeting site for an inflamed BBB.

Consequently, relevant ligands like integrin $\alpha v\beta 1$ are employed to augment the affinity for injured BMECs [74]. Stem cell membranes intrinsically display VLA-4, which serves as VCAM-1's ligand. As a result, when the stem cell membrane combines with liposomes to produce a targeted delivery vehicle, VLA-4 is also integrated into the construct. In a study by Wu et al., it was demonstrated that

biomimetic vehicles based on stem cell membranes exhibited the capability to bind to VCAM-1 and demonstrated a strong affinity for damaged BMECs [7]. This observation leads to the speculation that the interaction between VCAM-1 and VLA-4 serves as a crucial pathway for brain targeting by cell membrane-based biomimetic vehicles. A similar pattern emerged in a recent research: when the interaction between VCAM-1 and VLA-4 was disrupted, the accumulation of biomimetic vehicles based on stem cell membranes in the ischemic cerebral region ceased to occur [75]. Presently, the passage of cell membrane-based biomimetic vehicles across the BBB tends to occur primarily via endothelial cell transportation, rather than relying on the fenestration of compromised tight junctions . In order to gain deeper understanding of the potential mechanism governing the BBB passage during nanoparticle-mediated drug delivery, several investigations have indicated that clathrin-mediated endocytosis serves as a primary route for nanoparticles sized below 200 nm. In non-inflammatory conditions, stem cell membrane-based vehicles are internalized via clathrin-mediated endocytosis.

Nevertheless, following an inflammatory injury, micropinocytosis becomes the prevailing mode of BMECs endocytosis. It was speculated that this phenomenon might be linked to the specific recognition of the VCAM-1 protein, as stem cell membrane-based vehicles appeared more inclined to aggregate on the surface of injured BMECs. However, it must be acknowledged that whether this occurrence is a shared trait among various cell membrane-based vehicles or an exclusive capability exclusive to carriers based on stem cell membranes remains uncertain. Moreover, there remains a noticeable gap in the understanding of the precise mechanisms governing the endocytosis of cell membrane-based vehicle carriers. Nonetheless, this underscores the importance of recognizing that the intracellular destiny of cell membrane-based vehicles diverges from that of nanocarriers of similar dimensions and cannot be generalized. Undoubtedly, the mechanism behind the brain targeting of cell membrane-based biomimetic vehicles remains largely unexplored and necessitates further investigation. Approaches to studying this targeting mechanism are still in their preliminary stages. Many of the current research methods and concepts draw inspiration from the investigation of synthetic nano-delivery vehicles targeting the BBB, often overlooking the biological traits and functions inherent to incorporated cell membranes. These biomimetic vehicles based on cell membranes bear some resemblance to exosomes. Hence, exploring the strategies employed to understand how exosomes traverse the BBB could offer valuable insights for comprehending the mechanisms underpinning cell membrane-based biomimetic vehicle behavior.

6 PROSPECTS IN THE DEVELOPMENT OF BIOMIMETIC VEHICLES BASED ON CELL MEMBRANES

Drawing inspiration from cell membranes, biomimetic vehicles founded on cell membranes inherit inherent attributes such as innate inflammation targeting capabilities and immune evasion. By implementing a range of functional modifications, these delivery platforms can potentially attain targeted delivery, extended circulation periods, and biological compatibility while minimizing notable side effects. Recent endeavors have showcased that this top-down approach streamlines the functional enhancement of synthetic nanoscale delivery vehicles. Nevertheless, the progression of cell membrane-based biomimetic vehicles from laboratory settings to clinical utilization encounters distinct challenges compared to synthetic nanoscale delivery vehicles. This discrepancy arises from the biological complexity of cell membranes and the constraints posed by technical limitations [76]. Numerous hurdles hinder the transition from laboratory research to clinical application, encompassing challenges related to large-scale production, criteria for maintaining consistency, storage stability, and the assessment of biological effectiveness and safety. Primarily, the matter of large-scale manufacturing methods and the establishment of consistent rating criteria poses a bottleneck for clinical translation. On one hand, the substantial generation of cell membrane-based biomimetic vehicles is a pivotal prerequisite for their integration into biomedical applications. However, the existing techniques like mechanical coextrusion and sonication are confined to laboratory-scale operations [77]. When contemplating practical application, laboratory techniques frequently lack scalability and must be tailored to conform with industrial standards. Simultaneously, there is an imperative need to discover standardized and efficient methodologies for the isolation, purification, and integration of cell membranes with synthetic nanoparticles [78]. As the cornerstone material, cell membranes can be conveniently sourced and utilized on a laboratory scale. However, as production scales up, the efficient procurement and preservation of cell membranes become pressing concerns. Strategies such as cryopreservation of cells and the extraction of cell membranes at the point of utilization for carrier preparation might aid in achieving improved cell membrane storage. Furthermore, ensuring the uniformity of cell membrane protein components and their functionalities serves as the foundation for the scalable production of cell membrane-based biomimetic vehicles. Without this assurance, it becomes improbable to maintain consistent or comparable functionalities across each batch of these vehicles.

Regrettably, a standardized set of criteria for evaluating the functional attributes of distinct types or batches of cell membranes prior to production is lacking [79]. Similarly, when progressing to clinical trials, establishing consistent rating criteria and quality control for both the production process and the ultimate product remains a primary apprehension.

Cell membranes share certain similarities with cells, and the GLP standards for cell preparations are steadily advancing. The quality control and criteria for maintaining consistency during cell preparation might serve as useful references for the production of cell membrane-based biomimetic vehicles. Another issue revolves around the stability during manufacturing, storage, and transportation processes. In a previous study, it was examined the persistence of the intact structure of stem cell membrane-based biomimetic vehicles for a span of two weeks [7]. However, the resilience of these vehicles under conditions of extended storage and in dry powder form is still awaiting exploration [80]. The stability is substantially influenced by the size, shape, components, and physicochemical attributes of diverse cell membranes [81]. Additionally, a pressing need exists to investigate the stability of loaded drugs within cell membrane-based delivery vehicles and the potential for drug leakage across diverse storage and transportation conditions. To facilitate transport and storage, frozen or lyophilized formulations might be the favored dosage forms for creating cell membrane-based biomimetic vehicle formulations. Moreover, assessing the biological functionality of cell membranes during storage is also pivotal, even though no relevant studies have surfaced thus far. Given their susceptibility to degradation and deactivation, achieving stability levels that align with industrial manufacturing prerequisites remains a formidable challenge, impeding their prospects for large-scale production [82]. Lastly, the assessment of biological efficacy and safety in humans remains pending [83]. As discussed in the preceding section, the unclear BBB targeting mechanism can impede investigations into biodistribution and pharmacokinetics within CNS disorders. The dissimilarity between animal models and humans means that drugs exhibiting efficacy in animal experiments might display limited effectiveness in humans [84]. Notwithstanding this distinction, it's widely recognized that the potential of biomimetic vehicles as viable drug candidates can be preliminarily inferred from their physicochemical, biochemical, pharmacodynamic, and pharmacokinetic attributes [85]. Beyond assessing efficacy, it holds significant importance to incorporate predictive toxicological safety evaluations that are informed by thoughtful analyses of various aspects including absorption, distribution, metabolism, excretion, and toxicokinetic behavior [86].

7 CONCLUSION

To conclude, this study provides an overview of cell membrane-based biomimetic vehicles for delivering treatments to CNS disorders, emphasizing their pertinent biomedical applications. The diverse array of strategies hinging on cell membranes has ushered in a new era in targeted delivery approaches. Through cell membrane modification, these delivery vehicles acquire multifunctional attributes akin to the originating cells. Both cell membrane-derived vesicles and cell membrane-adapted NPs demonstrate potent therapeutic outcomes for recalcitrant CNS diseases. Furthermore, the potential BBB targeting mechanism of cell membrane-based biomimetic vehicles is explored within this research, proposing a potential study avenue and reference point. Ultimately, the continued exploration of the biology underlying cell membrane-based biomimetic vehicles, along with a comprehensive comprehension of the associated therapeutic challenges and limitations, will establish a firm footing for future clinical triumphs.

ABBREVIATIONS

CNS: central nervous system, BBB: blood-brain barrier
AD: Alzheimer's disease, PD: Parkinson's disease
NPs: nanoparticles, TJs: tight junctions
BMECs: brain microvascular endothelial cells, PLGA: poly lactic-co-glycolic acid
RBCs: red blood cells, CDX: candoxin-derived
ApoE: apolipoprotein E, MSCs: mesenchymal stem cells
NSC: neural stem cells, rtPA: recombinant tissue plasminogen activator
BBTB: brain blood tumor barrier, ROS: reactive oxygen species
SDF1: stromal cell-derived factor, MCAO: middle cerebral artery occlusion
ICAM-1: intercellular adhesion molecule-1, VCAM-1: vascular cell adhesion molecule-1
VLA-4: very late antigen-4, GLP: Good Laboratory Practice
CCL2: C-C motif chemokine ligand 2, CXCR4: C-X-C motif chemokine receptor 4

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