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Review Article

Exosomes: Traversing the blood-brain barrier and their therapeutic potential in brain cancer

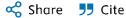
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Highlights

- The BBB presents a significant challenge in treating brain tumors due to its restricted permeability.
- Exosome-based drug delivery platforms can cross the BBB, presenting a promising approach for brain cancer treatment.
- Understanding exosome transport routes across the BBB may improve their efficacy in barrier penetration.

- Flexible use of various drug payload methods can enhance exosomal drug loading efficiency for clinical applications.
- The full potential of exosomes can be achieved by effectively applying various BBB targeting methods.

Abstract

The blood-brain barrier (BBB) presents a major challenge for the effective delivery of therapeutic agents to the brain tumor cells from the peripheral blood circulation, making the treatment of central nervous system (CNS)-related cancers more difficult and resistant to both standard treatments and emerging therapies. Exosomes, which serve as messengers for intercellular communication throughout the body, can naturally or be modified to penetrate the BBB. Recently, exosomes have been increasingly explored as an invasive or non-invasive approach for delivering therapeutic agents to the CNS. With their low immunogenicity, ease of modification, excellent cargo protection, and inherent ability to cross the BBB, exosomes hold great promise for revolutionizing targeted therapy for CNS-related diseases, including brain cancer. In this review, we highlight recent discoveries and insights into the mechanisms exosomes use to penetrate the BBB, the methods they employ to payload diverse therapeutics, and their roles in transporting therapeutic compounds for brain cancer and other neurological disorders.

Introduction

Brain tumors such as glioblastoma (GBM) have high morbidity and mortality [1]. Despite advancements in surgical resection techniques and the development of novel therapeutic agents, there has been no substantial improvement in patient survival rates [2,3]. A significant challenge in treating brain cancer is the presence of the blood-brain barrier (BBB), which, along with the non-specificity of conventional chemotherapy drugs, severely limits the efficacy of current therapeutic strategies [[4], [5], [6]]. The BBB is a highly selective and complex neurovascular structure that tightly regulates the exchange of molecules between the peripheral circulation and the central nervous system (CNS), thereby significantly restricting the delivery of therapeutic agents to the brain [7]. Consequently, the effective transport of drugs across the BBB remains a critical challenge in the treatment of brain cancer and other CNS-related disorders [8,9].

Various drug delivery systems, including synthetic biomaterials, self-assembled liposomes, and viral vectors, have been extensively explored to enhance the efficiency of therapeutic and diagnostic agent delivery to the brain [10,11]. However, these delivery systems present several limitations, including immunogenic responses, complex structural properties, challenges in quality control during manufacturing, poor biocompatibility, and potential toxicity [11]. In contrast, naturally secreted exosomes have emerged as a promising alternative for brain tumor therapy due to their biological stability and ability to traverse the BBB (Fig. 1) [[12], [13], [14]].

Exosomes exhibit low immunogenicity, extended circulation time, and innate brain-homing properties, making them effective carriers for various therapeutic agents, including small molecules, nucleic acids, and proteins (Fig. 1) [15].

Although substantial evidence suggests that exosomes can successfully cross the BBB, comprehensive reviews summarizing the key factors influencing exosomal entry into the CNS remain limited. This review aims to address this gap by examining the intrinsic biological properties of exosomes, including their surface proteins, packaged payloads, and cellular origins, to better understand the mechanisms governing their BBB penetration. Additionally, the potential of bioengineered and chemically modified exosomes to enhance BBB permeability is discussed. Finally, we summarize current exosome-based drug delivery strategies and evaluate their potential as targeted therapeutic carriers for brain cancer treatment, with a particular focus on their ability to deliver anti-cancer agents to the brain.

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Section snippets

Basics of exosome biology

Exosomes were first described by Tram and collaborators in the 1980s when they discovered that cellular ecto-enzymes were conserved in exfoliated membrane vesicles, and they proposed that these vesicles derived from the plasma membrane could be specified as exosomes in general [16,17]. Developing biological techniques provide many strategies to identify and characterize these extracellular and membrane-bounded vesicles, typically sized around 30–200nm [18,19]. Exosomes are composed of a large ...

Exosome-mediated BBB crossing: biological mechanisms and targeted modifications

Many reports have indicated that exosomes can cross the BBB due to their role in intercellular communication and physiological functions through the transport of packaged contents between cells (Fig. 3) [42] [43]. The key components of the BBB are endothelial cells, which form a tight and selective membrane that covers brain-associated capillaries (Fig. 4) [44,45]. The BBB separates the brain microenvironment from the rest of the body and strictly regulates the entry of substances into the CNS ...

Strategies for loading exosomes with therapeutics

The aqueous core and lipid bilayer membrane of exosomes make them naturally designed to be a nanosized drug delivery platform to transport different biological or chemical therapeutics across various cell and tissue barriers, including the BBB. We now focus on some of the current advances in exosome-based drug loading and delivery techniques, organized into the following three categories based on loading strategies: 1) passive and active physical methods for loading into the exosomal lumen; 2) ...

Exosome-based drug delivery systems for overcoming the BBB in brain cancer therapy

Building upon the ability of exosomes to traverse the BBB and encapsulate therapeutic agents, we now focus on their targeted application in brain cancer treatment. Since the initial demonstration of exosome-mediated siRNA delivery for brain-targeted gene transcription regulation, exosomes have been widely acknowledged for their exceptional drug-loading capacity and their ability to facilitate the transport of various genetic and chemotherapeutic agents to the brain with the goal of inhibiting ...

Discussion and future directions

In this review, we summarized research on the mechanisms behind exosomal ability to cross the BBB, focusing on intrinsic surface components, exosomal cargo manipulation, cell origin-dependent targeting, surface modification strategies, and alternative administration routes. We then highlighted recent advances in exosome-based drug loading methods, categorized into three strategies: physical lumen loading, chemical surface modifications, and biological engineering of parental cells to load ...

Author contribution

X.P. contributed with conceptualization, writing the first draft, and reviewing and editing the text. H.N., N.A., and D.A.S. all helped with the writing, reviewing, and editing. S.H. and A.B·S contributed to the concept, writing, reviewing, and editing, and were in charge of supervision and funding acquisition. ...

Declaration of competing interest

During the preparation of this work the authors used AI language models such as ChatGPT in order to refine sentence quality. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Shawn Hingtgen and Andrew Satterlee report financial support provided by National ...

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