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Therapeutic aspects of mesenchymal stems cells in medulloblastoma therapy: A review of the current knowledge

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Abstract

Medulloblastoma (MB), the most common malignant brain tumor in children, presents a significant therapeutic challenge. Despite advancements in treatment regimens, particularly for recurrence and leptomeningeal spread, achieving long-term survival for MB patients remains elusive. Multimodal therapies, including radiation, chemotherapy, and extensive surgical, have improved survival rates; however, roughly one-third of patients still face an incurable disease. Integrating mesenchymal stem cells (MSCs) from various sources is increasingly explored in novel therapeutic strategies. Hence, this review aims to comprehensively examine the migratory potential and therapeutic efficacy of MSCs in the context of experimental MB models. While MSCs are emerging as innovative cell-based delivery vehicles, their specific therapeutic potential in MB treatment requires further investigation.

Introduction

Medulloblastoma (MB), the most frequent malignant primary brain tumor in children, represents a significant challenge in pediatric oncology. Accounting for approximately 20% of all childhood brain tumors and 63% of intracranial embryonic malignancies (Huang *et al.* 2016; Z. Huang *et al.* 2023; Katsushima *et al.* 2023), MB primarily affects individuals between 5 and 7 years old, with a male predominance (1.8:1) (Penco-Campillo *et al.* 2023). Despite advancements in multimodal therapies integrating surgery, radiation, and chemotherapy, roughly one-third of patients experience treatment failure (Kim *et al.* 2006). While these standard approaches achieve a 70-75% success rate, they are often accompanied by long-term impairments and treatment-related toxicities (Borgenvik *et al.* 2022; Kim *et al.* 2006). Histologically classified as

a cerebellar embryonal neuroepithelial tumor by WHO (Mahapatra & Amsbaugh, 2017), MB comprises four main variants: classic, desmoplastic/nodular, MB with extensive nodularity, and the large cell/anaplastic (LCA) subtype Originating from neural stem cell precursors in the cerebellum's granular cell layer (G.-H. Huang *et al.* 2016), MB exhibits features suggestive of multipotency, captivating researchers due to its potential therapeutic implications (Calinescu *et al.* 2021; Fan & Eberhart, 2008). The 5-year survival rate, although reaching 70-80% for standard-risk patients and 55-76% for high-risk cases, remains overshadowed by the unfavorable prognosis associated with MB [10]. Moreover, survivors often face enduring side effects from these aggressive therapies (Huang *et al.* 2016). For children diagnosed at four years or older, the current approach typically involves maximal safe surgical resection followed by a combination of cytotoxic chemotherapy and craniospinal irradiation (CSI) (Cooney *et al.* 2023). Despite these efforts, poor outcomes necessitate ongoing exploration of novel therapeutic strategies.

Mesenchymal stem cells (MSCs), with their immunomodulatory, regenerative, and homing capabilities, have emerged as a promising therapeutic avenue for various diseases, including cancer (Aref Nezhad *et al.* 2021; Musial-Wysocka *et al.* 2019). While preliminary studies show promise for MSCs in treating COVID-19, significant hurdles remain before stem cell therapy can be considered a definitive treatment option (Hosseinzadeh *et al.* 2021). The unique properties of MSCs, particularly their ability to migrate toward and infiltrate tumor sites, make them attractive candidates for treating brain malignancies (Chastkofsky *et al.* 2021). This migration process is mediated by matrix metalloproteinases (MMPs), with MMP-2 playing a crucial role (Chastkofsky *et al.* 2021; Do *et al.* 2021). These fibroblast-like cells, residing in almost all organs, possess the potential to differentiate into various cell types (Najar *et al.* 2019). Their niche-specific features and mesodermal origin contribute to their immunomodulatory effects, influencing the behavior of both innate and adaptive immune cells (Bernardo & Fibbe, 2013). Genetically modified MSCs have been explored as delivery vehicles of therapeutic drugs, such as oncolytic viruses (OVs), for treating diverse brain tumors (Chastkofsky *et al.* 2021). MSC-derived extracellular vesicles (MSC-EVs) represent another promising avenue. Due to their inherent ability to home to the brain and cross the blood-brain barrier, they offer a safe and bioavailable means of delivering therapeutic payloads (Do *et al.* 2021). These innovative approaches hold promise for both autologous and allogeneic MSC use, with applications extending to acute tissue damage syndromes, chronic degenerative diseases, and inflammatory conditions, leveraging the regenerative and anti-inflammatory properties of MSCs (Galipeau & Sensébé, 2018). Notably, MSCs have been shown to migrate to tumor sites and exert anti-tumor effects through diverse mechanisms, including immune modulation, angiogenesis inhibition, and induction of apoptosis in cancer cells (Aref Nezhad *et al.* 2021; Musial-Wysocka *et al.* 2019). Safety studies suggest that *in vitro*-expanded human MSCs exhibit enhanced resistance to damage, further supporting their potential therapeutic application (Musial-Wysocka *et al.* 2019). Recent pre-clinical investigations have shed light on the potential of MSCs to target MB stem cells (MBSCs), critical players in tumor initiation, metastasis, and relapse (Huang *et al.* 2016). Elucidating the growth control mechanisms governing MB formation and progression is essential for refining current treatments and exploring novel therapeutic avenues.

Therefore, this review aims to comprehensively examine the migratory potential and therapeutic efficacy of MSCs in the context of experimental MB models. While MSCs are gaining traction as innovative cell-based delivery vehicles, their specific therapeutic potential in MB treatment requires further investigation.

Medulloblastoma and its pathogenesis

The categorization of brain tumors has traditionally relied on the morphological or functional resemblance of tumors to different types of non-neoplastic cells in the brain (Friedmann-Morvinski & Hambardzumyan, 2023). The investigation into the cellular basis of MB has been a subject of interest since its original characterization by Harvey Cushing and Percival Bailey. The tumor was called after the presumed medulloblast, an undifferentiated cell seen on the surface of the cerebellum that was believed to develop into both neurons and glia at that time (Fan & Eberhart, 2008). Although rare in adults, this rapidly progressing tumor exhibits complex genetic pathogenesis with distinct subgroups defined by demographics, transcriptomes, somatic mutations, and clinical outcomes, as revealed by transcriptomic analyses of patient cohorts. The significant vascularity of MB highlights the crucial roles of angiogenesis and lymphangiogenesis in tumor progression and dissemination (Penco-Campillo *et al.* 2023). Characteristically, MB presents as a poorly defined, pink-purple, soft, and friable mass in the cerebellar vermis, often arising from the inferior medullary velum. Metastasis typically occurs within the subarachnoid space (Kombogiorgas, 2017).

Signaling pathway in medulloblastoma

Hedgehog pathway

The Hedgehog (Hh) pathway or Sonic Hedgehog (SHH) plays a crucial role in the cerebellar embryonic germ layer (EGL) and has been shown to regulate neural stem cell formation across various species (Montagnani & Stecca, 2019). The REN gene, frequently lost in MB, located on chromosome 17, promotes cerebellar

granule cell precursor development partly by inhibiting Hh signaling (Luo *et al.* 2021). Sonic hedgehog ligand, produced by Purkinje cells migrating from the rhombic lip to the EGL, triggers rapid proliferation in granule cell precursors. SHH signaling seems essential for maintaining stem cells in the postnatal hippocampus and subventricular zone (SVZ). Mutations in the SHH signaling pathway contribute to dysregulated cell division and tumor development, particularly in children under three years old (Wijaya *et al.* 2020). The ATP-binding cassette transporter ABCC4 has emerged as a regulator of SHH-MB, with elevated ABCC4 expression linked to poorer patient survival. Among the regulatory elements of SHH-MB, the ATP-binding cassette transporter ABCC4 has been recognized, and elevated ABCC4 expression is associated with worse overall survival in patients (Wijaya *et al.* 2020). A deeper understanding of these molecular complexities and subgroup-specific features is crucial for improving prognostic evaluations and developing targeted therapy strategies for MB patients. Cerebellar granule cells and MB both target the N-myc oncogene, which is involved in cerebellar development and a crucial target of SHH signaling. Amplification or overexpression of myc oncogenes can occur in tumors progressing from less aggressive subtypes, associated with the large-cell/anaplastic MB subtype and poorer clinical outcomes (Fan & Eberhart, 2008). The SHH signaling pathway emerges as a primary therapeutic target, with the SHH pathway inhibitor vismodegib (a conventional drug) demonstrating efficacy in tumor reduction, specifically targeting Smoothened (Smo), causing the tumor to shrink rapidly. However, Smo mutations leading to treatment resistance and recurrence remain significant concerns. Promising targets include the Wnt, Hedgehog, and Notch signaling pathways, crucial for non-neoplastic neural stem cells (Huang *et al.* 2016).

Notch signaling pathway

Similar to the SHH pathway, Notch signaling is present in neural stem and progenitor cells of the embryonic ventral forebrain (VZ) and rhombic lip, as well as in the postnatal SVZ and EGL. This pathway acts upstream, regulating the Hh response in brain progenitor cells (Jacobs & Huang, 2019). Studies have reported dysregulation of the Notch pathway in both human and mouse models of MB. Evidence suggests that SHH signaling can influence Notch activity in these tumors. Hypoxia has been shown to stimulate neural stem cell growth through the Notch pathway, and a similar mechanism might be at play in medulloblastoma cancer stem cells (Fan & Eberhart, 2008).

WNT signaling pathway

Another canonical pathway, the Wnt signaling pathway, plays a role in both sporadic and syndromic medulloblastoma. It regulates the proliferation of stem and progenitor cells in the fetal VZ, the postnatal SVZ, and the hippocampus (Al-Dalahmah *et al.* 2020). A subset of medulloblastomas exhibit mutations or decreased expression of Axin2, a negative regulator of Wnt signaling. Up to 25% of cases show nuclear translocation of beta-catenin, indicating Wnt pathway activation, which is associated with improved clinical outcomes (Fan & Eberhart, 2008).

Other pathways

The PI3K/AKT signaling pathway, frequently activated in MB, is linked to tumor progression, metastasis, and chemotherapy resistance (Cooney *et al.* 2023). Inhibitors like GDC-0941 and BKM120 exhibit promise in targeting MB stem cell subpopulations and reducing tumor development in pre-clinical models (Cooney *et al.* 2023). Dysregulation of circular RNA circ_63706, observed across various cancers, presents a potential therapeutic target, particularly in children with Sonic Hedgehog subtype MB (Katsushima *et al.* 2023). The necessity for innovative treatment strategies remains paramount, demanding approaches that selectively target tumor cells while minimizing damage to surrounding healthy tissue, ensuring high efficacy and low toxicity for children diagnosed with MB.

Medulloblastoma subgroups and molecular landscape

MB is a heterogeneous pediatric brain tumor classified into four major subgroups: Wingless/integrated (WNT), Sonic Hedgehog (SHH), Group 3, and Group 4. WNT and SHH subgroups are driven by abnormal activation of their respective signaling pathways (Fang *et al.* 2022; Shiraishi & Kawauchi, 2021). Groups 3 and 4 lack a single dominant signaling pathway but exhibit overexpression of N-myc and c-myc with TP53 inactivation (Penco-Campillo *et al.* 2023). MB distinguishes itself from other brain tumors through its specific gene expression profile, with elevated BAIAP2 and CDC42 potentially contributing to metastasis (Ruiz *et al.* 2023). Notably, Elongator complex protein 1 (ELP1) mutations are particular to the SHH subgroup, occurring in 15-20% of pediatric cases, which is a scaffolding member of the Elongator complex, is crucial for posttranscriptional tRNA modification, effective translational elongation, and protein homeostasis (Garcia-Lopez *et al.* 2022).

Epidemiology and clinical presentation

The annual incidence is estimated at 5-6 cases per million in children, with around 450 new cases diagnosed annually in the US (Katsushima *et al.* 2023; Mahapatra & Amsbaugh, 2017). Males are 1.5 times more likely to be affected than females. The disease primarily affects young children (aged 4-9 years) at a rate of 44%, followed by teenagers (10-16 years old) at 23% and infants (0-3 years old) at 12%. Notably, MB in adults is much less common, with an incidence rate

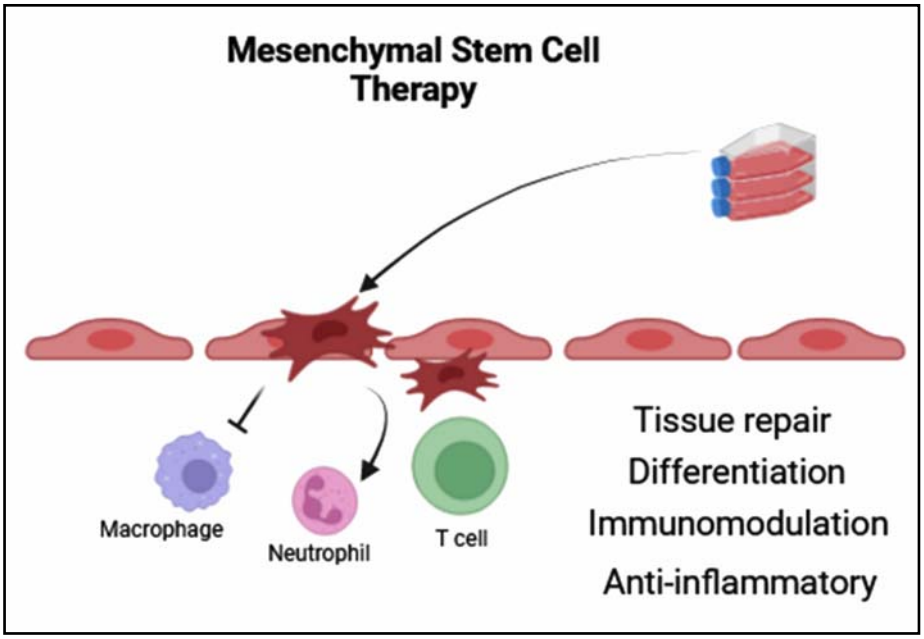

Fig. 1. Several benefits of using mesenchymal stem cell therapy (adapted and redesigned from Shi *et al.* (2021) (Shi *et al.* 2021)

of 0.05 cases per 100,000 (Mahapatra & Amsbaugh, 2017). Another research study conducted in Piedmont, Italy, between 1976 and 1995 aimed to elucidate the epidemiological features of adult MB. This study reported an annual incidence rate of 0.5 per million (Giordana *et al.* 1999). Consistent with an embryonic origin, the peak incidence (2.33 per million per year) was observed in the 15–19-year-old age range and gradually declined until age 40 (Giordana *et al.* 1999).

The precise etiology of MB remains elusive. However, some studies suggest associations with maternal nutrition, immune system disorders, and potential links to childhood viral infections (Mahapatra & Amsbaugh, 2017). The tumor typically originates in the fourth ventricle's roof and can spread through the cerebellar vermis and brainstem. Despite similar histological features, MB subgroups exhibit varying responses to standard therapies (surgery, radiation, and chemotherapy) (Giordana *et al.* 1999).

Hypoxia, prognostic, and treatment challenges

Hypoxia within the tumor microenvironment is a critical factor influencing MB progression, promoting dissemination, resistance to therapy, and a poorer prognosis (Blocher *et al.* 2023). Patient data highlight hypoxia-induced gene expression changes and alterations in proteomic, metabolomic, and lipidomic profiles. *In vitro* investigations further elucidate the involvement of HIF-1α in conferring resistance to chemotherapy (Blocher *et al.* 2023).

Several factors significantly influence MB's prognosis. Pre-radiotherapy neutrophil-lymphocyte ratio (NLR) exceeding 4.5, age, and Group 3 genotype is associated with increased risk (Li *et al.* 2022). Prognostic considerations also include molecular subgroup, extent of surgical resection, and radiation application (Dufour *et al.* 2021; Liu *et al.* 2022). Recurrence, particularly the M+ stage and large-cell/anaplastic histology, is associated with a lower progression-free survival rate (PFS) (Liu *et al.* 2019). Preoperative tumor infiltration into the medulla and a large tumor diameter (>5 cm) are linked to an increased risk of postoperative cerebellar mutism syndrome (pCMS) (Pettersson *et al.* 2022). Optimizing treatment for MB and supratentorial primitive neuroectodermal tumors (sPNET) in children remains a challenge. Tailoring therapy intensity based on risk stratification (high-risk vs. low-risk) is crucial for improving outcomes (Perkins *et al.* 2018).

However, recent advancements in multi-omics analysis have identified distinct MB subgroups with unique oncogenic drivers and biological origins (Shiraishi & Kawauchi, 2021). For instance, metabolomic studies have revealed disruptions in specific metabolic pathways potentially linked to MB development. These findings hold promise for developing targeted therapies to improve patient outcomes (Huang *et al.* 2023).

Mesenchymal stem cells: therapeutic promise and challenges

MSCs, originating from mesoblasts, reside in a variety of tissues including bone marrow, adipose tissue, and umbilical cord blood (Zhu *et al.* 2023a). However, their therapeutic application presents initial hurdles related to cell processing. Various factors can influence the final product's therapeutic efficacy, highlighting the critical need for standardization and stringent quality control measures in cell-based therapies. As an alternative solution, research efforts are exploring cell-free systems, such as MSC-derived extracellular vesicles (Do *et al.* 2021).

The immunomodulatory, regenerative, and homing properties of MSCs make them a promising therapeutic approach for various medical conditions, including cancer (Galipeau & Sensébé, 2018; Najar *et al.* 2019). Studies suggest their potential for treating various diseases, such as acute respiratory distress syndrome (ARDS) (Cao *et al.* 2022), connective tissue repair (Rehman *et al.* 2023), cardiac ailments (Zhu *et al.* 2023b), myocardial ischemia-reperfusion injury (Zhou *et al.* 2023), and severe burns (Eldaly *et al.* 2022). Despite these advantages, challenges associated with MSC use remain.

Therapeutic benefits of MSCs

Multiple studies have documented the therapeutic potential of MSCs due to their regenerative, immunomodulatory, and anti-inflammatory properties (Yasamineh *et al.* 2022). They can modulate the immune response and promote tissue repair. In the context of ARDS, MSC therapy has shown promising results with a high safety profile (Cao *et al.* 2022). Additionally, MSCs hold promise as a future therapeutic strategy for repairing cardiac damage. They can facilitate cardiomyocyte repair, stimulate angiogenesis (blood vessel growth), and regulate the immune system (Zhu *et al.* 2023b).

MSCs have demonstrated significant potential in soft tissue regeneration. They have been applied in various therapeutic settings, including craniofacial and oral tissue defects and the regeneration of blood vessels, muscle, and fibrous tissue (Rehman *et al.* 2023). Myocardial ischemia-reperfusion injury represents another condition where MSCs may be beneficial. Research suggests that MSC-derived small extracellular vesicles (sEVs) offer a promising therapeutic option due to their low tumorigenicity, easy accessibility, and minimal immunogenicity (Zhou *et al.* 2023). Studies have explored the use of MSCs in treating severe burns, where they may help reduce inflammation and burn-induced organ damage. Positive effects have been documented on renal function, tissue damage reduction, pro-inflammatory cytokine levels, and burn survival rates (Eldaly *et al.* 2022). The diverse benefits of MSC therapy are further illustrated in Figure 1.

Strict quality control measures, aligned with pharmaceutical manufacturing standards, are crucial for MSC therapy. Stem cell preparations must undergo rigorous quality inspections at accredited third-party institutions before clinical use (Shi *et al.* 2021). The ease of isolation and remarkable growth potential of MSCs make them attractive candidates for various cell therapies (Najar *et al.* 2019). Notably, MSCs are the most extensively studied experimental cell therapy system globally, despite lacking marketing authorization in the United States, following their pioneering use as a cellular therapeutic by Hillard Lazarus (Fung *et al.* 2017). In contrast, research supports the anti-tumor effects of MSCs through mechanisms like immune response modulation, suppression of angiogenesis, and tumor cell apoptosis induction (Galipeau & Sensébé, 2018; Najar *et al.* 2019), combining them with conventional therapies remains an option for targeting residual tumor cells, particularly in cases with subarachnoid space dissemination where neural stem cell (NSC) transplantation into the resection cavity can be beneficial (Kim *et al.* 2006). However, several challenges hinder the therapeutic application of MSCs.

A significant challenge is the inherent variability of MSCs, leading to inconsistent treatment responses across patients. This variability stems from differences in the characteristics of MSCs derived from various sources, such as bone marrow, adipose tissue, and umbilical cord blood (Jovic *et al.* 2022). Consequently, the reliability and efficacy of MSC-based treatments can be unpredictable. Furthermore, conflicting evidence exists regarding the impact of MSCs on tumors. While some studies support their anti-tumor properties, others suggest MSCs may promote tumor development and metastasis (Galipeau & Sensébé, 2018). This dual role underscores the importance of understanding the factors influencing whether MSCs exhibit pro- or anti-tumor actions. Another barrier to their therapeutic utility is the limited ability of MSCs to engraft and survive following transplantation (Fričová *et al.* 2020). Transplanted MSCs may fail to reach or integrate within the target tissue, potentially dying before exerting any therapeutic benefit. Ongoing research explores preconditioning and genetic manipulation techniques to improve engraftment and survival rates (Musial-Wysocka *et al.* 2019). The optimal dose, administration time, and delivery route for MSC-based therapies remain definitively established (Zhou *et al.* 2021). Developing MSC-based therapies faces additional regulatory and industrial hurdles. Standardizing protocols for MSC isolation, expansion, and characterization is essential to ensure MSC products' safety, efficacy, and reproducibility (Regmi *et al.* 2019). High manufacturing costs and the need for large-scale production methods pose further challenges concerning broad availability and cost-effectiveness (Hmadcha *et al.* 2020).

Cell-based therapies encounter three main types of problems related to their biological effectiveness and safety (Do *et al.* 2021):

1. **Biostability:** This includes homing and cell trafficking within the systemic circulation.
2. **Unanticipated differentiation:** This refers to the potential for tumorigenicity.
3. **Host immune system interactions:** These include the spread of infection, embolism from cell clumping, and similar phenomena (Table 1).

Several key factors influence the safety and efficacy of extracellular vesicles (EVs) for *in vivo* applications (Do *et al.* 2021). These include:

Tab. 1. Brain tumor treatment strategies based on MSCs and MSC-derived extracellular vesicles (MSC-EVs) are compared and contrasted concerning key challenges and impediments (adapted from Do *et al.* (2021)) (Do *et al.* 2021)

	MSCs	MSC-EVs
Difficulties shared by both approaches	– Low efficiency in targeting as a result of organ entrapment following systemic injection. – Inadequate production and characterization standards – Possible influences that promote tumor growth	
Issues with technology	– Difficulties in formulation, storage, and clinical use	– Processes with less complexity
	– *Ex vivo* growth and mass manufacture are both limited.	– Increased yield and simplified scalability
Concerns about *in vivo* applications	Possible dangers of infection, embolism, and immune system attacks due to unchecked differentiation.	Improved Risk Assessments
Therapeutic outcomes	– Options for enhancing treatment efficacy are restricted.	– Ability to accommodate a larger variety of methods
	– Lack of successful engraftment in desired tissues, such as the brain	– Superior ability to cross the blood-brain barrier (BBB) and accumulate in brain parenchyma

- Optimal administration route: Identifying the most effective route for EV delivery.
- Biodistribution and stability: Understanding how EVs distribute and maintain stability within the circulatory system.
- Tumor growth risk: Evaluating the potential for EVs to promote tumor development.
- EV behavior in the tumor microenvironment (TME): Elucidating how EVs interact with the specific environment surrounding tumors

These factors highlight the need for further research in EV-based cancer therapy. Promising areas of investigation include (Do *et al.* 2021):

1. Evaluation of novel anti-cancer drugs: Exploring how radiation therapy, chemotherapy, EV therapy, and surgical procedures can interact to enhance or re-sensitize each other's effects. Understanding these synergies holds the potential to improve overall treatment outcomes.
2. Investigating Synergistic Treatment Interactions: Exploring how radiation therapy, chemotherapy, EV therapy, and surgical procedures can interact to enhance or re-sensitize each other's effects. Understanding these synergies holds the potential to improve overall treatment outcomes.
3. Co-delivery of therapeutic pathways in EVs: Researching the possibility of co-loading multiple therapeutic pathways within a single EV for enhanced therapeutic benefit. This strategy aims to develop more versatile and convenient EV-based therapies.
4. Discovery of new glioma targets: Aggressively identification of novel therapeutic targets will expand treatment options for gliomas. Extensive research is needed to discover specific molecular targets that can effectively be exploited for glioma treatment.
5. Validation of MSC-EV delivery systems in CNS cancers: Confirming the efficacy and safety of MSC-EV delivery systems for treating various CNS malignancies. This requires further research to validate their effectiveness across different CNS cancers.

By focusing on these research avenues, scientists can develop improved cancer treatment strategies, investigate interactions between various therapeutic methods, and optimize the delivery of therapeutic agents for better clinical outcomes.

Challenges in the use of MSCs

Despite their promising therapeutic potential, several challenges hinder using MSCs for cardiac repair. A major obstacle is the short half-life of MSCs in the heart. This has prompted research into the potential of MSC-secreted exosomes for cardiac damage repair (Zhu *et al.* 2023b). Additional challenges include (Zhou *et al.* 2023):

- Difficulty acquiring stem cells: The isolation and expansion of MSCs can be complex and time-consuming.
- Slow homing rate: MSCs may have difficulty homing to the target tissue, limiting their therapeutic efficacy.
- Short *in vivo* survival: MSCs may not survive for a long period after transplantation, which can reduce their therapeutic benefit.

Mesenchymal stem cells and medulloblastoma

MB, a highly aggressive pediatric brain tumor, presents a significant therapeutic challenge (Nowak *et al.* 2021). MSCs have emerged as a promising avenue for MB treatment due to their immunomodulatory, regenerative, and anti-tumorigenic properties (Kim *et al.* 2012).

However, the impact of MSCs on MB remains complex and warrants further investigation.

Studies have yielded conflicting results regarding the efficacy of MSCs in MB treatment. Some reports suggest limited migration and differentiation of MSCs within the MB microenvironment (Calinescu *et al.* 2021). Conversely, other studies raise concerns about potential risks, such as enhanced tumor cell proliferation and invasion associated with MSCs (Lichá *et al.* 2023). These inconsistencies highlight the need to elucidate the underlying mechanisms governing the interaction between MSCs and MB (Tarasov *et al.* 2019). A crucial factor appears to be the expression of matrix metalloproteinases (MMPs) by MSCs (Bhoopathi *et al.* 2011). MMPs play a critical role in the invasive capacity of human MSCs, and their activity can be modulated by various inflammatory cytokines (Zhao *et al.* 2016).

The therapeutic potential of MSCs lies in their versatility and the possibility of tailored treatment methods based on their source (Nowak *et al.* 2021). MSCs can be derived from various sources, including bone marrow (BM-MSCs), adipose tissue (AD-MSCs), umbilical cord blood (UCB-MSCs), and dental pulp. Each source possesses distinct characteristics suitable for specific clinical applications.

Bone marrow (BM)-MSCs

Bone marrow-derived mesenchymal stem cells (BM-MSCs) are the most extensively studied source and have demonstrated anti-tumor properties in MB. These benefits are mediated through multiple mechanisms, such as immune response regulation and angiogenesis suppression (Zhu *et al.* 2023b). The anticancer effects of BM-MSCs in MB have been thoroughly investigated. As a case study, Lu *et al.* (2019) found that hBMSCs suppress the PI3K/AKT signaling pathway, which in turn inhibits U251 cell proliferation and epithelial-mesenchymal transition (EMT)-like (Lu *et al.* 2019).

Adipose-derived MSCs (AD-MSCs)

Adipose-derived mesenchymal stem cells (AD-MSCs) are a plentiful source that has been extensively researched due to their convenient harvestability and strong ability to multiply (Zhu *et al.* 2023a). The potential of AD-MSCs in MB therapy has also been explored. Choi *et al.* reported that AD-MSCs could be used as cellular vehicles to deliver a prodrug-converting enzyme, which would cause the glioma cells to be selectively killed while normal brain tissue is preserved (Choi *et al.* 2012). Research suggests that human AD-MSCs (hAT-MSCs) can inhibit MB cell proliferation through neurotrophin-3 (NT-3) secretion, leading to reduced Nestin expression (a neural progenitor cell marker) and cell death (Kim *et al.* 2012).

Umbilical cord blood (UCBSCs)

Research on the potential of MSCs produced from umbilical cords (UC-MSCs) to target medulloblastoma has paralleled that of BM-MSCs and AD-MSCs.

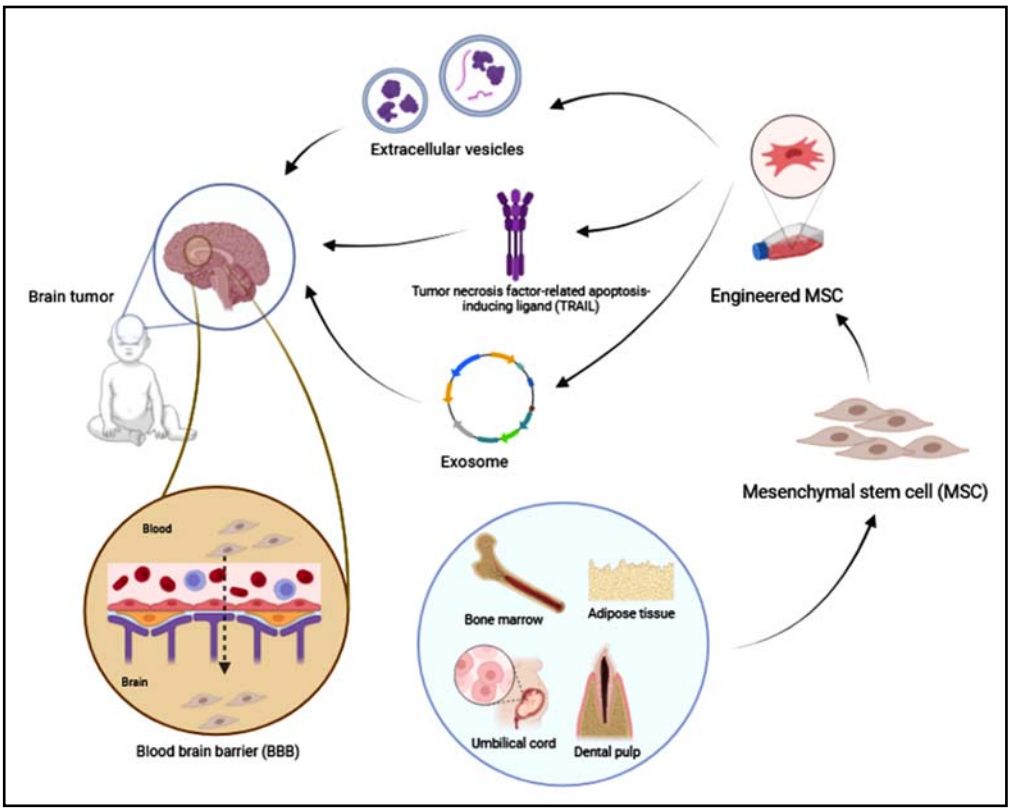

Fig. 2. Brain tumor growth can be inhibited from engineered MSCs (adapted and modified from Ghasempour *et al.* 2022)

According to research conducted by Fan *et al.* UC-MSCs have a strong ability to migrate towards glioma cells, which raises the possibility that they could be used as vehicles to deliver anticancer medicines (Fan *et al.* 2013). Bhoopathi *et al.* found that umbilical cord blood secretes the matrix metalloproteinase-2 (MMP-2), which mediates their tropism towards MB tumors (Bhoopathi *et al.* 2011). This tropism, or preferential migration of MSCs towards tumors, presents an exploitable feature for targeted therapy (Bhoopathi *et al.* 2011).

The instances mentioned above underscore the adaptability of MSCs derived from various origins within the realm of medulloblastoma treatment. The careful choice of the suitable MSC source, together with the manipulation of these cells to improve their ability to target tumors and provide therapeutic benefits, are essential factors to be taken into account in the advancement of efficacious MSC-based therapies for this debilitating pediatric brain tumor. The therapeutic potential of MSCs in MB treatment is promising due to two key features:

1. Inherent Tropism: MSCs naturally migrate towards MB tumors (tropism) (Bhoopathi *et al.* 2011). This characteristic allows for targeted therapeutic strategies.
2. Targeted Drug Delivery: Engineered MSCs can be used to deliver pro-apoptotic proteins like tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) directly to MB tumors (Do *et al.* 2021; Nesterenko *et al.* 2012). TRAIL selectively targets tumor cells while sparing healthy cells, making it an attractive therapeutic option. TRAIL binding to death domain-containing receptors (DR) on the tumor cell surface triggers a cascade of events leading to caspase activation and, ultimately, cell death (Nesterenko *et al.* 2012). Notably, this approach has demonstrated efficacy in both TRAIL-sensitive and TRAIL-resistant MB models.

However, utilizing MSCs in MB therapy faces significant challenges:

- Heterogeneity: MSC properties can vary depending on their source (bone marrow, adipose tissue, or

Tab. 2. Various mesenchymal stem cells in treating MB

Source of mesenchymal stem cells	Concentration	Results	Design of study *(in vivo/in vitro)*	Ref.
Ptch1 heterozygous mice	60 ng/mL	SHH MB CSCs have a mesenchymal phenotype compared to normal cerebellar neural stem cells due to reduced miR-466f-3p expression. Downregulation of miR-466f-3p increased Nrp2 activation, either through Nrp2 levels or its ligand Vegfa, preserving SHH MB CSCs' mesenchymal phenotype.	*in vitro*	(Besharat *et al.* 2018)
Human adipose tissue-derived mesenchymal stem cells (hAT-MSCs)	0-150 ng/mL	NT-3-secreting stem cells significantly increased death of D283-MED cells *in vitro*. High concentrations of NT-3 increased expression of class III b-tubulin.	*in vitro*	(Kim *et al.* 2012)
HB1.F3 cells (an immortalized, clonal human NSC line)	10-100 µg/mL	hNSCs can be genetically modified to express therapeutic genes against MB. In an animal model, hNSCs expressing the cytosine deaminase (CD) gene reduced tumor volume by 76%. No signs of local or systemic toxicity were observed in hNSC-treated groups.	*in vitro* and *in vivo*	(Kim *et al.* 2006)
Human BM-MCSs	5×10^4 cell per well	By suppressing the PI3K/AKT signaling pathway, hBMSCs impede the proliferation of U251 cells and the EMT-like.	A case study	(Lu *et al.* 2019)
Human adipose tissue	8×10^3 cell per well	Under optimal culture circumstances, the hAT-MSCs were able to transdifferentiate into a neural lineage and differentiate into a mesenchymal lineage. The hAT-MSC.rCE was able to transform CPT-11 into SN-38 while maintaining the hAT-MSCs' tumor tropism.	*in vitro*	(Choi *et al.* 2012)
Human mesenchymal stem cells (hMSCs)	0.5–2.0 µg/mL	In TRAIL-sensitive MB lines, MSC-S-TRAIL triggers caspase-3 mediated cell death.In mice with TRAIL-sensitive MBs or TRAIL-resistant MBs pre-treated with MS-275, MSC-S-TRAIL exerts a strong anti-tumor impact.	*in vitro* and *in vivo*	(Nesterenko *et al.* 2012)
Human mesenchymal stem cells using vector (lentivirus)	-	By regulating the expression of important target genes and coordinating its action at enhancer sites, OTX2 manages the regulatory landscape of Group 3 medulloblastoma.	*in vitro*	(Boulay *et al.* 2017)

umbilical cord), potentially leading to inconsistent therapeutic outcomes.
- Tumor Promotion: Despite evidence for MSCs' anti-tumor some studies suggest a potential risk for promoting tumor metastasis and growth (Do *et al.* 2021), as depicted in Figure 2 (Ghasempour *et al.* 2022).

MSC function is significantly influenced by microRNAs (miRNAs). One example is miR-383, a miRNA known to suppress tumor growth in various cancers, including MB. It achieves this by directly targeting the mRNA of pro-tumor genes, thereby inhibiting cancer-related activities like cell proliferation, invasion, migration, angiogenesis, and cancer stem cell formation. While the role of miR-383 highlights the potential for tumor suppression, other research explores different aspects of MB therapy. Besharat *et al.* (2018) investigated the importance of miR-466f-3p, Vegfa, and Nrp2 in the molecular network maintaining the mesenchymal phenotype of cancer stem cells (CSCs) in SHH-MB (Besharat *et al.* 2018). Additionally, Kim *et al.* explored the therapeutic effects NT-3 on MB tumor cells, highlighting potential avenues for improving patient prognosis (Kim *et al.* 2012). These diverse research areas, summarized in Table 2, showcase the complexity and potential of various approaches in addressing this challenging brain tumor.

Understanding MB recurrence and therapeutic targets

Understanding MB mechanisms is critical for developing more effective treatments, particularly for recurrent tumors (Borgenvik *et al.* 2022). Recent research has shed light on potential pathways contributing to recurrence and identified promising therapeutic targets.
- **SOX9 and MYC amplification:** Borgenvic *et al.* (2022) investigated the role of SOX9, a transcription factor associated with stem cell and glial fate, in high-risk MB with MYC amplification (Borgenvik *et al.* 2022). Their findings revealed limited SOX9 expression in rare, quiescent cells with the potential to develop into MYC-high tumors. Furthermore, recurrent tumors exhibited downregulation of the p53 tumor suppressor pathway and DNA repair mechanisms, alongside upregulation of MGMT, a DNA repair enzyme. These findings suggest that targeting these pathways may hold promise for preventing recurrence (Borgenvik *et al.* 2022).
- **Hand1 and Epithelial-Mesenchymal Transition (EMT):** Asuthkar *et al.* identified the transcription factor Hand1 as a potential target for inhibiting MB metastasis. Their research demonstrated that Hand1 overexpression reduces the expression of metastatic markers and suppresses the EMT process, a key driver of metastasis. Mechanistically, Hand1 overexpression inhibited the production of β-catenin and N-cadherin, proteins associated with EMT. This suggests that Hand1 may be a valuable therapeutic target for preventing MB metastasis (Asuthkar *et al.* 2016).
- **OTX2 and Gene Expression in Group 3 MB:** Boulay *et al.* (2017) focused on Group 3 MB, an aggressive subtype, investigating the role of the transcription factor OTX2 in gene expression regulation (Boulay *et al.* 2017). Their study revealed that OTX2 binds to specific DNA elements and collaborates with another factor, NEUROD1, to control the expression of critical genes, including NEK2 kinase, which plays a role in cell viability. This research provides insights into the molecular mechanisms of Group 3 MB and suggests potential targets for therapeutic intervention (Boulay *et al.* 2017).

This research provides vital insights into the molecular pathways that cause the recurrence and spread of MB, suggesting possible targets for treatment. Targeting SOX9, Hand1, and OTX2 represent promising avenues for preventing MB recurrence and metastasis.

Future directions and conclusions

Medulloblastoma MB, a highly malignant pediatric brain tumor, remains a significant therapeutic challenge despite advancements in multimodal therapy. The lack of effective screening methods, limited treatment options for aggressive subtypes, and therapeutic resistance contribute to poor patient outcomes. However, recent progress in omics research has shed light on the genetic heterogeneity of MB, paving the way for a new era of precision medicine (Do *et al.* 2021). While targeted therapies hold promise, further research is necessary to translate these findings into effective clinical applications.

The SHH signaling pathway and other molecular targets present opportunities for therapeutic intervention, although challenges remain in achieving efficient and specific delivery. The complex heterogeneity of MB subtypes, the dynamic nature of tumor development, and the influence of factors like hypoxia necessitate the development of novel therapeutic strategies. To fully realize the potential of MSC-based therapies, it is crucial to address existing limitations, including inconsistent treatment outcomes, the risk of tumor promotion, and limited engraftment and survival *in vivo*. Future research should prioritize improving the efficacy and safety of MSC therapies, establishing standardized protocols, and exploring alternative cell-free approaches.

Understanding the molecular mechanisms underlying MB recurrence, such as the roles of SOX9 and Hand1, is essential for developing targeted therapies. Omics data analysis has revealed distinct MB subgroups defined by unique oncogenic drivers, highlighting the potential for personalized therapeutic approaches.

Investigating arachidonic acid metabolism, steroid hormone generation, and folate-related pathways offers further avenues for targeted interventions. The unique pediatric onset of MB necessitates the development of age-specific treatment strategies. While multimodality therapy remains a cornerstone of MB treatment, optimizing treatment regimens for different risk profiles remains challenging. Future efforts should prioritize the development of targeted therapies based on molecular subtypes and patient risk factors.

In conclusion, MSCs hold significant potential as therapeutic agents for MB due to their regenerative capabilities, immunomodulatory properties, and targeted delivery potential. Research on MSC-based therapies has demonstrated promising results in suppressing MB cell growth and enabling targeted drug delivery. However, overcoming challenges associated with MSC heterogeneity and their potential to promote tumor growth is critical. Additionally, elucidating the molecular mechanisms of MSC action, including the role of miRNAs, is essential for optimizing treatment strategies. A comprehensive investigation of MB biology, coupled with standardized protocols for MSC therapy, is necessary to fully realize the potential of this approach. Ultimately, the goal is to develop more effective, precise, and less toxic treatments for children diagnosed with MB, paving the way for overcoming this devastating disease.

Compliance with ethical standards

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AMC and RA wrote and organized the first draft; MKG, MA, RH, FJG, and HG helped in providing data and wrote some sections, MKG and RA checked the latest version of manuscript. All authors read and approved the final manuscript.

Conflict of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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