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The Intersections between Neuroscience and Medulloblastoma

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Highlights

- Nervous system-medulloblastoma interplay drives tumor progression.
- Drug repurposing study targets medulloblastoma nervous system.
- Glial cells exert multifaceted influences on medulloblastoma .

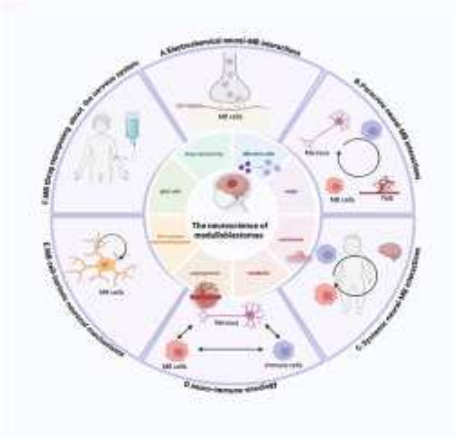
Abstract

Medulloblastoma (MB) represents the most common malignant central nervous system tumor in childhood. The nervous system plays a critical role in the progression of MB, with interactions between the nervous system and cancer significantly influencing oncogenesis, tumor growth, invasion, stemness, and metabolism. These interactions also regulate angiogenesis, metastatic dissemination, the tumor immune microenvironment, and drug resistance. Investigating the nervous system-MB axis holds promise for identifying diagnostic markers, prognostic biomarkers, and therapeutic targets. It also provides insights into the molecular mechanisms underlying MB and informs the development of novel therapeutic strategies.

This review summarizes the latest advancements in understanding the interplay between the nervous system and MB, including the role of glial cells in MB and the potential of drug repurposing targeting nervous system components for MB treatment. These findings underscore

promising diagnostic and therapeutic opportunities for MB management. Additionally, we outline future research directions in neurosciences that may pave the way for innovative therapeutic approaches and deepen our understanding of this complex disease.

Graphical abstract



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Introduction

Central nervous system (CNS) embryonal tumors (ETs) represent a heterogeneous group of aggressive malignancies, primarily affecting children and adolescents. These tumors are classified as grade IV neoplasms and are associated with a poor prognosis for patients[3]. Unlike adult tumors, pediatric cancers exhibit a unique biological characteristic that hinders their maturation rather than acquiring the ability to dedifferentiate [4].

Medulloblastoma (MB), the most common embryonal brain tumor in children, is closely related to the early development of the cerebellum and significantly contributes to the disease burden and mortality in this population [4], [5], [6], [7]. Historically, MB has been classified into four histological subtypes: Classic, Large Cell/Anaplastic, Desmoplastic/Nodular (DNMB), and MB with Extensive Nodularity (MBEN) [8], [9]. Beyond histological classification, the 2021 WHO CNS tumor classification introduced a molecular classification, dividing MB into four subgroups: Wingless/WNT-activated, Sonic Hedgehog (SHH), Group 3, and Group 4 [4]. Each subgroup exhibits cellular diversity[10], [11]. Despite standard treatment protocols, including surgery, radiation, and chemotherapy, yielding promising short-term outcomes, patients with intensively treated MB face an increased risk of developing secondary tumors (e.g., hematological cancers) and neurocognitive alterations, which encompass neurological complications, endocrine disruptions, auditory issues, and a higher likelihood of subsequent cancers. As a result, there is an urgent need for more precise and less harmful therapeutic strategies[12], [13], [14], [15], [16], [17], [18], [19], [20], [21]. The nervous system, composed of neurons, microglia, oligodendrocytes, astrocytes, and peripheral nerves, plays a crucial role in regulating normal tissue function.

Similar to its role in organ development, tissue homeostasis, plasticity, and regeneration, the nervous system can also influence the initiation, growth, and spread of malignant tumors. Cancer neuroscience, which governs the systemic and local tumor microenvironment (TME) aspects of cancer initiation and progression, has been extensively studied in various cancers, including breast, gliomas, and pancreatic [22], [23], [24], [25], [26], [27]. Although research has shed light on the mechanisms influencing MB progression, a comprehensive understanding of these phenomena remains elusive[1], [2], [24], [28].

In this review, we summarize the latest insights into the interactions between the nervous system and MB, including the stemness, genesis, dissemination, metabolism, angiogenesis, and TME of MB, as well as the role of glial cells in MB and drug repurposing targeting the nervous system for MB. These insights highlight potential diagnostic and therapeutic targets for MB management in cancer neuroscience. The future directions of cancer neuroscience in MB are also outlined [29], [30].

Section snippets

Literature Search Methodology

A systematic search was conducted using PubMed, Web of Science, and Scopus (2013–2024) with keywords: medulloblastoma neuroscience, neuro-tumor interactions, neurotransmitter signaling, glial cells in MB. Inclusion criteria: peer-reviewed studies in English focusing on neural mechanisms in MB biology. Clinical trials, preclinical models, and single-cell omics studies were prioritized. Excluded: non-CNS tumors or purely genetic/epigenetic analyses without neural context. …

Nervous System and MB stem cells

In the TME, cancer cells can imitate neural cells, taking advantage of electrical impulses from the nervous system to further their development, leading to drug resistance[31], [32], [33], [34], [35], [36].Pediatric nervous system tumors originate from stem or progenitor cells, including highly tumorigenic subpopulations with stem cell-like characteristics [37], [38]. In MB tumors, cancer stem cells (CSCs) have been identified, demonstrating the capacity for self-renewal under clonal conditions …

Nervous System and MB metabolism

The nervous system plays an important role in regulating MB metabolic reprogramming[91], [92], [93]. Neurotransmitter signaling, both local and distant, is critical for neurogenesis [16], [94].Metabolomic analyses of cerebrospinal fluid (CSF) from MB patients have shown upregulated pathways for aspartate and glutamate biosynthesis in various subtypes, suggesting that TCA cycle metabolites can serve as markers to differentiate MB from normal brain tissue[95], [96]. Comparative metabolomic …

Nervous system and MB angiogenesis

Recent studies show that neural innervation regulates tumor angiogenesis[114].Studies using snRNA-seq and ST-seq have shown that MB cells, vascular cells, and stromal cells are co-localizing[4]. The mechanism of how cell affects angiogenesis remains to be studied. The proliferation and spread of tumor cells are heavily reliant on the formation of new blood vessels, a process governed by a variety of cellular signals, including those involved in axon guidance. The molecules that guide axons …

Nervous system and the immune microenvironment in MB

In the complex landscape of cancer, the intricate interplay among neurons, immune cells, and cancer cells is increasingly recognized. This interaction shapes the tumor's immune context, the balance between pro- and anti-tumor immunity, and the potential for immunotherapy. Given that neural cells are sensitive to immune signaling molecules and immune cells are influenced by neurotransmitters and neuromodulators, it is not surprising that this interplay significantly affects both the nervous and …

Glial cells and MB

Glial cells, essential to the neurological system, are prevalent in the TME and play a major role in the initiation and spread of cancer. Different clusters of glial cells, such as astrocytic cells, oligodendrocytes/oligodendrocyte precursors, monocytes/endothelial cells, and fibroblast/perivascular cells, have been identified by recent studies using snRNA-seq and ST-seq[4].

Cerebellar astrocytes have been implicated in functions like synapse plasticity, metabolic processes, neuroprotection, and …

Cancer therapy effects on the nervous system in MB

Tumors can establish local neuron networks and communicate with the brain through adipokines, cytokines, neurotrophic factors, and neuron inputs, promoting cancer initiation, growth, and metastasis. The brain, in turn, can influence tumor development via neural, neuroimmune, or neurovascular pathways. Understanding these neural interactions offers potential for novel therapies [150].

Side effects related to cognition, neurology, and endocrine system function are frequently caused

by the current …

Drug repurposing

Drug repurposing, a strategic approach to identifying new uses for approved or experimental drugs, offers multiple advantages compared to developing entirely new medications[162]. It not only reduces the risk of failure but also speeds up the drug development process and cuts down on financial costs [134]. Many existing drugs in the fields of neurology and psychiatry, which target neurotransmitter receptors, ion channels, and neurophysiological pathways, have the potential to influence neural …

Conclusions and future directions

Recent studies have made significant progress in understanding MB. However, despite these achievements, several key issues remain unresolved. Many sequencing results have not been effectively integrated or utilized; research has primarily focused on cluster-level analyses without delving into experimental investigations of molecular and intercellular interactions. Additionally, while it is known that cancer can influence distant nervous systems through circulating factors or altered afferent …

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

Medulloblastoma	**MB**
Sonic Hedgehog	SHH
cancer stem cells	CSCs
inner granular layer	IGL
external granular layer	EGL.
single-cell RNA sequencing	scRNA-seq
Purkinje cells	PCs
granule neuron precursor	GNP
single-nuclei RNA sequencing	snRNA-seq
tumor microenvironment	TME
Tumor-associated astrocytes	TAAs
tumor-associated macrophages	TAMs

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