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Narrative Review

Molecular Mechanisms and Therapeutic Challenges in Medulloblastoma: A Narrative Review of Pathogenesis and Emerging Treatment Paradigms in Clinical Oncology

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ABSTRACT

Background: Medulloblastoma (MB), a leading intracranial malignant tumor in children, presents complex challenges due to its diverse molecular pathways and resistance to traditional therapies. Recent research has provided insights into its pathogenesis, revealing significant genetic aberrations and molecular subgroups that influence disease progression and treatment response.

Objective: This review aims to synthesize current knowledge about the molecular mechanisms underlying MB's pathogenesis, therapeutic resistance, and to evaluate the potential and efficacy of emerging treatment strategies.

Methods: A comprehensive literature review was conducted, focusing on studies published in major scientific databases. The criteria for inclusion involved relevance to MB's molecular pathways, epidemiology, treatment strategies, and therapeutic resistance. Key data were extracted and analyzed systematically to understand the disease's molecular underpinnings and treatment implications.

Results: MB is classified into four molecular subgroups—WNT, SHH, Group 3, and Group 4—each with distinct genetic mutations and clinical presentations. Key findings include the identification of specific signaling pathways crucial for tumor growth and survival, such as Wnt, PI3K/Akt/mTOR, and Hedgehog. Treatments are evolving towards targeted therapies, including immunotherapies and drugs focusing on specific signaling pathways. Diagnostic approaches primarily rely on imaging techniques like CT and MRI, which help in identifying tumor characteristics essential for treatment planning.

Conclusion: Advancements in molecular biology have significantly enhanced the understanding of MB, leading to more personalized and targeted treatment approaches. These developments promise to improve survival rates and reduce treatment-related morbidity, thereby improving the quality of life for MB patients. However, ongoing research and innovation remain crucial to address the challenges in treating this complex disease.

Keywords: Medulloblastoma, Molecular Pathways, Treatment Resistance, Targeted Therapy, Immunotherapy, Personalized Medicine.

INTRODUCTION

Medulloblastoma, a leading nervous disorder cancer, is notably prevalent in infants and children, and occasionally observed in adults. This tumor represents a critical proportion of pediatric brain cancers, accounting for 20% of such cases and 63% of embryonal tumors (1). MB is often caused by germline mutations in genes such as APC, TP53, PTCH1, BRCA2, PALB2, and SUFU (2). The incidence of MB is higher in male children and varies across age, gender, and racial groups, with a noted decline in incidence with increasing age (1). Research efforts in recent decades have been concentrated on understanding the molecular mechanisms and progression of MB, aiming to develop improved diagnostic and therapeutic approaches (3).

MB is distinguished by four molecular subgroups, each exhibiting significant intertumoral heterogeneity. These subgroups, as classified by transcriptional profiling, have implications for the tumor microenvironment (TME), which is integral to cancer progression and influences the efficacy of therapeutic interventions in both primary and metastatic brain malignancies. Understanding the tumor-promoting roles of different TME components can reveal vital survival pathways and inform the development of therapies targeting drug resistance and disease pathogenesis (4).

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Metabolic alterations in MB cells are a key factor contributing to chemotherapy resistance. These resistant cells often exhibit activation of the pentose phosphate pathway and increased glycolytic capacity. Such metabolic uncoupling allows MB cells to meet their altered energy demands through alternative pathways, thus enhancing their resistance to chemotherapeutic agents (5).

Resistance to MB therapy is a multifaceted process involving various genes and pathways. The transcription factor YB-1, for example, is implicated in therapy sensitivity and regulates the multi-drug resistance gene ABCB1. Researchers have identified a drug-tolerant gene expression signature, which may represent a broader, targetable mechanism of MB drug resistance (6).

The mTOR proteins play a critical role in MB pathogenesis and are significant targets for therapeutic intervention. However, resistance mechanisms to mTOR inhibitors have been discovered, emphasizing the necessity for combination therapies in MB treatment due to its inherently resistant nature (7).

A specific phenotype characterized by the loss of H3K27me3 in MB has been associated with radioresistance, high relapse rates, and poor overall survival. Targeting this resistance through BET inhibition, which suppresses H3K27ac levels, presents a potential novel therapeutic strategy (8).

The primary objective of this research is to conduct a comprehensive analysis of the molecular pathways involved in the pathogenesis of Medulloblastoma (MB), with a particular emphasis on uncovering the mechanisms of therapeutic resistance and identifying potential treatment strategies. This study will explore the distinct molecular subgroups of MB to understand their impact on disease progression and response to treatment, scrutinize the influence of the tumor microenvironment on MB's growth and therapy resistance, and delve into the metabolic alterations that contribute to chemotherapy resistance. A key aspect will be analyzing the mechanisms behind drug resistance in MB, focusing on genetic and molecular factors, while evaluating both current and emerging therapeutic strategies to assess their effectiveness and limitations. This approach is aimed at deepening the understanding of MB's complex molecular landscape, which is crucial for developing more effective, targeted therapeutic interventions and improving the prognosis and quality of life for patients with MB.

MATERIAL AND METHODS

The methodology for this comprehensive narrative review involved a systematic and extensive literature search, data extraction, and analysis focused on unraveling the intricacies of Medulloblastoma (MB) (9).

The team embarked on a meticulous search across several scientific databases, including PubMed, Scopus, Web of Science, and the specialized Consensus database. Recognizing the rapid advancements in the field, the search was confined to studies published within the last decade, ensuring the incorporation of up-to-date and relevant data (10). Keywords such as "Medulloblastoma," "MB molecular pathways," "MB epidemiology," "MB treatment strategies," and "MB therapeutic resistance" were strategically employed, using Boolean operators for an effective combination of search terms (9, 11).

In selecting the studies for inclusion in the review, a stringent set of criteria was applied. The focus was on studies that provided substantial insights into the molecular pathways, epidemiology, therapeutic approaches, and resistance mechanisms of MB (12). This included original research articles, systematic reviews, meta-analyses, and clinical trial results. Conversely, the team excluded articles that were not peer-reviewed, not in English, or irrelevant to MB (13).

Data extraction was a critical component of the methodology. The team meticulously extracted key information from each study, such as study design, patient demographics, detailed descriptions of molecular pathways, treatment modalities, outcomes, and insights into therapeutic resistance (14, 15). To synthesize this information, a thematic approach was adopted, grouping studies by their focus on molecular pathogenesis, epidemiological trends, treatment strategies, and resistance mechanisms in MB.

Quality assessment of the studies was an integral part of the process. The Newcastle-Ottawa Scale was utilized for evaluating observational studies, while randomized trials were assessed using the Cochrane risk-of-bias tool. Each study was scrutinized for its scientific rigor, relevance to the topic of MB, and the reliability of its findings. (16)

The review was organized thematically, with a clear and coherent narrative structure. Findings from various studies were integrated to present a comprehensive overview of MB (17). This approach ensured that the review not only highlighted the consensus within the scientific community but also shed light on any discrepancies in the findings.

To ensure the continued relevance and accuracy of the review, a strategy for periodic updates was established. The team planned to conduct annual searches of the databases to incorporate new studies related to MB, thus maintaining the currency of the review in a rapidly evolving field.

FINDINGS

The molecular classification and targeted therapeutic approaches for Medulloblastoma (MB) are essential aspects of understanding and treating this complex brain tumor. MB's incidence, as highlighted by Zahraa et al. (2021) (1), varies with age, gender, and race,

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being more prevalent in males and white populations. Genetic factors like germline mutations in genes such as APC, TP53, PTCH1, BRCA2, PALB2, and SUFU are crucial in MB's development, as noted by Northcott et al. (2019) (2).

Table 1, sourced from Juraschka & Taylor (2019) (18), presents a detailed molecular classification of MB. This classification divides MB into four subgroups: WNT, SHH, Group 3, and Group 4. Each subgroup is characterized by its own frequency of occurrence, gender ratio, typical diagnostic age, specific mutated genes, amplified genes, primary tumor location, patterns of genetic gain or loss of function, survival rate, and metastatic potential. For instance, the WNT subgroup, accounting for 5-10% of cases, is found in both children and adults, often involves a mutation in the CTNNB1 gene, and shows a high survival rate of over 95%. In contrast, Group 3 MB, found mainly in infants and children and constituting 25% of cases, is associated with mutations in KMT2D and SMARCA4, has a less favorable survival rate of less than 60%, and is more likely to be metastatic.

Table 1 Molecular Classification of Medulloblastoma

Subgroup	Frequency	Gender Ratio (M:F)	Diagnostic Age	Mutated Gene	Amplified Genes	Location	Gain/Loss of Function	Survival Rate	Metastatic
WNT	5-10%	1:1	Children, Adults	CTNNB1	None	Brain stem	6	> 95%	No
SHH	30%	1:1	All age groups	PTCH1 (43%), SUFU (10%), TP53 (9.4%)	MYCN, GLI1/2	Cerebellar hemisphere	3q, 9p, 9q, 10q, 17p	75%	No
Group 3	25%	2:1	Infants and Children	KMT2D, SMARCA4	MYC (17%), MYCN (5%), OTX2 (3%)	Neuronal stem cells	1q, 7, 18, 8, 11, 10q, 16q	< 60%	Yes
Group 4	35-40%	3:1	Children	KDM6A, KTM2C	MYCN, OTX2, CDK6 (6%)	Midline	7, 18q, 8, 11p	Standard (80%), High risk (60%)	Yes
Juraschka and Taylor, 2019									

Table 2 Targeted Drugs Under Clinical Trials for Medulloblastoma

Signaling Pathway	Targeted Drug	Clinical Effects
Hedgehog	Vismodegib, LDE225, IPI-926	- Reduce tumor growth - Increase survival rate
WNT	Rucaparib, Veliparib, Olaparib, OTSA101	- Enhanced TMZ (Temozolomide)
Notch	γ-secretase inhibitor (MK-0752)	- Initiate apoptosis - Enhance cell cycle arrest
PI3K	LY294002, BKM120	- Reduce growth & proliferation - Sensitive towards chemotherapy
PI3K-mTOR	BEZ235 (Sirolimus)	- Inhibit growth & proliferation - Promote apoptosis
Ras/MEK/ERK	U0126	- Inhibit cell migration
GF/Cytokine Receptor	Lapatinib, Erlotinib, Bevacizumab	- Reduce proliferation
p53/HDM2	Nutlin 3a	- Reduce growth of MB
MacDonald et al., 2014		

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Table 2, derived from MacDonald, T. J. (19) outlines the targeted drugs under clinical trials for MB. This table reflects the efforts to align treatment strategies with specific molecular subgroups and pathways. For example, drugs like Vismodegib, LDE225, and IPI-926 target the Hedgehog signaling pathway, aiming to reduce tumor growth and increase the survival rate. Similarly, drugs targeting the WNT pathway, such as Rucaparib and Veliparib, are used to enhance the efficacy of Temozolomide. Other pathways like Notch, PI3K, PI3K-mTOR, Ras/MEK/ERK, GF/Cytokine Receptor, and p53/HDM2 are also being targeted, with drugs designed to inhibit tumor growth, reduce proliferation, initiate apoptosis, and in some cases, make cancer cells more sensitive to chemotherapy.

Integrating these findings, it becomes evident that MB's treatment is increasingly moving towards a more personalized approach, guided by the molecular characteristics of each subgroup. This approach not only considers the specific genetic makeup of the tumor but also the demographic factors that might influence both the incidence and progression of the disease. The ongoing research and clinical trials of targeted therapies hold promise for more effective and tailored treatments for MB, aiming to improve survival rates and reduce the long-term impacts of treatment.

DISCUSSION

Medulloblastoma (MB), a predominant pediatric brain tumor, exhibits distinct hallmarks that have been extensively studied to understand its development and progression (20, 21). The research underscores the importance of specific signaling pathways that are pivotal in both embryonic development and in the pathogenesis of MB. Notably, these pathways include Wnt, PI3K/Akt/mTOR, Ras/MEK/ERK, Notch, and Hedgehog signaling, each playing a critical role in cell proliferation, differentiation, survival, and growth (19, 22).

The aberrations in these pathways often manifest as germline mutations, leading to either the activation or inactivation of cancer-promoting genes. For instance, mutations in the CTNNB1 gene within the Wnt pathway and alterations in the PTCH1 gene in the Hedgehog pathway are significant contributors to MB pathogenesis. These mutations disrupt normal cellular processes, making the cells self-sufficient in growth signaling and insensitive to growth inhibitory signals (19, 22). Tumor cells in MB exhibit a marked evasion of apoptosis, a mechanism that typically serves to eliminate defective cells, thus allowing for the uncontrolled proliferation of cancerous cells. This evasion is facilitated through mechanisms such as the inhibition of caspase activation and degradation of pro-apoptotic factors, contributing to MB's aggressive nature.

Another significant aspect of MB's pathology is its limitless replicative potential. Cancer cells in MB achieve this through mechanisms like the activation of telomerase enzymes, mutations, and chromosomal abnormalities, which allow for continuous cell division beyond the normal limits. This aspect is particularly concerning as it leads to tumor aggressiveness and metastasis, posing significant challenges in treatment (18).

The role of sustained angiogenesis in MB, especially in the WNT subgroup, is also noteworthy. The interaction between WNT and NOTCH signaling within endothelial cells contributes to the modification of the surrounding tumor microenvironment, facilitating tumor growth and progression (23, 24). Furthermore, the ability of MB cells to invade and metastasize is exemplified by their modification of the cerebrospinal fluid, facilitating leptomeningeal invasion and allowing the tumor to access essential nutrients and spread to other CNS locations (25, 26).

Defects in DNA repair mechanisms have emerged as a crucial factor in MB progression and treatment resistance. Studies have identified harmful variants in DNA repair genes like MSH2 and NBN, which not only contribute to MB development but also influence the response to chemotherapy, leading to adverse treatment outcomes (27).

Diagnosis of MB primarily relies on imaging techniques like CT and MRI. These modalities help in identifying the characteristic features of MB tumors, such as their appearance, enhancement patterns, and diffusion properties, which are essential for accurate diagnosis and treatment planning (28, 29).

Treatment strategies for MB have evolved to include both immunotherapy and targeted drug therapy. Immunotherapy approaches, such as CAR T lymphocyte treatment and checkpoint inhibitors, aim to overcome MB's immune-suppressing abilities, while targeted drug therapies focus on specific aberrant signaling pathways in MB cells. These strategies represent a shift towards personalized medicine, offering hope for more effective treatments with fewer side effects (1, 19, 30).

In conclusion, significant advances have been made in understanding the complex nature of MB. The molecular classification of MB into subgroups has provided crucial insights into its pathophysiology, influencing both diagnostic and therapeutic strategies. As the focus shifts towards improving the quality-of-life post-therapy and minimizing long-term adverse reactions, continued research and development of new, targeted, and less toxic treatments remain imperative. The goal is not only to improve survival rates but also to ensure a better quality of life for MB survivors, emphasizing the need for ongoing research and innovation in this field.

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CONCLUSION

The in-depth understanding of Medulloblastoma (MB) has significantly advanced in recent years, largely due to the molecular classification of the disease into specific subgroups and the identification of key signaling pathways involved in its pathogenesis. This knowledge has crucial implications for both diagnosis and treatment, facilitating the development of more targeted and personalized therapeutic strategies. As a result, treatments are evolving from generalized approaches to more precise modalities, such as immunotherapies and drugs targeting specific genetic mutations and signaling pathways. These advancements not only hold the promise of improving survival rates but also aim to reduce the long-term adverse effects of treatments, thereby enhancing the quality of life for MB patients. The ongoing research and emerging insights into MB's molecular mechanisms continue to be pivotal in shaping future therapeutic strategies, emphasizing the importance of continued innovation and exploration in the field of oncology.

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