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REVIEW

Metabolomic profiling of childhood medulloblastoma: contributions and relevance to diagnosis and molecular subtyping

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Abstract

The incidence of brain tumors among children is second only to acute lymphoblastic leukemia, but the mortality rate of brain tumors has exceeded that of leukemia, making it the most common cause of death among children. Medulloblastoma (MB) is the most common type of brain tumor among children. Malignant brain tumors have strong invasion and metastasis capabilities, can spread through cerebrospinal fluid, and have a high mortality rate. In 2010, the World Health Organization first divided MB into four molecular subtypes based on molecular markers: WNT, Sonic hedgehog (SHH), Group 3, and Group 4. MB is a highly heterogeneous tumor. Different molecular subtypes of MB have significantly different clinical, pathological, and molecular characteristics. The prognosis of MB varies significantly among patients with different subtypes of this cancer. Thus, it is needed to study new diagnostic and therapeutic strategies. Metabolomics is an advanced analytical technology that uses various spectroscopic, electrochemical, and data analysis technologies to study and analyze the body's metabolites. By detecting changes in metabolite types and quantities in different types of samples, it can sensitively discover the physiological and pathological changes in the body. It has great potential for clinical application and personalized medicine. It is promising and can help develop personalized treatment strategies based on the metabolic profiles of individuals. It can unravel the unique metabolic profiles of MB, which may revolutionize our understanding of the disease and improve patients' outcomes.

Keywords Medulloblastoma · Metabolomics · Biomarkers · Molecular typing · Central nervous system tumors in children

Introduction

In the past decade, integrated genomic studies have fundamentally changed the understanding of medulloblastoma. Four major molecular subtypes have been identified, namely WNT, SHH, Group 3, and Group 4, which have unique clinicopathological and molecular characteristics (Cotter and Hawkins 2022). The WNT and SHH subgroups are characterized by mutations that activate key regulators of the corresponding signaling pathways, while Group 3 and Group 4 are characterized by overlapping chromosomal changes (Fang et al. 2022a). The different genetic characteristics and different onset patterns of these molecular subgroups are associated with different clinical outcomes. WNT patients have a very good prognosis under current treatment regimens (5-year survival rate exceeds 95%), and there have been many studies in recent years on reducing treatment (Carrie et al. 2020). The prognosis of SHH type depends largely on the patient's age and specific genetic characteristics, among which children with TP53 mutations have a poor prognosis (Fang et al. 2022b). Group 3 has the worst prognosis, especially when accompanied by MYC amplification, while Group 4 has a moderate prognosis. A large number of studies have confirmed that the accuracy of molecular typing of medulloblastoma in predicting prognosis is significantly higher than that of tissue typing (Schwalbe et al. 2017). Molecular typing has also laid a solid theoretical foundation for the personalized treatment of medulloblastoma. Once the genotype is clear, we can stratify the risk according to the molecular typing, so as to carry out more precise treatment. Currently, molecular typing diagnosis

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is obtained by genomic analysis of postoperative tissue specimens, which takes 3–4 weeks, is relatively expensive, and is not conducive to the formulation of early treatment plans. Metabolomics is an emerging discipline. Due to their unique biological characteristics, in terms of metabolism, tumor cells have different characteristics compared to normal cells (An and Duan 2022). Compared to normal cells, tumor cells usually have high glucose metabolism and abnormal amino acid and lipid metabolism (Zhu et al. 2022). These metabolic characteristics provide energy and nutritional support for the rapid proliferation, invasion, and metastasis of tumors. Metabolomics is a technical means to systematically study cell or tissue metabolites (Ji et al. 2024a). In 1999, Nicholson et al. proposed a discipline that uses various spectral, electrochemical, and data analysis techniques to analyze the body's metabolites, especially small molecules with a molecular weight of less than 1000 Da after being stimulated by external stimuli (Danzi et al. 2023). By detecting and analyzing metabolites in tumor tissues or body fluids, the metabolic state of tumor cells can be fully reflected and their unique metabolic characteristics can be discovered (Zuo et al. 2022). It is another important part of systems biology after genomics, transcriptomics, and proteomics (Neagu et al. 2023; Dar et al. 2023). Metabolomics methods can be divided into targeted and non-targeted methods (Singh et al. 2019). The non-targeted method is usually used in the discovery stage of biomarker research, while the targeted method is mostly used for biomarker verification (Wang et al. 2023). Commonly used detection methods include gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), and nuclear magnetic resonance (NMR) technology (Hu et al. 2020) (Fig. 1). Their working mechanism is basically to identify and quantify the compounds in the sample through chromatography or mass spectrometry and electromagnetic radiation. This information not only helps understand the metabolism of tumors but also can be used to develop new diagnostic markers and therapeutic targets (Taunk et al. 2024). For example, lactate dehydrogenase levels can be elevated in various cancers, making it a non-specific marker which provide a new entry point for early diagnosis and personalized treatment (Yu et al. 2024a). This review focused on the metabolic changes associated with MB, emphasizing the potential of metabolomics to identify

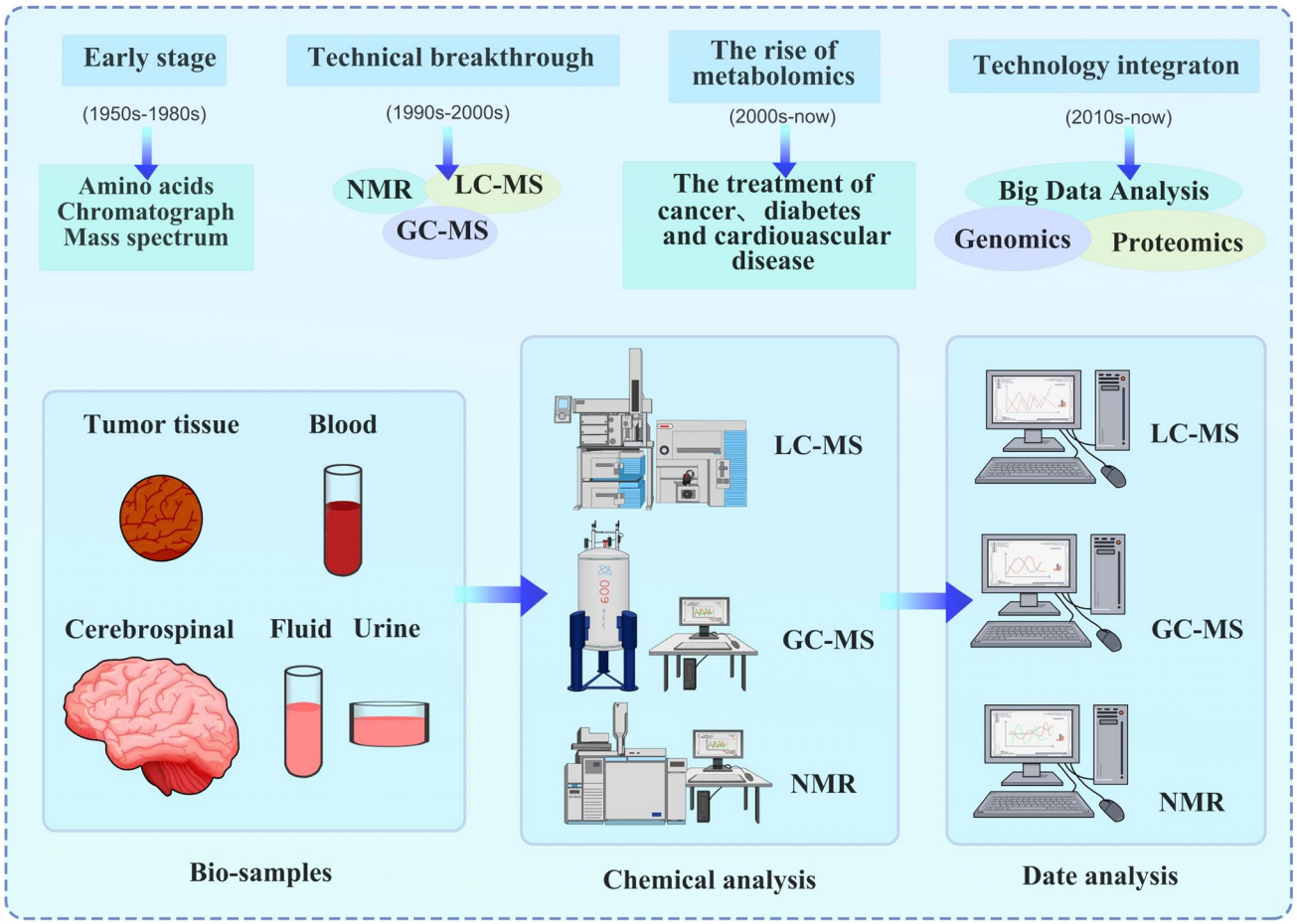

Fig. 1 Introduction to metabolomics

biomarkers for early detection, diagnosis, treatment, prognosis, and molecular subtyping.

Overview of the metabolic characteristics of tumors

The rapid proliferation, invasion, and metastasis of tumor cells largely depend on their special metabolic processes. Compared to normal cells, tumor cells usually exhibit the following metabolic characteristics:

Hyperglycolytic metabolism

Even under aerobic conditions, tumor cells tend to utilize the glycolytic metabolic pathway rather than the more efficient oxidative phosphorylation metabolism (Cheng et al. 2024; Ji et al. 2024b). Tumor cells highly rely on glycolytic metabolism to provide energy and metabolic intermediates for their own proliferation. In addition, tumor cells also increase the expression of lactate dehydrogenase, converting more pyruvate into lactate, further aggravating the tendency for glycolytic metabolism (Pereira et al. 2020; Peng et al. 2024).

Abnormal amino acid metabolism

Amino acids are important nutrients for tumor cell growth, and their metabolism undergoes a series of changes (Wang and Zhang 2024a; Majtan et al. 2024). For example, tumor cells generally show a high metabolism of glutamine and can use glutamine as a carbon and nitrogen source to provide energy and synthesize raw materials for themselves (Zhang et al. 2024a; Park et al. 2024). In addition, the metabolism of certain amino acids is different in tumor cells; For example, abnormal tryptophan metabolism is associated with increased immunosuppressive substances and accumulation of catecholamines. (Bickerdike et al. 2024; Zheng et al. 2024; Duan et al. 2024).

Abnormal lipid metabolism

Lipid metabolism is also an important component for the vigorous growth of tumor cells (Li et al. 2023). Tumor cells usually show enhanced fatty acid synthesis and hyperlipidemia, which provide essential lipid molecules for their own membrane structure and signal transduction (Zeng et al. 2024). In addition, tumor cells can also use exogenous lipids as an energy source to meet their needs for rapid proliferation (Chen et al. 2024; Cao et al. 2024).

Enhanced anaerobic metabolism

Since there is often a hypoxic microenvironment in solid tumors, tumor cells must adopt some metabolic strategies to cope with the hypoxic stress (Jayathilake et al. 2024). Compared to normal cells, tumor cells show a stronger capacity for anaerobic metabolism, such as glycolysis and glutamine metabolism, to provide energy for their growth (Qannita et al. 2024). At the same time, tumor cells can maintain their own anaerobic metabolism by regulating the expression and function of some metabolic enzymes (Zhang et al. 2024b) (Fig. 2).

Cancer cells can also reprogram their metabolism to meet energy and biosynthetic intermediates needs and maintain their integrity in hostile and hypoxic environments. These reprogramming activities are currently considered as hallmarks of cancer, but which pathways are involved in regulating metabolic plasticity remains unclear (Melone et al. 2018; Park et al. 2019). It has been reported that MYC-amplified medulloblastoma orthotopic xenografts exhibit upregulation of the TCA cycle and synthesis of nucleotides, hexosamine, amino acids, and glutathione compared with normal brain. Glucose uptake and utilization were significantly higher in orthotopic xenografts compared with flank xenografts and cultured cells (Pham et al. 2022). In general, these metabolic characteristics of tumor cells provide energy and nutritional support for their malignant characteristics, such as rapid proliferation, invasion, and metastasis, which make them new targets for tumor treatment.

Application of metabolomics research in the field of cancer

As our understanding of abnormal tumor metabolism continues to deepen, metabolomics technology is increasingly used in basic research on cancer and clinical practice (Mao et al. 2024). As a technical means of systematically studying cell or tissue metabolites, metabolomics can comprehensively reflect the metabolic state of tumor cells and provide an important tool for understanding the mechanism of tumor metabolism (Yu et al. 2024b).

Application of metabolomics in tumor diagnosis

The discovery of tumor cell-specific metabolic characteristics provides new opportunities for the early diagnosis of tumors. For example, some potential diagnostic biomarkers were found in the metabolomics study of lung cancer, such as lactate dehydrogenase and glutamine synthetase (Kinslow et al. 2024; Neves et al. 2024; Wu et al. 2024). These metabolites can reflect the metabolic characteristics of lung cancer cells and are expected to be used for early screening

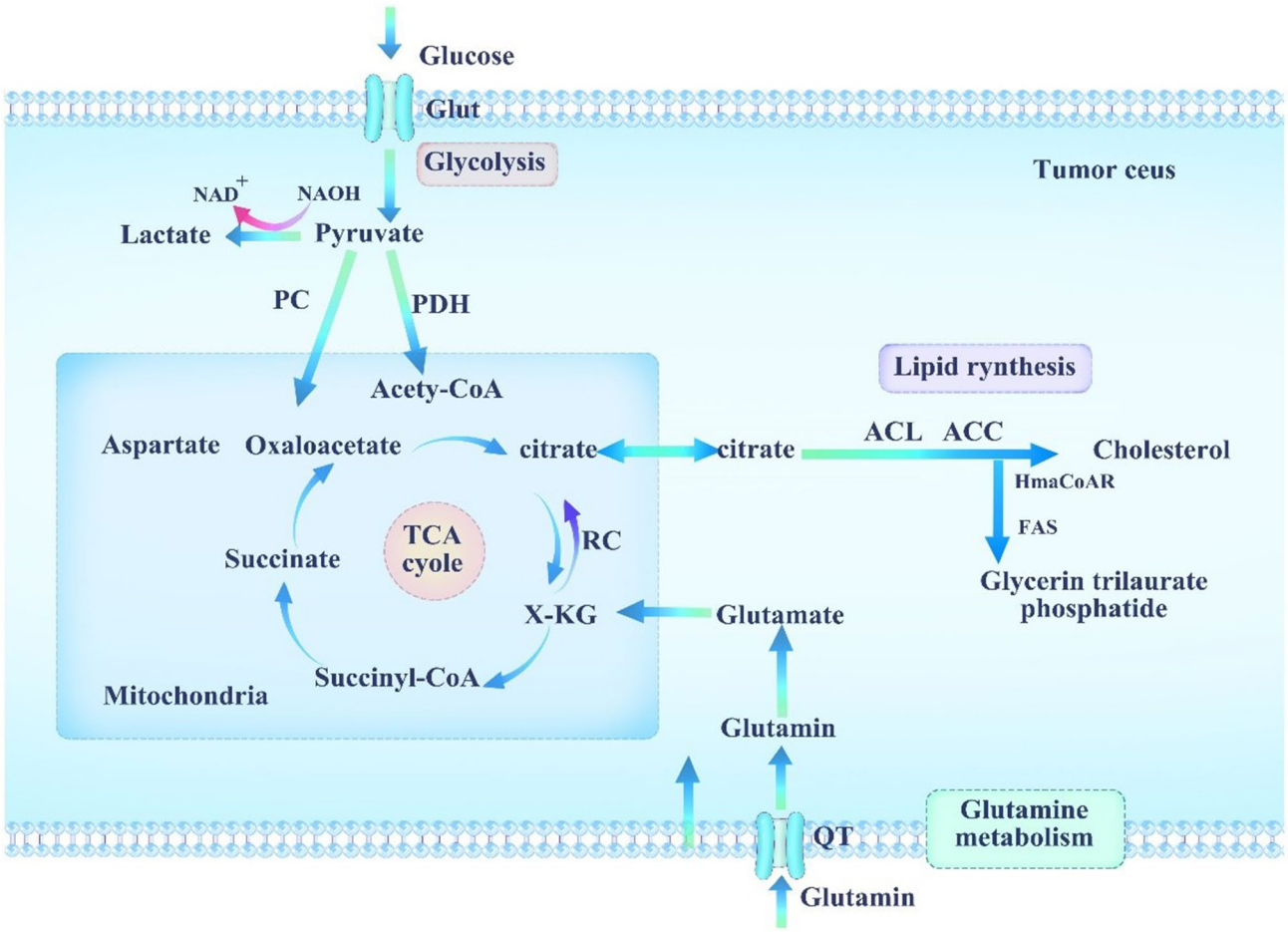

Fig. 2 Introduction to the metabolic characteristics of tumors

and auxiliary diagnosis of lung cancer. In the metabolomics study of breast cancer, Wang et al. established a metabolite biomarker model including glutamate, erythritol acid, docosahexaenoic acid, and propionylcarnitine for the diagnosis of breast cancer (Wang et al. 2024b). Zniber et al.'s study showed the capability of 1 H NMR urine metabolomics in detecting distinct metabolic profiles between prostate cancer and benign prostatic hyperplasia, as well as among different Gleason grade groups (Zniber et al. 2024). Noriega et al.'s study supports the potential use of urinary fatty acids as a stable and non-invasive alternative test for prostate cancer diagnosis (Noriega et al. 2024). In addition, there are some reports indicate that developing effective lactate dehydrogenase or glutamine synthetase inhibitors may inhibit tumor cell growth and become an effective strategy for treating tumors (Gubser et al. 2024).

The role of metabolomics in tumor classification and prognosis prediction

Tumor cells of different subtypes or stages exhibit marked differences in metabolic characteristics (Ma et al. 2024). Metabolomics analysis can discover these differences and provide a basis for tumor classification and prognosis prediction. For example, it was found that IDH gene-mutant glioma cells show unique metabolic phenotypes, characterized by the accumulation of hydroxyglutaric acid and 2-hydroxyglutaric acid (Maekawa et al. 2024). These metabolic markers help distinguish different subtypes of gliomas and provide a basis for clinical diagnosis and prognosis.

Application of metabolomics in personalized tumor treatment

The discovery of therapeutic targets is the key to achieving personalized tumor treatment. Metabolomics studies have found that tumor cells of different subtypes or stages have unique characteristics at the metabolic level, which can help find new therapeutic targets. For example, in the study of triple-negative breast cancer, metabolomics analysis found that this type of tumor cells has the characteristic of enhanced glutamine metabolism (Winter et al. 2023). Further studies have confirmed that drugs targeting glutamine metabolism can inhibit the proliferation of triple-negative

breast cancer, providing a new strategy for personalized treatment of this tumor (Carneiro et al. 2023; Berardi et al. 2022). In general, metabolomics provides us with an important technical means to deeply understand the metabolic characteristics of tumors and discover potential diagnostic and therapeutic targets. With the advancement of detection technologies and continuous improvements in bioinformatics analysis, metabolomics will play an important role in the clinical management of tumors.

Background and advances in metabolomics for diagnosis and prediction of molecular typing of childhood medulloblastoma

Metabolomics is a systematic research method that can comprehensively reflect the metabolic state and energy metabolism characteristics of tumor cells. Metabolomics analysis of childhood MB can identify some unique metabolic characteristics, helping design more accurate diagnostic methods and molecular typing strategies. These results not only enhance the accuracy of diagnosis but also provide a basis for individualized treatment and improve the prognosis of childhood MB. To date, only a few studies have reported comprehensive metabolomics analysis of a large cohort of MB patients, and all studies have only identified metabolic changes and did not find specific characteristics of subpopulations (Table 1). As early as 2014, Wilson et al. first identified glutamate as a predictive biomarker for survival in childhood MB using magnetic resonance spectroscopy (MRS) technology and highlighted the importance of detailed studies on MB metabolism (Wilson et al. 2014). In 2017, Woolman et al. used the handheld Picosecond InfraRed Laser (PIRL) technology developed by their team to perform mass spectrometry analysis and analyze 19 mouse xenograft tumors. They accurately distinguished the SHH group (with an accuracy of 98%), but no validation of human tissue samples was conducted (Woolman et al. 2017). In 2018, Bennett et al. used high-resolution magic-angle spinning (HR-MAS) to obtain tissue metabolite profiles from cerebellar ependymoma ($n=18$), medulloblastoma ($n=36$), pilocytic astrocytoma ($n=24$), and atypical teratoid/rhabdoid tumor ($n=5$) samples. The results showed that elevated inositol was a characteristic of ependymoma. In addition, they found that glutamine, hypotaurine, and N-acetylaspartate were elevated in pilocytic astrocytoma, while high taurine, phosphorylcholine, and glycine levels were used to distinguish MB (Bennett et al. 2018). Lee et al. analyzed cerebrospinal fluid samples

Table 1 Summary of metabolomics studies on MB among children

Researcher	Year	Methodology	Samples	Results
Wilson et al.	(2014)	Magnetic Resonance Spectroscopy	35 human MB tissue samples	Glutamate as a predictive biomarker for survival in children with medulloblastoma
Woolman et al.	(2017)	handheld Picosecond InfraRed Laser	6 different established MB cell lines: D341, D458, MED8A (for Group 3) and ONS76, DAOY, UW228 (for the SHH subgroup)	PIRL-MS analysis of ex vivo medulloblastoma tumors was successful in 98% of subgroups
Bennett et al.	(2018)	High Resolution Magic-angle Spinning	35 human MB tissue samples and 47 other brain malignant tumor tissue samples	High levels of taurine, phosphocholine, and glycine can be used to differentiate medulloblastoma from other brain tumors.
Lee et al.	(2022)	RNA sequencing and high-resolution mass spectrometry	40 human MB cerebrospinal fluid samples	The tricarboxylic acid cycle metabolites (such as citric acid, succinic acid, etc.) and other metabolites (such as differential propionic acid, N-acetyl aspartate, etc.) in the cerebrospinal fluid of MB patients were significantly increased, and the metabolic panel Both biological and lipidomic data revealed indicators of tumor hypoxia.
Liu et al.	(2022)	Liquid Chromatography-Mass Spectrometry	111 human MB urine samples, 31 patients with malignant brain cancer, 51 patients with benign brain disease, 118 healthy human controls	The combination of these two metabolites, tetrahydroacetone and corticosterone, showed diagnostic accuracy in distinguishing MB from non-MB with an AUC value of 0.851.
Huang et al.	(2023)	Ultra Performance Liquid Chromatography-Quadrupole / Electrospray-Mass Spectrometry/Mass Spectrometry	33 human MB serum samples, 16 healthy control	Six metabolites (Phosphatidic acid (8:0/15:0), 3'-Sialyllactose, Isocoproporphyrin, Acetylspermidine, Fructoseglycine and 3-Hydroxydodecanedioate) were identified as potential biomarkers for the diagnosis of MB with high specificity and accuracy (AUC > 0.98).
Funke et al.	(2023)	Bioinformatics Analysis	1288 Bulk RNA sequencing data	Genes involved in inositol phospholipid and nucleotide metabolism are significantly associated with patient prognosis
Kohe et al.	(2024)	in vivo Magnetic Resonance Spectroscopy	86 human MB tissue samples	Glutamate levels can independently predict survival in medulloblastoma

from 40 patients with MB and 11 normal controls in 2022. Although it is difficult to divide MB into different molecular subtypes solely based on the transcriptomics, metabolomics, and lipidomics analysis of cerebrospinal fluid, this study identified a group of metabolic characteristics that can distinguish cancer samples from normal samples. The metabolites of tricarboxylic acid cycle, such as citric acid, succinic acid, etc., and other metabolites, such as aberrant propionic acid and N-acetyl thiamine, were significantly elevated in the cerebrospinal fluid of patients with MB, and both metabolomics and lipidomics showed indicators of tumor hypoxia (Lee et al. 2022). This study provides new insights and candidate biomarkers for the metabolomics studies on MB based on cerebrospinal fluid samples, improving the diagnosis and monitoring of MB. In another study, metabolomic analysis of urine samples from patients with MB compared to patients with other brain tumors and healthy subjects showed that the combination of two metabolites, tetrahydrocortisone and cortolone, showed diagnostic accuracy for distinguishing MB from non-MB, with an AUC value of 0.851 (Liu et al. 2022). In 2023, Huang et al. used ultra-performance liquid chromatography-quadrupole (UPLC-Q)/electrospray-mass spectrometry (E-MS)/mass spectrometry (MS) to conduct metabolomics research and explore the pathogenesis of MB in children. They found 25 significantly changed metabolites, 6 of which (phosphatidic acid, 3'-sialyllactose, isoaerporphyrin, acetylspermidine, fructoseglycine, and 3-hydroxydodecanoic acid) had high diagnostic values (AUC > 0.98). Functional analysis found three impaired metabolic pathways, including arachidonic acid metabolism, steroid hormone biosynthesis, and folate-related metabolism. Modulation of these pathways may reduce the mortality rate of MB (Huang et al. 2023). These metabolic markers may also serve as potential diagnostic biomarkers. Funke et al. comprehensively explored metabolic differences between and within MB groups at the genome and transcriptome levels. The study analyzed data from 1,288 patients from 4 independent MB cohorts, including metabolic gene expression characteristics based on bulk RNA sequencing. Based on metabolic heterogeneity in single-cell RNA sequencing and metabolism-related gene mutations at the genome level, it was found that genes involved in inositol phospholipid and nucleotide metabolism are significantly associated with MB patients' prognosis. Frequently mutated metabolic genes play a central role in the development of MB, upregulation of pyrimidine metabolism was associated with significantly decreased overall survival, whereas inositol phosphate (IP) metabolism gene expression was associated with a better prognosis (Funke et al. 2023). In 2024, Kohe et al. analyzed the metabolite profiles of 86 MB tissue samples, used unsupervised cluster analysis and support vector machine (SVM) models to classify molecular subtypes, and evaluated the feasibility of in-vivo MRS metabolite quantitative data for predicting molecular subtypes. The results showed that the accuracy of the SVM classifier based on tissue metabolites reached 89% (including 100% for the WNT subtype). Furthermore, it was shown that glutamate levels can independently predict the survival of patients with MB. These findings are of great significance for improving the non-invasive diagnosis and molecular typing of MB (Kohe et al. 2024) (Table 1). In general, metabolomics provides an important technical means to unravel the metabolic characteristics of tumors and discover potential diagnostic and therapeutic targets.

Future perspectives

We continue to explore the metabolic network and regulatory mechanism of childhood MB, further verifying the application value of metabolic markers in diagnosis and molecular typing, exploring metabolic regulation as a new treatment strategy, and improving the prognosis of patients. Briefly, metabolomics research on childhood MB has brought new opportunities for the diagnosis and molecular typing of the disease and provided an important scientific basis for clinical practice. Continuous in-depth metabolomics research can help clarify the pathogenesis of the tumor and provide patients with more accurate diagnoses and treatment plans. There are also some studies that use machine learning to determine sample-related functions and use machine learning for more detailed classification (Zhou et al. 2024). In addition, large-scale studies have found that mutations and structural changes in metabolic modifiers, abnormal DNA methylation, and histone modification features can lead to abnormalities in the cancer epigenome. Therefore, the treatment of cancer with epigenetic modifiers has received increasing attention, and inhibitors of various epigenetic regulators have been intensively studied in clinical trials (Marquardt et al. 2023; Fang et al. 2022a). We believe this is a promising area of development.

Limitations

Although metabolomics has made significant progress in the field of cancer, there remain some challenges that need to be solved. The first is the problem of metabolomics data interpretation and integration. Tumor metabolism is a complex and systematic process. A single metabolomics analysis cannot fully explain its biological behavior. How to effectively integrate metabolomics data with multi-omics data, such as genomics and proteomics, is one of the focuses of future research. The second problem is the clinical transformation of metabolomics markers. Although some potential metabolomics markers have been discovered, most of them

are still limited to basic research and have not yet been clinically applied. How to promote these metabolomics markers from the laboratory setting to the clinical setting has become a bottleneck that needs to be solved urgently. There are also limitations of metabolic-targeted therapy. Although metabolic abnormalities provide new targets for tumor treatment, metabolic-targeted therapy alone is usually ineffective. How to effectively combine metabolic-targeted therapy with other treatment methods is the key to improving efficacy. Finally, there is continuous innovation in technical means. The continuous innovation and improvement of metabolomics technology, such as the development of new detection equipment and the optimization of big data analysis algorithms, can provide stronger technical support for tumor metabolism research.

Conclusion

There are still many unknown aspects of the development and evolution of MB, and the differences between genotype and phenotype need to be further explored. Only by comprehensively identifying metabolites and their concentrations at the whole tissue and single-cell levels, we can gain a deep understanding of the complex metabolic processes involved in cells and tissues and unravel the molecular mechanisms associated with tumorigenesis and cancer evolution. Spatial metabolomics technology can map the distribution of metabolites in tissues, revealing spatial heterogeneity that may play a key role in tumor development and treatment response (Hu et al. 2024; Zhu et al. 2024). Single-cell metabolomics can help unravel metabolic changes at the level of individual cells, reveal the diversity within tumor populations, and provide a deeper understanding of the cellular dynamics that drive disease progression (Bidgood et al. 2024; Fan et al. 2024). These cutting-edge technologies provide valuable means to fill the existing gap between genotype and phenotype, pave the way for improving diagnostic accuracy and personalized treatment strategies, and are expected to improve the prognosis of patients with MB. In general, tumor metabolomics research is in rapid development, and will surely bring new opportunities for early diagnosis, precise classification, and personalized treatment of tumors in the future. We believe that through continuous in-depth basic research and technological innovation, metabolomics can play an important role in the clinical management of tumors.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rong Huang, Xiaoxu Lu and Xueming Sun. The first draft of the manuscript was written by Rong Huang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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