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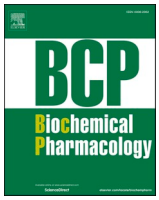

Review

Surviving the hunger games: Metabolic reprogramming in medulloblastoma

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ABSTRACT

Medulloblastoma is a highly malignant pediatric brain tumor characterized by its aggressive nature and limited treatment options. Metabolic changes have recently emerged as key factors in the development, progression, and response to therapy in various types of cancer. Cancer cells exhibit remarkable adaptability by modulating glucose, lipids, amino acids, and nucleotide metabolism to survive in nutrient- and oxygen-deprived environments. Although medulloblastoma has been extensively studied from a genomic perspective, leading to the identification of four subgroups and their respective subcategories, the investigation of its metabolic phenotype has remained relatively understudied. This review focus on the available literature, aiming to summarize the current knowledge about the main metabolic pathways that are deregulated in medulloblastoma tumors, while emphasizing the controversial aspects and the progress that is yet to be made. Furthermore, we underscored the insights gained so far regarding the impact of metabolism on the development of drug resistance in medulloblastoma and the therapeutic strategies employed to target specific metabolic pathways.

Abbreviations: ABAT, 4-Aminobutyrate aminotransferase; ACC1, Ccetyl-CoA Carboxylase 1; ACOX1, Acyl-CoA Oxidase 1; ALDO, Aldolase; ARHGAP11B, Rho GTPase Activating Protein 11B; ATP, Adenosine triphosphate; ATRTs, Atypical Teratoid Rhabdoid Tumors; BMI1, Polycomb Group RING Finger Protein 4; BTICs, Brain Tumor-Initiating Cells; CDK, Cyclin-dependent kinase; CHD7, Chromodomain Helicase DNA Binding Protein 7; CNS, Central Nervous System; *CREBBP*, CREB Binding Protein; CSC, Cancer Stem Cell; CSF, Cerebrospinal Fluid; CSI, Craniospinal Irradiation; CtBP2, C-Terminal Binding Protein 2; CTNNB1, Catenin Beta 1; DCA, Dichloroacetate; *DDX3X*, DEAD-box helicase 3 X-linked; DHODH, Dihydroorotate Dehydrogenase; E2F1, E2F Transcription Factor 1; ENO, Enolase; ETC, Electron Transport Chain; FAO, Fatty acid oxidation; FASN, Fatty Acid Synthase; FDA, Food And Drug Administration; GAPDH, Glyceraldehyde-3-Phosphate Dehydrogenase; *GFI1*, Growth Factor Independent 1 Transcriptional Repressor; *GLI1-2*, GLI family zinc finger 1–2; GLS2, Glutaminase 2; GLUT1, Glucose Transporter 1; GPI, Glucose Transporter 3; GSEA, Geneset Enrichment Analysis; GTK, Glutamine Transaminase K; HDAC, Histone deacetylase; HIF-1a, Hypoxia-inducible factor 1-alpha; HK, Hexokinase; HMG-CoA, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; *KDM*, Lysine demethylase; *KMT2D*, Lysine Methyltransferase 2D; LDH, Lactate Dehydrogenase; LDHA, Lactate Dehydrogenase A; LDHB, Lactate Dehydrogenase B; MAGIC, Medulloblastoma Advanced Genomic International Consortium; MB, Medulloblastoma; MCAD, Medium-chain acyl-coenzyme A dehydrogenase; MCT1, Monocarboxylate transporter 1; mGPD, Mitochondrial Glycerol Phosphate Dehydrogenase; *MYCN*, Proto-Oncogene, BHLH Transcription Factor; NADH, Nicotinamide adenine dinucleotide; NEAT1, Nuclear Paraspeckle Assembly Transcript 1; NSCs, Neural Stem Cells; *OTX2*, Orthodenticle Homeobox 2; OXPHOS, Oxidative Phosphorilation; PDH, Pyruvate Dehydrogenase; PDK, Pyruvate Dehydrogenase Kinase; PDOX, Patient-Derived Orthotopic Xenograft; PDX, Patient-derived xenografts; PFK, Phosphofructokinase; PFKP, Phosphofructokinase, Platelet; PGAM, Phosphoglycerate mutase; PGK, Phosphoglycerate kinase; PI3K, PhosphatidylInositol 3-Kinase; *PRDM6*, PR-Domain Zinc Finger Protein 6; *PTCH1*, Patched 1; rMSLCs, radioresistant MB stem-like clones; ROS, Reactive Oxygen Species; SCD, Stearoyl-CoA desaturase; SHH, Sonic Hedgehog; *SMARCA4*, SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 4; SMO, Smoothened Receptor; *SUFU*, Negative Regulator Of Hedgehog Signaling; SVZ-BPs, Sub Ventricular Zone Basal Progenitors; TCA, Tricarboxylic Acid Cycle; *TERT*, Telomerase Reverse Transcriptase; TME, Tumor Microenvironment; WHO, World Health Organization; WNT, Wingless.

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1. Introduction

Embryonal tumors are the most common group of malignant neoplasms occurring in the Central Nervous System (CNS) [1,2]. Medulloblastoma (MB) is a cerebellar embryonal tumor that comprises 15% of all pediatric CNS malignancies and is a leading cause of cancer-related death in childhood [3]. MB patients undergo a multimodal treatment schedule which includes maximal safe resection, craniospinal irradiation (CSI), and adjuvant platinum- and alkylating agents-based chemotherapy. With the implementation of this aggressive therapeutic approach, along with proper risk stratification, the long-term survival rate of patients has significantly improved, with approximately 70–80% of patients now able to survive for extended periods. [4,5]. However, up to 30% of MB patients still experience tumor relapse, eventually dying for the progression of an almost incurable disease. Moreover, even in survivors, the frequent consequence of this treatment regimen is a high burden of long-term morbidity due to the application of aggressive therapies during the developmental age, heavily impacting the patient's quality of life [6–8]. Indeed, aggressively treated MB patients display a high incidence of secondary tumors (i.e., hematological malignancies) and neurotoxicity, including neurocognitive and endocrine disorders, and auditory sequelae [9–11].

During the last two decades, the deep molecular analysis of a large number of MB tumors allowed to recognize at least four MB subgroups, characterized by distinct molecular, biological, and clinical features [12] (Summarized in Table 1). It is now widely accepted that the observed MB intertumoral heterogeneity may be well resembled by these molecular subgroups which include: the wingless (WNT), the sonic hedgehog (SHH), the Group 3, and the Group 4 [13–16]. Accordingly, in 2016, with a recent update in 2021, the World Health Organization (WHO) introduced this paradigm classification into the clinical management of MB, now considering both the transcriptome and methylome analysis of these tumors as invaluable tools for their correct diagnosis, even replacing the histology-based classification employed until then [17–19]. Indeed, although all MBs are generally classified as highly malignant (grade IV) tumors, their molecular subgrouping better resembles their cell of origin and clinical behavior, identifying some patients that would benefit from treatment intensification or chemotherapy de-escalation [20–22]. More recently, based on additional molecular investigations performed on increasingly larger patient cohorts [20,23–27], this molecular classification has evolved beyond the four consensus subgroups by identifying additional smaller subcategories within each subgroup: the so-called MB "subtypes" [28–30]. In this context, it is now clear that MB subgrouping (and subtyping) should be considered an irrevocable *modus operandi* to be employed both experimentally and clinically to reliably approach MB heterogeneity [20].

1.1. Molecular classification

1.1.1. WNT medulloblastoma

WNT MB account for 10% of all MB cases, occurring primarily in older children (from 4 years of age; median 10–11 years) and very rarely in infants (<3 years of age). Tumors belonging to this subgroup usually develop in the midline cerebellum and are generally characterized by the absence of metastases at diagnosis (less than 5% of patients) and excellent outcome (>90% at 5 years) [25,31,32]. Wnt signaling overactivation is the clear hallmark of WNT MB, with most of them carrying *CTNNB1* (encoding for β-catenin) mutations (>85%) or pathogenic germline variants of *APC* [13,33]. Other frequently mutated genes are *DDX3X*, *SMARCA4*, *CREBBP*, and *KMT2D*, which encode for activated β-catenin interacting proteins [29,33]. In addition, monosomy of chromosome 6 is very frequently observed in *CTNNB1* mutated tumors [29,34]. Despite being consistently homogeneous, WNT MBs have been further subdivided into the α and β subtypes, characterized by differential age at diagnosis (10 versus 20, respectively) and frequency of monosomy of 6 [28]. Due to their intrinsic favorable prognosis, several ongoing trials are testing if a potential reduction of CSI and/or chemotherapy may still exert therapeutic efficacy, although displaying decreased long-term toxicity [22].

Table 1
Medulloblastoma subgroups. The table summarizes the clinical and the molecular features of medulloblastoma subgroups, based on data reported in references [12,13,16,25,29]. Created with Biorender.com.

	WNT	SHH	Group 3	Group 4
% of cases	10	30	25	35
Age				
Histology	Classic, LCA	Desmoplastic, Classic, LCA	Classic, LCA	Classic, LCA
% of metastases	5-10	15-20	40-45	35-40
Recurrence pattern	Local or metastatic	Local	Metastatic	Metastatic
Prognosis	Very good	Infants good Others intermediate	Poor	Intermediate
Recurrent mutation	CTNNB1 DDX3X SMARCA4 TP53	PTCH1 TERT SUFU SMO TP53	SMARCA4 KBTBD4 CTDNEP1 KMT2D	KDM6A ZMYM3 KTM2C KBTBD4
Cytogenetic events	6-	3q+, 9p+ 9q-, 10q-, 17p-	1q+, 7+, 18+ 8-, 10q-, 11-, 16q-, i17q-	7+, 18q+ 8-, 11p-, X-, i17q-

1.1.2. SHH medulloblastoma

SHH MBs occur in 25% of patients and display a peculiar bimodal age distribution, representing most of the infant and young adult patients [25]. These MBs generally arise from the cerebellar hemispheres, with very few of them localizing at the midline [31]. According to their title, SHH MB are characterized by mutations or copy number alterations at the level of SHH pathway-related genes, including inactivating mutations and deletions of *PTCH1* [17], *SUFU* mutations (mostly in infants) [29,35], and activating aberrations of *SMO* (almost exclusively in young adults)[36]. *GLI1-2* and *MYCN* amplifications and *TP53* mutations have been retrospectively associated with a poorer outcome in patients belonging to this subgroup [37–39]. Moreover, almost all these MBs also harbor mutations of the *TERT* promoter [40]. Hallmark cytogenetic events comprise loss of chromosomes 9q and 10q (inducing *PTCH1* and *SUFU* loss of heterozygosity), as well as 14q and 17p [23]. More recently, four molecular subtypes have been identified in SHH MB: SHH-β and SHH-γ tumors, mostly occurring in infants (with SHH-β displaying the worst outcome), and SHH-α and SHH-δ, corresponding to childhood and adolescent/adult MB cases, respectively. In particular, SHH-α MBs are enriched in *TP53* mutated tumors (30%), also displaying inferior survival relative to SHH-δ cases [28,30,36]. *TP53* mutant, *GLI2*- and *MYCN*-amplified SHH tumors display the most refractory behavior in this subgroup [39]. In this context, different studies are exploring the potential benefit of using SMO inhibitors, although with only initial encouraging results due to acquired resistance [41,42] and the obvious insensitivity of MB with downstream SHH pathway mutations (different from *SMO* and *PTCH1*) [36].

1.1.3. Group 3 medulloblastoma

Group 3 MB comprises 25% of all MB, mainly in infants and young children, and displays a significantly inferior outcome (40–60%) relative to the other subgroups. Moreover, up to 50% of these patients display metastases at diagnosis. They usually localize at the midline, with the involvement of the fourth ventricle [25]. *MYC* amplifications represent a recurrent hallmark of Group 3 MB (17%), clearly associated with a particularly dismal prognosis [15,16]. In contrast to WNT and SHH MBs, Group 3 is not defined by aberrations occurring in specific signaling pathways or recurrent genes, but rather by a defined transcriptional profile. In general, these tumors are characterized by genomic instability (frequently displaying isochromosome 17q) downstream affecting the proto-oncogenes *GFI1* and *GFI1B*. Mutations of *SMARCA4*, *KDM* genes, and *OTX2* have also been reported [23,43,44]. From a therapeutic point of view, Group 3 MB is subjected to treatment intensification and the potential adjuvant administration of Carboplatin as a radio-sensitizing agent [45]. BET-bromodomain, CDK, and HDAC inhibitors are also under investigation for Group 3 MB patients [46–49].

1.1.4. Group 4 medulloblastoma

Group 4 is the most common MB subgroup (35% of all MB) and occurs across all ages [25]. Differently from Group 3, these MBs are frequently driven by enhancer hijacking mediated *PRDM6* overexpression (17%), also bearing *MYCN* and *CDK6* mutations. Similar to Group 3, isochromosome 17q represents the most common cytogenetic aberration of Group 4 MB (80%), however without affecting patient outcome [24,29,50,51]. As the molecular landscape of Group 4 MB is very similar to Group 3, most of the above-mentioned therapeutic strategies have been proposed also for this subgroup. However, despite current therapy being sufficient to cure a large amount of Group 4 patients, further studies are needed to improve our understanding of the molecular drivers of these MBs for a properly tailored treatment [52].

Intriguingly, combined analysis of Group 3 and Group 4 MB cases disclosed the presence of eight different subtypes, with some of them sharing tumors from both subgroups. Collectively, each subtype seems to bear different driver events, peculiar cytogenetic alterations, and different prognoses [53]. In particular, subtypes I, V, and VII are mixed groups, with subtype I frequently displaying *OTX2* amplifications and *GFI* activation. Subtypes II, III, and IV comprise almost exclusively Group 3 MB. Subtypes II and III are classified as high-risk tumors since they are characterized by *MYC/MYCN* amplifications, whereas subtype IV is enriched for younger patients with a favorable prognosis (only in non-infants). Subtype VIII is considered a pure Group 4 subtype, occurring in older patients displaying a favorable 5-year outcome [29].

Based on the above-described heterogeneity displayed by MB tumors across, but also within, the four molecular subgroups, their upcoming management will undoubtedly need to account for individual tumor features. MB heterogeneity may be at least partially explained by the presence of small populations of cancer stem cells (CSC) within the tumors, which have been recognized as a main contributing factor to cancer onset, progression, and resistance to treatments in several tumor types, including MB [54]. Then, intra- and intertumoral heterogeneity displayed by MB, potentially sustained by peculiar amounts and types of tumor-driving CSCs [55,56], may also result in differential metabolic needs, with (cancer) stem cell functions relying on distinct metabolic adjustments [57,58]. Accordingly, in the last years, the metabolic behavior of cancer cells has gained brand new interest for its potential ability to contribute to treatment resistance and even provide novel intriguing targets to overcome it, with metabolic adaptation engaged by cancer cells during tumor growth now considered as a major hallmark of several cancers [59]. Indeed, since cancer cells are exposed to a dramatically different microenvironment from that of normal cells, they must adapt to these challenging conditions by rewiring their metabolic activities, to eventually overcome the deficiency of oxygen and nutrients. The best-studied mechanism by which cancer cells can reprogram their metabolic activity to fulfill their differential energetic demand is the so-called “Warburg effect”, also known as “aerobic glycolysis”, through which cancer cells can switch their energetic production towards glycolysis, even in properly oxygenated conditions [60]. In this context, extensive reprogramming in cell metabolism has been reported in MB, also displaying a non-uniform profile across MB subtypes [61,62]. In particular, Park *et al.* recently recognized that several metabolic pathways may serve as relevant prognostic markers in MB subgroups, which are therefore each characterized by specific metabolic signatures [63]. However, our knowledge of how the different metabolic pathways can interact with each other and even contribute to the above-described subgroup-specific features is still limited and frustrated by the engagement of complex molecular mechanisms and the coordinated action of several signaling molecules.

In this review we provide a comprehensive view of the state of the art of metabolic adaptation in the context of MB progression, describing the main metabolic pathways that are deregulated in this pediatric malignancy, with a particular focus on the areas that remain controversial and the progress that is yet to be made. In addition, this review analyzes the metabolic properties that sustain stemness and therapy resistance of MB cells, and the influence of tumor microenvironment in MB metabolism. Finally, considering that, in supporting tumor progression, the metabolic rewiring exposes malignant cells to potential vulnerability, this review summarizes the pharmacological strategies that have been reported to interfere with metabolic addiction of MB cells, suggesting potential therapy combinations as effective approaches to successfully treat pediatric patients.

2. Metabolic pathways in medulloblastoma

2.1. Glucose metabolism

The normal brain is a highly respiratory organ and requires a high and continuous supply of glucose to fuel physiological brain function. In normal neurons, glycolysis metabolizes glucose into pyruvate, which under aerobic conditions, supplies the tricarboxylic acid cycle (TCA) to provide ATP through oxidative phosphorylation (OXPHOS) and provide reducing equivalent to manage oxidative stress (Fig. 1). Differentially, astrocytes consume glucose mainly through glycolysis to produce L-

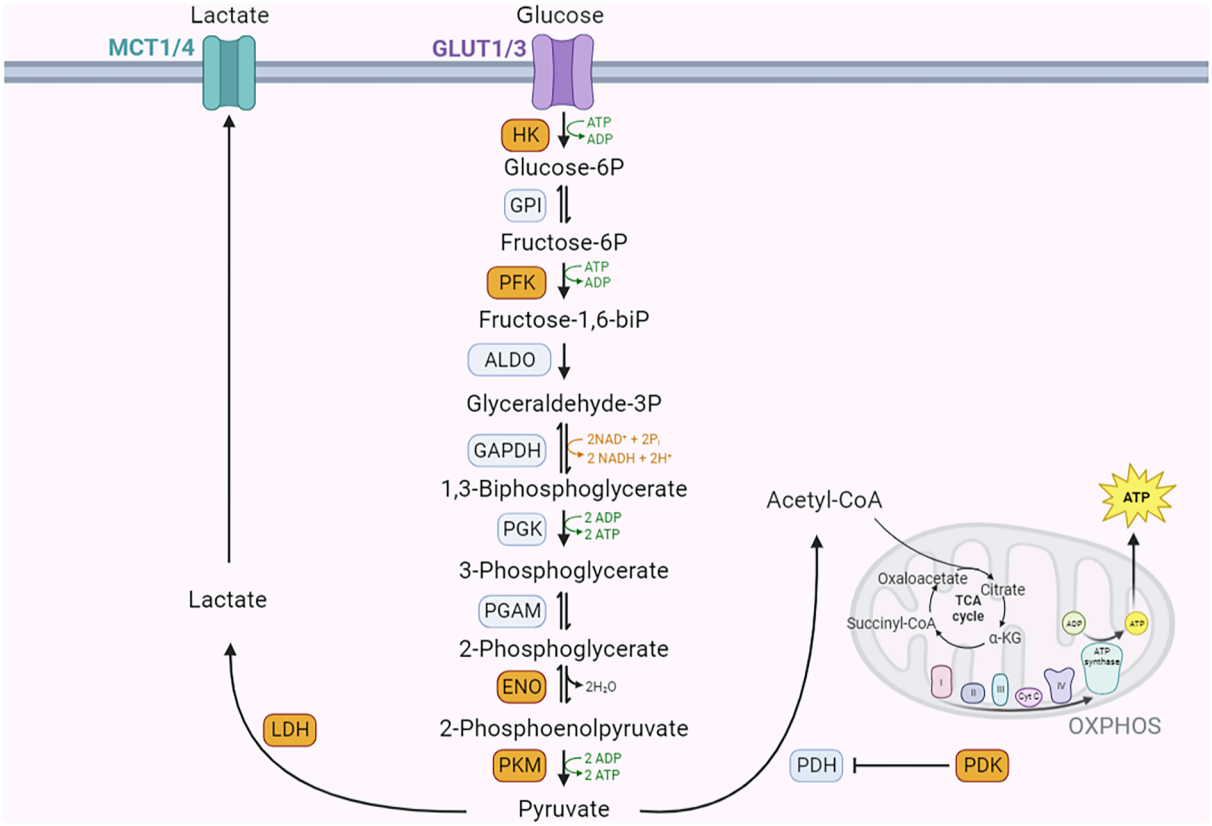

Fig. 1. Glucose metabolism. The simplified scheme depicts the main pathway by which glucose is metabolized by cells for energy generation and building block biosynthesis. Through glycolytic pathway, glucose is metabolized into pyruvate that can be converted into acetyl-CoA to fuel TCA cycle or into lactate which is then secreted. Yellow boxes highlight enzymes that are relevant in medulloblastoma metabolism. Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lactate that is delivered to neurons to sustain neuronal oxidative metabolism thanks to the astrocyte–neuron lactate shuttle. Indeed, high glucose metabolism and therefore high glucose influx into the cells, in addition to the energy supply, is required by proliferating cells and more in particular by proliferating cancer cells to provide building blocks for anabolic pathways and redox homeostasis [64].

Oncogene-directed metabolic reprogramming of cancer cells has been considered an emerging hallmark of cancer [65] and, like most cancers, MB undergoes metabolic adaptation to survive and hyperproliferate in harsh and nutrient-restricted conditions [61]. In this context, the decreased mitochondrial function with a concomitant enhancement of glycolytic activity even in the presence of oxygen is a common feature in metabolic adaptation in many cancers. This phenomenon, known also as the Warburg effect [60], empowers cancer cells with a survival advantage by contributing to a lower level of Reactive Oxygen Species (ROS), thus reducing the cytotoxic effects of oxidative damage, and supporting the biosynthesis of metabolic precursors required for nucleic acid, amino acid, and lipid synthesis to fuel proliferation [65].

In addition, brain tumors, including MB, are characterized by the presence of regions of intratumoral hypoxia obtained by the rapid and uncontrolled proliferation of cancer cells that overtake the ability of the pre-existing blood vessel to satisfy the oxygen demand. One of the main regulators of metabolic adaptation in hypoxic conditions is the Hypoxia-inducible factor-1 (HIF-1α() transcription factor which is induced by microenvironmental hypoxic conditions and controls the expression of glycolytic genes in adult and cancer stem cells [66,67]. In particular, HIF-1α controls glucose uptake by the expression of glucose transporter GLUT1 and GLUT3, induces the expression of glycolytic enzymes and promotes pyruvate conversion to lactate by inducing LDHA and pyruvate dehydrogenase kinase PDK1 expression [68]. Hypoxia and HIF-1α over-activation have been correlated with tumor aggressiveness and progression in several cancers[69], including MB [70,71], where they are crucial for stem cell survival and stem cell maintenance [72].

Despite a high expression of the key gatekeeper enzymes involved in glycolysis and improved aerobic glycolytic rates have been found among group 3 MYC-driven MB [73] SHH MB [74,75] and group 4 [76], the role of glycolysis in sustaining MB tumorigenesis is currently debated.

Gershon et al, demonstrated that SHH together with PI3K signal induces the expression of Hexokinase2 (HK2), and its cre-mediate deletion abrogates aerobic glycolysis and interferes with Smoothened-induced tumorigenesis reducing the aggressiveness of MB in Smo-M2 mice models [74]. In addition, SHH signaling has been found to induce the expression of the M2 isoform of pyruvate kinases (PKM2) that catalyze the last step of glycolysis also in the presence of normal oxygen rate and treatment with the pyruvate kinase inhibitor dichloroacetate (DCA) efficiently represses MB growth in vitro and in vivo[75]. In contrast, more recently, Tech et al demonstrated that PKM2 deletion boosts MB cell proliferation and tumorigenesis and highlighted that patients with low PKM2 expression trended shorter survival times [77].

During aerobic glycolysis, lactate dehydrogenase enzyme (LDH) converts pyruvate into lactate with the regeneration of NAD+ which is required for the maintenance of the glycolytic pathway and ATP generation. Lactate is finally exported outside the cells through monocarboxylate transporter 1 (MCT1) which mediates the import/export of lactate, pyruvate, and ketone bodies throughout the plasma membrane. MB group 3/4 exhibits a high level of lactate and the overexpression of LDHA and MCT1 suggesting that MB is sustained by a glycolytic phenotype [78]. The inhibition of LDHA using oxamate significantly suppresses MB lactate production, aerobic glycolysis, proliferation, and

motility [78].

As we mentioned above, glucose is the major source of energy in the brain and lactate is highly produced also in the normal brain, where it provides a supplementary energy source through the astrocyte–neuron lactate shuttle. Through an isotopic tracing experiment, using uniformly labeled glucose, Pham et al recently described the glucose carbons contribution to the downstream metabolic pathway in MYC MB orthotopic tumors and normal brain. In contrast with the "Warburg effect", the presented data demonstrate higher glucose incorporation in TCA in MYC MB models than in normal brain suggesting that tumor cells simultaneously use glycolysis and OXPHOS [79]. The high rate of glucose anaplerosis in MYC MB provides intermediate metabolites for the synthesis of glutamate which is then incorporated into glutathione and glutamine [79]. In agreement, RNAseq analysis of MYC-driven Group 3 MB demonstrates the upregulation of metabolic pathways involved in both in glycolysis and TCA cycle and the measurement of TCA metabolites revealed enhanced OXPHOS and TCA activity in this MB subtype [71]. In addition, Electron Transfer Chain (ETC) proteins were found highly expressed in group 3 orthotopic PDXs confirming that mitochondrial energy metabolism in upregulated in MYC group 3 MB [80].

Recently, Badodi and colleagues identified mTOR and inositol signaling contribution in the modulation of metabolic adaptation of the molecular subgroup G4 characterized by a $BMI1^{High}$; $CHD7^{Low}$ signature [76]. In particular, they found that $BMI1^{High}$; $CHD7^{Low}$ signature induces the deregulation of inositol metabolism and the activation of mTOR signaling leading to an impairment of the mitochondrial respiration and enhanced aerobic glycolysis, suggesting the administration of inositol (IP6) to reduce cell survival and improve chemotherapy response. Consistently, they found increased expression of key enzymes of glucose metabolism, HK2, PFKP, ENO4, PDK1 and LDHB, $BMI1^{High}$; $CHD7^{Low}$ G4 MB tumor samples but not in G3 MB samples with the same signature, suggesting the correlation between the signature and this metabolic pathway being specifically pertinent to the G4 subgroup [76].

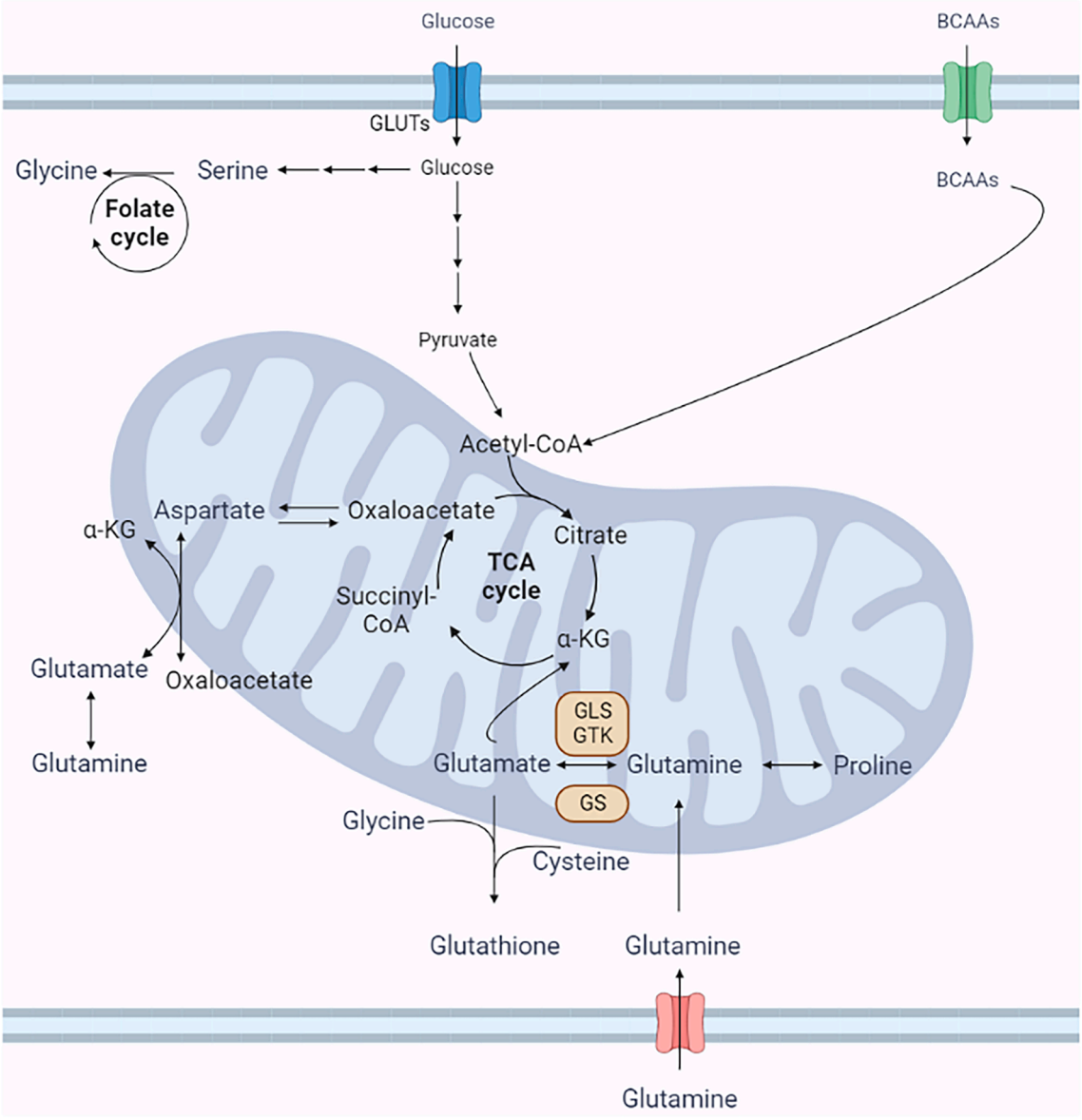

Fig. 2. Amino acid metabolism. This simplified cartoon represents the main metabolic pathways used by cells to produce and use amino acids. Intermediates derived from the catabolism of branched-chain amino acid (val, leu, ile) can fuel the TCA cycle, Serine contributes to one-carbon metabolism, while glutamine is metabolized by mitochondrial enzymes into glutamate and α-KG, which serves as an important intermediate in the TCA cycle. Yellow boxes represent enzymes that are relevant in medulloblastoma metabolism. Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Currently, there is no clear consensus regarding the relevance of glucose metabolism in sustaining tumorigenesis and the aggressiveness of MB. However, certain enzymes involved in the glycolytic pathway have been identified as having prognostic relevance in this malignancy. In particular, HK2 expression has been correlated with SHH patient clinical outcome, while ENO1 encoding enolase 1 has been detected in all 3 subgroups [63].

2.2. Amino acid metabolism

Amino acid metabolism is a complex and tightly regulated process that involves various interconnected pathways (Fig. 2). When cells receive amino acids from dietary sources or protein breakdown, they undergo a series of reactions to ensure the proper utilization and balance of these crucial building blocks. Amino acids can be used for protein synthesis or can be metabolized through pathways such as transamination, where the amino group of one amino acid is transferred to a keto acid, producing a new amino acid and a new keto acid. The amino acids can also undergo deamination, where the amino group is removed as ammonia, which is further converted into less toxic compounds like urea or used in other metabolic processes. The remaining carbon skeleton can be utilized for energy production or converted into other molecules like glucose, fatty acids, or neurotransmitters. Amino acid metabolism is crucial for maintaining cellular homeostasis, providing the necessary materials for protein synthesis, energy production, and the synthesis of other important biomolecules. Dysregulation of amino acid metabolism is a well-known characteristic of cancer cells, highlighting the importance of altered amino acid processes in cancer development. A common feature observed in cancer cells is the heightened uptake and utilization of amino acids, which facilitates their accelerated growth and proliferation. This enhanced amino acid metabolism in cancer cells plays a crucial role in regulating redox state, maintaining homeostasis, controlling energy levels, and supporting biosynthesis. One example is the increased uptake of the amino acid glutamine by cancer cells, which can be used as a carbon and nitrogen source for the synthesis of nucleotides and other macromolecules (reviewed in [81]). For example, elevated levels of the amino acid serine have been observed in many cancer types, and serine metabolism has been implicated in promoting cancer cell survival and proliferation [82] but also drug resistance [83,84]. In addition, cancer cells often exhibit alterations in amino acid catabolism, with increased levels of certain amino acid metabolites. All these processes are regulated by several oncogenes and tumor suppressor genes, including MYC [85,86] and p53 [65,87,88]. Targeting amino acid metabolism has emerged as a promising therapeutic strategy in cancer, with several amino acid metabolism inhibitors currently being evaluated in clinical trials. However, the complex interplay between amino acid metabolism and other cellular processes in cancer cells makes it challenging to develop effective therapies targeting this pathway [89]. Glutamine is the most extensively studied amino acid concerning MB, and its metabolism is crucial in sustaining this type of tumor. At the neuronal level, glutamine is involved in significant functions related to the production of the neurotransmitter glutamate. The metabolism of glutamine is comprised of two primary reactions: the first reaction involves the enzyme glutaminase, which catalyzes the conversion of glutamine into glutamate. In the second reaction, glutamate dehydrogenase converts glutamate into alpha-ketoglutarate, which subsequently supports the Krebs cycle. Pham et al's findings indicate that in orthotopic high-MYC Group3 MB, glutamine is primarily metabolized by the enzyme glutamine transaminase K (GTK) to produce glutathione that sustains detoxing activity within the cells [79]. Moreover, recent research has shown that p73, a member of the p53 family, supports glutamine metabolism in MB by promoting the expression of GLS2 and other enzymes involved in glutamine metabolism [90,91]. Additionally, a study by Ge et al. revealed that the long non-coding RNA NEAT1 contributes to chemoresistance in MB cell lines through the miR-23a-3p-GLS axis [92]. These findings further support the idea that glutamine metabolism plays a significant role in the behavior of MB.

2.3. Lipid metabolism

Lipid metabolism in cells is a dynamic and tightly regulated process that involves the synthesis, breakdown, and interconversion of various lipid molecules (Fig. 3). Lipids are used as essential components of cell membranes, energy storage molecules, and signaling molecules. In cells, lipids are synthesized through *de novo* lipogenesis, where acetyl-CoA molecules are converted into fatty acids, which can further undergo modification to produce different lipid species. Lipid metabolism also involves the breakdown of lipids through processes such as beta-oxidation, where fatty acids are broken down into acetyl-CoA to generate energy. Cells regulate lipid metabolism in response to nutrient availability, hormonal signals, and cellular energy status and this gains much importance in the contest of cancer.

Over the past few years, there has been a significant increase in research exploring the role of fatty acid metabolism in cancer, leading to numerous important discoveries. Fatty acid metabolism modulates cancer cells in multiple ways, mediate membrane composition and fluidity (depending on glycerophospholipid composition), modulates secondary messenger signaling, and controls the presence of substrates for mitochondrial ATP and NADH production [93–95]. Notably, fatty acid metabolism, through both beta-oxidation and the synthesis of fatty acids, can also contribute to drug resistance in various cancers (reviewed in Hoy et al., 2011 [96]). However, research on the metabolism of fatty acids in MB remains limited, leaving ample space for future studies. To date, what is known is that the metabolism of fatty acids is heterogeneous according to the molecular subgroup of MB [62]. For instance, SHH-MBs result in higher lipid levels due to the overactivation of SHH signaling that regulates fatty acid metabolism towards increased lipogenesis. This is due to the upregulation of fatty acid synthase (FASN) and Acetyl-CoA carboxylase (ACC1), induced by E2F1, and the concurrent downregulation of well-known fatty acid catabolic enzymes like MCAD and ACOX1 [97,98]. FASN and stearoyl-CoA desaturase (SCD), both encoding enzymes involved in the fatty acid synthesis pathway, were also detected as prognostic genes in all three subgroups [63].

The mevalonate pathway is a central player in fatty acid metabolism, and it is well-established that this pathway contributes significantly to the growth and development of tumors [99]. The inhibition of cholesterol biosynthesis, using statins, has proved to be a valid strategy to target MB cells. Specifically, it has been demonstrated that in the context of SHH group MB, inhibition of cholesterol biosynthesis through the inhibition of HMG-CoA reductase by the use of statins or gene silencing can repress cell proliferation. Exogenous oxysterols resulting from cholesterol oxidation have been observed to activate Smo, which is the main receptor responsible for SHH signaling, thus causing this effect. Indeed, by inhibiting the synthesis of cholesterol, the levels of its oxidized derivatives would also be reduced. In addition, statins can synergize with vismodegib, an inhibitor of Smo [100,101].

Inhibition of HMG-CoA reductase is effective in inducing cell death even in non-SHH models of MB, for example, Myc-driven Group3 and Group4 [49,102,103]. This evidence indicates that lipid metabolism is likely to be involved in the development, growth, and maintenance of MB cells. However, other metabolic processes related to fatty acids, such as fatty acids beta-oxidation, are still not well-understood in this type of tumor.

Furthermore, these outlined mechanisms are critical in causing recurrences and drug resistance in other types of tumors [96] but remain unexplored in the contest of MB.

2.4. Nucleotide metabolism

Nucleotide metabolism is now widely recognized as a crucial feature of cancer. Numerous studies have demonstrated that this metabolic pathway represents a vulnerability that can be exploited by drugs

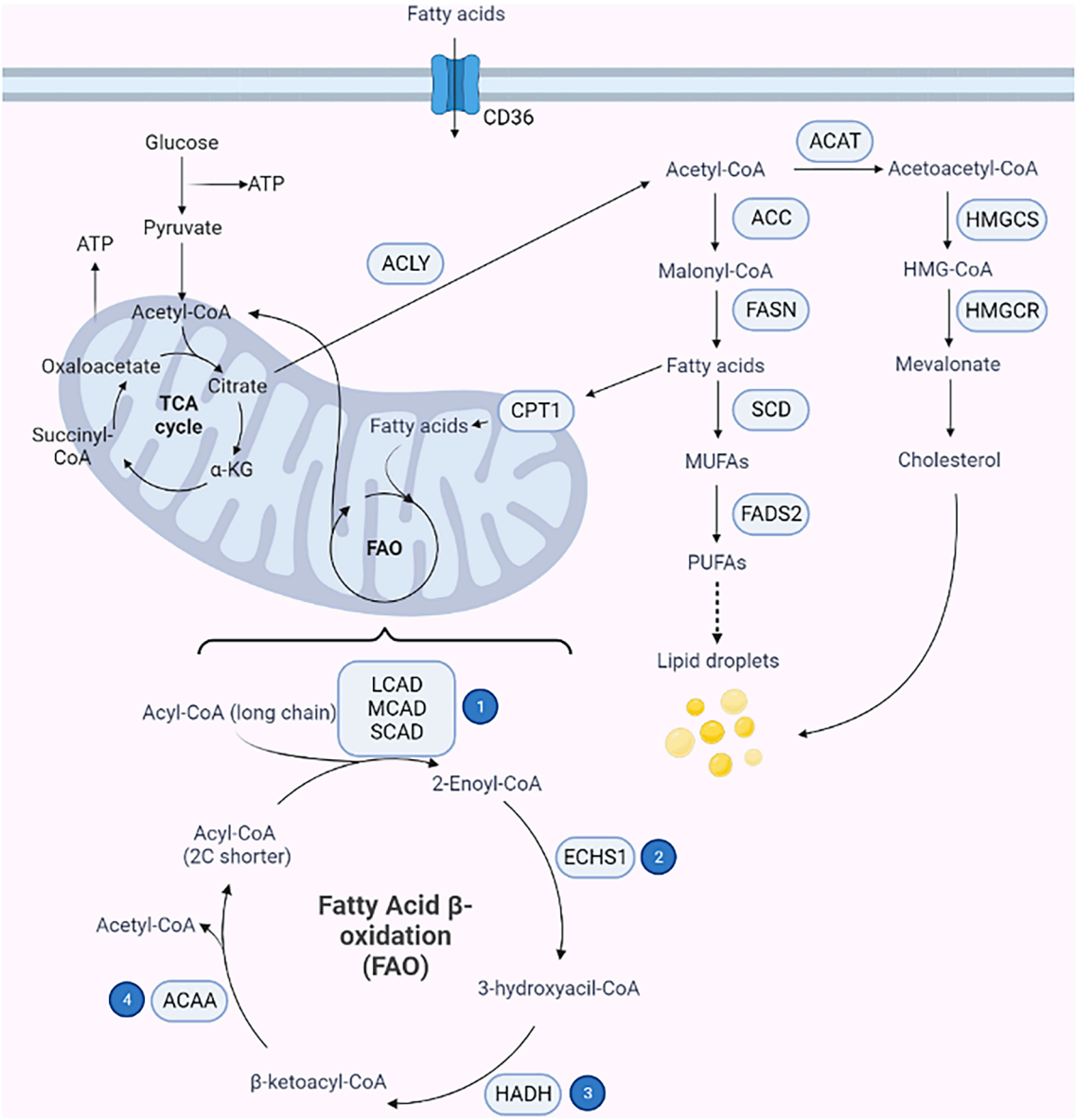

Fig. 3. This cartoon provides an overview of the key enzymes and metabolic pathways involved in lipid metabolism in cancer cells. Lipid metabolism comprises fatty acid uptake, fatty acid catabolism through the fatty acid oxidation cycle, fatty acid synthesis, and cholesterol synthesis. Blue boxes represent the main enzymes involved in lipid metabolism. Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

already available in the market and commonly used in clinical practice to treat different types of tumors. As a result, the field of nucleotide metabolism holds great promise for significant breakthroughs in cancer therapy.

Within cells, there are two distinct pathways responsible for nucleotide synthesis: the *de novo* pathway and the salvage pathway (Fig. 4). The *de novo* pathway provides nucleotide synthesis using simple building blocks such as ribose 5-phosphate, amino acids, CO_2, and NH_3. In contrast, the salvage pathway functions by recycling nucleotides and free bases that are released during the breakdown of nucleic acids. In the context of cancer, an elevated nucleotide metabolism, usually controlled by oncogenic signaling, has been linked to a range of pathological behaviors, including uncontrolled cell proliferation, resistance to chemotherapy, the formation of metastases, and evasion of the immune system [104–107] New research indicates that nucleotide metabolism may have a role in the development of MB, particularly in the group3 myc-amplified subgroup [79,108]. In a recent study, Gwynne and colleagues utilized a genome-wide loss-of-function genetic screening to provide compelling evidence that this specific subgroup of MB is highly reliant on nucleotide metabolism, specifically the *de novo* synthesis pathway [109]. Out of the proteins essential for cell survival, Dihydroorotate dehydrogenase (DHODH) has emerged as the most promising candidate. DHODH is a key enzyme in de novo pyrimidine biosynthesis, catalyzing the oxidation of dihydroorotate in orotate. Furthermore, the research provided evidence that inhibiting DHODH, both in vitro and in vivo, can specifically target brain tumor-initiating cells (BTICs), through a mTORC1 inhibition that leads to cell cycle arrest and the induction of apoptosis. While there is robust evidence supporting nucleotide metabolism importance in MYC-amplified Group 3 MBs, little is currently understood about the remaining subgroups [109].

The main metabolic features of MB subgroups are summarized in Fig. 5.

3. Metabolic behavior of medulloblastoma stem cells

One of the first steps during vertebrate development is the

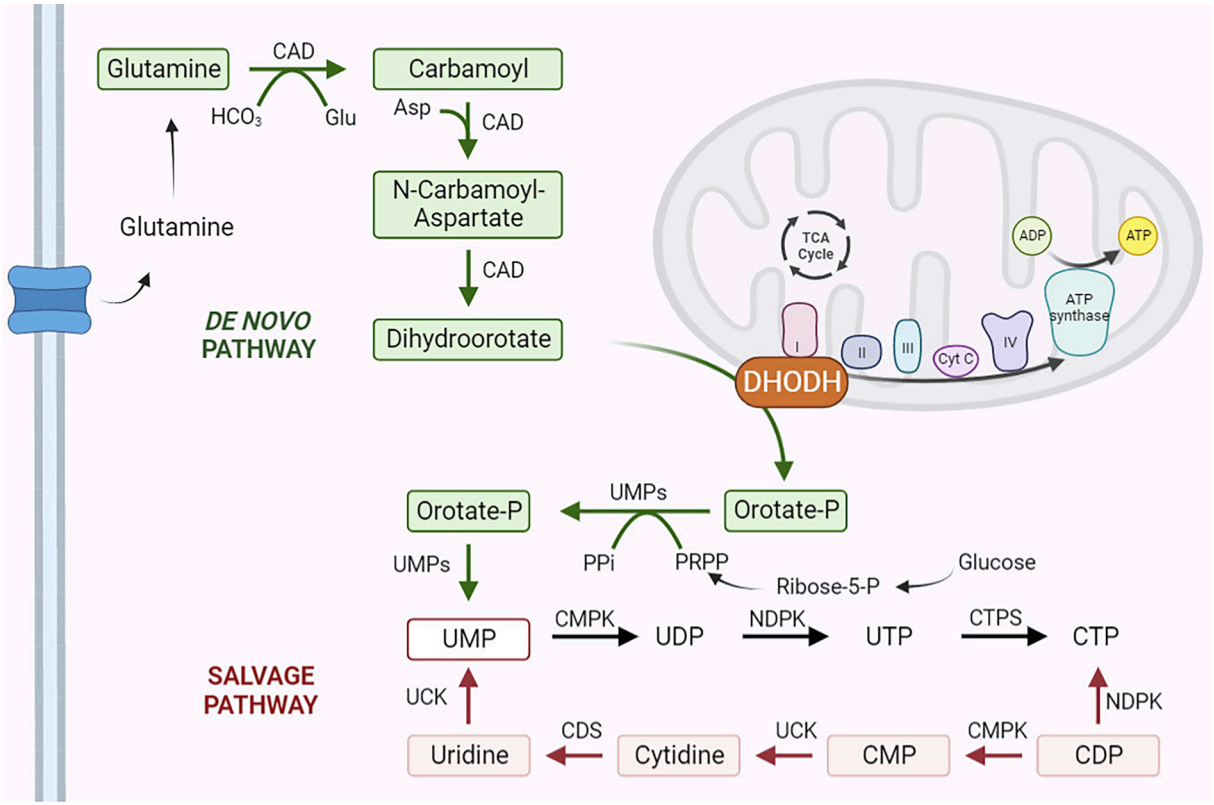

Fig. 4. The pyrimidine metabolism. Pyrimidine synthesis is composed of *de novo* pathway highlighted in green and salvage pathway in red. DHODH, in the orange box, has been found to be relevant in MYC-amplified Group 3 MBs Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

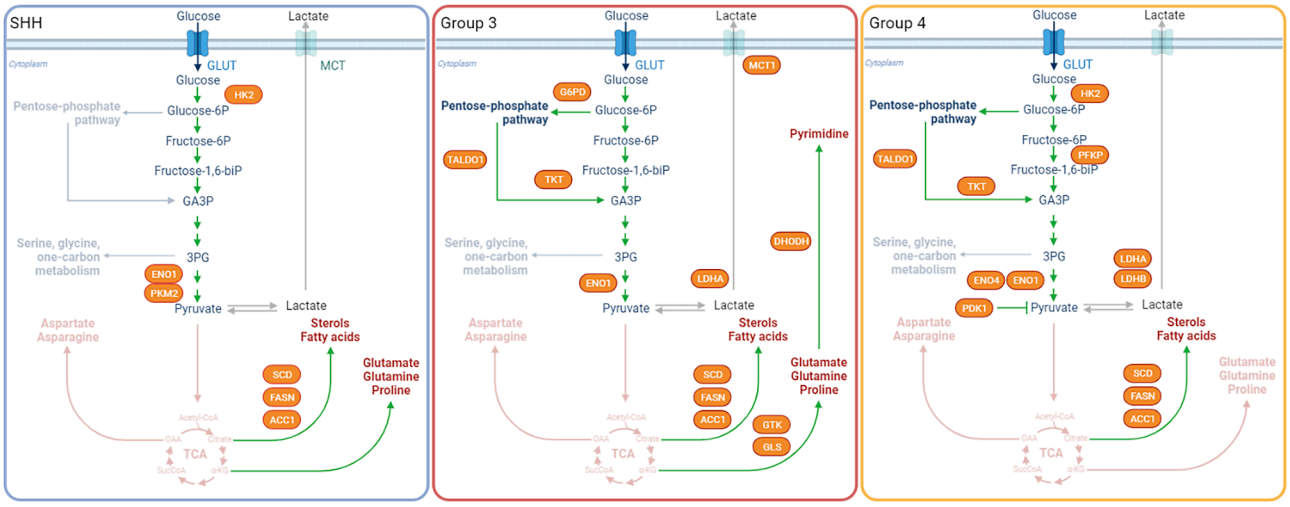

Fig. 5. MB subgroup-specific alteration of metabolic pathways. Schematic cartoon of metabolic genes and pathways that are found to be upregulated in MB subgroups. Green arrows highlight upregulated pathways, orange boxes represent overexpressed genes. Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

construction of the nervous system. Neural development is a tightly regulated process orchestrated by several signaling pathways whose gradient and combination specify at first the dorso-ventral/rostro-caudal morphogenesis and, in a second wave of development, determine neural cell fate.

In this context, neurogenesis is the key event of neural development, by which neural stem cells (NSCs) divide, self-renew, and convert to postmitotic neurons. The balance between self-renewal and cell-specific differentiation of NSCs is controlled both by intrinsic and extrinsic cues such as transcription factors, morphogen signals, and cell contact-mediated signaling. In the last years, many researches uncovered and described another pivotal cellular mechanism able to influence and determine neural cell fate: cellular metabolism.

NSCs metabolism has been demonstrated to determine the balance between cellular proliferation, differentiation, or quiescence. Specifically, a connection × between NSCs proliferating state and higher levels of glycolysis has been proved, while the maturation of neural stem cells into fully differentiated neurons, requires a switch in the cellular energy

source thus linking differentiation to an upregulation of genes involved in the mitochondrial-mediated OXPHOS [110,111]. This metabolic shift is not only a means to increase cellular energy production but is considered a specific mechanism to drive NSC fate decisions depending on the microenvironmental cues. Paradoxically, the human brain has been demonstrated to be highly hypoxic with the partial pressure of oxygen ranging between 0.55 and 8 %. Despite this evidence, the brain is a highly oxidative organ, accounting for 20 % of bodily oxygen consumption [112]. Indeed, neural cells strictly regulate metabolites and in particular the ROS balance [113] that can function as signaling molecules able to coordinate developmental pathways activation (i.e. HIF-1α; Wnt/β-catenin and Notch).

Lipid metabolism has been found to be important in NSC fate and in particular in adult hippocampal neurogenesis where it has been shown to control the proliferative potential of NSCs. Of note, Knobloch et al. demonstrated that the rate of fatty acid oxidation (FAO) in NSCs in the hippocampal region, regulated the balance between quiescent and proliferative states and, specifically, that FASN is upregulated in NSCs whereas FASN knockout mice showed decreased neurogenesis [114]. Moreover, the mechanism by which FAO maintains NSC stemness whereas lipogenesis drives them toward differentiation has been highlighted also in humans [115].

Another metabolic pathway that plays a crucial role in NSC's fate decisions is also Glutaminolysis. Namba et al in 2020 demonstrated that glutaminolysis regulates NSC fate decisions in humans and promotes NSC proliferation throughout a Rho GTPase Activating Protein 11B (ARHGAP11B)-mediated promotion of the sub ventricular zone basal progenitors (SVZ-BPs) proliferation during the embryonic life [116].

All the neural metabolic cues considered so far, acquired a particular meaning in the cancer context since human cerebral cancers contain cell types resembling all the stages of neural development, from cancer stem cells, to progenitors-like cells to phenotypically differentiated cancer cells, both in adults and children [55,117].

It has been always considered that the energy metabolic pathways are largely different between cancer and normal cells. However, as it has been described for NSCs, cancer stem cells exhibit higher glycolytic activity compared to more differentiated cells. This phenomenon is crucial for cancer cells since glycolysis represents the starting point for nucleotides and lipids production and also amino acids, fundamental "build blocks" necessary for proliferation and stress resistance [118]. In this context, cerebellar MBs have been deeply investigated during the last two decades and their mass structure has been finely delineated and compared to the normal cerebellar development to define the cerebellar tumors as a mirror of the embryonic cell populations. Luo et al. demonstrated that MB is composed of heterogeneous cancer cell populations including cancer stem-like cells, neuroblast-like cells, and more differentiated cells opening the way to speculation and hypothesis on the metabolic paradigm linking bioenergetics and cell fate [119]. As for many brain tumors also in MB the existence of a cancer stem cells population has been postulated and characterized. In particular, MB CSCs are endowed with tumor reconstruction capacity being more resistant to radiotherapy and chemotherapy compared to more differentiated cells, suggesting their role in MB recurrence [120]. Very little is known about the specific metabolism of this subpopulation, and the metabolic properties that sustain stemness and therapy resistance of MB-CSCs remain areas worthy of further investigation. Tsuboi research group identified suppressed mitochondrial respiration together with a lower level of ROS as the driving mechanism of radio resistance of MB CSCs. Specifically, they linked increased endogenous mitochondria ROS production with augmented oxidative stress-mediated DNA damage after irradiation with a final result of stemness loss [121]. This paper lay the ground for further studies starting from the notion that every stage of neural development has a complex but very specific cellular metabolic state that could potentially be engaged by cancer cells to arise, survive, and proliferate [122].

4. Modulation of medulloblastoma metabolism by tumor microenvironment

Currently, the concept of a tumor as a singularity has been replaced by the idea of a tumor as a complex ecosystem composed of various cell types, including pathological and non-pathological cells, with different chemical and physical properties such as stiffness [123], pH [124], O2 tension [125], and metabolites [126]. These factors collectively influence the development, growth, progression, response to treatment, and recurrence of tumors, including brain tumors [127–133].

Above all, from the metabolic point of view, it has been amply demonstrated that the microenvironment, through the modulation of the concentration of metabolites and the exchange of them between tumor cells and cells present in the microenvironment, can support the growth of the tumor itself [134–137].

Very little is known about how the tumor microenvironment can modulate MB [138] and its metabolic phenotype, however, a very recent paper demonstrated that MB cells can metabolize GABA under conditions of low nutrient availability in the microenvironment. More specifically, this work demonstrates that, when MB cells find themselves in a nutrient-deprived environment such as cerebrospinal fluid (CSF), and this happens in cells that express high levels of 4-Aminobutyrate aminotransferase (ABAT) and spread in CSF, they can modify their metabolism by increasing their ability to make OXPHOS using GABA as a source. This promotes their survival capacity in a low-nutrient environment. The authors hypothesize that the increase in the metabolism of GABA mediated by ABAT and of OXPHOS in CSF induces the cell to use acetyl-CoA as a metabolic mediator (e.g. to be metabolized for ATP production in mitochondria), preventing its use to acetylate histones, also modifying epigenetic [139]. To date, this work appears to be one of the first pieces of evidence demonstrating how the tumor microenvironment can modulate the metabolism and characteristics of MB cells and future research will be necessary to clarify TME-induced metabolic alteration in MB.

5. Metabolic rewiring sustains medulloblastoma resistance

Resistance to therapeutic agents is one of the major issues in the treatment and clinical management of MB patients [140]. Besides the alteration in many signaling pathways that are affected by genetic mutations, genomic rearrangements, or alterations in epigenetic control, recent studies have highlighted the relevance of the metabolic plasticity of cancer cells in response and adaptation to therapies [66,67]. Tumors are not static entities and rewire their metabolism depending on several factors, intrinsic to the cancer cells or influenced by external factors such as the microenvironment, chemotherapy, or radiotherapy, and increasing evidence suggests that metabolic requirements and dependencies evolve throughout cancer progression [141]. Nevertheless, to date, there is no clear consensus on how metabolic changes can support drug resistance, as different tumors can manifest different and sometimes even opposite metabolic changes in response to therapy [66,142]. In the context of MB, radioresistant MB stem-like clones (rMSLCs) obtained by irradiation of the human MB cell line ONS-76 showed lower oxygen consumption rate, higher pyruvate kinase (PK) activity, and lactate production than parental cells [121]. Indeed, the treatment with the PDK1 inhibitor DCA resulted in increased cellular oxidative stress and altered mitochondria morphology, thus suppressing cancer stem cell-like phenotypes and radioresistance. These findings highlight the relevance of metabolism in sustaining radioresistance and in maintaining cancer stem cell-like phenotypes, providing new insight into the identification of metabolic vulnerability to be exploited for the development of metabolic targeting radiotherapy [121].

In a more recent paper, Bakhshinyan and colleagues presented interesting data about comprehensive and dynamic profiling of MB cells at engraftment, after radiation, after chemoradiotherapy, and at relapse, in a therapy-adapted patient-derived xenograft (PDX) model of group 3

MB recurrence. Temporal transcriptomic profiling at different disease stages of this model highlighted that malignant cells rewire metabolic pathways including OXPHOS and de novo lipogenesis [143].

6. Pharmacologic targeting of medulloblastoma metabolism

In the last years, successful improvements in the treatment and standard of care of patients suffering from several types of cancers have been made, nevertheless, chemotherapy resistance still constitutes a severe problem to be solved to improve the cure of oncologic patients. This issue becomes particularly relevant in the context of pediatric MB, where despite the administration of a high dosage of chemotherapeutics with unacceptable toxicity, the chance of therapeutic success after the onset of relapse, is very low. In the last years, the study of metabolic dependencies of MB cells has contributed to the development of metabolically-targeted therapies (summarized in Fig. 6) that gave encouraging results in preclinical models and clinical trials for more effective and less toxic cures.

The fast glucose consumption rate and the high expression of glycolytic enzymes in all MB subgroups suggest a vulnerability toward therapies that target glycolysis. Despite many studies highlighting these metabolic features of MB cells [74,75,78], only the Lactate Dehydrogenase A (LDHA) inhibitor Oxamate has been reported to inhibit glycolysis and to affect cell proliferation and migration of both group 3 and SHH MB cell lines [78]. In vivo studies conducted on mice models of nasopharyngeal carcinoma, Ehrlich carcinoma, and nonsmall cell lung cancer demonstrate very low toxicity and high cancer cell selectivity of oxamate.However, no in vivo studies has been reported for medulloblastoma models [144]. Concerning glucose metabolism, but not strictly related to the inhibition of the glycolytic pathway, the antidiabetic drug Phenformin, which displays also potent activity in several cancers, demonstrated encouraging results in SHH-MB mouse models. L. di Magno et al., in their elegant study, demonstrate that Phenoformin affects SHH MB tumor growth through the inhibition of mitochondrial glycerophosphate dehydrogenase (mGPD), a component of the glycerophosphate shuttle, leading to a raise of the intracellular NADH levels. This redox imbalance induces an association between the corepressor CtBP2 and Gli1, thereby inhibiting Hh transcriptional output and tumor growth [145]. Phenformin was used for the treatment of type 2 diabetes mellitus but was retired from the market due to a high risk of fatal lactic acidosis. However, phenformin's anticancer effect has been described for many tumor types with higher effectiveness and greater tissue availability compared to non-toxic metformin. Considering that the combination with other anticancer agents seems to be a good strategy in the treatment of several cancer types, thus reducing the dosage and the toxic effects of phenformin, preclinical and clinical trials have been started to determine therapeutic doses and safety profile [146].

Antimetabolites have been successfully used for decades for the treatments of many cancer types and nowadays are standard in many modern chemotherapy regimens [147]. In MB important results, obtained from a high throughput screening of FDA-approved drugs and a preclinical study in xenograft models, suggest that pemetrexed and gemcitabine can be added to currently used chemotherapy for the treatment of group 3 patients, with an improved effect and little additional myelosuppressive toxicity [148].

Another target that has been considered for group 3 treatment is DHODH whose inhibition with BAY2402234, Brequinar, and PTC299 induces a reduction in uridine metabolite availability and hyperlipidemia, together with a decrease of protein O-GlcNAcylation and c-Myc degradation, leading to cell cycle arrest and apoptosis. BAY2402234, already under clinical investigation for AML and in recurrent glioma, showed good efficacy in a preclinical study in PDOX-model of group 3 MB, suggesting a possible clinical use of this agent alone or in combination with standard chemotherapy [109].

Also, the inhibition of fatty acid metabolism has gained attention in the last years, and in particular, the inhibition of HMG-CoA reductase by the use of statins is effective in all MB subgroups [102,103]. Relevant data has been published concerning the use of simvastatin for the treatment of SHH-MB. The study, published by Fan and colleagues,

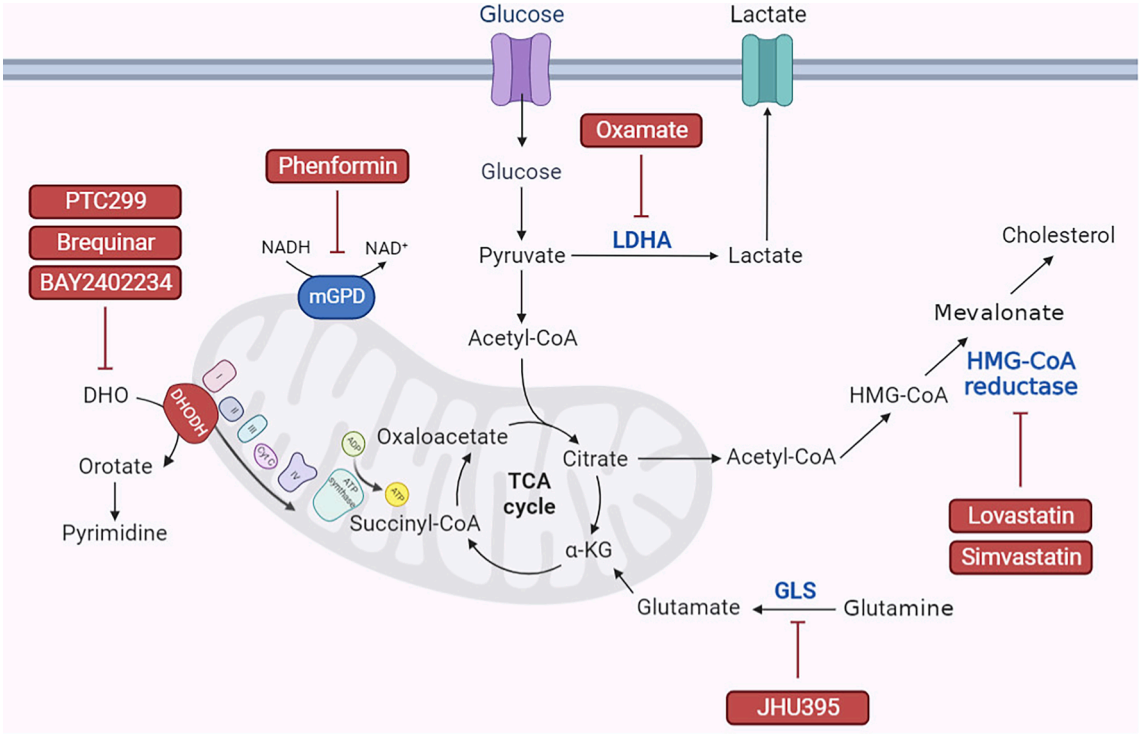

Fig. 6. Cartoon summary of drugs targeting key enzymes involved in medulloblastoma metabolism. Drug are represented by red boxes. Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reveals that statins reduce MB tumor growth in allograft SHH-MB mouse models by repressing SHH pathway activation without affecting bone development, and suggest their use in combination with a low dosage of the SMO antagonist vismodegib [100]. In addition, Lovastatin has been found to reduce the proliferation of DAOY cells in vitro and xenograft models, via upregulation of miR-33b, a negative regulator of c-MYC [103]. Statins are well tolerated by adolescents and children and are used for the treatment of dyslipidemia since many years [149], however, despite the promising preclinical studies, no clinical trials have been started for the treatment of childhood cancers.

Further considering the glutamine addiction as a targetable vulnerability in MB, the novel glutamine antagonist prodrug JHU395 was found to be effective in multiple human high-MYC MB cell lines in reducing cell proliferation and inducing apoptosis. JHU395 displayed high activity also in MYC-driven MB orthotopic xenografts extending also the median of survival in comparison with vehicle-control treated mice [150].

7. Conclusions

The first evidence that cancer cells are endowed with peculiar metabolic features date back to a century ago and now, thanks to new tools and technologies for biochemical and molecular biology studies, metabolism has become a widely studied aspect of tumorigenesis and cancer progression. A common feature of cancer cells is the constant requirement of metabolites and building blocks to improve the biomass and allow uncontrolled and rapid proliferation, without affecting redox homeostasis. Cancer-associated metabolic changes profoundly influence and can be influenced by the tumor microenvironment and have been associated with cancer stem cell maintenance and resistance to therapy [65]. Despite a plethora of research articles regarding the study of metabolism in the tumoral context has been published in the last decade, only a few and sometimes discordant results are related to medulloblastoma.

Although an extensive exploration of the transcriptional and mutational landscape of large MB patient cohorts has been performed to identify the molecular basis of MB, only a paper recently published by Park and colleagues highlights some metabolic pathways as subgroup-specific prognostic factors [63]. In addition, it is important to note that the results presented by Park et al. were obtained by employing subgroup-specific Gene Set Enrichment Analysis (GSEA) combined with disease progression data analysis using transcriptomic data from Medulloblstoma Advanced Genomic International Consortium (MAGIC) projet. However, a study that associates the metabolomic profile of MB patients with prognosis or subgroup signatures has not already been published. Indeed, until now, only a few studies report comprehensive metabolomics analysis of a wide cohort of MB patients and all of them identified metabolic alterations without finding specific subgroups signatures. Metabolomics data of CSF of MB patients reveal that the TCA cycle, alanine, aspartate, glutamate metabolism, and arginine biosynthesis pathways are all upregulated in SHH, group 3/4, and group 4 MB. Thus, the metabolic profile of CSF is unable to differentiate between molecular subgroups, however, it suggests that metabolites of the TCA cycle can be used to distinguish MB from the normal brain [151]. In another study, the metabolomics analysis of urine samples from MB patients in comparison to other brain tumor patients and healthy donors reveals alterations in fatty acid oxidation, steroid hormone biosynthesis, dopamine metabolism, and leukotriene B4 metabolism [152]. In addition, C. Bennet and his group compared the tissue metabolite profile of different paediatric cerebellar tumor types finding that MBs displayed significantly higher concentrations of ascorbate, aspartate, phosphocholine, taurine, and lipids and significantly lower glucose and scyllo-inositol in comparison to pilocytic astrocytomas ependymomas and ATRTs. Additionally, this work suggests that choline metabolism is a good candidate for the development of targeted therapies [153].

Despite in the last years genomics and transcriptomics have provided countless and unprecedented information about tumorigenesis and cancer evolution, a gap between genotype and phenotype remains opened and needs to be filled, in particular in the context of pediatric brain tumors. However, emerging technologies such as spatial metabolomics and single-cell metabolomics hold significant promise in bridging this divide. By comprehensively identifying metabolites and their concentrations in both entire tissues and at the single cell level, these technologies provide a direct representation of the molecular phenotype in cancer cells. This newfound capability allows researchers to gain insights into the intricate metabolic processes occurring within cells and tissues, shedding light on the underlying mechanisms of tumorigenesis and cancer evolution. Spatial metabolomics techniques enable the mapping of metabolite distributions within tissues, unveiling spatial heterogeneity that may play a crucial role in tumor development and response to therapy [154]. Moreover, single-cell metabolomics allows for the examination of metabolic variations at the individual cell level, unraveling the diversity within tumor populations and offering a deeper understanding of the cellular dynamics that drive disease progression [155]. Together, these cutting-edge technologies provide a valuable means to fill the existing gap between genotype and phenotype, paving the way for enhanced diagnostic precision, personalized treatment strategies, and ultimately improved outcomes for pediatric brain tumor patients, MB included.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

[1] D.R. Withrow, A.B. De Gonzalez, C.J.K. Lam, K.E. Warren, M.S. Shiels. Trends in pediatric central nervous system tumor incidence in the United States, 1998–2013, Cancer Epidemiol. Biomarkers Prev. 28. (2019). 522–530. 10.1158/1055-9965.EPI-18-0784.

[2] M. Tulla, F. Berthold, N. Graf, S. Rutkowski, D. Von Schweinitz, C. Spix, P. Kaatsch, Incidence, trends, and survival of children with embryonal tumors, Pediatrics. 136 (2015) e623, https://doi.org/10.1542/peds.2015-0224.

[3] Q.T. Ostrom, M. Price, C. Neff, G. Cioffi, K.A. Waite, C. Kruchko, J.S. Barnholtz-Sloan, CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015–2019, Neuro, Oncol. 24 (2022) v1–v95, https://doi.org/10.1093/neuonc/noac202.

[4] A.O. Von Bueren, R.D. Kortmann, K. Von Hoff, C. Friedrich, M. Mynarek, K. Müller, T. Goschzik, A. Zur Mühlen, N. Gerber, M. Warmuth-Metz, N. Soerensen, F. Deinlein, M. Benesch, I. Zwiener, R. Kwiecien, A. Faldum, U. Bode, G. Fleischhack, V. Hovestadt, M. Kool, D. Jones, P. Northcott, J. Kuehl, S. Pfister, T. Pietsch, S. Rutkowski, Treatment of children and adolescents with metastatic medulloblastoma and prognostic relevance of clinical and biologic parameters, J. Clin. Oncol. 34 (2016) 4151–4160, https://doi.org/10.1200/JCO.2016.67.2428.

[5] A. Gajjar, M. Chintagumpala, D. Ashley, S. Kellie, L.E. Kun, T.E. Merchant, S. Woo, G. Wheeler, V. Ahern, M.J. Krasin, M. Fouladi, A. Broniscer, R. Krance, G. A. Hale, C.F. Stewart, R. Dauser, R.A. Sanford, C. Fuller, C. Lau, J.M. Boyett, D. Wallace, R.J. Gilbertson, Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial, Lancet Oncol. 7 (2006) 813–820, https://doi.org/10.1016/S1470-2045(06)70867-1.

[6] R.J. Packer, T. Zhou, E. Holmes, G. Vezina, A. Gajjar. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. (n.d.). 10.1093/neuonc/nos267.

[7] B. Pizer, P.H.J. Donachie, K. Robinson, R.E. Taylor, A. Michalski, J. Punt, D. W. Ellison, S. Picton, Treatment of recurrent central nervous system primitive neuroectodermal tumours in children and adolescents: Results of a Children's Cancer and Leukaemia Group study, Eur. J. Cancer. (2011), https://doi.org/10.1016/j.ejca.2011.03.004.

[8] P.A. Northcott, G.W. Robinson, C.P. Kratz, D.J. Mabbott, S.L. Pomeroy, S. C. Clifford, S. Rutkowski, D.W. Ellison, D. Malkin, M.D. Taylor, A. Gajjar, S. M. Pfister, Medulloblastoma, Nat. Rev. Dis. Prim. 5 (2019), https://doi.org/10.1038/s41572-019-0063-6.

[9] R. Salloum, Y. Chen, Y. Yasui, R. Packer, W. Leisenring, E. Wells, A. King, R. Howell, T.M. Gibson, K.R. Krull, L.L. Robison, K.C. Oeffinger, M. Fouladi, G. T. Armstrong, Late morbidity and mortality among medulloblastoma survivors diagnosed across three decades: A report from the Childhood Cancer Survivor Study, J. Clin. Oncol. 37 (2019) 731–740, https://doi.org/10.1200/JCO.18.00969.

[10] S.J. Laughton, T.E. Merchant, C.A. Sklar, L.E. Kun, M. Fouladi, A. Broniscer, E. B. Morris, R.P. Sanders, M.J. Krasin, J. Shelso, Z. Xiong, D. Wallace, A. Gajjar, Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial, J. Clin. Oncol. 26 (2008) 1112–1118, https://doi.org/10.1200/JCO.2008.13.5293.

[11] C.F. Levitch, A.A. Holland, J. Bledsoe, S.Y. Kim, M. Barnett, S. Ramjan, S. A. Sands, Comparison of neuropsychological functioning in pediatric posterior fossa tumor survivors: Medulloblastoma, low-grade astrocytoma, and healthy controls, Pediatr. Blood, Cancer. 69 (2022) 1–9, https://doi.org/10.1002/pbc.29491.

[12] M.D. Taylor, P.A. Northcott, A. Korshunov, M. Remke, Y.J. Cho, S.C. Clifford, C. G. Eberhart, D.W. Parsons, S. Rutkowski, A. Gajjar, D.W. Ellison, P. Lichter, R. J. Gilbertson, S.L. Pomeroy, M. Kool, S.M. Pfister, Molecular subgroups of medulloblastoma: The current consensus, Acta Neuropathol. 123 (2012) 465–472, https://doi.org/10.1007/s00401-011-0922-z.

[13] M.C. Thompson, C. Fuller, T.L. Hogg, J. Dalton, D. Finkelstein, C.C. Lau, M. Chintagumpala, A. Adesina, D.M. Ashley, S.J. Kellie, M.D. Taylor, T. Curran, A. Gajjar, R.J. Gilbertson, Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations, J. Clin. Oncol. 24 (2006) 1924–1931, https://doi.org/10.1200/JCO.2005.04.4974.

[14] M. Kool, J. Koster, J. Bunt, N.E. Hasselt, A. Lakeman, P. van Sluis, D. Troost, N. Schouten-van Meeteren, H.N. Caron, J. Cloos, A. Mršić, B. Ylstra, W. Grajkowska, W. Hartmann, T. Pietsch, D. Ellison, S.C. Clifford, R. Versteeg, Integrated genomics identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features, PLoS One. 3 (2008), https://doi.org/10.1371/journal.pone.0003088.

[15] P.A. Northcott, A. Korshunov, H. Witt, T. Hielscher, C.G. Eberhart, S. Mack, E. Bouffet, S.C. Clifford, C.E. Hawkins, P. French, J.T. Rutka, S. Pfister, M. D. Taylor, Medulloblastoma comprises four distinct molecular variants, J. Clin. Oncol. 29 (2011) 1408–1414, https://doi.org/10.1200/JCO.2009.27.4324.

[16] Y.J. Cho, A. Tsherniak, P. Tamayo, S. Santagata, A. Ligon, H. Greulich, R. Berhoukim, V. Amani, L. Goumnerova, C.G. Eberhart, C.C. Lau, J.M. Olson, R. J. Gilbertson, A. Gajjar, O. Delattre, M. Kool, K. Ligon, M. Meyerson, J.P. Mesirov, S.L. Pomeroy, Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome, J. Clin. Oncol. 29 (2011) 1424–1430, https://doi.org/10.1200/JCO.2010.28.5148.

[17] D.N. Louis, A. Perry, G. Reifenberger, A. von Deimling, D. Figarella-Branger, W. K. Cavenee, H. Ohgaki, O.D. Wiestler, P. Kleihues, D.W. Ellison, The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary, Acta Neuropathol. 131 (2016) 803–820, https://doi.org/10.1007/s00401-016-1545-1.

[18] D.N. Louis, A. Perry, P. Wesseling, D.J. Brat, I.A. Cree, D. Figarella-Branger, C. Hawkins, H.K. Ng, S.M. Pfister, G. Reifenberger, R. Soffietti, A. Von Deimling, D.W. Ellison, The 2021 WHO classification of tumors of the central nervous system: A summary, Neuro. Oncol. 23 (2021) 1231–1251, https://doi.org/10.1093/neuonc/noab106.

[19] J.A. Cotter, C. Hawkins, Medulloblastoma: WHO 2021 and Beyond, Pediatr. Dev. Pathol. 25 (2022) 23–33, https://doi.org/10.1177/10935266211018931.

[20] V. Hovestadt, O. Ayrault, F.J. Swartling, G.W. Robinson, S.M. Pfister, P. A. Northcott, Medulloblastomics revisited: biological and clinical insights from thousands of patients, Nat. Rev. Cancer. 20 (2020) 42–56, https://doi.org/10.1038/s41568-019-0223-8.

[21] A.M. Martin, E. Raabe, C. Eberhart, K.J. Cohen, Management of Pediatric and Adult Patients with Medulloblastoma, Curr. Treat. Options Oncol. 15 (2014) 581–594, https://doi.org/10.1007/s11864-014-0306-4.

[22] A. Thomas, G. Noël, Medulloblastoma: Optimizing care with a multidisciplinary approach, J. Multidiscip. Healthc. 12 (2019) 335–347, https://doi.org/10.2147/JMDH.S167808.

[23] P.A. Northcott, D.J.H. Shih, J. Peacock, L. Garzia, A. Sorana Morrissy, T. Zichner, A.M. Stútz, A. Korshunov, J. Reimand, S.E. Schumacher, R. Beroukhim, D. W. Ellison, C.R. Marshall, A.C. Lionel, S. MacK, A. Dubuc, Y. Yao, V. Ramaswamy, B. Luu, A. Rolider, F.M.G. Cavalli, X. Wang, M. Remke, X. Wu, R.Y.B. Chiu, A. Chu, E. Chuah, R.D. Corbett, G.R. Hoad, S.D. Jackman, Y. Li, A. Lo, K. L. Mungall, K. Ming Nip, J.Q. Qian, A.G.J. Raymond, N. Thiessen, R.J. Varhol, I. Birol, R.A. Moore, A.J. Mungall, R. Holt, D. Kawauchi, M.F. Roussel, M. Kool, D. T.W. Jones, H. Witt, A. Fernandez-L, A.M. Kenney, R.J. Wechsler-Reya, P. Dirks, T. Aviv, W.A. Grajkowska, M. Perek-Polnik, C.C. Haberler, O. Delattre, S. S. Reynaud, F.F. Doz, S.S. Pernet-Fattet, B.K. Cho, S.K. Kim, K.C. Wang, W. Scheurlen, C.G. Eberhart, M. Fèvre-Montange, A. Jouvet, I.F. Pollack, X. Fan, K.M. Muraszko, G. Yancey Gillespie, C. Di Rocco, L. Massimi, E.M.C. Michiels, N. K. Kloosterhof, P.J. French, J.M. Kros, J.M. Olson, R.G. Ellenbogen, K. Zitterbart, L. Kren, R.C. Thompson, M.K. Cooper, B. Lach, R.E. McLendon, D.D. Bigner, A. Fontebasso, S. Albrecht, N. Jabado, J.C. Lindsey, S. Bailey, N. Gupta, W. A. Weiss, L. Bognár, A. Klekner, T.E. Van Meter, T. Kumabe, T. Tominaga, S. K. Elbabaa, J.R. Leonard, J.B. Rubin, L.M. Liau, E.G. Van Meir, M. Fouladi, H. Nakamura, G. Cinalli, M. Garami, P. Hauser, A.G. Saad, A. Iolascon, S. Jung, C. G. Carlotti, R. Vibhakar, Y. Shin Ra, S. Robinson, M. Zollo, C.C. Faria, J.A. Chan, M.L. Levy, P.H.B. Sorensen, M. Meyerson, S.L. Pomeroy, Y.J. Cho, G.D. Bader, U. Tabori, C.E. Hawkins, E. Bouffet, S.W. Scherer, J.T. Rutka, D. Malkin, S. C. Clifford, S.J.M. Jones, J.O. Korbel, S.M. Pfister, M.A. Marra, M.D. Taylor, Subgroup-specific structural variation across 1,000 medulloblastoma genomes, Nature. 487 (2012) 49–56, https://doi.org/10.1038/nature11327.

[24] T.J. Pugh, S.D. Weeraratne, T.C. Archer, D.A. Pomeranz Krummel, D. Auclair, J. Bochicchio, M.O. Carneiro, S.L. Carter, K. Cibulskis, R.L. Erlich, H. Greulich, H. Greulich, N.J. Lennon, A. Mc Kenna, J. Meldrim, A.H. Ramos, M.G. Ross, C. Russ, E. Shefler, A. Sivachenko, B. Sogoloff, P. Stojanov, P. Tamayo, J. P. Mesirov, V. Amani, N. Teider, S. Sengupta, J.P. Francois, P.A. Northcott, M. D. Taylor, F. Yu, G.R. Crabtree, A.G. Kautzman, S.B. Gabriel, G. Getz, N. Jäger, D. T.W. Jones, P. Lichter, S.M. Pfister, T.M. Roberts, J.L. Dangl, S.L. Pomeroy, Y. J. Cho, Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations, Nature. 488 (2012) 106–110, https://doi.org/10.1038/nature11329.

[25] M. Kool, A. Korshunov, M. Remke, D.T.W. Jones, M. Schlanstein, P.A. Northcott, Y.J. Cho, J. Koster, A. Schouten-Van Meeteren, D. Van Vuurden, S.C. Clifford, T. Pietsch, A.O. Von Bueren, S. Rutkowski, M. McCabe, V.P. Collins, M. L. Bäcklund, C. Haberler, F. Bourdeaut, O. Delattre, F. Doz, D.W. Ellison, R. J. Gilbertson, S.L. Pomeroy, M.D. Taylor, P. Lichter, S.M. Pfister, Molecular subgroups of medulloblastoma: An international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas, Acta Neuropathol. 123 (2012) 473–484, https://doi.org/10.1007/s00401-012-0958-8.

[26] V. Hovestadt, M. Remke, M. Kool, T. Pietsch, P.A. Northcott, R. Fischer, F.M. G. Cavalli, V. Ramaswamy, M. Zapatka, G. Reifenberger, S. Rutkowski, M. Schick, M. Bewerunge-Hudler, A. Korshunov, P. Lichter, M.D. Taylor, S.M. Pfister, D.T. W. Jones, Robust molecular subgrouping and copy-number profiling of medulloblastoma from small amounts of archival tumour material using high-density DNA methylation arrays, Acta Neuropathol. 125 (2013) 913–916, https://doi.org/10.1007/s00401-013-1126-5.

[27] E.C. Schwalbe, D. Williamson, J.C. Lindsey, D. Hamilton, S.L. Ryan, H. Megahed, M. Garami, P. Hauser, B. Dembowska-Baginska, D. Perek, P.A. Northcott, M. D. Taylor, R.E. Taylor, D.W. Ellison, S. Bailey, S.C. Clifford, DNA methylation profiling of medulloblastoma allows robust subclassification and improved outcome prediction using formalin-fixed biopsies, Acta Neuropathol. 125 (2013) 359–371, https://doi.org/10.1007/s00401-012-1077-2.

[28] F.M.G. Cavalli, M. Remke, L. Rampasek, J. Peacock, D.J.H. Shih, B. Luu, L. Garzia, J. Torchia, C. Nor, A.S. Morrissy, S. Agnihotri, Y.Y. Thompson, C.M. Kuzan-Fischer, H. Farooq, K. Isaev, C. Daniels, B.-K. Cho, S.-K. Kim, K.-C. Wang, J.Y. Lee, W.A. Grajkowska, M. Perek-Polnik, A. Vasiljevic, C. Faure-Conter, A. Jouvet, C. Giannini, A.A. Nageswara Rao, K.K.W. Li, H.-K. Ng, C.G. Eberhart, I.F. Pollack, R.L. Hamilton, G.Y. Gillespie, J.M. Olson, S. Leary, W.A. Weiss, B. Lach, L. B. Chambless, R.C. Thompson, M.K. Cooper, R. Vibhakar, P. Hauser, M.-L. van Veelen, J.M. Kros, P.J. French, Y.S. Ra, T. Kumabe, E. López-Aguilar, K. Zitterbart, J. Sterba, G. Finocchiaro, M. Massimino, E.G. Van Meir, S. Osuka, T. Shofuda, A. Klekner, M. Zollo, J.R. Leonard, J.B. Rubin, N. Jabado, S. Albrecht, J. Mora, T.E. Van Meter, S. Jung, A.S. Moore, A.R. Hallahan, J.A. Chan, D.P. C. Tirapelli, C.G. Carlotti, M. Fouladi, J. Pimentel, C.C. Faria, A.G. Saad, L. Massimi, L.M. Liau, H. Wheeler, H. Nakamura, S.K. Elbabaa, M. Perezpeña-Diazconti, F. Chico Ponce de León, S. Robinson, M. Zapotocky, A. Lassaletta, A. Huang, C.E. Hawkins, U. Tabori, E. Bouffet, U. Bartels, P.B. Dirks, J.T. Rutka, G.D. Bader, J. Reimand, A. Goldenberg, V. Ramaswamy, M.D. Taylor, Intertumoral Heterogeneity within Medulloblastoma Subgroups, Cancer Cell. 31 (6) (2017) 737–754.e6.

[29] P.A. Northcott, I. Buchhalter, A.S. Morrissy, V. Hovestadt, J. Weischenfeldt, T. Ehrenberger, S. Gröbner, M. Segura-Wang, T. Zichner, V.A. Rudneva, H. J. Warnatz, N. Sidiropoulos, A.H. Phillips, S. Schumacher, K. Kleinheinz, S. M. Waszak, S. Erkek, D.T.W. Jones, B.C. Worst, M. Kool, M. Zapatka, N. Jäger, L. Chavez, B. Hutter, M. Bieg, N. Paramasivam, M. Heinold, Z. Gu, N. Ishaque, C. Jäger-Schmidt, C.D. Imbusch, A. Jugold, D. Hübschmann, T. Risch, V. Amstislavskiy, F.G.R. Gonzalez, U.D. Weber, S. Wolf, G.W. Robinson, X. Zhou, G. Wu, D. Finkelstein, Y. Liu, F.M.G. Cavalli, B. Luu, V. Ramaswamy, X. Wu, J. Koster, M. Ryzhova, Y.J. Cho, S.L. Pomeroy, C. Herold-Mende, M. Schuhmann, M. Ebinger, L.M. Liau, J. Mora, R.E. McLendon, N. Jabado, T. Kumabe, E. Chuah, Y. Ma, R.A. Moore, A.J. Mungall, K.L. Mungall, N. Thiessen, K. Tse, T. Wong, S.J. M. Jones, O. Witt, T. Milde, A. Von Deimling, D. Capper, A. Korshunov, M. L. Yaspo, R. Kriwacki, A. Gajjar, J. Zhang, R. Beroukhim, E. Fraenkel, J.O. Korbel, B. Brors, M. Schlesner, R. Eils, M.A. Marra, S.M. Pfister, M.D. Taylor, P. Lichter, The whole-genome landscape of medulloblastoma subtypes, Nature. 547 (2017) 311–317, https://doi.org/10.1038/nature22973.

[30] E.C. Schwalbe, J.C. Lindsey, S. Nakjang, S. Crosier, A.J. Smith, D. Hicks, G. Rafiee, R.M. Hill, A. Iliasova, T. Stone, B. Pizer, A. Michalski, A. Joshi, S. B. Wharton, T.S. Jacques, S. Bailey, D. Williamson, S.C. Clifford, Novel molecular subgroups for clinical classification and outcome prediction in childhood

medulloblastoma: a cohort study, Lancet Oncol. 18 (2017) 958–971, https://doi.org/10.1016/S1470-2045(17)30243-7.
[31] S. Perreault, V. Ramaswamy, A.S. Achrol, K. Chao, T.T. Liu, D. Shih, M. Remke, S. Schubert, E. Bouffet, P.G. Fisher, S. Partap, H. Vogel, M.D. Taylor, Y.J. Cho, K. W. Yeom, MRI surrogates for molecular subgroups of medulloblastoma, Am. J. Neuroradiol. 35 (2014) 1263–1269, https://doi.org/10.3174/ajnr.A3990.
[32] D.W. Ellison, J. Dalton, M. Kocak, S.L. Nicholson, C. Fraga, G. Neale, A. M. Kenney, D.J. Brat, A. Perry, W.H. Yong, R.E. Taylor, S. Bailey, S.C. Clifford, R. J. Gilbertson, Medulloblastoma: Clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups, Acta Neuropathol. 121 (2011) 381–396, https://doi.org/10.1007/s00401-011-0800-8.
[33] D.W. Ellison, O.E. Onilude, J.C. Lindsey, M.E. Lusher, C.L. Weston, R.E. Taylor, A. D. Pearson, S.C. Clifford, β-catenin status predicts a favorable outcome in childhood medulloblastoma: The United Kingdom Children's Cancer Study Group Brain Tumour Committee, J. Clin. Oncol. 23 (2005) 7951–7957, https://doi.org/10.1200/JCO.2005.01.5479.
[34] S.C. Clifford, M.E. Lusher, J.C. Lindsey, J.A. Langdon, R.J. Gilbertson, D. Straughton, D.W. Ellison, Wnt/Wingless pathway activation and chromosome 6 loss characterize a distinct molecular sub-group of medulloblastomas associated with a favorable prognosis, Cell Cycle. 5 (2006) 2666–2670, https://doi.org/10.4161/cc.5.22.3446.
[35] M.J. Smith, C. Beetz, S.G. Williams, S.S. Bhaskar, J. O'Sullivan, B. Anderson, S. B. Daly, J.E. Urquhart, Z. Bholah, D. Oudit, E. Cheesman, A. Kelsey, M.G. McCabe, W.G. Newman, D.G.R. Evans, Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations, J. Clin. Oncol. 32 (2015) 4155–4161, https://doi.org/10.1200/JCO.2014.58.2569.
[36] M. Kool, D.T.W. Jones, N. Jäger, P.A. Northcott, T.J. Pugh, V. Hovestadt, R. M. Piro, L.A. Esparza, S.L. Markant, M. Remke, T. Milde, F. Bourdeaut, M. Ryzhova, D. Sturm, E. Pfaff, S. Stark, S. Hutter, H. Sxeker-Cin, P. Johann, S. Bender, C. Schmidt, T. Rausch, D. Shih, J. Reimand, L. Sieber, A. Wittmann, L. Linke, H. Witt, U.D. Weber, M. Zapatka, R. König, R. Beroukhim, G. Bergthold, P. Van Sluis, R. Volckmann, J. Koster, R. Versteeg, S. Schmidt, S. Wolf, C. Lawerenz, C.C. Bartholomae, C. Von Kalle, A. Unterberg, C. Herold-Mende, S. Hofer, A.E. Kulozik, A. Von Deimling, W. Scheurlen, J. Felsberg, G. Reifenberger, M. Hasselblatt, J.R. Crawford, G.A. Grant, N. Jabado, A. Perry, C. Cowdrey, S. Croul, G. Zadeh, J.O. Korbel, F. Doz, O. Delattre, G.D. Bader, M. G. McCabe, V.P. Collins, M.W. Kieran, Y.J. Cho, S.L. Pomeroy, O. Witt, B. Brors, M.D. Taylor, U. Schüller, A. Korshunov, R. Eils, R.J. Wechsler-Reya, P. Lichter, S. M. Pfister, Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition, Cancer Cell. 25 (2014) 393–405, https://doi.org/10.1016/j.ccr.2014.02.004.
[37] H. Coltin, L. Sundaresan, K.S. Smith, P. Skowron, L. Massimi, C.G. Eberhart, K. C. Schreck, N. Gupta, W.A. Weiss, D. Tirapelli, C. Carlotti, K.K.W. Li, M. Ryzhova, A. Golanov, O. Zheludkova, O. Absalyamova, K. Okonechnikov, D. Stichel, A. von Deimling, C. Giannini, S. Raskin, E.G. Van Meir, J.A. Chan, D. Fults, L. B. Chambless, S.K. Kim, A. Vasiljevic, C. Faure-Conter, R. Vibhakar, S. Jung, S. Leary, J. Mora, R.E. McLendon, I.F. Pollack, P. Hauser, W.A. Grajkowska, J. B. Rubin, M.L.C. van Veelen, P.J. French, J.M. Kros, L.M. Liau, S.M. Pfister, M. Kool, N. Kijima, M.D. Taylor, R.J. Packer, P.A. Northcott, A. Korshunov, V. Ramaswamy, Subgroup and subtype-specific outcomes in adult medulloblastoma, Acta Neuropathol. 142 (2021) 859–871, https://doi.org/10.1007/s00401-021-02358-4.
[38] V. Ramaswamy, M. Remke, E. Bouffet, S. Bailey, S.C. Clifford, F. Doz, M. Kool, C. Dufour, G. Vassal, T. Milde, O. Witt, K. von Hoff, T. Pietsch, P.A. Northcott, A. Gajjar, G.W. Robinson, L. Padovani, N. André, M. Massimino, B. Pizer, R. Packer, S. Rutkowski, S.M. Pfister, M.D. Taylor, S.L. Pomeroy, Risk stratification of childhood medulloblastoma in the molecular era: the current consensus, Acta Neuropathol. 131 (2016) 821–831, https://doi.org/10.1007/s00401-016-1569-6.
[39] N. Zhukova, V. Ramaswamy, M. Remke, E. Pfaff, D.J.H. Shih, D.C. Martin, P. Castelo-Branco, B. Baskin, P.N. Ray, E. Bouffet, A.O. Von Bueren, D.T.W. Jones, P.A. Northcott, M. Kool, D. Sturm, T.J. Pugh, S.L. Pomeroy, Y.J. Cho, T. Pietsch, M. Gessi, S. Rutkowski, L. Bognar, A. Klekner, B.K. Cho, S.K. Kim, K.C. Wang, C. G. Eberhart, M. Fevre-Montange, M. Fouladi, P.J. French, M. Kros, W. A. Grajkowska, N. Gupta, W.A. Weiss, P. Hauser, N. Jabado, A. Jouvet, S. Jung, T. Kumabe, B. Lach, J.R. Leonard, J.B. Rubin, L.M. Liau, L. Massimi, I.F. Pollack, Y.S. Ra, E.G. Van Meir, K. Zitterbart, U. Schüller, R.M. Hill, J.C. Lindsey, E. C. Schwalbe, S. Bailey, D.W. Ellison, C. Hawkins, D. Malkin, S.C. Clifford, A. Korshunov, S. Pfister, M.D. Taylor, U. Tabori, Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma, J. Clin. Oncol. 31 (2013) 2927–2935, https://doi.org/10.1200/JCO.2012.48.5052.
[40] M. Remke, V. Ramaswamy, J. Peacock, D.J.H. Shih, C. Koelsche, P.A. Northcott, N. Hill, F.M.G. Cavalli, M. Kool, X. Wang, S.C. Mack, M. Barszczyk, A.S. Morrissy, X. Wu, S. Agnihotri, B. Luu, D.T.W. Jones, L. Garzia, A.M. Dubuc, N. Zhukova, R. Vanner, J.M. Kros, P.J. French, E.G. Van Meir, R. Vibhakar, K. Zitterbart, J. A. Chan, L. Bognár, A. Klekner, B. Lach, S. Jung, A.G. Saad, L.M. Liau, S. Albrecht, M. Zollo, M.K. Cooper, R.C. Thompson, O.O. Delattre, F. Bourdeaut, F.F. Doz, M. Garami, P. Hauser, C.G. Carlotti, T.E. Van Meter, L. Massimi, D. Fults, S. L. Pomeroy, T. Kumabe, Y.S. Ra, J.R. Leonard, S.K. Elbabaa, J. Mora, J.B. Rubin, Y.J. Cho, R.E. McLendon, D.D. Bigner, C.G. Eberhart, M. Fouladi, R.J. Wechsler-Reya, C.C. Faria, S.E. Croul, A. Huang, E. Bouffet, C.E. Hawkins, P.B. Dirks, W. A. Weiss, U. Schüller, I.F. Pollack, S. Rutkowski, D. Meyronet, A. Jouvet, M. Fèvre-Montange, N. Jabado, M. Perek-Polnik, W.A. Grajkowska, S.K. Kim, J. T. Rutka, D. Malkin, U. Tabori, S.M. Pfister, A. Korshunov, A. Von Deimling, M. D. Taylor, TERT promoter mutations are highly recurrent in SHH subgroup medulloblastoma, Acta Neuropathol. 126 (2013) 917–929, https://doi.org/10.1007/s00401-013-1198-2.
[41] G.W. Robinson, B.A. Orr, G. Wu, S. Gururangan, T. Lin, I. Qaddoumi, R.J. Packer, S. Goldman, M.D. Prados, A. Desjardins, M. Chintagumpala, N. Takebe, S. C. Kaste, M. Rusch, S.J. Allen, A. Onar-Thomas, C.F. Stewart, M. Fouladi, J. M. Boyett, R.J. Gilbertson, T. Curran, D.W. Ellison, A. Gajjar, Vismodegib exerts targeted efficacy against recurrent sonic hedgehog - Subgroup medulloblastoma: Results from phase II Pediatric Brain Tumor Consortium studies PBTC-025B and PBTC-032, J. Clin. Oncol. 33 (2015) 2646–2654, https://doi.org/10.1200/JCO.2014.60.1591.
[42] C. Metcalfe, F.J. De Sauvage, Hedgehog fights back: Mechanisms of acquired resistance against smoothened antagonists, Cancer Res. 71 (2011) 5057–5061, https://doi.org/10.1158/0008-5472.CAN-11-0923.
[43] P.A. Northcott, C. Lee, T. Zichner, A.M. Stütz, S. Erkek, D. Kawauchi, D.J.H. Shih, V. Hovestadt, M. Zapatka, D. Sturm, D.T.W. Jones, M. Kool, M. Remke, F.M. G. Cavalli, S. Zuyderduyn, G.D. Bader, S. Vandenberg, L.A. Esparza, M. Ryzhova, W. Wang, A. Wittmann, S. Stark, L. Sieber, H. Seker-Cin, L. Linke, F. Kratochwil, N. Jäger, I. Buchhalter, C.D. Imbusch, G. Zipprich, B. Raeder, S. Schmidt, N. Diessl, S. Wolf, S. Wiemann, B. Brors, C. Lawerenz, J. Eils, H.J. Warnatz, T. Risch, M.L. Yaspo, U.D. Weber, C.C. Bartholomae, C. Von Kalle, E. Turányi, P. Hauser, E. Sanden, A. Darabi, P. Siesjö, J. Sterba, K. Zitterbart, D. Sumerauer, P. Van Sluis, R. Versteeg, R. Volckmann, J. Koster, M.U. Schuhmann, M. Ebinger, H.L. Grimes, G.W. Robinson, A. Gajjar, M. Mynarek, K. Von Hoff, S. Rutkowski, T. Pietsch, W. Scheurlen, J. Felsberg, G. Reifenberger, A.E. Kulozik, A. Von Deimling, O. Witt, R. Eils, R.J. Gilbertson, A. Korshunov, M.D. Taylor, P. Lichter, J.O. Korbel, R.J. Wechsler-Reya, S.M. Pfister, Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma, Nature. 511 (2014) 428–434, https://doi.org/10.1038/nature13379.
[44] P.A. Northcott, Y. Nakahara, X. Wu, L. Feuk, D.W. Ellison, S. Croul, S. Mack, P. N. Kongkham, J. Peacock, A. Dubuc, Y.S. Ra, K. Zilberberg, J. Mcleod, S. W. Scherer, J. Sunil Rao, C.G. Eberhart, W. Grajkowska, Y. Gillespie, B. Lach, R. Grundy, I.F. Pollack, R.L. Hamilton, T. Van Meter, C.G. Carlotti, F. Boop, D. Bigner, R.J. Gilbertson, J.T. Rutka, M.D. Taylor, Multiple recurrent genetic events converge on control of histone lysine methylation in medulloblastoma, Nat. Genet. 41 (2009) 465–472, https://doi.org/10.1038/ng.336.
[45] S.E.S. Leary, R.J. Packer, Y. Li, C.A. Billups, K.S. Smith, A. Jaju, L. Heier, P. Burger, K. Walsh, Y. Han, L. Embry, J. Hadley, R. Kumar, J. Michalski, E. Hwang, A. Gajjar, I.F. Pollack, M. Fouladi, P.A. Northcott, J.M. Olson, Efficacy of Carboplatin and Isotretinoin in Children with High-risk Medulloblastoma: A Randomized Clinical Trial from the Children's Oncology Group, JAMA Oncol. 7 (2021) 1313–1321, https://doi.org/10.1001/jamaoncol.2021.2224.
[46] P. Bandopadhayay, G. Bergthold, B. Nguyen, S. Schubert, S. Gholamin, Y. Tang, S. Bolin, S.E. Schumacher, R. Zeid, S. Masoud, F. Yu, N. Vue, W.J. Gibson, B.R. Paolella, S.S. Mitra, S.H. Cheshier, J. Qi, K.W. Liu, R. Wechsler-Reya, W.A. Weiss, F.J. Swartling, M.W. Kieran, J.E. Bradner, R. Beroukhim, Y.J. Cho. BET bromodomain inhibition of MYC-amplified medulloblastoma. Clin. Cancer Res. 20. (2014). 912–925. 10.1158/1078-0432.CCR-13-2281.
[47] M.L. Cook Sangar, L.A. Genovesi, M.W. Nakamoto, M.J. Davis, S.E. Knobluagh, P. Ji, A. Millar, B.J. Wainwright, J.M. Olson. Inhibition of CDK4/6 by palbociclib significantly extends survival in medulloblastoma patient-derived xenograft mouse models. Clin. Cancer Res. 23. (2017). 5802–5813. 10.1158/1078-0432.CCR-16-2943.
[48] S. Bolin, A. Borgenvik, C.U. Persson, A. Sundström, J. Qi, J.E. Bradner, W. A. Weiss, Y.J. Cho, H. Weishaupt, F.J. Swartling, Combined BET bromodomain and CDK2 inhibition in MYC-driven medulloblastoma, Oncogene. 37 (2018) 2850–2862, https://doi.org/10.1038/s41388-018-0135-1.
[49] Y. Pei, K.W. Liu, J. Wang, A. Garancher, R. Tao, L.A. Esparza, D.L. Maier, Y. T. Udaka, N. Murad, S. Morrissy, H. Seker-Cin, S. Brabetz, L. Qi, M. Kogiso, S. Schubert, J.M. Olson, Y.J. Cho, X.N. Li, J.R. Crawford, M.L. Levy, M. Kool, S. M. Pfister, M.D. Taylor, R.J. Wechsler-Reya, HDAC and PI3K Antagonists Cooperate to Inhibit Growth of MYC-Driven Medulloblastoma, Cancer Cell. 29 (2016) 311–323, https://doi.org/10.1016/j.ccell.2016.02.011.
[50] G. Robinson, M. Parker, T.A. Kranenburg, C. Lu, X. Chen, L. Ding, T.N. Phoenix, E. Hedlund, L. Wei, X. Zhu, N. Chalhoub, S.J. Baker, R. Huether, R. Kriwacki, N. Curley, R. Thiruvenkatam, J. Wang, G. Wu, M. Rusch, X. Hong, J. Becksfort, P. Gupta, J. Ma, J. Easton, B. Vadodaria, A. Onar-Thomas, T. Lin, S. Li, S. Pounds, S. Paugh, D. Zhao, D. Kawauchi, M.F. Roussel, D. Finkelstein, D.W. Ellison, C. C. Lau, E. Bouffet, T. Hassall, S. Gururangan, R. Cohn, R.S. Fulton, L.L. Fulton, D. J. Dooling, K. Ochoa, A. Gajjar, E.R. Mardis, R.K. Wilson, J.R. Downing, J. Zhang, R.J. Gilbertson, Novel mutations target distinct subgroups of medulloblastoma, Nature. 488 (2012) 43–48, https://doi.org/10.1038/nature11213.
[51] J.H. Shih, P.A. Northcott, M. Remke, A. Korshunov, V. Ramaswamy, M. Kool, B. Luu, Y. Yao, X. Wang, A.M. Dubuc, L. Garzia, J. Peacock, S.C. Mack, X. Wu, A. Rolider, A.S. Morrissy, F.M.G. Cavalli, D.T.W. Jones, K. Zitterbart, C.C. Faria, U. Schüller, L. Kren, T. Kumabe, T. Tominaga, Y.S. Ra, M. Garami, P. Hauser, J. A. Chan, S. Robinson, L. Bognár, A. Klekner, A.G. Saad, L.M. Liau, S. Albrecht, A. Fontebasso, G. Cinalli, P. De Antonellis, M. Zollo, M.K. Cooper, R.C. Thompson, S. Bailey, J.C. Lindsey, C. Di Rocco, L. Massimi, E.M.C. Michiels, S.W. Scherer, J. J. Phillips, N. Gupta, X. Fan, K.M. Muraszko, R. Vibhakar, C.G. Eberhart, M. Fouladi, B. Lach, S. Jung, R.J. Wechsler-Reya, M. Fèvre-Montange, A. Jouvet, N. Jabado, I.F. Pollack, W.A. Weiss, J.Y. Lee, B.K. Cho, S.K. Kim, K.C. Wang, J. R. Leonard, J.B. Rubin, C. De Torres, C. Lavarino, J. Mora, Y.J. Cho, U. Tabori, J. M. Olson, A. Gajjar, R.J. Packer, S. Rutkowski, S.L. Pomeroy, P.J. French, N. K. Kloosterhof, J.M. Kros, E.G. Van Meir, S.C. Clifford, F. Bourdeaut, O. Delattre, F.F. Doz, C.E. Hawkins, D. Malkin, W.A. Grajkowska, M. Perek-Polnik, E. Bouffet, J.T. Rutka, S.M. Pfister, M.D. Taylor, Cytogenetic prognostication within

medulloblastoma subgroups, J. Clin. Oncol. 32 (2014) 886–896, https://doi.org/10.1200/JCO.2013.50.9539.
[52] M.A. Lazow, J.D. Palmer, M. Fouladi, R. Salloum, Medulloblastoma in the Modern Era: Review of Contemporary Trials, Molecular Advances, and Updates in Management, Neurotherapeutics. 19 (2022) 1733–1751, https://doi.org/10.1007/s13311-022-01273-0.
[53] T. Sharma, E.C. Schwalbe, D. Williamson, M. Sill, V. Hovestadt, M. Mynarek, S. Rutkowski, G.W. Robinson, A. Gajjar, F. Cavalli, V. Ramaswamy, M.D. Taylor, J.C. Lindsey, R.M. Hill, N. Jäger, A. Korshunov, D. Hicks, S. Bailey, M. Kool, L. Chavez, P.A. Northcott, S.M. Pfister, S.C. Clifford, Second-generation molecular subgrouping of medulloblastoma: an international meta-analysis of Group 3 and Group 4 subtypes, Acta Neuropathol. 138 (2019) 309–326, https://doi.org/10.1007/s00401-019-02020-0.
[54] S.K. Singh, I.D. Clarke, M. Terasaki, V.E. Bonn, C. Hawkins, J. Squire, P.B. Dirks, Identification of a cancer stem cell in human brain tumors, Cancer Res. 63 (2003) 5821–5828.
[55] M.C. Vladoiu, I. El-Hamamy, L.K. Donovan, H. Farooq, B.L. Holgado, Y. Sundaravadanam, V. Ramaswamy, L.D. Hendrikse, S. Kumar, S.C. Mack, J.J. Y. Lee, V. Fong, K. Juraschka, D. Przelicki, A. Michealraj, P. Skowron, B. Luu, H. Suzuki, A.S. Morrissy, F.M.G. Cavalli, L. Garzia, C. Daniels, X. Wu, M.A. Qazi, S.K. Singh, J.A. Chan, M.A. Marra, D. Malkin, P. Dirks, L. Heisler, T. Pugh, K. Ng, F. Notta, E.M. Thompson, C.L. Kleinman, A.L. Joyner, N. Jabado, L. Stein, M. D. Taylor, Childhood cerebellar tumours mirror conserved fetal transcriptional programs, Nature. 572 (2019) 67–73, https://doi.org/10.1038/s41586-019-1158-7.
[56] V. Hovestadt, K.S. Smith, L. Bihannic, M.G. Filbin, M.K.L. Shaw, A. Baumgartner, J.C. DeWitt, A. Groves, L. Mayr, H.R. Weisman, A.R. Richman, M.E. Shore, L. Goumnerova, C. Rosencrance, R.A. Carter, T.N. Phoenix, J.L. Hadley, Y. Tong, J. Houston, R.A. Ashmun, M. DeCuypere, T. Sharma, D. Flasch, A. Silkov, K. L. Ligon, S.L. Pomeroy, M.N. Rivera, O. Rozenblatt-Rosen, J.M. Rusert, R. J. Wechsler-Reya, X.N. Li, A. Peyrl, J. Gojo, D. Kirchhofer, D. Lötsch, T. Czech, C. Dorfer, C. Haberler, R. Geyeregger, A. Halfmann, C. Gawad, J. Easton, S. M. Pfister, A. Regev, A. Gajjar, B.A. Orr, I. Slavc, G.W. Robinson, B.E. Bernstein, M.L. Suvà, P.A. Northcott, Resolving medulloblastoma cellular architecture by single-cell genomics, Nature. 572 (2019) 74–79, https://doi.org/10.1038/s41586-019-1434-6.
[57] P. Martín-Rubio, P. Espiau-Romera, A. Royo-García, L. Caja, P. Sancho, Metabolic determinants of stemness in medulloblastoma, World, J Stem Cells. 14 (2022) 587–598, https://doi.org/10.4252/WJSC.V14.I8.587.
[58] V. Marabitti, M. Giansanti, F. De Mitri, F. Gatto, A. Mastronuzzi, F. Nazio, Pathological implications of metabolic reprogramming and its therapeutic potential in medulloblastoma, Front. Cell, Dev. Biol. 10 (2022) 1–19, https://doi.org/10.3389/fcell.2022.1007641.
[59] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: The next generation, Cell. 144 (2011) 646–674, https://doi.org/10.1016/j.cell.2011.02.013.
[60] O. WARBURG. On respiratory impairment in cancer cells. Science. (80). (n.d.).
[61] K. Tech, T.R. Gershon, Energy metabolism in neurodevelopment and medulloblastoma, Transl. Pediatr. 4 (2015) 12–19, https://doi.org/10.3978/j.issn.2224-4336.2015.01.03.
[62] S. Blüml, A.S. Margol, R. Sposto, R.J. Kennedy, N.J. Robison, M. Vali, L.T. Hung, S. Muthugounder, J.L. Finlay, A. Erdreich-Epstein, F.H. Gilles, A.R. Judkins, M. D. Krieger, G. Dhall, M.D. Nelson, S. Asgharzadeh, Molecular subgroups of medulloblastoma identification using noninvasive magnetic resonance spectroscopy, Neuro, Oncol. 18 (2016) 126–131, https://doi.org/10.1093/neuonc/nov097.
[63] A.K. Park, J.Y. Lee, H. Cheong, V. Ramaswamy, S.H. Park, M. Kool, J.H. Phi, S. A. Choi, F. Cavalli, M.D. Taylor, S.K. Kim, Subgroup-specific prognostic signaling and metabolic pathways in pediatric medulloblastoma, BMC Cancer. 19 (2019) 1–15, https://doi.org/10.1186/s12885-019-5742-x.
[64] S. Agnihotri, Z. Gelareh. Metabolic reprogramming in glioblastoma: the influence of cancer metabolism on epigenetics and unanswered questions. 18. (2016). 160–172. 10.1093/neuonc/nov125.
[65] N.N. Pavlova, C.B. Thompson, The Emerging Hallmarks of Cancer Metabolism, Cell Metab. (2016), https://doi.org/10.1016/j.cmet.2015.12.006.
[66] E.A. Zaal, C.R. Berkers, The influence of metabolism on drug response in cancer, Front. Oncol. (2018), https://doi.org/10.3389/fonc.2018.00500.
[67] Y. Zhao, E.B. Butler, M. Tan, Targeting cellular metabolism to improve cancer therapeutics, Cell Death Dis. (2013), https://doi.org/10.1038/cddis.2013.60.
[68] K.E. Hawkins, S. Joy, J.M.K.M. Delhove, V.N. Kotiadis, E. Fernandez, L. M. Fitzpatrick, J.R. Whiteford, P.J. King, J.P. Bolanos, M.R. Duchen, S. N. Waddington, T.R. McKay, NRF2 Orchestrates the Metabolic Shift during Induced Pluripotent Stem Cell Reprogramming, Cell Rep. (2016), https://doi.org/10.1016/j.celrep.2016.02.003.
[69] C. Bernauer, Y.K.S. Man, J.C. Chisholm, E.Y. Lepicard, S.P. Robinson, J. M. Shipley, Hypoxia and its therapeutic possibilities in paediatric cancers, Br. J. Cancer. 124 (2021) 539–551, https://doi.org/10.1038/s41416-020-01107-w.
[70] G.A.V. Cruzeiro, M.B. Dos Reis, V.S. Silveira, R.C.P. Lira, C.G.J. Carlotti, L. Neder, R.S. Oliveira, J.A. Yunes, S.R. Brandalise, S. Aguiar, A.K. Eterovic, L.G. Tone, C. A. Scrideli, E.T. Valera, HIF1A is Overexpressed in Medulloblastoma and its Inhibition Reduces Proliferation and Increases EPAS1 and ATG16L1 Methylation, Curr. Cancer Drug Targets. 18 (2018) 287–294, https://doi.org/10.2174/1568009617666170315162525.
[71] F. Linke, J.E.C. Johnson, S. Kern, C.D. Bennett, A. Lourdusamy, D. Lea, S. C. Clifford, C.L.R. Merry, S. Stolnik, M.R. Alexander, A.C. Peet, D.J. Scurr, R. L. Griffiths, A.M. Grabowska, I.D. Kerr, B. Coyle, Identifying new biomarkers of aggressive Group 3 and SHH medulloblastoma using 3D hydrogel models, single cell RNA sequencing and 3D OrbiSIMS imaging, Acta Neuropathol. Commun. 11 (2023) 1–18, https://doi.org/10.1186/s40478-022-01496-4.
[72] F. Pistollato, E. Rampazzo, L. Persano, S. Abbadi, C. Frasson, L. Denaro, D. D'Avella, D.M. Panchision, A. Della Puppa, R. Scienza, G. Basso, Interaction of hypoxia-inducible factor-1α and Notch signaling regulates medulloblastoma precursor proliferation and fate, Stem Cells. 28 (2010) 1918–1929, https://doi.org/10.1002/stem.518.
[73] R. Tao, N. Murad, Z. Xu, P. Zhang, K. Okonechnikov, M. Kool, S. Rivero-Hinojosa, C. Lazarski, P. Zheng, Y. Liu, C.G. Eberhart, B.R. Rood, R. Packer, Y. Pei, MYC drives group 3 medulloblastoma through transformation of Sox2 þ astrocyte progenitor cells, Cancer Res. 79 (2019) 1967–1980, https://doi.org/10.1158/0008-5472.CAN-18-1787.
[74] T.R. Gershon, A.J. Crowther, A. Tikunov, I. Garcia, R. Annis, H. Yuan, C.R. Miller, J. Macdonald, J. Olson, M. Deshmukh, Hexokinase-2-mediated aerobic glycolysis is integral to cerebellar neurogenesis and pathogenesis of medulloblastoma, Cancer Metab. (2013), https://doi.org/10.1186/2049-3002-1-2.
[75] L. Di Magno, D. Manzi, D. D'Amico, S. Coni, A. Macone, P. Infante, L. Di Marcotullio, E. De Smaele, E. Ferretti, I. Screpanti, E. Agostinelli, A. Gulino, G. Canettieri, Druggable glycolytic requirement for Hedgehog-dependent neuronal and medulloblastoma growth, Cell Cycle. 13 (2014) 3404–3413, https://doi.org/10.4161/15384101.2014.952973.
[76] S. Badodi, N. Pomella, X. Zhang, G. Rosser, J. Whittingham, M.V. Niklison-Chirou, Y.M. Lim, S. Brandner, G. Morrison, S.M. Pollard, C.D. Bennett, S. C. Clifford, A. Peet, M.A. Basson, S. Marino, Inositol treatment inhibits medulloblastoma through suppression of epigenetic-driven metabolic adaptation, Nat. Commun. 12 (2021) 1–16, https://doi.org/10.1038/s41467-021-22379-7.
[77] K. Tech, A.P. Tikunov, H. Farooq, A.S. Morrissy, J. Meidinger, T. Fish, S.C. Green, H. Liu, Y. Li, A.J. Mungall, R.A. Moore, Y. Ma, S.J.M. Jones, M.A. Marra, M.G. Vander Heiden, M.D. Taylor, J.M. MacDonald, T.R. Gershon. Pyruvate kinase inhibits proliferation during postnatal cerebellar neurogenesis and suppresses medulloblastoma formation. Cancer Res. 77. (2017). 3217–3230. 10.1158/0008-5472.CAN-16-3304.
[78] C.J. Valvona, H.L. Fillmore, Oxamate, but not selective targeting of LDH-A, inhibits medulloblastoma cell glycolysis, growth and motility, Brain Sci. 8 (2018), https://doi.org/10.3390/brainsci8040056.
[79] K. Pham, A.R. Hanaford, B.A. Poore, M.J. Maxwell, H. Sweeney, A. Parthasarathy, J. Alt, R. Rais, B.S. Slusher, C.G. Eberhart, E.H. Raabe, Comprehensive Metabolic Profiling of MYC-Amplified Medulloblastoma Tumors Reveals Key Dependencies on Amino Acid, Tricarboxylic Acid and Hexosamine Pathways, Cancers (Basel). 14 (2022), https://doi.org/10.3390/cancers14051311.
[80] K.L. Leskoske, K. Garcia-Mansfield, R. Sharma, A. Krishnan, J.M. Rusert, J. P. Mesirov, R.J. Wechsler-Reya, P. Pirrotte, Subgroup-Enriched Pathways and Kinase Signatures in Medulloblastoma Patient-Derived Xenografts, J. Proteome Res. 21 (2022) 2124–2136, https://doi.org/10.1021/acs.jproteome.2c00203.
[81] E.L. Lieu, T. Nguyen, S. Rhyne, J. Kim, Amino acids in cancer, Exp. Mol. Med. 52 (2020) 15–30, https://doi.org/10.1038/s12276-020-0375-3.
[82] M. Yang, K.H. Vousden, Serine and one-carbon metabolism in cancer, Nat. Rev. Cancer. 16 (2016) 650–662, https://doi.org/10.1038/nrc.2016.81.
[83] E. Pranzini, E. Pardella, L. Muccillo, A. Leo, I. Nesi, A. Santi, M. Parri, T. Zhang, A. H. Uribe, T. Lottini, L. Sabatino, A. Caselli, A. Arcangeli, G. Raugei, V. Colantuoni, P. Cirri, P. Chiarugi, O.D.K. Maddocks, P. Paoli, M.L. Taddei, SHMT2-mediated mitochondrial serine metabolism drives 5-FU resistance by fueling nucleotide biosynthesis, Cell Rep. 40 (2022), 111233, https://doi.org/10.1016/j.celrep.2022.111233.
[84] T. Van Nyen, M. Planque, L. van Wagensveld, J.A.G. Duarte, E.A. Zaal, A. Talebi, M. Rossi, P.R. Körner, L. Rizzotto, S. Moens, W. De Wispelaere, R.E.M. Baiden-Amissah, G.S. Sonke, H.M. Horlings, G. Eelen, E. Berardi, J.V. Swinnen, C. R. Berkers, P. Carmeliet, D. Lambrechts, B. Davidson, R. Agami, S.M. Fendt, D. Annibali, F. Amant, Serine metabolism remodeling after platinum-based chemotherapy identifies vulnerabilities in a subgroup of resistant ovarian cancers, Nat. Commun. 13 (2022), https://doi.org/10.1038/s41467-022-32272-6.
[85] P. Gao, I. Tchernyshyov, T.C. Chang, Y.S. Lee, K. Kita, T. Ochi, K.I. Zeller, A.M. De Marzo, J.E. Van Eyk, J.T. Mendell, C.V. Dang, C-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism, Nature. 458 (2009) 762–765, https://doi.org/10.1038/nature07823.
[86] L. Sun, L. Song, Q. Wan, G. Wu, X. Li, Y. Wang, J. Wang, Z. Liu, X. Zhong, X. He, S. Shen, X. Pan, A. Li, Y. Wang, P. Gao, H. Tang, H. Zhang, CMyc-mediated activation of serine biosynthesis pathway is critical for cancer progression under nutrient deprivation conditions, Cell Res. 25 (2015) 429–444, https://doi.org/10.1038/cr.2015.33.
[87] O.D.K. Maddocks, C.R. Berkers, S.M. Mason, L. Zheng, K. Blyth, E. Gottlieb, K. H. Vousden, Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells, Nature. 493 (2013) 542–546, https://doi.org/10.1038/nature11743.
[88] S. Suzuki, T. Tanaka, M.V. Poyurovsky, H. Nagano, T. Mayama, S. Ohkubo, M. Lokshin, H. Hosokawa, T. Nakayama, Y. Suzuki, S. Sugano, E. Sato, T. Nagao, K. Yokote, I. Tatsuno, C. Prives, Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 7461–7466, https://doi.org/10.1073/pnas.1002459107.
[89] J. Jin, J.K. Byun, Y.K. Choi, K.G. Park, Targeting glutamine metabolism as a therapeutic strategy for cancer, Exp. Mol. Med. (2023), https://doi.org/10.1038/s12276-023-00971-9.
[90] M.V. Niklison-Chirou, I. Erngren, M. Engskog, J. Haglöf, D. Picard, M. Remke, P. H.R. McPolin, M. Selby, D. Williamson, S.C. Clifford, D. Michod,

M. Hadjiandreou, T. Arvidsson, C. Pettersson, G. Melino, S. Marino, TAp73 is a marker of glutamine addiction in medulloblastoma, Genes Dev. 31 (2017) 1738–1753, https://doi.org/10.1101/gad.302349.117.
[91] T. Velletri, F. Romeo, P. Tucci, A. Peschiaroli, M. Annicchiarico-Petruzzelli, M. V. Niklison-Chirou, I. Amelio, R.A. Knight, T.W. Mak, G. Melino, M. Agostini, GLS2 is transcriptionally regulated by p73 and contributes to neuronal differentiation, Cell Cycle. 12 (2013) 3564–3573, https://doi.org/10.4161/cc.26771.
[92] J. Ge, B. Wang, S. Zhao, J. Xu, Inhibition of lncRNA NEAT1 sensitizes medulloblastoma cells to cisplatin through modulating the miR-23a-3p-glutaminase (GLS) axis, Bioengineered. 13 (2022) 7670–7682, https://doi.org/10.1080/21655979.2021.2008695.
[93] N. Koundouros, G. Poulogiannis, Reprogramming of fatty acid metabolism in cancer, Br. J. Cancer. (2020), https://doi.org/10.1038/s41416-019-0650-z.
[94] J. Zhu, C.B. Thompson, Metabolic regulation of cell growth and proliferation, Nat. Rev. Mol. Cell Biol. 20 (2019), https://doi.org/10.1038/s41580-019-0123-5.
[95] L.M. Butler, Y. Perone, J. Dehairs, L.E. Lupien, V. De Laat, A. Talebi, M. Loda, W. B. Kinlaw, J.V. Swinnen, Lipids and cancer : Emerging roles in pathogenesis, diagnosis and therapeutic intervention, Adv. Drug Deliv. Rev. 159 (2020) 245–293, https://doi.org/10.1016/j.addr.2020.07.013.
[96] A.J. Hoy. Tumour fatty acid metabolism in the context of therapy resistance and obesity. 21. (2021). 753–766. 10.1038/s41568-021-00388-4.
[97] B. Bhatia, M. Hsieh, Z. Nahle. Mitogenic Sonic hedgehog signaling drives E2F1-dependent lipogenesis in progenitor cells and medulloblastoma. (2011). 410–422. 10.1038/onc.2010.454.
[98] K. Tech, M. Deshmukh, T.R. Gershon, Adaptations of energy metabolism during cerebellar neurogenesis are co-opted in medulloblastoma, Cancer Lett. 356 (2015) 268–272, https://doi.org/10.1016/j.canlet.2014.02.017.
[99] D. Juarez, D.A. Fruman, Targeting the Mevalonate Pathway in Cancer, Trends in Cancer. 7 (2020) 525–540, https://doi.org/10.1016/j.trecan.2020.11.008.
[100] Q. Fan, T. Gong, C. Zheng, J.M.Y. Ng, J. Chen, C. Myers, H. Hensley, T. Curran, Z. jie Yang, Statins repress hedgehog signaling in medulloblastoma with no bone toxicities, Oncogene. 40 (2021) 2258–2272, https://doi.org/10.1038/s41388-021-01701-z.
[101] R.E. Gordon, L. Zhang, S. Peri, Y.M. Kuo, F. Du, B.L. Egleston, J.M.Y. Ng, A.J. Andrews, I. Astsaturov, T. Curran, Z.J. Yang. Statins synergize with hedgehog pathway inhibitors for treatment of medulloblastoma, Clin. Cancer Res. 24. (2018). 1375–1388. 10.1158/1078-0432.CCR-17-2923.
[102] K. Sheikholeslami, A.A. Sher, S. Lockman, D. Kroft, M. Ganjibakhsh, K. Nejati-Koshki, S. Shojaei, S. Ghavami, M. Rastegar, Simvastatin induces apoptosis in medulloblastoma brain tumor cells via mevalonate cascade prenylation substrates, Cancers (Basel). 11 (2019), https://doi.org/10.3390/cancers11070994.
[103] A.A.L. Takwi, Y. Li, L.E. Becker Buscaglia, J. Zhang, S. Choudhury, A.K. Park, M. Liu, K.H. Young, W.Y. Park, R.C.G. Martin, Y. Li, A statin-regulated microRNA represses human c-Myc expression and function, EMBO Mol. Med. 4 (2012) 896–909, https://doi.org/10.1002/emmm.201101045.
[104] N. Santana-Codina, A.A. Roeth, Y. Zhang, A. Yang, O. Mashadova, J.M. Asara, X. Wang, R.T. Bronson, C.A. Lyssiotis, H. Ying, A.C. Kimmelman, Oncogenic KRAS supports pancreatic cancer through regulation of nucleotide synthesis, Nat. Commun. 9 (2018), https://doi.org/10.1038/s41467-018-07472-8.
[105] K.K. Brown, J.B. Spinelli, J.M. Asara, A. Toker. Adaptive reprogramming of De novo pyrimidine synthesis is a metabolic vulnerability in triple-negative breast cancer. Cancer Discov. 7. (2017). 391–399. 10.1158/2159-8290.CD-16-0611.
[106] D.E. Biancur, K.S. Kapner, K. Yamamoto, R.S. Banh, J.E. Neggers, A.S.W. Sohn, W. Wu, R.T. Manguso, A. Brown, D.E. Root, A.J. Aguirre, A.C. Kimmelman, Functional Genomics Identifies Metabolic Vulnerabilities in Pancreatic Cancer, Cell Metab. 33 (2021) 199–210.e8, https://doi.org/10.1016/j.cmet.2020.10.018.
[107] D.B. Sykes, Y.S. Kfoury, F.E. Mercier, M.J. Wawer, J.M. Law, M.K. Haynes, T. A. Lewis, A. Schajnovitz, E. Jain, D. Lee, H. Meyer, K.A. Pierce, N.J. Tolliday, A. Waller, S.J. Ferrara, A.L. Eheim, D. Stoeckigt, K.L. Maxcy, J.M. Cobert, J. Bachand, B.A. Szekely, S. Mukherjee, L.A. Sklar, J.D. Kotz, C.B. Clish, R. I. Sadreyev, P.A. Clemons, A. Janzer, S.L. Schreiber, D.T. Scadden, Inhibition of Dihydroorotate Dehydrogenase Overcomes Differentiation Blockade in Acute Myeloid Leukemia, Cell. 167 (2016) 171–186.e15, https://doi.org/10.1016/j.cell.2016.08.057.
[108] I.I. Ozbek, K.O. Ulgen, Identification of Therapeutic Targets for Medulloblastoma by Tissue-Specific Genome-Scale Metabolic Model, Molecules. 28 (2023), https://doi.org/10.3390/molecules28020779.
[109] W.D. Gwynne, Y. Suk, S. Custers, N. Mikolajewicz, J.K. Chan, Z. Zador, S.C. Chafe, K. Zhai, L. Escudero, C. Zhang, O. Zaslaver, C. Chokshi, M.V. Shaikh, D. Bakhshinyan, I. Burns, I. Chaudhry, O. Nachmani, D. Mobilio, W.T. Maich, P. Mero, K.R. Brown, A.T. Quaile, C. Venugopal, J. Moffat, J.R. Montenegro-Burke, S.K. Singh, Cancer-selective metabolic vulnerabilities in MYC-amplified medulloblastoma, Cancer Cell. 40 (2022) 1488–1502.e7, https://doi.org/10.1016/j.ccell.2022.10.009.
[110] C. Maffezzini, J. Calvo-Garrido, A. Wredenberg, C. Freyer, Metabolic regulation of neurodifferentiation in the adult brain, Cell. Mol. Life Sci. 77 (2020) 2483–2496, https://doi.org/10.1007/s00018-019-03430-9.
[111] M. Agostini, F. Romeo, S. Inoue, M.V. Niklison-Chirou, A.J. Elia, D. Dinsdale, N. Morone, R.A. Knight, T.W. Mak, G. Melino, Metabolic reprogramming during neuronal differentiation, Cell Death Differ. 23 (2016) 1502–1514, https://doi.org/10.1038/cdd.2016.36.
[112] M. Erecińska, I.A. Silver, Tissue oxygen tension and brain sensitivity to hypoxia, Respir. Physiol. 128 (2001) 263–276, https://doi.org/10.1016/S0034-5687(01)00306-1.
[113] D.Y. Kim, I. Rhee, J. Paik, Metabolic circuits in neural stem cells, Cell. Mol. Life Sci. 71 (2014) 4221–4241, https://doi.org/10.1007/s00018-014-1686-0.
[114] M. Knobloch, G.A. Pilz, B. Ghesquière, W.J. Kovacs, T. Wegleiter, D.L. Moore, M. Hruzova, N. Zamboni, P. Carmeliet, S. Jessberger, A Fatty Acid Oxidation-Dependent Metabolic Shift Regulates Adult Neural Stem Cell Activity, Cell Rep. 20 (2017) 2144–2155, https://doi.org/10.1016/j.celrep.2017.08.029.
[115] T. Namba, J. Nardelli, P. Gressens, W.B. Huttner, Metabolic Regulation of Neocortical Expansion in Development and Evolution, Neuron. 109 (2021) 408–419, https://doi.org/10.1016/j.neuron.2020.11.014.
[116] T. Namba, J. Dóczi, A. Pinson, L. Xing, N. Kalebic, M. Wilsch-Bräuninger, K. R. Long, S. Vaid, J. Lauer, A. Bogdanova, B. Borgonovo, A. Shevchenko, P. Keller, D. Drechsel, T. Kurzchalia, P. Wimberger, C. Chinopoulos, W.B. Huttner, Human-Specific ARHGAP11B Acts in Mitochondria to Expand Neocortical Progenitors by Glutaminolysis, Neuron. 105 (2020) 867–881.e9, https://doi.org/10.1016/j.neuron.2019.11.027.
[117] A.A. Hamed, D.J. Kunz, I. El-Hamamy, Q.M. Trinh, O.D. Subedar, L.M. Richards, W. Foltz, G. Bullivant, M. Ware, M.C. Vladoiu, J. Zhang, A.M. Raj, T.J. Pugh, M. D. Taylor, S.A. Teichmann, L.D. Stein, B.D. Simons, P.B. Dirks, A brain precursor atlas reveals the acquisition of developmental-like states in adult cerebral tumours, Nat. Commun. 13 (2022), https://doi.org/10.1038/s41467-022-31408-y.
[118] M.G.V. Heiden, L.C. Cantley, C.B. Thompson, Understanding the warburg effect: The metabolic requirements of cell proliferation, Science 80 (324) (2009) 1029–1033, https://doi.org/10.1126/science.1160809.
[119] Z. Luo, M. Xia, W. Shi, C. Zhao, J. Wang, D. Xin, X. Dong, Y. Xiong, F. Zhang, K. Berry, S. Ogurek, X. Liu, R. Rao, R. Xing, L.M.N. Wu, S. Cui, L. Xu, Y. Lin, W. Ma, S. Tian, Q. Xie, L. Zhang, M. Xin, X. Wang, F. Yue, H. Zheng, Y. Liu, C. B. Stevenson, P. de Blank, J.P. Perentesis, R.J. Gilbertson, H. Li, J. Ma, W. Zhou, M.D. Taylor, Q.R. Lu, Human fetal cerebellar cell atlas informs medulloblastoma origin and oncogenesis, Nature. 612 (2022) 787–794, https://doi.org/10.1038/s41586-022-05487-2.
[120] A. Casciati, M. Tanori, R. Manczak, S. Saada, B. Tanno, P. Giardullo, E. Porcù, E. Rampazzo, L. Persano, G. Viola, C. Dalmay, F. Lalloué, A. Pothier, C. Merla, M. Mancuso, Human medulloblastoma cell lines: Investigating on cancer stem cell-like phenotype, Cancers (Basel). 12 (2020) 1–14, https://doi.org/10.3390/cancers12010226.
[121] L. Sun, T. Moritake, K. Ito, Y. Matsumoto, H. Yasui, H. Nakagawa, A. Hirayama, O. Inanami, K. Tsuboi, Metabolic analysis of radioresistant medulloblastoma stem-like clones and potential therapeutic targets, PLoS One. 12 (2017) 1–24, https://doi.org/10.1371/journal.pone.0176162.
[122] I. Angelopoulos, G. Gakis, K. Birmpas, C. Kyrousi, E.E. Habeos, K. Kaplani, Z. Lygerou, I. Habeos, S. Taraviras, Metabolic regulation of the neural stem cell fate: Unraveling new connections, establishing new concepts, Front. Neurosci. 16 (2022) 1–14, https://doi.org/10.3389/fnins.2022.1009125.
[123] Z. Hajjarian, E.F. Brachtel, D.M. Tshikudi, S.K. Nadkarni. Mapping Mechanical Properties of the Tumor Microenvironment by Laser Speckle Rheological Microscopy. 2. (n.d.). 19–21. 10.1158/0008-5472.CAN-20-3898.
[124] E. Boedtkjer, S.F. Pedersen, The Acidic Tumor Microenvironment as a Driver of Cancer, Annu. Rev. Physiol. 82 (1) (2020) 103–126.
[125] V. Petrova, M. Annicchiarico-Petruzzelli, G. Melino, I. Amelio, The hypoxic tumour microenvironment, Oncogenesis. 7 (2018), https://doi.org/10.1038/s41389-017-0011-9.
[126] I. Elia, M.C. Haigis, Metabolites and the tumour microenvironment: from cellular mechanisms to systemic metabolism, Nat. Metab. 3 (2021) 21–32, https://doi.org/10.1038/s42255-020-00317-z.
[127] L.N.G. Castro, I. Liu, M. Filbin. Characterizing the biology of primary brain tumors and their microenvironment via single-cell profiling methods. 25. (2023). 234–247.
[128] R.L. Bowman, F. Klemm, L. Akkari, V. Tabar, P.H. Gutin, J.A. Joyce, R. L. Bowman, F. Klemm, L. Akkari, S.M. Pyonteck, L. Sevenich, D.F. Quail, V. Tabar, P.H. Gutin, J.A. Joyce, Macrophage Ontogeny Underlies Differences in Tumor-Specific Education in Brain Malignancies Resource Macrophage Ontogeny Underlies Differences in Tumor-Specific Education in Brain Malignancies, Cell Reports. 17 (2016) 2445–2459, https://doi.org/10.1016/j.celrep.2016.10.052.
[129] N. Brösicke, A. Faissner, A. Faissner. Role of tenascins in the ECM of gliomas Role of tenascins in the ECM of gliomas. 6918. (2015). 10.1080/19336918.2014.1000071.
[130] C. Calabrese, H. Poppleton, M. Kocak, T.L. Hogg, C. Fuller, B. Hamner, E.Y. Oh, M.W. Gaber, D. Finklestein, M. Allen, A. Frank, I.T. Bayazitov, S.S. Zakharenko, A. Gajjar, A. Davidoff, R.J. Gilbertson, A Perivascular Niche for Brain Tumor Stem Cells (2007) 69–82, https://doi.org/10.1016/j.ccr.2006.11.020.
[131] N. Charles, T. Ozawa, M. Squatrito, A. Bleau, C.W. Brennan, D. Hambardzumyan, E.C. Holland, Perivascular Nitric Oxide Activates Notch Signaling and Promotes Stem-like Character in PDGF-Induced Glioma Cells, Stem, Cell. 6 (2010) 141–152, https://doi.org/10.1016/j.stem.2010.01.001.
[132] Q. Chen, A. Boire, X. Jin, M. Valiente, E.E. Er, A. Lopez-soto, L.S. Jacob, R. Patwa, H. Shah, K. Xu, J.R. Cross, J. Massagué, Carcinoma – astrocyte gap junctions promote brain metastasis by cGAMP transfer, (2016). 10.1038/nature18268.
[133] S.J. Coniglio, E. Eugenin, K. Dobrenis, E.R. Stanley, B.L. West, Microglial Stimulation of Glioblastoma Invasion Involves Epidermal Growth Factor Receptor (EGFR) and Colony Stimulating Factor 1 Receptor (CSF-1R), Signaling (2012) 519–527, https://doi.org/10.2119/molmed.2011.00217.
[134] I. Vitale, G. Manic, L.M. Coussens, G. Kroemer, L. Galluzzi, Macrophages and Metabolism in the Tumor Microenvironment, Cell Metab. 30 (2018) 36–50, https://doi.org/10.1016/j.cmet.2019.06.001.

[135] K.M. Nieman, H.A. Kenny, C.V. Penicka, A. Ladanyi, R. Buell-gutbrod, M. R. Zillhardt, I.L. Romero, M.S. Carey, G.B. Mills, G.S. Hotamisligil, S.D. Yamada, M.E. Peter, K. Gwin, E. Lengyel, Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth 17 (2011), https://doi.org/10.1038/nm.2492.

[136] M. Zhang, J.S. Di Martino, R.L. Bowman, N.R. Campbell, S.C. Baksh, T. Simon-vermot, I.S. Kim, P. Haldeman, C. Mondal, V. Yong-gonzales, M. Abu-akeel, T. Merghoub, D.R. Jones, X.G. Zhu, A. Arora, C.E. Ariyan, K. Birsoy, J. D. Wolchok, K.S. Panageas, T. Hollmann, J.J. Bravo-cordero, R.M. White, Adipocyte-Derived Lipids Mediate Melanoma Progression via FATP, Proteins (2018) 1006–1025, https://doi.org/10.1158/2159-8290.CD-17-1371.

[137] C.M. Sousa, D.E. Biancur, X. Wang, C.J. Halbrook, M.H. Sherman, L. Zhang, D. Kremer, R.F. Hwang, A.K. Witkiewicz, H. Ying, J.M. Asara, R.M. Evans, L. C. Cantley, C.A. Lyssiotis, A.C. Kimmelman, Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion, Nature. 536 (2016) 479–483, https://doi.org/10.1038/nature19084.

[138] M. Yao, P.B. Ventura, Y. Jiang, F.J. Rodriguez, L. Wang, J.S.A. Perry, Y. Yang, K. Wahl, R.B. Crittenden, M.L. Bennett, L. Qi, C.-C. Gong, X.-N. Li, B.A. Barres, T. P. Bender, K.S. Ravichandran, K.A. Janes, C.G. Eberhart, H. Zong, Astrocytic trans -Differentiation Completes a Multicellular Paracrine Feedback Loop Required for Article Astrocytic trans -Differentiation Completes a Multicellular Paracrine Feedback Loop Required for Medulloblastoma Tumor Growth, Cell. 180 (3) (2020) 502–520.e19.

[139] H. Zhou, C. Danilov, T. Chen, J. Neman, V. Martirosian, K. Deshpande, H. Zhou, K. Shen, K. Smith, P. Northcott, M. Lin, Medulloblastoma uses GABA transaminase to survive in the cerebrospinal fluid microenvironment and promote leptomeningeal dissemination ll Medulloblastoma uses GABA transaminase to survive in the cerebrospinal fluid microenvironment and promote leptomening, Cell Reports. 35 (2021), 109302, https://doi.org/10.1016/j.celrep.2021.109302.

[140] V. Kumar, V. Kumar, T. McGuire, D.W. Coulter, J.G. Sharp, R.I. Mahato, Challenges and Recent Advances in Medulloblastoma Therapy, Trends Pharmacol. Sci. (2017), https://doi.org/10.1016/j.tips.2017.09.002.

[141] B. Faubert, A. Solmonson, R.J. DeBerardinis, Metabolic reprogramming and cancer progression, Science 80- (2020) 368, https://doi.org/10.1126/science.aaw5473.

[142] L. Liang, F. Sun, H. Wang, Z. Hu, Metabolomics, metabolic flux analysis and cancer pharmacology, Pharmacol. Ther. 224 (2021), 107827, https://doi.org/10.1016/J.PHARMTHERA.2021.107827.

[143] D. Bakhshinyan, A.A. Adile, J. Liu, W.D. Gwynne, Y. Suk, S. Custers, I. Burns, M. Singh, N. McFarlane, M.K. Subapanditha, M.A. Qazi, P. Vora, M.M. Kameda-Smith, N. Savage, K.L. Desmond, N. Tatari, D. Tran, M. Seyfrid, K. Hope, N. A. Bock, C. Venugopal, G.D. Bader, S.K. Singh, Temporal profiling of therapy resistance in human medulloblastoma identifies novel targetable drivers of recurrence, Sci. Adv. 7 (2021) 1–13, https://doi.org/10.1126/sciadv.abi5568.

[144] M.A. Altinoz, A. Ozpinar, Oxamate targeting aggressive cancers with special emphasis to brain tumors, Biomed. Pharmacother. 147 (2022), 112686, https://doi.org/10.1016/j.biopha.2022.112686.

[145] L. Di Magno, S. Manni, F. Di Pastena, S. Coni, A. Macone, S. Cairoli, M. Sambucci, P. Infante, M. Moretti, M. Petroni, C. Nicoletti, C. Capalbo, E. De Smaele, L. Di Marcotullio, G. Giannini, L. Battistini, B.M. Goffredo, E. Iorio, E. Agostinelli, M. Maroder, G. Canettieri, Phenformin Inhibits Hedgehog-Dependent Tumor Growth through a Complex I-Independent Redox/Corepressor Module, Cell Rep. 30 (2020) 1735–1752.e7, https://doi.org/10.1016/j.celrep.2020.01.024.

[146] M.E.G. Rubiño, E. Carrillo, G.R. Alcalá, A. Domínguez-Martín, J.A. Marchal, H. Boulaiz, Phenformin as an anticancer agent: Challenges and prospects, Int. J. Mol. Sci. 20 (2019) 1–17, https://doi.org/10.3390/ijms20133316.

[147] A. Luengo, D.Y. Gui, M.G. Vander Heiden, Targeting Metabolism for Cancer Therapy, Cell, Chem. Biol. 24 (2017) 1161–1180, https://doi.org/10.1016/j.chembiol.2017.08.028.

[148] M. Morfouace, A. Shelat, M. Jacus, B. Freeman, D. Turner, S. Robinson, F. Zindy, Y.-D. Wang, D. Finkelstein, O. Ayrault, L. Bihannic, S. Puget, X.-N. Li, J. Olson, G. Robinson, R.K. Guy, C. Stewart, A. Gajjar, M. Roussel, Pemetrexed and gemcitabine as combination therapy for the treatment of group3 medulloblastoma, Cancer Cell. 25 (4) (2014) 516–529.

[149] R. Fiorentino, F. Chiarelli, Statins in Children, an Update, Int. J. Mol. Sci. 24 (2023), https://doi.org/10.3390/ijms24021366.

[150] K. Pham, M.J. Maxwell, H. Sweeney, J. Alt, R. Rais, C.G. Eberhart, B.S. Slusher, E. H. Raabe, Novel Glutamine Antagonist JHU395 Suppresses MYC-Driven Medulloblastoma Growth and Induces Apoptosis, J. Neuropathol. Exp. Neurol. 80 (2021) 336–344, https://doi.org/10.1093/jnen/nlab018.

[151] B. Lee, I. Mohamad, R. Pokhrel, R. Murad, M. Yuan, S. Stapleton, C. Bettegowda, G. Jallo, C.G. Eberhart, T. Garrett, R.J. Perera, Medulloblastoma cerebrospinal fluid reveals metabolites and lipids indicative of hypoxia and cancer-specific RNAs, Acta Neuropathol. Commun. 10 (2022) 1–14, https://doi.org/10.1186/s40478-022-01326-7.

[152] X. Liu, J. Li, X. Hao, H. Sun, Y. Zhang, L. Zhang, L. Jia, Y. Tian, W. Sun, LC–MS-Based Urine Metabolomics Analysis for the Diagnosis and Monitoring of Medulloblastoma, Front, Oncol. 12 (2022) 1–9, https://doi.org/10.3389/fonc.2022.949513.

[153] C.D. Bennett, S.E. Kohe, S.K. Gill, N.P. Davies, M. Wilson, L.C.D. Storer, T. Ritzmann, S.M.L. Paine, I.S. Scott, I. Nicklaus-Wollenteit, D.A. Tennant, R. G. Grundy, A.C. Peet, Tissue metabolite profiles for the characterisation of paediatric cerebellar tumours, Sci. Rep. 8 (2018) 1–10, https://doi.org/10.1038/s41598-018-30342-8.

[154] T. Alexandrov, Spatial Metabolomics and Imaging Mass Spectrometry in the Age of Artificial Intelligence, Annu. Rev. Biomed. Data Sci. 3 (2020) 61–87, https://doi.org/10.1146/annurev-biodatasci-011420-031537.

[155] I. Lanekoff, V.V. Sharma, C. Marques, Single-cell metabolomics: where are we and where are we going? Curr. Opin. Biotechnol. 75 (2022) 1–7, https://doi.org/10.1016/j.copbio.2022.102693.