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Targeting metabolic dependencies in pediatric cancer

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Abstract

Purpose of Review: In an attempt to identify potential new therapeutic targets, efforts to describe the metabolic features unique to cancer cells are increasingly being reported. While current standard of care regimens for several pediatric malignancies incorporate agents that target tumor metabolism, these drugs have been part of the therapeutic landscape for decades. More recent research has focused on the identification and targeting of new metabolic vulnerabilities in pediatric cancers. The purpose of this review is to describe the most recent translational findings in the metabolic targeting of pediatric malignancies.

Recent Findings: Across multiple pediatric cancer types, dependencies on a number of key metabolic pathways have emerged through study of patient tissue samples and preclinical modeling. Among the potentially targetable vulnerabilities are glucose metabolism via glycolysis, oxidative phosphorylation, amino acid and polyamine metabolism, and NAD^+ metabolism. While few agents have yet to move forward into clinical trials for pediatric cancer patients, the robust and promising preclinical data that has been generated suggests that future clinical trials should rationally test metabolically-targeted agents for relevant disease populations.

Summary: Recent advances in our understanding of the metabolic dependencies of pediatric cancers represent a source of potential new therapeutic opportunities for these diseases.

Keywords

cancer metabolism; pediatric cancer; glycolysis; oxidative phosphorylation; amino acid metabolism

INTRODUCTION

Proliferating cancer cells exhibit significantly different metabolic needs compared to normal differentiated cells, including rapid ATP production to maintain energy status, increased macromolecular biosynthesis, and tightened maintenance of appropriate cellular redox status (1, 2). To meet the increased demands necessary to support cancer cell survival and

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CONFLICTS OF INTEREST

None.

proliferation, cellular metabolism is altered through changes in signaling pathways that are affected by genetic and microenvironmental factors (1–3). Given their importance across many different cancer types, altered cellular metabolism has been recognized as a hallmark of cancer (4, 5).

Research into how cancer cell metabolism differs from that of normal cells may uncover therapeutic opportunities to exploit the differential metabolic dependencies of cancer cells while potentially sparing normal cells from toxicity (6). In the field of pediatric oncology, therapies targeting cancer metabolism have been in use for decades. The first report of a metabolic inhibitor demonstrating clinical activity was published in 1948 by the pediatric pathologist Sidney Farber, who reported that use of aminopterin, a folate analog that competitively inhibits dihydrofolate reductase (DHFR), resulted in temporary remissions in children with leukemia (7, 8). Mechanistically, folate analogs deplete tetrahydrofolate, impairing thymidylate production and impeding DNA synthesis, which is required for rapidly dividing cancer cells (9). Even today, DHFR inhibitors like methotrexate are currently incorporated into standard first-line treatments for pediatric acute lymphoblastic leukemia (ALL) (10) and osteosarcoma (11), and ongoing research has revealed that the metabolic consequences of methotrexate may also include effects on glucose metabolism and altered response to oxidative stress (12).

Following the identification of folate analogs as anticancer agents, analogs of purine, pyrimidine, thymidine, and other nucleosides were developed, forming the class of agents known as antimetabolites (13). Several antimetabolites, such as 6-mercaptopurine and cytarabine, have endured in standard regimens to treat ALL (14) and acute myeloid leukemia (AML) in children (15). In addition to antimetabolites, asparaginase is another standard of care agent targeting cancer metabolism for pediatric patients. Asparaginase exploits the lack of asparagine synthetase activity in ALL cells by depleting necessary serum asparagine (16, 17). While asparaginase remains an integral part of the therapeutic backbone for pediatric ALL (14), research efforts to enhance its efficacy in ALL (18–20) reduce its associated toxicity (21), and identify other pediatric malignancies that share asparagine dependency (22–24) are ongoing.

Several recent studies have focused on characterizing the metabolic profiles of tumor cells, determining the effects of genetic drivers on tumor metabolism, and gaining new insights into the unique metabolic dependencies of pediatric cancer cells with the goal of improving upon current therapies. The purpose of this review is to describe the most recent translational findings in metabolic targeting of pediatric cancers.

GLYCOLYSIS

Among the earliest insights into the metabolic differences between normal and cancer cells was the observation by Otto Warburg that many cancer cells exhibit an increased dependence on aerobic glycolysis, preferentially catalyzing the conversion of glucose to lactate, as opposed to carbon dioxide, in the presence of oxygen (25). Dependence on glycolysis is frequently a consequence of genetic alterations which result in overexpression or silencing of key enzymes along the glycolytic pathway (26).

Recent work has shown that despite a relatively low mutational burden, numerous pediatric cancers have altered expression of key glycolytic enzymes, suggestive of an increased dependence on glycolysis. Specifically, expression of hexokinase 2 (HK2), an isoform of the first enzyme of glycolysis that converts glucose to glucose-6-phosphate, was found to be increased in clinical samples and preclinical models of pediatric malignancies. These included the SHH subtype of medulloblastoma (27, 28) and diffuse large B-cell lymphoma (DLBCL), where high HK2 expression correlated with poor prognosis (29). Similarly, in osteosarcoma tissue samples, elevated *HK2* expression was correlated with Ki-67 expression (30), and was directly regulated by NF-KB (31).

In addition, high expression of several isoforms of lactate dehydrogenase (LDH), the terminal enzyme in glycolysis that converts pyruvate to lactate, has been described. High LDHA expression has been linked to poor prognoses in neuroblastoma, where it correlated with *MYCN*-amplification (32), and in medulloblastoma, where it was associated with two of the genetically-defined subtypes, including the aggressive group 3 subtype which portends a very poor prognosis (33). Increased expression of LDHB was also observed in embryonal hepatoblastoma cell lines, as compared to normal liver and fetal hepatoblastoma cell lines (34). In preclinical models of Ewing sarcoma, the driver oncogenic fusion protein EWS-FLI1 was found to regulate a pro-glycolytic phenotype (35), specifically through direct upregulation of *LDHA* (36).

Altered expression of transporters of the substrates and products of glycolysis has also been identified in several pediatric cancers. Glucose transporters, such as GLUT1, GLUT3, and GLUT4 have been found to be more highly expressed in tumor samples of medulloblastoma (Bhatia 2012) aggressive neuroblastoma (37), Wilms' tumor (38), and embryonal hepatoblastoma (34). Loss of expression of the monocarboxylate transporter 4 (MCT4), which functions to efflux lactate in highly glycolytic tissues was noted in a majority of Burkitt lymphoma and DLBCL patient samples, suggesting that these cancers may be more dependent on compensatory mechanisms of lactate transport (39).

From a translational perspective, recent preclinical studies investigating the utility of inhibiting aspects of glycolysis as a strategy for treating pediatric cancers suggest that there may be a role for this approach. Inhibition of HK with 2-Deoxy-D-glucose (2-DG) resulted in apoptotic death in Ewing sarcoma (40), alveolar rhabdomyosarcoma (41), and embryonal hepatoblastoma (34) cell lines. In medulloblastoma, genetic depletion of HK2 abrogated the aggressive phenotype of these cells *in vivo* (42); in osteosarcoma, genetic depletion of HK2 induced apoptosis in some, but not all preclinical models (30, 31). Genetic depletion of LDHA was effective in inhibiting the growth of preclinical models of neuroblastoma (32) and Ewing sarcoma, which was also sensitive to pharmacological targeting of LDH (36). Pharmacological targeting of glycolysis in medulloblastoma and neuroblastoma using other glycolytic inhibitors reduced cellular viability (33, 43) through potentially distinct mechanisms of growth inhibition. In Burkitt lymphoma and DLBCL models with low MCT4 expression, targeting the compensatory monocarboxylate transporter 1 (MCT1) with a small molecule inhibitor profoundly reduced proliferation *in vitro* and *in vivo* (39). Additionally, a compensatory increase in oxidative phosphorylation (OXPHOS) has been

reported with glycolytic inhibition in numerous preclinical studies, suggesting that resistance may be mediated through this mechanism (33, 36, 39).

Finally, several studies have investigated the role of glycolysis in relation to resistance to standard therapies. In models of pediatric AML, resistance to adriamycin was associated with increased glycolysis and *HK2* expression in patient samples. Notably, use of 2-DG in resistant models of this disease restored sensitivity to chemotherapy (44). Similarly, acquired resistance to chemotherapy plus rituximab in DLBCL models was associated with increased *HK2* expression and could be overcome by the HK inhibitors 2-DG or lonidamine (29). In pediatric ALL models, resistance to glucocorticoid agents could be mitigated by the addition of 2-DG (45), and in Ewing sarcoma cell lines, the addition of 2-DG to standard chemotherapy drugs enhanced their antiproliferative effect (40). Taken together, these studies suggest there may be a role for targeting glycolysis through inhibition of key enzymes or substrate transporters in a subset of pediatric cancers. While clinical investigation of 2-DG has been conducted for adult patients with cancer (46) and a trial using an MCT1 inhibitor is currently open for adults (NCT01791595), clinical testing of these agents in children has not yet been performed.

OXIDATIVE PHOSPHORYLATION

More recent insights into tumor metabolism have revealed that in addition to increased glycolysis, mitochondrial metabolism also plays a major role in tumor growth and survival (47). As a result, there have been increased efforts to understand tumor-specific dependencies on the tricarboxylic acid (TCA) cycle and to identify targetable vulnerabilities in this pathway in pediatric cancers. Recent studies indicate that mitochondrial number and function differed from the surrounding normal tissue in Wilms' tumor (48), neuroblastoma (49), and pediatric brain tumors like high grade glioma (HGG), in which an aggressive phenotype may be partly related to a relatively low mitochondrial DNA (mtDNA) copy number (50–52).

Most preclinical studies in pediatric malignancies have targeted OXPHOS with metformin, a widely prescribed type 2 diabetes medication that can inhibit Complex I of the mitochondrial respiratory chain (53). Metformin treatment was associated with cancer cell growth inhibition in preclinical models of several pediatric solid tumors, including Ewing sarcoma (40), rhabdomyosarcoma (54), neuroblastoma (55–57), HGG (50) and osteosarcoma, in which antitumor effects against primary tumor cells (58) and microenvironmental factors (59) were reported. In preclinical models of pediatric hematological malignancies, including FLT3-ITD AML (60) and ALL (61), metformin negatively impacted cellular viability. In addition to metformin, other hypoglycemic agents such as the thiazolidinediones had activity against pediatric cancers, including neuroblastoma (56). CCI-006, a non-hypoglycemic agent that induces mitochondrial depolarization, had potent activity against MLL-rearranged leukemias (62), as did genetic depletion of mtDNA in HGG (50).

Another potential target relevant to OXPHOS regulation is pyruvate dehydrogenase kinase 1 (PDK1), which catalyzes the phosphorylation and inactivation of pyruvate dehydrogenase

(PDH), thus inhibiting the conversion of pyruvate into acetyl-CoA through the TCA cycle. PDK1 was found to be overexpressed in retinoblastoma (63). Functionally, inhibition of PDK1, which permits more entry of pyruvate into the TCA cycle, resulted in decreased cell growth in models of AML (64) and retinoblastoma, where it also sensitized cells to the effects of chemotherapy (63). Inhibition of OXPHOS also improved responses to chemotherapy in osteosarcoma (58). Another combination approach that has been studied in Ewing sarcoma (40), HGG (50), and AML (60) involved dual targeting of OXPHOS and glycolysis, which addresses the reported compensatory induction of one pathway upon inhibition of the other (33, 36, 40, 60). Combining metformin with other DNA damaging agents such as radiation in HGG (50) or molecularly targeted therapies in neuroblastoma or AML (55, 60) was also efficacious preclinically.

Unlike glycolytic inhibitors, OXPHOS inhibitors such as metformin (65), DCA (66, 67), and the PDH inhibitor CPI-613 (68–71), remain in the clinic for testing in adult cancer patients. Notably, a recently completed phase 1 study for pediatric patients with relapsed ALL investigated the addition of metformin to a 28-day pre-transplant induction regimen, concluding that the combination was safe and reporting pharmacodynamic evidence of on-target metformin activity in blood cells (72). An additional phase 1 study (NCT01528046) combining metformin with chemotherapy for pediatric patients with relapsed solid tumors is ongoing.

AMINO ACID METABOLISM

Major differences exist in the uptake and metabolism of amino acids in tumors relative to normal tissues. Amino acids play key roles in cancer cell proliferation, as they provide precursors for macromolecular biosynthesis, control redox status and antioxidant systems, and serve as substrates for post-translational and epigenetic modifications. Consequently, there is significant interest in understanding and targeting amino acid metabolism for cancer therapy (73, 74).

Glutamine Metabolism

Glutamine, the most abundant amino acid in serum, is metabolized in multiple pathways supporting cellular proliferation (2, 75–77). Several pediatric cancers display altered glutamine metabolism and increased dependence on glutamine. Specifically, an enriched glutaminolysis gene signature associated with *MYCN*-amplification was identified in neuroblastoma patient tumor samples (78), and unbiased metabolic profiling of atypical teratoid/rhabdoid tumors (AT/RT) revealed increased glutamine metabolism in high versus low MYC-expressing patient-derived cell lines (79). In medulloblastoma, glutamine addiction was identified in a subset of tumors of the non-Wnt subtypes where it was essential for sustained cell growth and proliferation (80). Rhabdomyosarcoma and Ewing sarcoma cell lines were also shown to be dependent on glutamine for maximal proliferation and were able to increase the expression of glutamine synthetase, which drives *de novo* glutamine synthesis, to overcome glutamine withdrawal. In Ewing sarcoma tumors, high glutamine synthetase expression correlated with worse survival (81).

Several recent preclinical studies have reported the effects of targeting glutamine metabolism in pediatric cancer models. In AT/RT, both glutamine restriction and treatment with the glutamine analog 6-diazo-5-oxo-L-norleucine (DON) selectively affected high-MYC expressing cell lines, slowing proliferation *in vitro* and *in vivo*, and extending survival when combined with carboplatin in orthotopic mouse models (79). In medulloblastoma, dietary glutamine restriction increased survival in a mouse xenograft model and synergized with cisplatin treatment (80). Mechanistically, both DON treatment and glutamine restriction resulted in reduced levels of the antioxidant glutathione (GSH), and increased levels of reactive oxygen species (ROS). This relationship between glutamine depletion and increased oxidative stress in glutamine-dependent cells has also been described in osteosarcoma models (82). Similarly, the glutaminase inhibitor CB-839, which impairs conversion of glutamine to glutamate, decreased GSH production in AML, resulting in accumulation of ROS and apoptosis. Glutaminase inhibition also sensitized AML and ALL cells to redox-targeted agents *in vitro* and *in vivo* (83). In rhabdomyosarcoma and Ewing sarcoma, inhibition of glutamine synthetase with methionine sulfoximine selectively abolished the ability of glutamine-deprived cells to proliferate. Mechanistically, glutamine metabolism supported sarcoma nucleotide biosynthesis and mitochondrial bioenergetics. Pharmacological and genetic inhibition of glutamine synthetase significantly reduced Ewing sarcoma orthotopic xenograft tumor growth (81). In the clinic, multiple studies of CB-839 are ongoing, including one phase 1 trial (NCT03528642) that includes adolescent patients with IDH-mutant brain tumors.

Serine, Glycine and One-carbon Metabolism

Serine, glycine, and downstream one-carbon metabolism (involving the folate and methionine cycles) support several biological processes that are crucial for the growth and survival of proliferating cells. Overexpression of enzymes in these pathways has been linked to more aggressive cancer phenotypes (84–86). Several recent studies have indicated that altered serine-glycine-one-carbon metabolism may play an essential role in certain pediatric cancers. In neuroblastoma, high expression of a serine-glycine-one-carbon metabolism gene signature (87) or of glycine decarboxylase (GLDC), the enzyme which catalyzes glycine breakdown producing the one-carbon unit 5,10-methylene-tetrahydrofolate (88), was identified in *MYCN*-amplified patient tumor samples and was associated with advanced disease stage and poor prognosis. Both studies demonstrated that MYC transcriptionally activated targets in the serine-glycine-one-carbon metabolism pathway. In Ewing sarcoma call lines, several components of the serine-glycine synthesis pathway were also found to be direct transcriptional targets of EWS-FLI1. These genes were also found to be highly expressed in Ewing sarcoma patient tumors, and their expression was correlated with high-risk disease and poor survival (35, 89, 90).

Preclinical studies targeting serine-glycine-one-carbon metabolism have shown promise as a potential therapeutic strategy for pediatric malignancies and indicate that perturbation of these pathways impacts multiple other metabolic processes in pediatric cancer models. In AML models, knockdown of methylenetetrahydrofolate dehydrogenase (MTHFD2), which is essential for mitochondrial one-carbon folate metabolism, decreased cell growth in culture and prolonged survival in murine models. Mechanistically, loss of MTHFD2 increased

glycine dependence and depleted TCA cycle intermediates in these models (91). In *MYCN*-amplified neuroblastoma cell lines, *GLDC* knockdown inhibited cellular proliferation and tumorigenicity by disrupting glycolysis, the TCA cycle, lipid synthesis, and purine metabolism (88). *MYCN*-amplified neuroblastoma cell lines were also susceptible to pharmacological inhibition of 3-phosphoglycerate dehydrogenase (PHGDH), the enzyme that catalyzes the first committed step in *de novo* serine synthesis, using the small-molecule NCT-503, which selectively decreased proliferation and xenograft tumor growth (87). Similarly, in several studies using Ewing sarcoma models, both pharmacological and genetic inhibition of PHGDH decreased proliferation and induced apoptosis in cell lines and xenografts through induction of ROS and DNA damage (35, 89, 90). While there are no inhibitors of serine or glycine metabolism currently being tested the clinic, these data suggest that if and when they enter clinical development, there may be a role for targeting these pathways in certain pediatric malignancies.

Arginine Metabolism

Arginine represents another critical amino acid for cancer cell survival. Arginine is produced via argininosuccinate synthetase 1 (ASS1), the rate-limiting enzyme in arginine synthesis. Immunohistochemical analysis of primary sarcomas including pediatric histologies such as malignant peripheral nerve sheath tumor, synovial sarcoma, rhabdomyosarcoma, desmoplastic small round cell tumor, osteosarcoma, and Ewing sarcoma, revealed that >85% of samples had undetectable or very low expression of ASS1, rendering cells dependent on extracellular arginine. Consequently, arginine deprivation therapy with pegylated arginine deiminase (ADI-PEG20) resulted in growth arrest in ASS1-deficient models of osteosarcoma, Ewing sarcoma, synovial sarcoma, and alveolar soft part sarcoma (92). Arginine has also been found to be an important metabolic target specifically in EVI1-positive AML, where suppression of arginine-creatine metabolism by genetic or pharmacological means selectively decreased cellular viability and prolonged survival in mouse models (93). In preclinical models of osteosarcoma, Ewing sarcoma, synovial sarcoma, and rhabdomyosarcoma, efficacy was noted using ADI-PEG20 plus gemcitabine and docetaxel, and this combination is currently being evaluated in a phase II trial (NCT03449901) for patients with soft tissue sarcoma, including adolescents (94). Similarly, arginine depletion with BCT-100 (pegylated recombinant human arginase) treatment was effective against *in vitro* and *in vivo* models of ALL, and is currently being evaluated in a phase I/II study (NCT03455140) in children and young adults with relapsed/refractory leukemia, neuroblastoma, sarcoma, and HGG (95).

Polyamine Metabolism

The amino acid-derived polyamines are involved in many fundamental processes related to cell growth and survival. Polyamine metabolism is frequently dysregulated in cancer, where elevated polyamine levels can affect transformation and tumor progression. Intracellular polyamine levels are maintained through a highly-regulated metabolic pathway and import/export systems. Arginase produces the non-proteinogenic amino acid ornithine from arginine. In turn, ornithine decarboxylase (ODC), the first, rate-limiting enzyme in polyamine synthesis, produces the diamine putrescine, which is the precursor of the polyamines spermidine and spermine (96, 97).

Several studies have suggested a critical role for polyamine metabolism in pediatric cancers. In neuroblastoma patient tumors, elevated mRNA levels of *ODC* correlated with poor prognosis (98). Further, high expression of each polyamine biosynthetic gene and low expression of genes driving polyamine catabolism correlated with poor event-free and overall survival and were associated with *MYCN*-amplification and unfavorable tumor stage in neuroblastoma. MYCN directly increased polyamine synthesis and promoted neuroblastoma cell proliferation by regulating the key polyamine transporter *SLC3A2* in neuroblastoma, along with other regulatory components of polyamine metabolism (99).

From a translational perspective, several preclinical and clinical studies have investigated the utility of targeting polyamine metabolism in pediatric cancer. In osteosarcoma, the ODC inhibitor difluoromethylornithine (DFMO) reduced intracellular polyamine levels, induced differentiation, and caused growth suppression *in vitro* (100). In a number of studies in preclinical models of neuroblastoma, single-agent and combination treatment approaches using DFMO plus chemotherapy or other agents targeting polyamine homeostasis have been shown to effectively inhibit cellular proliferation and tumor growth (98, 99, 101, 102). Additionally, there are ongoing research efforts focused on defining the interactions between polyamine homeostasis and other metabolic pathways in neuroblastoma (103).

Targeting polyamine synthesis with DFMO has been evaluated in several early phase clinical trials in children with neuroblastoma where it was shown to be safe (104, 105). Clinical studies to further determine the efficacy of DFMO in this population and preclinical studies to optimize its use are ongoing (106, 107).

NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD^+) METABOLISM

For some cancer cells, increased requirements for NAD^+ result in altered dependency on NAD^+ production pathways to maintain efficient growth and survival (108). Mounting evidence that depletion of NAD^+ may inhibit cellular proliferation in some malignancies has led to the development of therapeutics targeting the NAD^+ production enzyme nicotinamide phosphoribosyltransferase (NAMPT) (109). Ewing sarcoma has emerged as a particularly sensitive tumor type to NAMPT inhibitors which, when applied to cells, resulted in NAD^+ depletion, metabolic collapse, impaired DNA synthesis, increased DNA damage, and cell death *in vitro* and *in vivo*. NAMPT inhibitor-sensitivity in Ewing sarcoma has been linked to several factors, including increased reliance on the NAD^+-dependent enzyme poly (ADP-ribose) polymerase (PARP) as well as EWS-FLI1-mediated dependency on NAD^+ (110, 111).

In addition to Ewing sarcoma, recent insights have revealed that other pediatric cancers may also be susceptible to NAMPT inhibition. Preclinical models of pediatric hematologic malignancies, including B- and T-cell leukemias (112, 113), and AML (114, 115) underwent growth inhibition upon treatment with single agent NAMPT inhibitors. Models of pediatric HGG, including diffuse pontine gliomas (DIPG) were also sensitive to inhibition of NAMPT, which may be mediated by genetic silencing of compensatory enzymes (116).

Several combination therapies using NAMPT inhibitors have been identified as active in preclinical models of pediatric cancers and represent potential future regimens for clinical testing. These include combinations with PARP inhibitors in Ewing sarcoma (111), and etoposide in T-cell leukemia (112). In addition, Vacor, a rodenticide that has recently been found to have dual inhibitory activity against NAMPT and nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2), a compensatory enzyme in the biosynthetic NAD^+ pathway, was noted to be active against NMNAT2-expressing neuroblastoma cells (117). While there are a number of completed (118, 119) and ongoing studies testing various NAMPT inhibitors in adult cancer patients, a pediatric trial has yet to be initiated.

ADDITIONAL METABOLIC PATHWAYS

In addition to the pathways already described, several other potential metabolic vulnerabilities have been defined in various pediatric cancers. These include reports of metabolic phenotypes that differ from untransformed cells due to the influence of a particular oncogenic driver such as EWS-FLI1 (35), RAS (22), or MYC (120–124), mutations of metabolic enzymes (122, 125–129), or factors based on tissue of origin (130), or microenvironmental conditions (131, 132), as well as alterations in specific pathways such as lipid synthesis (133) and maintenance of antioxidant homeostasis(134–137).

CONCLUSIONS

It is evident that much like the metabolic landscape that has been described in adult cancers, pediatric cancers share some common metabolic vulnerabilities across subtypes. As preclinical evidence and the translational potential of targeting these pathways grows, efforts should be made to formally test these interventions in the setting of clinical trials for children with these cancers.

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KEY POINTS

- The understanding that the metabolic needs of cancer cells are significantly different from those of normal cells has spurred an increase in research efforts to identify metabolic vulnerabilities specific to pediatric malignancies.
- Across multiple pediatric cancer types, a number of dependencies in key metabolic pathways, including glycolysis, oxidative phosphorylation, and amino acid, polyamine, and NAD^+ metabolism have recently been identified.
- These promising preclinical findings represent opportunities for potential new therapeutic interventions for children with cancer and suggest that future clinical trials should rationally test metabolically-targeted agents for relevant pediatric cancer populations.