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EDITED BY

Ming Yue,
The First Affiliated Hospital of Nanjing Medical
University, China

REVIEWED BY

Jiaxiong Tan,
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Hospital, China
Kaijun Wang,
Hunan Agricultural University, China
Ralf Stohwasser,
Brandenburg University of Technology
Cottbus-Senftenberg, Germany

*CORRESPONDENCE

Lei Miao

✉ miaoleimolly@126.com;

✉ miaolei@gzhmu.edu.cn

[†]These authors have contributed equally to
this work

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Ubiquitination in lipid metabolism reprogramming: implications for pediatric solid tumors

Weixin Zhang^{1†}, Yile Xu^{1†}, Yingjin Fang^{2,3,4†}, Meng Li¹, Di Li¹,
Huiqin Guo¹, Hang Li¹, Jing He¹ and Lei Miao^{1*}

¹Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangdong Provincial Key
Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical
Center, Guangzhou Medical University, Guangdong Provincial Clinical Research Center for Child
Health, Guangzhou, Guangdong, China, ²Department of Pancreatic Surgery, Fudan University
Shanghai Cancer Center, Shanghai, China, ³Department of Oncology, Shanghai Medical College,
Fudan University, Shanghai, China, ⁴Shanghai Key Laboratory of Precision Medicine for Pancreatic
Cancer, Shanghai, China

Pediatric solid tumors represent a significant subset of childhood cancers, accounting for approximately 60% of new diagnoses. Despite advancements in therapeutic strategies, survival rates remain markedly disparate between high-income and resource-limited settings, underscoring the urgent need for novel and effective treatments. Lipid metabolic reprogramming is a fundamental hallmark of cancer, driving tumor progression, therapeutic resistance, and immune evasion through enhanced fatty acid uptake, increased *de novo* lipid synthesis, and activated fatty acid β -oxidation (FAO). Ubiquitination, a dynamic post-translational modification mediated by the ubiquitin-proteasome system (UPS), plays a crucial role in regulating lipid metabolism by modulating the stability and activity of key metabolic enzymes and transporters involved in cholesterol and fatty acid pathways. This review comprehensively examines the complex interplay between ubiquitination and lipid metabolic reprogramming in pediatric solid tumors. It delineates the mechanisms by which ubiquitination influences cholesterol biosynthesis, uptake, efflux, and fatty acid synthesis and oxidation, thereby facilitating tumor growth and survival. Furthermore, the review identifies potential UPS-mediated therapeutic targets and explores the feasibility of integrating ubiquitination-based strategies with existing treatments. By targeting the UPS to disrupt lipid metabolism pathways, novel therapeutic avenues may emerge to enhance treatment efficacy and overcome resistance in pediatric oncology. This synthesis of current knowledge aims to provide a foundation for the development of innovative, precision medicine approaches to improve clinical outcomes for children afflicted with solid tumors.

KEYWORDS

ubiquitin-proteasome system (UPS), lipid metabolism, pediatric solid tumor, cholesterol biosynthesis, fatty acid β -oxidation

1 Introduction

Pediatric cancer, defined as malignancies in individuals under 19 years, poses a significant global health challenge due to its unique biological characteristics arising from developmental differences compared to adults (1–3). From 2018–2020, a research from China indicates that nearly 60% of newly diagnosed patients are solid tumor patients, followed by leukemia (30.56%) and lymphoma (10.06%) (4). Despite treatment advancements, five-year survival rates exceed 80% in high-income countries but drop below 30% in resource-limited settings, highlighting stark disparities in treatment access and the urgent need for novel therapies (5, 6).

Lipid metabolic reprogramming is a hallmark of cancer, driving tumor progression, therapeutic resistance, and immune evasion (7). Tumor cells exploit lipid metabolism by upregulating fatty acid uptake, enhancing *de novo* synthesis, and activating fatty acid β -oxidation (FAO) to meet their energy and biosynthetic demands (8–10). This dysregulated lipid metabolism also supports cancer cell survival in hypoxic and nutrient-deprived environments. Although FAO and the TCA cycle are typically oxygen-dependent, tumor cells adapt to hypoxia through metabolic reprogramming, including HIF-1 α -mediated lipid uptake and storage, as well as alternative substrates such as short-chain fatty acids that may sustain FAO activity (10–16). Elevated *de novo* fatty acid synthesis and cholesterol levels further contribute to tumor progression, immune evasion, and drug resistance, making lipid metabolism a compelling therapeutic target (17–21). Moreover, aberrant lipid metabolism modulates immune cell functions within the tumor microenvironment; for example, a lipid-rich milieu can skew tumor-associated macrophages (TAMs) toward an immunosuppressive M2 phenotype (22–28) and impair T cell (29–31) antitumor activity via excessive fatty acid uptake that leads to ferroptosis and reduced expression of key cytotoxic molecules (32–37). In addition, enzymes involved in arachidonic acid metabolism—such as cytosolic phospholipase A2, cyclooxygenase, and lipoxygenase—have been linked to tumor resistance to radiotherapy (38). Targeting key lipid metabolic enzymes, including ACAT2 and SOAT, may help overcome these challenges and improve therapeutic outcomes (39).

The ubiquitin-proteasome system (UPS) is a key regulator of intracellular protein turnover and metabolic homeostasis. By governing the degradation of approximately 80% of intracellular proteins (40), ubiquitination orchestrates processes such as metabolic adaptation, tumor progression, and immune regulation (41–43). Recent studies reveal its crucial role in lipid metabolism, where ubiquitination of enzymes and transporters like CD36 modulates lipid uptake and utilization. Dysregulation of this system contributes to metabolic rewiring, fueling tumor growth (44–46).

This review explores the interplay between ubiquitination and lipid metabolic reprogramming in pediatric solid tumors. By examining how ubiquitination drives lipid metabolism and tumor progression, we identify potential therapeutic targets and discuss the integration of ubiquitination-based strategies with current

treatments to disrupt tumor metabolism and improve outcomes in pediatric oncology.

2 Overview of ubiquitination

Ubiquitination is a fundamental post-translational modification that regulates protein stability, localization, and activity by attaching ubiquitin molecules to target proteins through a cascade of enzymatic reactions involving three core enzymes: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases (47–49). Beyond its primary role in protein degradation, ubiquitination also governs various non-proteolytic processes, including the regulation of protein activity, subcellular localization, and protein complex formation (50). Notably, ubiquitin (Ub) chains linked through alternative residues (K6, K27, K33, K63, and M1) are predominantly involved in non-degradative functions, such as selective autophagy, DNA damage repair, and innate immunity (51, 52). Furthermore, ubiquitination plays a crucial role in maintaining DNA integrity and regulating gene expression, thereby facilitating the activation of diverse metabolic pathways in response to environmental changes (13). While comprehensive reviews, such as those by Liu (47) and Zhu (49), have extensively characterized the ubiquitination machinery and its roles in various cancers, their focus is primarily on adult malignancies, leaving the unique aspects of pediatric tumors largely unaddressed.”

In mammals, the ubiquitination system comprises two E1 enzymes, approximately 40 E2 enzymes, and over 600 E3 ligases, with E3 ligases conferring substrate specificity. E3 ligases are classified into three families based on their ubiquitin transfer mechanisms: RING (Really Interesting New Gene), HECT (Homologous to the E6AP Carboxyl Terminus), and RBR (RING-between-RING) ligases (53, 54).

Ubiquitination primarily determines protein fate through proteasomal or lysosomal degradation, with most ubiquitinated proteins being processed by the 26S proteasome. Deubiquitinating enzymes (DUBs) recycle ubiquitin molecules during this process. Beyond protein degradation, ubiquitination regulates diverse cellular processes, including protein trafficking, DNA repair, and signal transduction (55).

Dysregulated ubiquitination, driven by genetic or epigenetic aberrations such as mutations, amplifications, or deletions of ubiquitination-related genes, is strongly implicated in cancer (9). The functional outcomes of ubiquitination are influenced by the type of ubiquitin linkage and site of attachment, which affect processes like proteasomal degradation, protein activity, and subcellular localization. While lysine residues are the primary ubiquitination sites, other amino acids, such as N-terminal residues and cysteines, contribute to the complexity of ubiquitination’s regulatory roles (56).

The versatility of ubiquitination, driven by its diverse enzymes and linkages, is essential for maintaining cellular homeostasis and responding to stress. Its dysregulation in cancer underscores its potential as a promising therapeutic target.

3 Lipid metabolism reprogramming in tumors: distinct mechanisms in adult and pediatric cancers

Adult and pediatric tumors exhibit significant differences in biological characteristics, metabolic profiles, and nutritional intervention strategies. Adult tumors typically develop following long-term environmental exposures, lifestyle factors, chronic inflammation, and the gradual accumulation of genetic mutations, resulting in a high mutation burden and adaptive metabolic reprogramming. In contrast, pediatric tumors are more often driven by congenital genetic alterations and abnormal developmental signaling, leading to notable heterogeneity and distinct metabolic requirements—partly due to embryonic regulatory influences (57, 58).

3.1 Differences in lipid metabolism

3.1.1 Differential dependency on fatty acid metabolism

Adult tumors generally rely on high levels of *de novo* fatty acid synthesis. For instance, cancers such as breast, prostate, and liver cancer commonly exhibit significant upregulation of fatty acid synthase (FASN) (59–61). In pediatric tumors, however, the reliance on fatty acid synthesis versus degradation varies by tumor type. For example, neuroblastoma (NB) primarily depends on FAO for energy metabolism (62), whereas medulloblastoma tends to favor lipid synthesis (63). Moreover, pediatric tumors may depend on alternative targets for exogenous lipid uptake. For instance, Fatty acid transport protein 2 (FATP2) plays a critical role in MYCN-amplified NB (64), whereas adult tumors more commonly depend on fatty acid transport proteins such as CD36 to enhance lipid absorption and metabolic reprogramming (65).

3.1.2 Distinct regulation of cholesterol metabolism

Cholesterol metabolism plays a crucial role in both adult and pediatric tumors, though its regulation and clinical intervention strategies differ markedly. In adult tumors—such as prostate cancer and certain subtypes of breast cancer—upregulated cholesterol metabolism can promote cancer cell proliferation. Statins block HMG-CoA reductase and have been shown to slow disease progression in both precursor T-cell acute lymphoblastic leukemia and adult cancers like prostate and breast cancer (66, 67). In contrast, the application of statins in pediatric patients is generally limited due to safety concerns (68). In pediatric solid tumors, research on cholesterol metabolism remains sparse, and no specific clinical interventions targeting this pathway have been established, indicating a need for further exploration into its role in tumorigenesis and progression.

3.2 Impact of other regulatory factors and environmental influences

Recent studies suggest that the fatty acid-binding protein (FABP5) exerts age-dependent effects in tumor biology. In adult tumors, such as glioma, cervical cancer, and liver cancer, FABP5 promotes malignant transformation via activation of the NF- κ B pathway (69–71). Conversely, in high-risk pediatric gliomas, elevated FABP5 levels have been associated with a more favorable prognosis, highlighting clear differences in regulatory mechanisms between age groups (72). Furthermore, dietary factors and obesity influence lipid metabolism differently across age groups. In adults, high-fat diets—particularly those rich in saturated and trans fats—are closely linked to colorectal, prostate, and liver cancers, underscoring the role of diet-induced metabolic dysregulation in tumor development (73–75). In the pediatric population, maternal high-fat diets during pregnancy may increase the risk of offspring developing leukemia and NB (76, 77), although some large-scale epidemiological studies have not confirmed a strong association (78). Additionally, despite children generally having lower fat reserves and muscle mass, their higher basal energy requirements render their lipid metabolic balance more vulnerable (79). Certain cancer treatments may also elevate triglyceride and free cholesterol levels, potentially increasing long-term health risks and recurrence probabilities (79–82).

3.3 The role of MYCN in lipid metabolic reprogramming

In NB, the proto-oncogene MYCN serves as a key driver of tumorigenesis by regulating the expression of multiple proteins involved in lipid metabolism, including FASN, stearoyl-CoA desaturase 1 (SCD1), and FATP2. These targets are particularly critical in MYCN- or MYC-driven tumors, while they may not be the primary oncogenic regulators in other cancer types (64).

In summary, the regulation of lipid metabolism varies markedly between tumors arising in different age groups. This heterogeneity reflects distinct underlying molecular biology and metabolic needs, emphasizing the importance of developing age-specific metabolic intervention strategies in future precision oncology.

4 Cholesterol metabolism in pediatric tumors

Cholesterol metabolism plays a critical role in pediatric tumor progression by supporting rapid cell proliferation (83), immune evasion (84, 85), and therapy resistance (86). Beyond serving as a structural component of cellular membranes, cholesterol mediates key signaling pathways that protect tumor cells from lipid peroxidation and enhance their metabolic adaptability within the

tumor microenvironment (87). Additionally, cholesterol accumulation promotes immune suppression by altering dendritic cell maturation and dampening anti-tumor immune responses (88).

Cholesterol biosynthesis is essential for tumor growth and survival in pediatric cancers. Elevated cholesterol levels are linked to poor prognosis in NB (89). Moreover, combining caffeine treatment or FOXM1 inhibition with statins enhances the anti-tumor efficacy of statins against NB (90). Similarly, enhanced cholesterol biosynthesis drives tumor progression and oncogenic signaling, such as Hedgehog pathway activation, in Wilms' tumor and medulloblastoma (91, 92).

The UPS plays a key role in this regulatory network by modulating the stability of proteins involved in cholesterol metabolism. When intracellular cholesterol levels are high, the UPS promotes the ubiquitination and subsequent degradation of proteins responsible for cholesterol biosynthesis and uptake, while the ubiquitination of proteins involved in cholesterol efflux is reduced to maintain adequate export function. Conversely, when

cholesterol levels decrease, the UPS reduces the ubiquitination of biosynthetic and uptake proteins—thereby prolonging their half-life—while enhancing the ubiquitination of efflux transporters to limit cholesterol loss (93). In this way, the UPS tightly regulates cholesterol metabolism, and dysregulation of this system contributes to the metabolic reprogramming observed in pediatric tumors, involving specific E3 ligases and deubiquitinases (Figure 1) (94).

4.1 Transcriptional regulation of cholesterol metabolism in pediatric solid tumors

In pediatric solid tumors, cholesterol metabolism is tightly regulated by two key transcription factors: sterol regulatory element-binding protein 2 (SREBP2) and liver X receptors (LXR). SREBP2 primarily drives cholesterol biosynthesis and

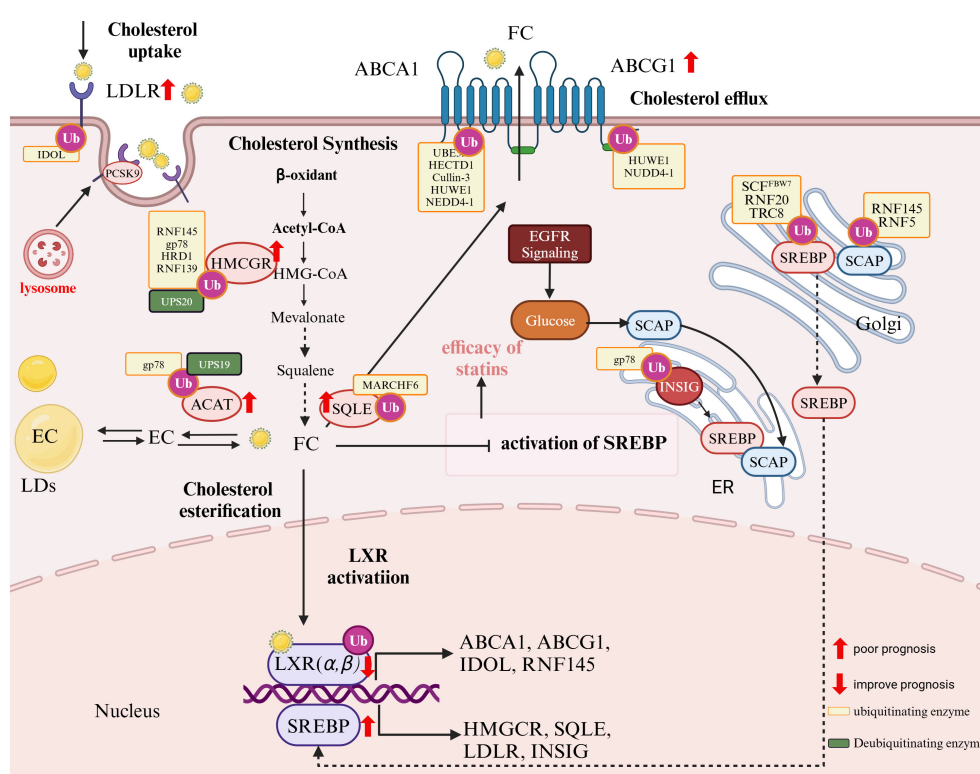


FIGURE 1

Ubiquitination and fatty acid (FA) metabolism in pediatric cancers. (Created in <https://BioRender.com>.) FA metabolism is driven by key enzymes and regulators, many of which are subject to ubiquitination and deubiquitination, marked in orange and green boxes, respectively. Sterol regulatory element-binding protein 1 (SREBP1) plays a central role in regulating FA synthesis. It is ubiquitinated by the Skp1-Cul1-FBW7 (SCF^{FBW7}) E3 ligase complex and Ring Finger Protein 20 (RNF20). Stabilized expression of SREBP1 promotes tumor progression. FA also activates peroxisome proliferator-activated receptors (PPARs), which are fine-tuned by UPS. PPAR activation induces the expression of cluster of differentiation 36 (CD36), a receptor involved in FA uptake. CD36, regulated by PARKIN-dependent ubiquitination, is associated with tumor progression, immune evasion, and metastasis in pediatric cancers, correlating with poor prognosis. However, the TSP-1/CD36 axis can inhibit angiogenesis under certain conditions. Internalized free fatty acids (FFAs) are converted into monoglycerides (MGs), diglycerides (DGs), and triglycerides (TGs), which are stored in lipid droplets (LDs). Upon energy demand, TGs are hydrolyzed by adipose triglyceride lipase (ATGL), which is ubiquitinated by COP1 and RNF213. FFAs can also be used to generate unsaturated fatty acids (e.g., MUFAs and PUFAs), a process requiring carnitine palmitoyltransferase 2 (CPT2), ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), stearoyl-CoA desaturase 1 (SCD1), and fatty acid-binding proteins FABP4 and FABP5. CPT2 is essential for FA transport into mitochondria. These enzymes (CPT2, ACLY, ACC, FASN, SCD1, FABP4, and FABP5) are frequently overexpressed in pediatric cancers and are drivers of tumor progression and poor prognosis.

uptake, while LXRs promote cholesterol efflux by inducing genes such as ABCA1, ABCG1, and APOE. Their activities are interlinked in a feedback loop that maintains cholesterol homeostasis; under high intracellular cholesterol conditions, LXRs can antagonize SREBP2 activity to prevent excessive cholesterol accumulation. Disruption of this balance—either through hyperactivation of SREBP2 or insufficient LXR-mediated clearance—leads to cholesterol accumulation that supports tumor growth, membrane synthesis, and oncogenic signaling.

4.2 The SREBP axis: sculpting tumor cholesterol homeostasis through UPS fine-tuning

SREBP2 plays a critical role in tumor cholesterol metabolism, driving proliferation and survival by inducing the expression of mevalonate pathway genes to enhance cholesterol and isoprenoid synthesis (95). Normally, the SCAP-SREBP2 complex is retained in the ER by insulin-inducible gene protein (Insig), preventing activation. Tumor cells bypass this regulation through mechanisms such as EGFR-induced the SREBP cleavage-activating protein (SCAP) glycosylation, enabling SREBP2 activation and increased lipogenesis (96). This dysregulation supports rapid proliferation and metabolic adaptability in glioblastoma, hepatocellular carcinoma, and NB. Inhibiting SREBP2 enhances statin efficacy and overcomes drug resistance, highlighting its therapeutic potential in pediatric tumors (90, 97, 98).

The UPS imposes an additional layer of control on SREBP2. The E3 ligase translocation in renal cancer from chromosome 8 (TRC8), initially identified as a tumor suppressor in renal cell carcinoma (99), inhibits tumor growth by regulating SREBP activation, likely through blocking ER-to-Golgi transport or promoting precursor degradation (100, 101). Similarly, the ring finger protein 145 (RNF145) targets SCAP for ubiquitination, limiting SREBP2 activation and cholesterol biosynthesis (102). gp78, another key E3 ligase, targets HMG-CoA reductase, a rate-limiting enzyme in the mevalonate pathway, for degradation to maintain cholesterol homeostasis (103). This differential regulation highlights the nuanced interplay between UPS components in balancing cholesterol synthesis and efflux.

Insig proteins further modulate this process. Insig-1, which is ubiquitinated and rapidly degraded, facilitates SREBP2 activation, while Insig-2 resists degradation under oxidative stress, protecting against lipid overload (104, 105). This interplay between SCAP, Insig proteins, and UPS ensures a balance between cholesterol synthesis and efflux.

Deubiquitination fine-tunes SREBP2 activity. Ubiquitin-specific protease 28 (USP28) stabilizes the active nuclear form of SREBP2 by removing ubiquitin chains, enhancing the expression of mevalonate pathway enzymes and supporting tumor metabolic demands. This dynamic regulation allows tumor cells to adapt to the metabolic requirements of growth and survival (106).

4.3 LXRs: cholesterol-sensing nuclear receptors in tumor metabolism

LXRs function as cholesterol sensors and are central to maintaining cholesterol homeostasis. Upon activation, LXRs induce the transcription of cholesterol efflux genes, including ATP-binding cassette transporter A1 (ABCA1), ATP binding cassette transporter G1 (ABCG1), and apolipoprotein E (APOE), which reduce intracellular cholesterol levels. LXRs also regulate cholesterol uptake by inducing E3 ligases such as low-density lipoprotein (LDL) receptor (LDLR) (107) and RNF145, which ubiquitinate and degrade the low-density lipoprotein receptor (LDLR) to prevent cholesterol overaccumulation (108, 109).

In pediatric tumors, LXRs exhibit context-specific roles that influence tumor progression and prognosis. In NB, LXR activation upregulates ABCG1, promoting cholesterol efflux, protecting cells from oxidative stress, and enhancing survival (110). Conversely, in osteosarcoma (OS), LXR α functions as a tumor suppressor, with its activation reducing proliferation and sensitizing tumors to chemotherapy through mTOR signaling modulation. Combining LXR agonists with chemotherapeutics such as doxorubicin has shown to enhance efficacy and overcome chemoresistance (111).

The UPS adds another layer of regulation to LXR activity. SIRT1-mediated deacetylation increases LXR ubiquitination and turnover, altering its transcriptional activity in a context-dependent manner (112). However, the roles of specific E3 ligases or DUBs in regulating LXRs remain unclear.

4.4 Cholesterol uptake: LDL receptor pathway and its dysregulation

Cholesterol uptake is essential for tumor cells to meet their increased energy and biosynthetic demands. LDLR family mediates cholesterol endocytosis, playing a central role in lipid homeostasis. In pediatric tumors like osteosarcoma, LR3, a member of the LDLR family, promotes tumor proliferation and invasion, underscoring the role of LDLR signaling in metabolic reprogramming (113). Targeting the mTOR-LDLR axis with agents such as rapamycin has been shown to restore LDLR regulation and suppress tumor growth by limiting cholesterol uptake (114).

LDLR expression is tightly controlled by intracellular cholesterol levels. SREBP2 upregulates LDLR during cholesterol scarcity, enhancing cholesterol uptake, while LXRs induce the E3 ligase IDOL (Inducible Degradation of LDLR) under high cholesterol conditions, targeting LDLR for ubiquitination and lysosomal degradation (115–117). In pediatric tumors, this balance is often disrupted. Pathways such as mTOR activation bypass the LXR-IDOL axis, leading to persistent LDLR expression and excessive cholesterol uptake. In osteosarcoma, sustained LDLR activity supports tumor growth and metastasis (114).

Beyond transcriptional control, LDLR levels are modulated post-translationally. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDLR and directs it to lysosomal degradation,

exacerbating LDLR dysregulation in tumors (107, 118, 119). In pediatric cancers such as medulloblastoma, PCSK9 acts as a tumor-specific neoantigen, triggering T-cell responses and presenting potential as an immunotherapy target (120). Elevated PCSK9 expression has been associated with poor prognosis, drug resistance, and reduced progression-free survival (PFS) in certain cancers, highlighting its dual role in cancer progression and immune modulation (84, 121).

4.5 Cholesterol biosynthesis: from acetyl-CoA to cholesterol

Cholesterol biosynthesis is a tightly regulated pathway essential for tumor growth and metabolic reprogramming. Key enzymes, including HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase) and squalene monooxygenase (SQLE), play central roles in maintaining cholesterol homeostasis and supporting cancer cell proliferation.

4.5.1 HMGCR: a key regulator in cholesterol biosynthesis

HMGCR, the rate-limiting enzyme of cholesterol biosynthesis, is extensively regulated by UPS. E3 ligases such as RNF145, gp78, and HRD1 promote HMGCR degradation, while ubiquitin-specific protease 20 (USP20) stabilizes HMGCR, enhancing cholesterol synthesis and driving tumor growth (122–126). Dysregulation of this balance, such as reduced RNF139 activity, results in HMGCR overexpression, contributing to drug resistance and tumor progression.

Clinically, HMGCR overexpression is frequently observed in pediatric cancers such as NB, rhabdomyosarcoma, and osteosarcoma, where it promotes proliferation, invasion, and survival while reducing therapy efficacy (127–130). Statins, including lovastatin, inhibit HMGCR, blocking cholesterol biosynthesis, inducing apoptosis, and sensitizing tumor cells to chemotherapy and radiotherapy. Statins also target the mevalonate pathway, disrupting Ras/Rho protein prenylation and enhancing antitumor immunity (131, 132).

4.5.2 Squalene monooxygenase

SQLE catalyzes a critical step in cholesterol biosynthesis and is strongly associated with chemoresistance and poor prognosis in cancers, including osteosarcoma. Inhibitors like FR194738 deplete intracellular cholesterol, suppress FAK/PI3K/Akt/mTOR signaling, reduce malignancy, and restore chemosensitivity (133–135).

Beyond its role in cholesterol biosynthesis, SQLE plays a pivotal role in regulating ferroptosis and cuproptosis, modulating the tumor microenvironment and potentially enhancing immunotherapy efficacy (134). Ferroptosis, characterized by iron-dependent lipid peroxidation and reduced glutathione peroxidase 4 (GPX4) activity, leads to oxidative damage and cell death (136). SQLE promotes ferroptosis by enhancing reactive oxygen species (ROS) production and lipid peroxidation. Cuproptosis, a form of cell death triggered by copper toxicity, disrupts the TCA cycle via protein–lipid interactions in mitochondria, leading to protein

aggregation and cell death (134, 137–140). SQLE may regulate cuproptosis by modulating intracellular copper metabolism and mitochondrial function.

Like HMGCR, SQLE is regulated by the UPS via the E3 ligase Membrane-associated ring-CH-type finger 6 (MARCHF6), which promotes its degradation under conditions of elevated cholesterol. MARCHF6 also regulates other enzymes in the cholesterol biosynthetic pathway, including DHCR24 and LDM, highlighting the UPS's central role in maintaining cholesterol homeostasis. Cholesterol enhances MARCHF6 activity to degrade SQLE, whereas unsaturated fatty acids inhibit this process by disrupting their interaction (141–143).

4.6 Cholesterol efflux: transport and removal mechanisms

Cholesterol efflux is critical for maintaining cellular cholesterol balance, preventing cytotoxic accumulation, and supporting cellular integrity. ATP-binding cassette (ABC) transporters, particularly ABCA1 and ABCG1, mediate cholesterol efflux to apolipoproteins and HDL, enabling reverse cholesterol transport (144). Dysregulated cholesterol efflux in pediatric tumors drives metabolic reprogramming, therapy resistance, and immune evasion.

4.6.1 ABCA1 and ABCG1: key transporters in cholesterol homeostasis

ABCA1 and ABCG1 exhibit context-specific roles in pediatric cancers. ATP-binding cassette subfamily B member 1 (ABCB1) effluxes doxorubicin, reducing its intracellular accumulation and diminishing both its toxicity and the immunogenic cell death it induces, thereby contributing to chemoresistance in osteosarcoma (145). In contrast, ABCA1 expels isopentenyl pyrophosphate (IPP), a molecule that activates anti-tumor Vγ9Vδ2 T cells. Enhancing ABCA1-dependent IPP efflux may help overcome ABCB1-mediated resistance (145). Conversely, in medulloblastoma, ABCA1 overexpression confers radiation resistance, likely by altering cholesterol efflux and membrane lipid composition, which could affect DNA repair and stress response pathways (146). Although the molecular basis underlying this discrepancy remains to be fully elucidated, these differences may reflect tumor-specific downstream signaling or microenvironmental factors that modulate ABCA1 function. In NB, ABCA1-mediated cholesterol efflux protects tumor cells from oxidative stress, facilitating survival under metabolic stress (110).

ABCG1 supports cancer stem-like cells (CSCs) in osteosarcoma and Ewing sarcoma, enhancing cholesterol efflux to sustain CSC viability and multidrug resistance. In NB, the LXR-ABCG1 axis protects tumor cells from oxidative damage caused by oxidized cholesterol. Targeting ABCG1 in CSCs could reduce tumor recurrence and improve therapeutic outcomes (110, 147).

UPS tightly regulates ABCA1 and ABCG1 by modulating their degradation and stability. E3 ligases such as HUWE1, NEDD4-1, and HECTD1 ubiquitinate these transporters, reducing their cholesterol efflux capacity and contributing to metabolic

dysregulation (148, 149). Additionally, ubiquitin-protein E3 ligase A (UBE3A)-mediated ubiquitination of ABCA1 has been implicated in myelin-induced foam cell formation in models of CNS repair (M. Loix et al., unpublished). Furthermore, Cullin-3, a cullin-RING ubiquitin E3 ligase, is activated through thrombin-protease-activated receptor (PAR1) signaling, leading to the degradation of ABCA1 and further disrupting cholesterol homeostasis (150, 151). Activation of Cullin-3 requires neddylation, a post-translational modification in which the ubiquitin-like protein NEDD8 conjugates to cullins, enhancing their ubiquitin ligase activity (152). The COP9 signalosome (CSN) acts as a key regulatory complex that counteracts this process by removing NEDD8 from Cullin-3, thereby modulating its activity in a reversible manner (153).

4.6.2 Other cholesterol transporters in tumor progression

Other ABC transporters also contribute to pediatric tumor progression. For instance, ABCG8, degraded by E3 ligases such as RNF5 and HRD1, correlates with metastasis in osteosarcoma, serving as a prognostic biomarker (154, 155). Conversely, ABCA6 exhibits tumor-suppressive properties in Ewing sarcoma, reducing intracellular cholesterol levels and inhibiting oncogenic pathways like IGF1R/AKT/MDM2. Enhancing ABCA6 expression improves chemosensitivity, particularly in combination with statins (156). Meanwhile, ABCB1 (P-glycoprotein) overexpression in NB promotes therapy resistance by effluxing cytotoxic drugs, with signaling pathways like Ras/ERK1/2/HIF-1 α further exacerbating ABCA1 suppression and cholesterol dysregulation (145, 157).

4.7 Cholesterol esterification

Cholesterol esterification, mediated by ACAT1 and ACAT2, is essential for converting free cholesterol into cholesteryl esters, promoting lipid droplet formation and supporting tumor survival in cholesterol-rich environments. This metabolic adaptation drives tumor progression and therapy resistance in pediatric cancers.

ACAT1 plays a central role in NB by facilitating cholesterol esterification and lipid droplet accumulation. While this process supports tumor survival, it can induce oxidative stress and cell death under ER dysfunction. Silencing ACAT1 reduces COX2 expression and restores protective PKC/ERK signaling, highlighting its potential as a therapeutic target (158, 159). In glioblastoma, ACAT1 enhances cholesteryl ester synthesis to support membrane production and proliferation (160). Interestingly, ACAT1 inhibition also enhances the cytotoxic function of CD8 (+) T cells, suggesting a potential immunomodulatory role in controlling tumor growth (161).

The UPS tightly controls ACAT enzyme stability, influencing cholesterol esterification and tumor metabolism. gp78 and INSIG mediate ROS-induced ubiquitination of ACAT2, promoting sterol storage and metabolic adaptation (161). In contrast, USP19 stabilizes ACAT1 by removing ubiquitin chains, enhancing

cholesterol esterification and supporting tumor growth, as observed in hepatocellular carcinoma (162).

5 UPS-mediated regulation of FA in pediatric tumors

Fatty acids (FAs) are essential for membrane synthesis, energy production, and cellular signaling. Dysregulated FA metabolism in pediatric tumors supports proliferation, therapy resistance, and survival by balancing lipid storage and oxidative stress, such as lipid peroxidation (LPO) and ferroptosis (163). The UPS plays a central role in regulating key aspects of FA metabolism, including *de novo* synthesis, uptake, and β -oxidation (Figure 2).

5.1 Ubiquitination in *de novo* fatty acid synthesis

De novo fatty acid synthesis provides critical lipids for tumor membrane production and growth, with its key enzymes tightly regulated by the UPS.

ATP Citrate Lyase (ACLY), which links glucose metabolism to lipid synthesis, is ubiquitinated by the CUL3-KLHL25 E3 ligase, suppressing tumor growth by reducing lipid production (164). Conversely, deubiquitinases USP13 and USP30 stabilize ACLY, promoting tumor progression in cancers such as ovarian and liver cancers (165, 166). In osteosarcoma, ACLY drives tumor growth and metastasis via the XIST/miR-655/ACLY axis, while miR-22 downregulates ACLY to inhibit lipogenesis, highlighting its potential as a therapeutic target (167, 168).

Acetyl-CoA Carboxylase (ACC), a rate-limiting enzyme in FA synthesis, is ubiquitinated by COP1 under normal conditions to suppress lipogenesis (169). However, in certain cancers, ACC evades degradation through interactions with AKR1B10, enhancing FA synthesis and driving tumor progression (170). Additionally, AKR1B10 is strongly associated with chemotherapy resistance (171).

FASN, a key enzyme in lipogenesis, is upregulated in pediatric tumors such as osteosarcoma, NB, and medulloblastoma. In osteosarcoma, FASN promotes anoikis resistance and metastasis to the lungs (172, 173). In NB, FASN and SCD1 regulate unsaturated FA metabolism to enhance immune evasion and survival (173–176). Similarly, in medulloblastoma, FASN-driven lipid synthesis sustains tumor proliferation (177). The UPS critically regulates FASN. COP1 ubiquitinates FASN to prevent excessive lipid accumulation, while mutations in SPOP impair FASN degradation, promoting tumor growth (170). Deubiquitinases such as USP2a and USP14 stabilize FASN, enhancing lipogenesis and contributing to therapy resistance. For example, in retinoblastoma, USP14-mediated FASN stabilization suppresses ferroptosis and promotes resistance to cisplatin (61, 178, 179). Conversely, USP2a binds to and stabilizes MDM4, which in turn increases the mitochondrial localization of p53 and promotes apoptosis in glioma cells (180).

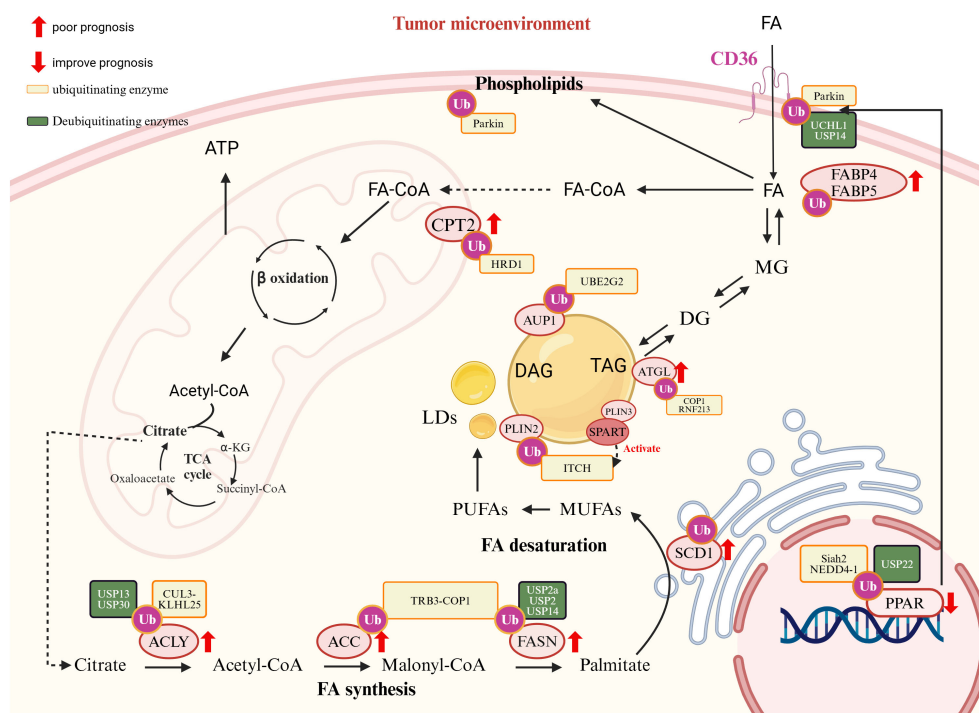


FIGURE 2

The role of ubiquitination in cholesterol metabolism and tumor prognosis. Cholesterol uptake: LDL receptor (LDLR) mediates cholesterol uptake. PCSK9 promotes LDLR degradation via the lysosome, while the E3 ubiquitin ligase IDOL ubiquitinates LDLR, targeting it for proteasomal degradation, reducing cholesterol uptake; Cholesterol Synthesis: The rate-limiting enzyme HMG-CoA reductase (HMGCR) is ubiquitinated by RNF145, gp78, HRD1, and RNF139, leading to degradation. Squalene epoxidase (SQLE) is ubiquitinated by MARCH6, affecting cholesterol biosynthesis; Cholesterol Efflux: ATP-binding cassette transporters ABCA1 and ABCG1 mediate cholesterol efflux. Their regulation involves ubiquitination by HUWE1, NEDD4-1, and others; Cholesterol Esterification: Acyl-CoA:cholesterol acyltransferase (ACAT) facilitates cholesterol storage in lipid droplets (LDs), regulated by gp78 and UPS19; Transcriptional Regulation: The sterol regulatory element-binding protein (SREBP) pathway controls cholesterol biosynthesis. SCAP facilitates SREBP transport from the ER to the Golgi, where it is activated. The INSIG-SCAP-SREBP complex is regulated via ubiquitination by gp78 and TRC8, while RNF145 and RNF5 ubiquitinate SCAP to modulate its stability. LXR activation induces genes like ABCA1, ABCG1, and IDOL, affecting cholesterol homeostasis. Cancer Metabolism and Prognostic Markers: EGFR signaling and glucose metabolism enhance SREBP activation, contributing to tumor lipid metabolism. Ubiquitination (orange boxes) and deubiquitination (green boxes) modulate key enzymes and pathways, influencing tumor progression and prognosis. Markers with red arrows (↑,↓) indicate prognostic impact, where upregulated elements are linked to poor prognosis, while downregulated components improve prognosis.

5.2 UPS-mediated control of fatty acid uptake and transport

Fatty acid (FA) uptake and transport are vital for tumor metabolism, influencing tumor cell proliferation, immune evasion, and the tumor microenvironment (TME). The UPS regulates key FA transporters, such as CD36 and fatty acid-binding proteins (FABPs), modulating lipid metabolism and tumor progression.

5.2.1 CD36: a dual role in tumor metabolism and immunity

CD36, a key FA transporter, plays a complex role in tumor metabolism and immunity. Parkin-mediated mono-ubiquitination enhances CD36 activity, increasing FA uptake, while deubiquitinases like UCHL1 and USP14 stabilize CD36, preventing degradation (44, 181, 182). Dysregulated CD36 activity impacts both tumor growth and immune cell function.

In immune cells, CD36 overexpression impairs antitumor immunity. Excessive FA uptake in CD8⁺ T cells induces lipid peroxidation and ferroptosis, reducing cytotoxicity and immunotherapy efficacy (29). In TAMs and Tregs, CD36 promotes an immunosuppressive environment, supporting tumor growth. Targeting CD36 restores immune function and enhances antitumor responses (30, 183).

In pediatric tumors, CD36 has diverse effects. In osteosarcoma, CD36 drives proliferation and immune evasion through the CD36-MYD88 axis, correlating with poor prognosis. However, its interaction with Thrombospondin-1 (TSP-1) produces anti-angiogenic vasculostatin, suppressing tumor growth (184–186). In NB, CD36-mediated uptake of long-chain FAs like palmitic acid induces metabolic stress and cell damage, which can be alleviated by CD36 inhibition (187, 188). Beyond pediatric settings, CD36 enrichment in glioblastoma stem cells and other adult tumors associates with metastatic potential and poor outcomes (189, 190).

Fatty acid-binding proteins (FABPs) regulate intracellular FA transport and contribute to tumor progression. Although direct UPS regulation of FABPs is unclear, their roles in tumor metabolism and immune evasion are well-documented. FABP4 enhances pro-tumoral TAM phenotypes in NB, driving tumor progression. FABP4+ macrophage enrichment in metastatic osteosarcoma correlates with immune evasion and poor prognosis (191–193). FABP5 promotes growth in osteosarcoma through the Akt/mTOR pathway and mediates therapy resistance in medulloblastoma, underscoring its role in tumor survival and progression (194–196).

5.3 Ubiquitination in FAO

FAO is a crucial energy source for lipid-dependent pediatric tumors. The UPS regulates key enzymes in this pathway, influencing tumor progression, metastasis, and therapeutic outcomes.

Carnitine Palmitoyltransferase 1A (CPT1A), the rate-limiting enzyme in FAO, is regulated by UPS-mediated ubiquitination, which modulates its mitochondrial localization and activity. Elevated CPT1A expression promotes epithelial-mesenchymal transition (EMT), cancer stemness, and metastasis. In NB, high CPT1A levels correlate with poor prognosis, linking FAO activation to aggressive tumor behavior (21, 197). Conversely, CPT1B, a paralog of CPT1A, is associated with improved outcomes in osteosarcoma, highlighting isoform-specific roles in pediatric tumors (198).

CPT2, another key FAO enzyme, is regulated by the E3 ligase HRD1, which restricts FAO by targeting CPT2 for ubiquitination and degradation. Reduced HRD1 expression enhances CPT2 activity, driving FAO and tumorigenesis, as observed in triple-negative breast cancer (TNBC). Although direct evidence in pediatric tumors is limited, similar regulatory mechanisms are likely involved (199). Furthermore, Acyl-CoA Dehydrogenases (ACADs), key enzymes in the FAO pathway, are degraded by the UPS, restricting FAO activity and sensitizing tumor cells to energy deprivation. This regulation may present therapeutic opportunities by targeting energy metabolism in lipid-dependent tumors.

5.4 Cross-talk between ubiquitination and lipid droplets

Lipid droplets (LDs) act as dynamic energy reserves, releasing free fatty acids (FFAs) and cholesterol through cytosolic lipolysis or lipophagy to prevent lipotoxicity and support tumor metabolic demands. The UPS plays a crucial role in regulating LD turnover, enabling tumor cells to adapt to fluctuating energy needs.

The LD-associated protein AUP1 links LDs to the UPS by recruiting the E2 conjugase Ube2g2, facilitating ubiquitination on the LD surface (200). Coating proteins such as PLIN2 is ubiquitinated by the Itch E3 ligase, facilitating lipid droplet (LD) degradation and releasing free fatty acids (FFAs) to support tumor metabolism (201). SPART/SPG20 (Spartin)

functions as an adaptor for Itch by binding to the LD-associated protein PLIN3, promoting the recruitment and activation of Itch. This leads to the ubiquitination of PLIN2 and the subsequent recruitment of the autophagy receptor SQSTM1/p62, triggering macrolipophagy (201, 202). Additionally, under nutrient stress, LDs can also undergo autophagy through ubiquitin-independent mechanisms (203).

Key enzymes regulating LD dynamics, such as ATGL and FSP27 (204), are also modulated by the UPS. For example, E3 ligases like COP1 and RNF213 ubiquitinate ATGL, reducing triglyceride hydrolysis and leading to increased LD accumulation. This shift not only augments the energy reserve of tumor cells but also enhances their metabolic flexibility—that is, the capacity to adjust fuel utilization and energy production in response to varying nutrient and stress conditions—which in turn supports tumor progression (205, 206). RNF213 suppresses carcinogenesis and affects MAPK/JNK signaling pathway in glioblastoma (207). These UPS-mediated mechanisms allow tumors to optimize energy utilization, contributing to their survival and growth under varying metabolic conditions (204, 208).

5.5 Transcriptional regulation of FA metabolism by UPS

The UPS regulates transcription factors such as PPAR γ and SREBP1, which are central to fatty acid (FA) metabolism.

5.5.1 Peroxisome proliferator-activated receptors (PPARs)

PPAR γ , a nuclear receptor regulating FA metabolism and glucose homeostasis, plays dual roles in lipid metabolism and tumor biology. Highly expressed in pediatric cancers, PPAR γ activation promotes tumor differentiation, inhibits proliferation, and induces apoptosis. For instance, PPAR γ agonists enhance pro-apoptotic pathways (e.g., p21 and Bax), suppressing osteosarcoma growth (209, 210), and improve therapeutic responses in high-risk NB by promoting differentiation and metabolic reprogramming (211, 212). PPAR γ is a critical regulator in tumor progression, and its expression is modulated by factors such as miR-27b and TRIM46, which in turn influence its impact on diseases like OS (213, 214).

The UPS provides post-translational control of PPAR γ activity. Ligand-bound PPAR γ undergoes K48-linked ubiquitination, limiting transcriptional activity (215). Under inflammatory conditions, E3 ligases such as Siah2 and NEDD4-1 mediate the ubiquitination and degradation of PPAR γ . In contrast, deubiquitinases (DUBs) like USP22 remove K48-linked ubiquitin chains from PPAR γ , stabilizing it. This stabilization enhances PPAR γ 's transcriptional activity, leading to increased expression of lipogenic enzymes, including ACC and ACLY, which promote *de novo* fatty acid synthesis (216–218). Interestingly, PPAR γ also acts as an E3 ligase, mediating ubiquitination at Lys28 and leading to p65 proteasomal degradation, directly linking lipid metabolism to immune modulation in the tumor microenvironment (219). Targeting the UPS-PPAR γ axis holds potential for

modulating FA metabolism and inflammation, particularly in pediatric cancers like osteosarcoma and NB (209–214, 220).

5.5.2 Sterol regulatory element-binding protein 1 (SREBP1)

SREBP1 is a master regulator of lipogenic genes, driving FA synthesis to support tumor growth and metabolic adaptation. Although its role in pediatric cancers is underexplored, UPS-mediated regulation is essential for maintaining lipid homeostasis. The SCF-FBXW7 E3 ligase complex degrades SREBP1 via GSK3-dependent phosphorylation, restricting FA synthesis under metabolic stress (221). In contrast, another study demonstrates that SREBP2 targets FBXW7 to regulate miR-182, establishing a feedback loop that modulates SREBP transcriptional activity (222, 223). Conversely, SREBP1 acetylation stabilizes the protein by competing with ubiquitination, enhancing lipogenic activity (224). Other E3 ligases, such as RNF20 and RNF139, promote SREBP1 degradation or inhibit precursor synthesis under nutrient-limiting conditions (221, 225). Additionally, SIRT1-mediated deacetylation facilitates SREBP1 ubiquitination and degradation, linking lipid metabolism to cellular stress responses (226).

Upstream, mTORC1 integrates SREBP1 activation with tumor cell biosynthetic and energy demands, particularly under lipid-rich conditions, further enhancing SREBP1-driven FA synthesis to meet the needs of rapidly proliferating tumor cells (221, 227). We summarized lipid metabolism-related genes and their roles in tumor prognosis: regulation by the UPS in (Table 1).

6 Ubiquitin ligases indirectly influence tumor lipid reprogramming

E3 ubiquitin ligases play critical roles in tumor lipid reprogramming by targeting regulatory proteins for degradation, driving tumor progression and therapy resistance. In Group 3 medulloblastoma, RNF126 ubiquitinates FSP1, altering its plasma membrane localization and disrupting the CoQ/CoQH2 balance, thereby suppressing ferroptosis and preventing phospholipid peroxidation. RNF126 overexpression correlates with poor prognosis in this subtype (228). In triple-negative breast cancer (TNBC), depletion of RNF126 increased sensitivity to irradiation (229). Similarly, in NB, TRIM59 promotes chemoresistance and tumor growth by degrading p53 and suppressing ferroptosis, enabling tumor survival under stress (230).

FBW7 regulates lipid metabolism by targeting c-Myc for degradation. Loss of FBW7 stabilizes c-Myc, resulting in abnormal lipid accumulation, uncontrolled proliferation, and therapy resistance (231). In osteosarcoma, FBW7 downregulation reduces the degradation of KCa1.1, a potassium channel localized in lipid rafts, which enhances drug resistance. Pharmacological inhibition of KCa1.1 restores chemosensitivity, demonstrating its therapeutic potential (232).

By modulating ferroptosis, lipid raft dynamics, and energy metabolism, E3 ligases such as RNF126, TRIM59, and FBW7 enable tumors to adapt to metabolic stress and evade apoptosis, making them promising targets for disrupting tumor lipid reprogramming.

7 Lipid regulation of ubiquitination in tumor progression and resistance

Lipids, categorized into eight classes by the LIPID MAPS system, are essential for cellular metabolism and signaling (233). Their interplay with ubiquitination reprograms tumor lipid metabolism, influencing key protein degradation and regulation. Imbalances in lipid ratios and dysregulated lipid metabolism-related genes drive abnormal lipid synthesis, uncontrolled cell growth, and tumor progression.

In Ewing sarcoma, ceramide triggers cleavage of the intracellular domain of GPR64, which translocates to the nucleus and promotes ubiquitination of RIF1 through the Cullin3-RING E3 ligase complex and SPOP, driving tumor growth (234). Similarly, lyso-Gb3, a deacylated lipid derivative, enhances ubiquitination of molecular chaperones like HSP90 and HSP60, inducing cytotoxicity and disrupting protein homeostasis (235). In osteosarcoma, M2 macrophage-derived exosomal Apoc1 facilitates ACSF2 ubiquitination and degradation, suppressing ferroptosis and promoting tumor progression (236).

Lipid metabolites also contribute to therapeutic resistance. For example, Prostaglandin E1 (PGE1) activates cAMP-PKA signaling via the EP4 receptor, promoting GLI2 ubiquitination and degradation to suppress Hedgehog signaling, overcoming GLI2 amplification-associated drug resistance in medulloblastoma models (237). Additionally, FASN modulates cell cycle regulation by stabilizing p27^{Kip1} through Skp2 suppression, linking lipid metabolism to tumor cell cycle arrest (238). Mitochondrial lipids like cardiolipin and phosphatidic acid regulate mitochondrial dynamics via MARCH5 ubiquitination. Cardiolipin accelerates MARCH5 self-ubiquitination, promoting mitochondrial turnover, while phosphatidic acid stabilizes MARCH5 to preserve mitochondrial homeostasis (239). Furthermore, PD-1 signaling facilitates MARCH5-mediated γ -chain ubiquitination, impairing antitumor immunity. Combining PD-1 blockade with MARCH5 inhibitors and IL-2 enhances immune responses and therapeutic efficacy (240).

A recent study by Sakamaki et al. demonstrated that phospholipids, such as phosphatidylethanolamine (PE), can be ubiquitinated in endosomal and lysosomal compartments by the ubiquitin enzymes Uba1 (E1), Ubc4/5 (E2), and Tul1 (E3). These findings provide insights into the novel roles of lipids beyond metabolic substrates (241). This reciprocal interaction between lipid metabolism and ubiquitination offers novel insights into tumor biology and identifies potential therapeutic targets.

8 Therapeutic strategies and discussion: targeting the UPS in pediatric tumors

Current research has demonstrated that the UPS plays a crucial role in the regulation of pediatric solid tumors, including NB (242). The ubiquitination pathway has been explored for drug

TABLE 1 Lipid metabolism-related genes and their roles in tumor prognosis: regulation by the UPS.

Gene/ Protein	Ub/Dub Enzyme	Disease Relevance	Effect	Impact on lipid Metabolism/Other Functions	Notes	Reference
De Novo Synthesis						
ACLY	CUL3-KLHL25	OS, RMS, Various Cancers	poor prognosis	Regulates lipid deposition, β -catenin activation, and interacts with Wnt and mTOR pathways in tumor growth.	Therapeutic targeting of XIST/ACLY or miR-22 shows promise in reducing tumor progression; preclinical models suggest synergy with immune checkpoint inhibitors	(167, 168, 314, 315)
	USP13, USP30					
FASN	COP1	WT, OS, NB, MB, GC	Poor prognosis	Regulates lipid metabolism and tumor progression via HER2/PI3K/Akt, NF κ B, and AMPK pathways. Promotes lipid accumulation, immune evasion, and unsaturated fatty acid synthesis.	Therapeutic targeting of FASN (e.g., Cerulenin, siFASN, miR-195, miR-424) reduces proliferation, metastasis, and invasion in various cancers. Combinatorial strategies improve outcomes by inhibiting Rb/AMPK signaling or reducing autophagy.	(174, 176, 177, 289, 316–321)
	USP2a, USP2, USP14					
ACC	COP1	Undefined	Poor prognosis	Ubiquitination by COP1 degrades ACC, inhibiting fatty acid synthesis. AKR1B10 stabilizes ACC, enhancing lipid synthesis and promoting tumor progression.	ACC degradation reduces lipid synthesis, providing a potential therapeutic target. AKR1B10 prevents ACC degradation, making it a target in lipid-driven cancers.	(169, 170)
	AKR1B10					
SCD1	Undefined	OS, HCC	Poor prognosis	Auto-protective role via PPAR δ and Smad1/5 signaling in OS. ER stress induced by lipid desaturation suppresses MYCN in HCC, reducing proliferation.	Regulation under high shear force conditions in OS requires further examination. ACR reduces unsaturated fatty acids, inducing ER stress and MYCN inhibition in HCC.	(175, 322)
Fatty Acid Uptake and Transport						
CD36	Parkin	OS	Poor prognosis via inflammation; improved prognosis via anti-angiogenesis	High-risk ARGs (e.g., CBS, MYC, MMP3, CD36) promote tumor growth, immune evasion, and metastasis. TSP-1/CD36 axis inhibits angiogenesis and tumor progression	High-risk ARGs (e.g., CBS, CD36) correlate with poor survival in OS. Anti-CD36 therapies targeting TSP-1/CD36 loops reduce angiogenesis and tumor growth; identified drugs (e.g., Bortezomib, Sunitinib) show potential.	(184–187)
	UCHL1, USP14					
FABP4	Undefined	NB, OS	Poor prognosis	FABP4 binds ATPB, accelerating ubiquitination and reducing ATP levels in NB. In OS, FABP4 enhances lipid metabolism (FFAs, TGs) via the RPARP-AS1/Akt/mTOR pathway.	FABP4 promotes NB migration and invasion, suppressed by blocking IL1 α . FABP4+ macrophages in metastatic OS are pro-inflammatory and linked to immunosuppressive microenvironments. Circulating FABP4 correlates with advanced stages.	(191, 194, 195)
FABP5	Undefined	NB, MB, OS	Poor prognosis	NBASP downregulates FABP5 in NB, inactivating MAPK and suppressing carcinogenesis. FABP5 enhances tumorigenic pathways (e.g., MYCN, E2F1, SREBF1/2) and lipid metabolism in NB and OS. Imbalanced CRABP-II \downarrow /FABP5 \uparrow leads to RA resistance in MB.	NBASP encoded by FAM201A is a potential therapeutic target. FABP5 knockdown reduces MYCN, survivin, and HMGA1 expression in NB. NSUN2-mediated m5C stabilizes FABP5 mRNA in OS, promoting fatty acid metabolism and tumor progression.	(192, 193, 196, 323)
Fatty Acid Oxidation						
CPT1B	Undefined	OS	improved prognosis	CPT1B expression correlates with immune cell regulation and better outcomes in OS.	SERPINE2 is linked to poor survival, while CPT1B suggests better prognosis. Biomarkers validated through AI and immunohistochemistry; potential for prognostic and therapeutic utility.	(198)
CPT2	HRD1	Undefined	Possibly Linked to Poor Prognosis	Undefined	Undefined	(199)

(Continued)

TABLE 1 Continued

Gene/ Protein	Ub/Dub Enzyme	Disease Relevance	Effect	Impact on lipid Metabolism/Other Functions	Notes	Reference
Lipid Droplets (LDs)						
<i>AUP1</i>	<i>UBE2G2</i>	Undefined	Undefined	Links lipid droplets (LDs) to UPS, mediating protein ubiquitination on the LD surface through Ube2g2.	AUP1 regulates LD turnover and protein quality control, suggesting a role in tumor metabolic adaptation and potential therapeutic targeting.	(200)
<i>PLIN2</i> , <i>PLIN5</i>	<i>Itch</i>	Undefined	Poor prognosis	PLIN2 and PLIN5 are ubiquitinated by Itch, linking lipid droplets (LDs) to the UPS for protein turnover and metabolic regulation.	Itch-mediated ubiquitination of PLIN2/PLIN5 regulates LD protein turnover, influencing tumor metabolic adaptation.	(202, 324)
<i>Spartin</i>	<i>Itch</i>	Undefined	Poor prognosis	Acts as an adaptor factor for autophagy-dependent lipid droplet (LD) turnover during nutrient deprivation.	Regulates LD degradation under metabolic stress, linking autophagy and lipid metabolism.	(202, 324)
<i>ATGL</i>	<i>COP1</i> , <i>RNF213</i>	Undefined	Undefined	Ubiquitination inhibits triglyceride hydrolysis, increasing lipid droplet (LD) content and disrupting lipid metabolism.		(205, 206)
<i>FSP27</i>	<i>COP1</i> , <i>RNF213</i>	Undefined	Undefined	UPS regulates the stability of FSP27, indirectly affecting lipid droplet homeostasis.		(204)
Transcriptional Regulation of Fatty Acid Metabolism						
<i>PPAR</i>	<i>Siah2</i> , <i>NEDD4-1</i> , <i>TRIM46</i>	MB, NB, OS	Improve prognosis	PPAR activation promotes tumor differentiation, apoptosis, and metabolic regulation. TRIM46-mediated PPAR ubiquitination enhances NF- κ B signaling, promoting tumor growth and poor prognosis in OS.	PPAR agonists (e.g., fenofibrate, troglitazone) reduce tumor progression in MB, NB, and OS by modulating IGF-I, lipid metabolism, and pro-apoptotic pathways. TRIM46 regulates PPAR signaling, influencing tumor outcomes.	(211, 214, 220, 325–328)
	<i>USP22</i>					
<i>SREBP1</i>	<i>SCF-FBXW7</i> , <i>RNF20</i> , <i>RNF139</i> , <i>SIRT1</i> ,	Undefined	poor prognosis	Ubiquitination (via SCF-FBXW7, RNF20, RNF139) or deacetylation (via SIRT1) promotes SREBP1 degradation, inhibiting fatty acid metabolism and maintaining lipid homeostasis. mTORC1 activation and SREBP1 acetylation enhance its stability and promote lipid metabolism, supporting tumor growth.	SCF-FBXW7, RNF20, and RNF139 promote SREBP1 degradation, reducing fatty acid synthesis. SIRT1 deacetylation links SREBP1 degradation to cellular stress responses. Acetylation or mTORC1 activation stabilizes SREBP1, driving tumor progression.	(213, 224, 226, 227)
Transcriptional Regulation of Cholesterol Metabolism						
<i>SREBP2</i>	<i>RNF145</i> , <i>SCF-FBXW7</i> , <i>TRC8</i>	NB	poor prognosis	Ubiquitination (via RNF145, SCF-FBXW7, TRC8) inhibits SREBP2 activation, reducing cholesterol synthesis and tumor growth. Deubiquitination by USP28 stabilizes SREBP2, enhancing cholesterol synthesis and lipid metabolism.	RNF145 and TRC8 inhibit SREBP2 activation via SCAP ubiquitination or ER-to-Golgi transport blockade. USP28 promotes tumor growth by stabilizing SREBP2, enhancing cholesterol metabolism.	(100–102, 106, 329)
	<i>USP28</i>					
<i>LXRs</i> (<i>LXRα</i> , <i>LXRβ</i>)	<i>IDOL</i> , <i>RNF145</i> , <i>SIRT1</i>	NB	Improve prognosis	24SOHC induces LXR-mediated adaptive responses; enhanced ABCG1 expression protects against 7KC-induced cytotoxicity; ABCA1 plays a less critical role in NB. 24(S)-hydroxycholesterol upregulates ApoE, ABCA1, and ABCG1 in astrocytes; NR Modulators inhibit mTOR signaling via DDIT4 in OS.	Adaptive responses enhanced by co-treatment with 9-cis retinoic acid; knockdown of LXR diminishes protective effects of 24SOHC. Statins show therapeutic potential; MES-NB addicted to mevalonate pathway.	(108)

(Continued)

TABLE 1 Continued

Gene/ Protein	Ub/Dub Enzyme	Disease Relevance	Effect	Impact on lipid Metabolism/Other Functions	Notes	Reference
Cholesterol uptake and LDLR (Low-Density Lipoprotein Receptor) pathway						
<i>LDLR</i>	SREBP2, mTOR, IDOL, PCSK9	NB, OS	poor prognosis	Activation of LXR induces IDOL, which ubiquitinates LDLR, promotes lysosomal degradation, and inhibits cholesterol uptake. During cholesterol deprivation, LDLR expression is induced, enhancing cholesterol uptake; PCSK9 binds to LDLR and directs it to lysosomal degradation, reducing LDLR levels on the cell surface and subsequently decreasing LDL uptake. mTOR activation can bypass the LXR-IDOL axis, maintaining high LDLR expression, thereby promoting cholesterol uptake and tumor metabolism.		(107–109, 118, 119, 330)
Cholesterol biosynthesis pathway						
<i>HMGR</i>	RNF145, gp78, HRD1, RNF139	NB, RMS, MES-NB, OS	Poor Prognosis	Lovastatin modulates cholesterol biosynthesis and induces apoptosis in neuroblastoma; hyperactive Akt1 signaling promotes tumor progression in RMS; mesenchymal neuroblastomas depend on HMGR-driven protein geranylgeranylation; inhibition of the mevalonate pathway reduces OS metastasis by suppressing Yes-associated protein 1 (YAP1) activity.	Statins exhibit therapeutic potential in neuroblastoma and osteosarcoma, reducing metastasis and tumor growth; combination therapy effective in RMS; mesenchymal subtype neuroblastomas show addiction to the mevalonate pathway.	(116, 122–126)
	USP20					
<i>SQLE, DHCR24, LDM</i>	MARCHF6	OS (High-Risk)	Poor Prognosis	Elevated SQLE promotes chemoresistance; suppression reduces malignancy, enhances chemosensitivity; regulates ferroptosis and cuproptosis.	SQLE is a metabolic vulnerability in OS; inhibitor FR194738 shows synergistic effects with chemotherapy.	(134, 141–143)
Cholesterol efflux						
<i>ABCA1</i>	HUWE1, NEDD4-1, HECTD1,UBE3A, Cullin-3	OS, MB, GBM, NB, Astrocytoma, AD	Poor prognosis in OS and GBM Protective role in NB and AD	Reduced cholesterol efflux impairs anti-tumor immune responses and promotes drug resistance in osteosarcoma and glioblastoma while enhanced efflux reduces oxidative stress in neuroblastoma and Alzheimer's disease	Restoration of ABCA1 enhances chemo-immune sensitivity in osteosarcoma ABC inhibitors improve radiation sensitivity in medulloblastoma TP70 shows neuroprotective properties in Alzheimer's disease	(145–147, 150)
<i>ABCG1</i>	HUWE1, NEDD4-1, HECTD1	NB, ES, OS	Poor/ Protective Prognosis	Enhances cholesterol efflux and protects against oxidative damage in NB and astrocytoma. High expression in ES-CSCs and OST-CSCs confers drug resistance and promotes chemoresistance.	Targeting ABCG1 improves cholesterol efflux in neurodegenerative diseases and reduces chemoresistance in ES-CSCs and OST-CSCs.	(147–149)
<i>ABCA6</i>	Undefined	ES	Improve prognosis	Reduces intracellular cholesterol levels, inhibits IGF1R/AKT/MDM2 and IGF1R/AKT/mTOR signaling, increases chemosensitivity.	Acts as a tumor suppressor, enhancing statin efficacy and linking high expression to favorable outcomes in ES patients.	(156)
<i>ABCG8</i>	RNF5, HRD1	OS	poor prognosis	Identified as a hub gene associated with metastasis and survival; regulates osteosarcoma progression and metastatic potential.	Prognostic biomarker and therapeutic target; drugs targeting ABCG8 and co-regulated hub genes show potential for clinical application.	(154)

(Continued)

TABLE 1 Continued

Gene/ Protein	Ub/Dub Enzyme	Disease Relevance	Effect	Impact on lipid Metabolism/Other Functions	Notes	Reference
Cholesterol efflux						
<i>ABCB1</i>	Undefined	NB	poor prognosis	Increased expression linked to drug resistance in OS, NB, and GBM; reduces intracellular drug accumulation, impairing treatment efficacy.	Promotes chemoresistance in OS via Ras/ERK1/2/HIF-1 axis; lapatinib inhibits efflux in NB to enhance YM155 cytotoxicity; associated with methylation-driven drug resistance in GBM.	(157)
Cholesterol esterification						
<i>ACAT1</i>	USP19	NB, GBM	poor prognosis	Promotes cholesteryl ester formation in GBM and 24S-OHC-induced neurotoxicity in NB.	Excessive 24S-OHC esterification in NB causes neuronal death; ACAT1 activity drives cholesteryl ester biosynthesis in GBM.	(158)
<i>ACAT2</i>	gp78	Undefined	poor prognosis	ROS-induced ubiquitination of ACAT2 enhances its degradation, promoting cholesterol storage and metabolic adaptation.		(161)

Tumor types – OS, osteosarcoma; RMS, rhabdomyosarcoma; NB, neuroblastoma; MB, medulloblastoma; GC, gastric cancer; HCC, hepatocellular carcinoma; WT, wild type; GBM, glioblastoma; ES, Ewing sarcoma; AD, Alzheimer’s disease; Astrocytoma.
Enzymes/Proteins – ACLY, ATP citrate lyase; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase; SCD1, stearoyl-CoA desaturase 1; CD36, FABP4/5, fatty acid-binding protein 4/5; CPT1B/CPT2, carnitine palmitoyltransferase 1B/2; AUP1, PLIN2/5, Spartin, ATGL, FSP27.
Transcriptional Regulators – PPAR, peroxisome proliferator-activated receptor; SREBP1/2, sterol regulatory element-binding protein 1/2; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; YAP1 denotes Yes-associated protein 1.
Cholesterol Metabolism Components – IDOL, inducible degrader of the LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; ABCA1/ABCG1/ABCA6/ABCG8/ABCB1, ATP-binding cassette transporters; ACAT1/2, acyl-CoA cholesterol acyltransferase 1/2.
Ubiquitination/Deubiquitination Enzymes – CUL3-KLHL25, USP13, USP30, COP1, USP2a/USP2, AKR1B10, HRD1, UBE2G2, Itch, RNF213, Siah2, NEDD4-1, TRIM46, USP22, SCF-FBXW7, RNF20, RNF139, SIRT1, RNF145, TRC8, USP28, gp78, USP20, MARCHF6, HUWE1, NEDD4-1, HECTD1, UBE3A, Cullin-3, RNF5.
Others – XIST, miR-22, miR-195, miR-424, NBASP, CRABP-II, MAPK, MYCN, E2F1, SREBF1/2, ER, ACR, ATPB, TSP-1, RPARP-AS1, mTOR, NFκB, AMPK, HER2, PI3K/Akt, Rb, SERPINE2, DDIT4, 24SOHC, 7KC, ApoE, IGF-I, MDM2.

development in various diseases, including cancer (243–246). However, directly targeting E3 ligases is challenging due to their multiple substrates, which may lead to unintended effects. A more effective approach could be inhibiting downstream pathways or specific protein-protein interactions (PPIs) relevant to cancer.

Currently, drug development targeting the ubiquitination pathway focuses on three main strategies:

Inhibiting proteasome-mediated proteolysis to disrupt protein degradation and affect tumor cell homeostasis.

Targeted protein degradation (TPD) using techniques like PROTACs to selectively degrade oncogenic proteins.

Inhibiting key factors, particularly E3 ligases, to regulate tumor progression.

The ubiquitination pathway is highly complex and can have oncogenic or tumor-suppressive effects depending on the specific context (243, 244, 247, 248). Notably, both E3 ligases and deubiquitinating enzymes (DUBs) play key roles in lipid biosynthesis and degradation, processes closely linked to tumor progression. However, a comprehensive understanding of the clinical relevance of these lipid metabolism-related UPS components in pediatric tumors is still lacking.

The following sections summarize current strategies, preclinical findings, and future perspectives.

8.1 Proteasome inhibitors

Bortezomib—a proteasome inhibitor approved by the FDA for multiple myeloma and mantle cell lymphoma—has demonstrated promising preclinical activity in pediatric tumor models (249). In animal studies, bortezomib not only suppressed the growth of NB cells injected into mice (249) but also induced apoptosis in human medulloblastoma cells by inhibiting key signaling pathways, including AKT and NF- κ B (250). Based on both *in vitro* experiments and mouse xenograft models, Yang et al. proposed that bortezomib might be effective for treating pediatric MBs (250). Additionally, bortezomib effectively inhibits NB cell growth and angiogenesis (251). However, its limited ability to cross the blood-brain barrier may restrict its efficacy in treating central nervous system (CNS) tumors (252). In the clinical setting, besides bortezomib (252–254), other FDA-approved proteasome inhibitors such as carfilzomib (255, 256) and ixazomib (257, 258) are currently used to treat myeloma (248, 259, 260).

The effects of proteasome inhibitors on apoptosis are multifaceted and depend heavily on the cellular context. The UPS governs a variety of proteins involved in programmed cell death. For example, in HL60 leukemia cells, these inhibitors promote apoptosis (261), yet in sympathetic neurons, they might have a protective, anti-apoptotic effect (262). Research by Bobba et al. demonstrated that in 7-day-old rat cerebellar granule neurons, proteasome inhibition can prevent the release of cytochrome c during apoptosis, suggesting that normal proteasomal function is crucial for initiating cell death and that its inhibition may rescue

cells from dying (263). Complementary work by Butts et al. revealed a dual-phase response in 7- to 8-day-old rat cerebellar granule cells: brief inhibition boosts cell survival by upregulating factors like MEF2D, whereas extended inhibition elevates pro-death molecules such as c-JUN and Bim, ultimately causing toxicity (264). These results emphasize that the duration and concentration of proteasome inhibitor exposure are key factors in determining whether the response will be protective or deleterious, with malignant cells generally undergoing apoptosis in response (264–266).

8.2 Deubiquitination module

8.2.1 USP22

USP22 plays a pivotal role in tumor cell tolerance to chemotherapy by promoting the repair of DNA strand breaks (267). In osteosarcoma, silencing ALKBH5 increases m6A modifications that destabilize USP22 and RNF40, leading to the downregulation of genes involved in the cell cycle, DNA replication, and repair, whereas enhanced ALKBH5 activity drives USP22/RNF40-dependent oncogenic processes (268). Moreover, USP22 contributes to osteosarcoma progression by modulating glycolytic pathways that affect cell proliferation, apoptosis, migration, and invasion (269). In hepatocellular carcinoma, USP22 knockdown or inhibition via agents like SO₂ markedly increases the sensitivity of HCC LR and primary HCC cells to lenvatinib, while also diminishing Treg-mediated immunosuppression and enhancing CD8⁺ T cell infiltration, suggesting a promising role in cancer immunotherapy (270, 271). Similarly, in non-small cell lung cancer, USP22 inhibition improves gefitinib sensitivity and induces ferroptosis, offering a novel strategy to overcome chemoresistance (272).

Structure-based virtual screening has identified selective USP22 inhibitors such as rottlerin and morusin, which elevate histone monoubiquitination and lower Sirt1 and PD-L1 expression, thereby exhibiting significant antitumor activity *in vivo* (273). Additionally, overexpression of miR-200b-5p, a regulator of USP22, suppresses gastric cancer cell proliferation and migration by targeting the NF- κ B pathway, highlighting its potential as a new therapeutic target in gastric cancer (274).

8.2.2 USP13

Recent studies highlight USP13's critical role in tumor progression. In osteosarcoma, Spautin-1-mediated inhibition of USP13 degrades METTL3, destabilizing ATG5 mRNA and impairing autophagy and glycolysis, which ultimately suppresses tumor growth (275). In glioblastoma, both Spautin-1 treatment and USP10/USP13 knockdown reduce cell proliferation and migration (276). Notably, high USP13 expression in glioma stem cells stabilizes c-Myc, while its depletion enhances c-Myc ubiquitination and degradation, effectively inhibiting tumor growth; conversely, overexpression of FBXL14 promotes c-Myc degradation, leading to stem cell differentiation and further tumor suppression (277).

8.2.3 USP30

Biochemical and structural studies have identified selective inhibitors for USP30. For instance, the benzosulfonamide compound USP30inh shows high selectivity and potency for USP30 over 49 other deubiquitylating enzymes in a NB cell line (278). Similarly, the N-cyano pyrrolidine FT3967385 is a highly selective USP30 inhibitor that accelerates the PINK1-dependent generation of phospho-Ser65 ubiquitin in cells (279). In parallel, the long non-coding RNA USP30-AS1 has emerged as a valuable prognostic marker; high expression of USP30-AS1 is associated with poor survival in both primary and recurrent glioma patients, likely due to its repression of mitophagy and disruption of mitochondrial homeostasis (280). Moreover, USP30-AS1 is currently under investigation as a potential biomarker for osteosarcoma prognosis (281).

8.2.4 USP2

USP2 is a deubiquitinating enzyme that modulates key signaling pathways by regulating protein stability. It stabilizes β -catenin, thereby promoting epithelial-to-mesenchymal transition (EMT) and altering chemosensitivity (282). In sorafenib-resistant Huf7-SR cells, USP2 inhibition reduces cFILP expression, induces apoptosis, and enhances sorafenib sensitivity (283), whereas USP2 overexpression in renal carcinoma cells (A498 and CAKi-1) suppresses proliferation, migration, and invasion (284). Therapeutically, USP2 is an attractive target; ML364 is the most extensively studied USP2 inhibitor, with other inhibitors like Q29, STD1T, and LCAHA under investigation (285). In mantle cell lymphoma, ML364 facilitates the degradation of CCND1 and β -catenin, arresting the cell cycle and impeding tumor growth (286). Moreover, agents such as 6-thioguanine (6-TG) are clinically employed for AML and CML (287, 288). Additionally, USP2, recruited by VCP, enhances the stability of fatty acid synthase (FASN) by removing K48-linked ubiquitin chains, a process whose inhibition reverses pro-tumorigenic effects in osteosarcoma cells (289). Elevated USP2 expression is also associated with poor prognosis in medulloblastoma (290).

8.2.5 USP28

Additionally, inhibitors of USP25/28 (e.g., CT1113) effectively lower MYCN expression in NB, as confirmed in patient-derived xenograft models (291). USP28 is similarly overexpressed in glioblastoma, contributing to tumorigenicity through MYC regulation (292).

8.3 Ubiquitination module

8.3.1 ITCH

ITCH, a HECT-type E3 ubiquitin ligase, plays critical roles in regulating apoptosis, cell growth, and inflammation. Dysregulated ITCH expression can impair the apoptotic response to conventional chemotherapy (293–295). In NB, ITCH downregulates TAp73 levels, thereby contributing to chemoresistance (296). Desmethyl-clomipramine (DCMI), the active metabolite of clomipramine,

inhibits both ITCH autoubiquitylation and its ubiquitylation of p73, enhancing the cytotoxic effects of standard chemotherapeutics in various cancers (297, 298). In glioblastoma, gain-of-function TP53 mutations in astrocytes upregulate ITCH, leading to ferritin heavy chain (FTH) degradation and increased free iron levels (299). Conversely, in NB, ITCH cooperates with UBE4B to promote the polyubiquitination of Ku70 and c-FLIPL, thereby enhancing apoptosis (300). Additionally, nanoparticle-mediated silencing of ITCH sensitizes tumor cells to irradiation, offering a potential strategy for combined chemo- and radiotherapy, particularly in p53-deficient tumors (301).

8.3.2 NEDD4

I3C, a natural inhibitor derived from Brassicaceae, effectively targets NEDD4 and WWP1, and has been shown to inhibit NEDD4-1 activity (302). In temozolomide (TMZ)-resistant glioblastoma cells, NEDD4-1 contributes to redox imbalance by promoting PTEN degradation and activating the AKT/NRF2/HO-1 pathway, while I3C treatment suppresses tumorsphere formation, migration, and invasion in resistant cell lines (303).

8.3.3 FBXW7

FBXW7 is a key tumor suppressor whose dysregulation contributes to malignant progression across multiple cancer types. In Ewing sarcoma, for instance, KDM5B attenuates FBXW7 transcription, leading to CCNE1 accumulation and enhanced proliferation (304). Similarly, in glioblastoma, miR-92b targets FBXW7 and TRIP13 suppresses its transcription, thereby stabilizing oncogenic proteins like c-MYC and driving tumorigenesis (305, 306). In osteosarcoma, the lncRNA GCLnc1 facilitates tumor progression by stabilizing NONO and preventing FBXW7-mediated ubiquitination (307), whereas targeting miR-27a-3p can restore FBXW7 expression to sensitize Taxol-resistant cells (308). Exosomal miR-25-3p in glioblastoma also promotes proliferation and temozolomide resistance by targeting FBXW7 (309).

Our own findings further support the pivotal role of FBXW7. Agents such as IPA and N6-BA modulate GBM cell proliferation by regulating the turnover of key proteins—like SREBPs and Mcl1—thereby influencing malignant progression and chemoresistance (306). In MYC-driven medulloblastoma, inhibition of PLK1 stabilizes FBXW7, underscoring its tumor-suppressive function, while blocking ELK1-mediated transcription activates FBXW7 and suppresses MCL1, leading to cytotoxicity (310) (311). In the context of MYCN-amplified neuroblastoma, Aurora-A inhibitors (e.g., MLN8054 and MLN8237) disrupt the protective Aurora-A/N-Myc complex, promoting FBXW7-mediated degradation of N-Myc and thus inhibiting tumor growth (291).

Moreover, insights from yeast have provided a structural basis for targeting this pathway. SCF-I2, an inhibitor of the yeast F-box protein Cdc4 (the homolog of human FBXW7), binds to the Skp1-Cdc4 complex through an allosteric mechanism—a mode of action distinct from inhibitors like nutlin, which block protein-protein interactions directly (PDB: 3MKS) (312).

8.3.4 RNF5

High RNF5 expression in neuroblastoma and melanoma is associated with improved patient survival, suggesting a tumor-suppressive role. Activation of RNF5 with the agonist Analog-1 reduces cell viability by inhibiting F_1F_0 ATPase activity (313). This inhibition limits glutamine supply and elevates oxidative stress, together delaying tumor growth (313).

8.4 Future challenges and innovative directions

8.4.1 Mechanistic complexity

A deeper, context-specific understanding of the UPS's regulatory networks in pediatric tumors is essential. Future research must elucidate how distinct E3 ligases and deubiquitinases coordinate to regulate lipid metabolic pathways, thereby offering insight into novel, age-specific vulnerabilities.

8.4.2 Selective targeting and drug development

Given the complex, large-scale interactions involved in substrate-E3 binding, the development of small-molecule inhibitors that are both selective and minimally toxic remains a formidable challenge. Innovative strategies—such as leveraging high-throughput screening and structure-based drug design—are needed to identify agents that precisely modulate these interactions.

8.4.3 Resistance mechanisms and combination therapies

Tumor cells may develop resistance through adaptive metabolic rewiring and alterations in UPS regulation. Addressing this requires exploring combination therapies that integrate UPS inhibitors with established modalities (chemotherapy, radiotherapy, or immunotherapy) to preempt and overcome resistance.

8.4.4 Age-specific therapeutic strategies

The distinct metabolic and developmental characteristics of pediatric tumors call for tailored therapeutic approaches. Future clinical strategies must account for these differences, optimizing dosing and safety profiles to ensure effective, child-specific treatments.

8.4.5 Integration of immune modulation

As lipid metabolism also shapes the tumor immune microenvironment, future research should investigate how targeting the UPS could concurrently modulate immune responses. This dual approach might not only impede tumor growth but also enhance immunotherapeutic efficacy, paving the way for more comprehensive treatment regimens.

In summary, while the UPS-driven regulation of lipid metabolism presents a promising frontier in pediatric oncology, realizing its full therapeutic potential will require overcoming

significant mechanistic and translational challenges. Advancing our understanding in these areas promises to yield innovative, targeted strategies that can more effectively disrupt tumor metabolism and improve outcomes for pediatric cancer patients.

Author contributions

WZ: Writing – original draft, Writing – review & editing, Conceptualization, Investigation, Supervision, Visualization. YX: Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. YF: Investigation, Supervision, Visualization, Writing – review & editing. ML: Investigation, Writing – review & editing. DL: Conceptualization, Investigation, Supervision, Writing – review & editing. HG: Conceptualization, Investigation, Writing – review & editing. HL: Investigation, Supervision, Writing – review & editing. JH: Software, Supervision, Writing – review & editing. LM: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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