REVIEW

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Posttranslational control of lipogenesis in the tumor microenvironment

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Abstract

Metabolic reprogramming of cancer cells within the tumor microenvironment typically occurs in response to increased nutritional, translation and proliferative demands. Altered lipid metabolism is a marker of tumor progression that is frequently observed in aggressive tumors with poor prognosis. Underlying these abnormal metabolic behaviors are posttranslational modifications (PTMs) of lipid metabolism-related enzymes and other factors that can impact their activity and/or subcellular localization. This review focuses on the roles of these PTMs and specifically on how they permit the re-wiring of cancer lipid metabolism, particularly within the context of the tumor microenvironment.

Keywords: Posttranslational modification, Cancer, Tumor microenvironment, Lipid metabolism reprogramming

Introduction

Over the past few years, it has been increasingly appreciated that enhanced macromolecular biosynthesis, altered energy metabolism and maintenance of REDOX homeostasis are fundamental features of cancer [1]. The metabolic changes that accompany tumor cells have attracted particular attention, especially with regard to how such changes could be harnessed for therapeutic benefit [2]. Lipid metabolic reprogramming is one such recently appreciated marker of tumor malignancy that has attracted considerable attention [3].

Molecularly, lipids are highly heterogeneous and, as a group, are comprised of thousands of different types of triglycerides, phospholipids, sphingolipids, glycolipids, cholesterol and cholesterol esters [4]. Intracellular lipids levels reflect a dynamic balance among their highly variable rates of biosynthesis, uptake, output and esterification, with excesses being secreted as lipoproteins and/or stored in lipid droplets [5]. An example of lipid

metabolism reprogramming can occur in cancer-associated fibroblasts, where it promotes colorectal cancer cell metastasis in vitro and in vivo [6]. Similar, but deliberate reprogramming of lipid metabolism by tumor-associated T cell represents a new strategy for therapeutic immuno-metabolic modulation [7].

Cancer cells increase the uptake of preformed lipids from external sources in response to changes in environmental conditions. Meanwhile, these cells also activate de novo synthesis of fatty acids and transcriptional regulators of lipid biosynthesis are well-known positive targets of oncogenes and negative targets of tumor suppressor pathways [8–10]. Therefore, various lipid-metabolizing and lipid-modifying enzymes are potentially high-value candidates for therapeutic targeting in cancer [11]. Several recent reviews have summarized the multiple functions of lipid metabolism reprogramming in cancers, cancer-associated fibroblasts and other cells residing in the tumor microenvironment generally with an eye toward targeting these altered pathways as potential therapeutic options [12–14]. However, the precise function of the posttranslational modification of lipid metabolic enzyme has never reviewed in cancer and tumor microenvironment.

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Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 2 of 18

Overview of lipid metabolism

In mammalian cells, lipids can be made available both through de novo synthesis and the external uptake and transport of preformed lipids via lysosomal–peroxisomal–ER pathways [15]. Most such cells take up cholesterol from low-density lipoproteins (LDLs) through receptor-mediated endocytosis. Upon reaching the lysosome, cholesterol is transported via NPC1/2 to the ER and other downstream organelles, to meet specific structural and functional needs. Peroxisomes also obtain cholesterol from the lysosome through direct lysosomal–peroxisome membrane contact. Peroxisomes directly engage the ER via peroxisomal PI(4,5)P2 and ER-resident extended synaptotagmin-1, 2 and 3 (e-syts). Cholesterol is transferred from peroxisomes or liposomes containing PI (4,5) P2 to the ER in vitro, and the presence of peroxisomes promotes the transfer of cholesterol from lysosomes to the ER [16]. The uptake and direct use of preformed fatty acids and cholesterol in the manner described above, rather than synthesizing them de novo, represent a significant energy-saving strategy for cells whose environment is often depleted of the relevant anabolic nutrients or which are being utilized for other tumor-sustaining purposes.

Sources

Glucose, glutamine and acetate are the main source for de novo lipid synthesis, with the former being the most important dietary source. Acetate, derived directly from dietary sources, the gut microbiome, intracellular deacetylation reactions or directly from pyruvate, is converted into acetyl-CoA in the cytoplasm for lipid synthesis [17–19]. Glutamine can be utilized as an anaplerotic TCA cycle substrate and then, via reverse carboxylation, be converted to citrate, transported to the cytoplasm and then converted to acetyl-CoA via the action of ATP citrate lyase (ACLY) [17–19]. Ammonia, released from glutamine, activates the dissociation of glucose-regulated, N-glycosylated sterol regulatory element-binding proteins (SREBPs)-cleavage-activating protein (SCAP) from insulin-inducible gene protein (Insig), an endoplasmic reticulum-retention protein, leading to SREBP translocation and lipogenic gene expression to promote lipogenesis. SCAP is a critical sensor of glutamine, glucose and sterol levels to precisely control lipid synthesis [20].

De novo *lipid synthesis*

Key regulatory factors and enzymes of lipogenesis include SREBPs, acetyl coenzyme A carboxylase (ACC), ACLY and fatty acid synthase (FASN), all of which are up-regulated to varying degrees in human cancers [21]. SREBPs are a family of basic helix–loop–helix leucine zipper transcription factors that regulate de novo fatty acid and cholesterol synthesis as well as cholesterol uptake [22]. Of the three subtypes of SREBPs, SREBP1a regulates fatty acid and cholesterol synthesis and cholesterol uptake, SREBP1c mainly controls fatty acid synthesis and SREBP-2 overlaps functionally with SREBP1 to regulate cholesterol synthesis and uptake [22]. EGFR signaling increases glucose uptake to promote N-glycosylation of SCAP. Glycosylation stabilizes SCAP and reduces its association with Insig-1, allowing movement of SCAP/SREBP to the Golgi and consequent proteolytic activation of SREBP, leading to increasing fatty acid synthesis and tumor growth [23]. ACLY is a downstream target of SREBPs and, via its conversion of cytoplasmic citrate to acetyl-CoA, serves to generate the both the most lipid precursor and the substrate for acetylation reactions [24]. Acetyl-CoA synthases (ACSSs) convert acetate into acetyl-CoA, thus ensuring a proper balance between these two pools of critical substrates. Following the conversion of citrate and acetate to acetyl-CoA, ACC catalyzes the ATP-dependent carboxylation of acetyl-CoA to malonyl-CoA, which is used in the synthesis of fatty acids. FASN is a key and rate-limiting lipogenic enzyme that catalyzes the last step in de novo fatty acid biogenesis [25].

Lipid uptake, storage and secretion

CD36, also known as fatty acid translocase, transports fatty acids into cells and thus plays an important role in regulating the growth, metastasis and epithelial–mesenchymal transformation of many cancers [26]. Cholesterol can be synthesized de novo and also be obtained from intestinal absorption by internalizing it in the form of LDLs. LDLs bind to membrane-bound LDL receptors (LDLR), are internalized and then enter the lysosome where they release free cholesterol [27]. Sterol O-acyltransferase/acyl coenzyme A: cholesterol acyltransferase (SOAT1, SOAT2) attaches acyl-CoA to free cholesterol, generating CoA and cholesterol ester, and allowing the latter to be incorporated into lipid droplets [28]. ABCA1 is a plasma membrane transporter that promotes cholesterol export, thereby reducing intracellular levels [29, 30]. ABCA1 has particularly important roles in macrophages, where it promotes removal of excess cholesterol, thereby preventing their transformation into foam cells [31]. Transcription of ABCA1 is up-regulated by LXRs and RXR. In human macrophages, the LXRα-ABCA1 cholesterol efflux pathway is elevated by AMP-activated protein kinase (AMPK) [32].

Fatty acid oxidation

Activation of peroxisome proliferator-activated receptor alpha (PPARα) induces the transcription of many genes related to mitochondrial beta type fatty acid oxidation

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 3 of 18

(FAO) in the mitochondria and peroxisomes, thereby reducing lipid levels [33, 34]. Carnitine palmityl transferase I (CPT1) converts fatty acids to acyl carnitines, which are transported to the mitochondria where they are converted to fatty acyl-CoAs prior to entering the FAO cycle, thereby providing acetyl-CoA to drive the TCA cycle and produce ATP [35].

Lipid metabolism reprogramming in tumors

Lipid metabolism, specifically its synthesis, is significantly reprogrammed and up-regulated in cancer as is the uptake and storage of exogenous lipid (Fig. 1) [36–38]. It is generally believed that the metabolic characteristics of cancer cells are highly reliant upon lipid metabolism remodeling, including fatty acid regeneration and transport, lipid droplet formation and oxidation of these fatty acids to generate ATP [39].

Most tumors have abnormally active lipid metabolism, enabling them to synthesize, lengthen and desaturate fatty acids to support growth and rapid proliferation. Stearoyl-CoA desaturase (SCD)-dependent fatty acid desaturation is the most common way to desaturate fatty acids although some studies have shown that cancer cell

lines may activate other desaturation pathways. Hepatocellular carcinoma (HCC) cells and primary hepatocytes desaturate palmitic acid to sapienate, a rare fatty acid that supports membrane biosynthesis during proliferation [40]. The utilization of other metabolites such as glucose and glutamine for fatty acid synthesis is a common feature of tumors. For example, glucose can be converted to fatty acids and cholesterol through de novo lipid biosynthesis pathways, metabolites of glucose and lipid are dynamically transported and then converted to other molecules in specific regions of cells [41].

Sphingolipid metabolism is generally up-regulated in tumors and inflammatory cells, with changes in sphingolipid balance being particularly prominent in colon cancer. Examples of sphingosine metabolism-related enzymes that are abnormally activated include sphingosine kinases (spHKs) 1 and 2. These produce sphingosin-1-phosphate (S1P), which promotes the development and progression of esophageal, gastric and colon cancers [42, 43]. S1P levels are elevated in both plasma and the peripheral lymphocytes of some cancer patients and S1P can initiate and/or support many inflammatory reactions, including lymphocyte infiltration of tumors [44]. In
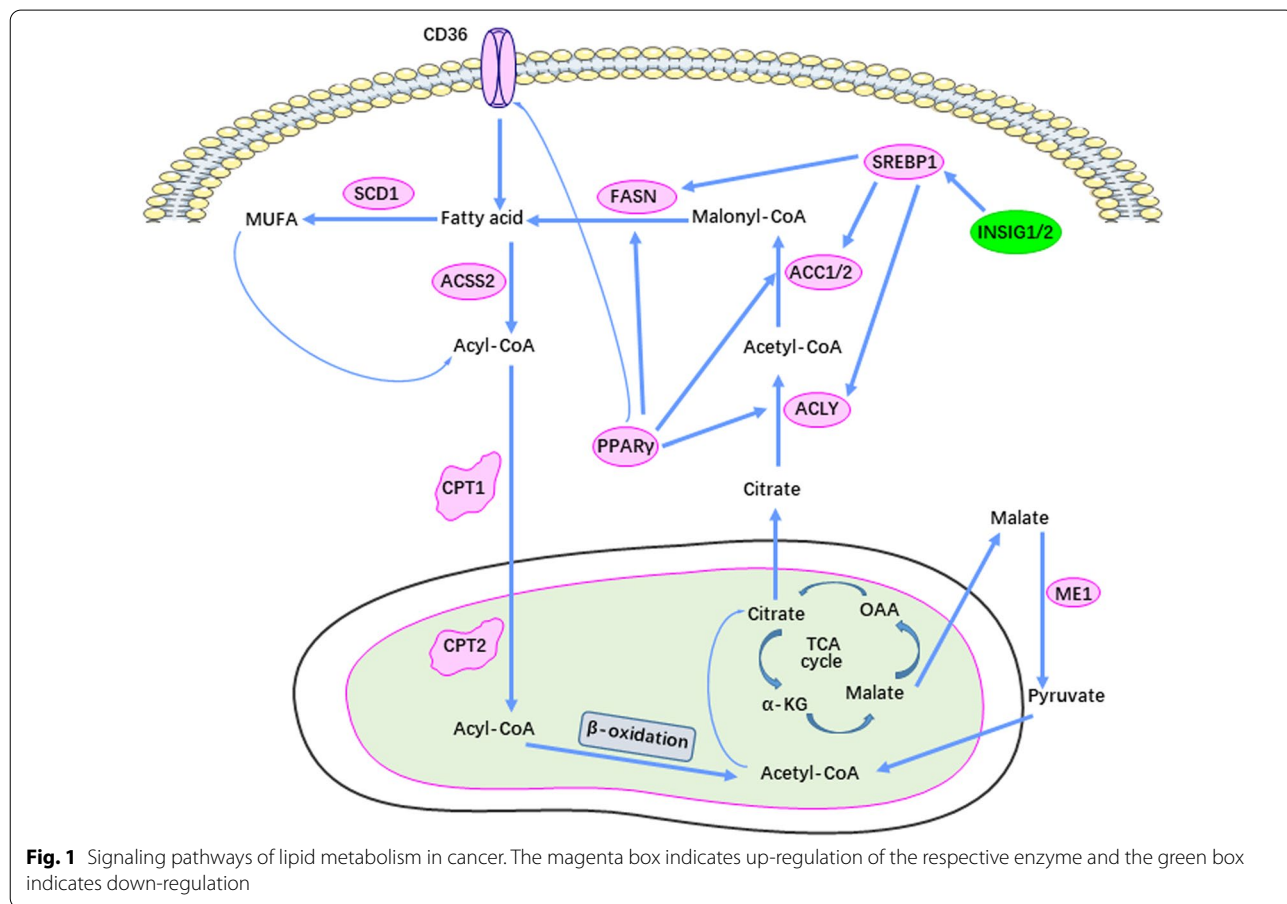

Fig. 1 Signaling pathways of lipid metabolism in cancer. The magenta box indicates up-regulation of the respective enzyme and the green box indicates down-regulation

Zhu *et al. Journal of Hematology & Oncology* (2022) 15:120

Page 4 of 18

doing so, S1P is thought to promote the growth and progression of cancer cells, including proliferation, survival, migration, invasion and inflammation [45, 46].

Lipid metabolism in the tumor microenvironment (TME)

While actual tumor cells have long been and continue to be the focus of many metabolic studies, those involving the tumor microenvironment (TME) and its non-transformed cellular populations are receiving increasing scrutiny [47]. Indeed, a full understanding of how and why tumors reorganize their metabolic landscapes requires an understanding of both cellular communities, along with an appreciation for how and why they communicate. Accumulation of the long-chain fatty acids in the TME enhances the differentiation of Th1 and Th17 cells and promotes dendritic cell maturation and T cell activation [48, 49]. Tumor-infiltrating CD8$^+$ T cells accumulate large amounts of fatty acids from the TME via through CD36. This can induce lipid peroxidation and ferroptosis, leading to a loss of this tumor-inhibitory CD8$^+$ population and allowing for unrestrained tumor growth. In support of this, inhibiting CD36 reduces lipid uptake by CD8$^+$ cells, increases their survival and allows them to better suppress tumor growth [50].

Cholesterol and cholesterol esters also regulate CD8$^+$ T cells proliferation and anti-tumor activity in many cancers [51]. OXPHOS and FAO can support Treg survival and differentiation, which is partially provided through fatty acids mediated by the AMPK and mTORC1 pathways [52]. Additional, M2-like macrophages and Treg cells also rely on FAO for both differentiation and activation during the course of tumorigenesis [53, 54]. Therefore, combined targeting of lipid metabolism and TME is a good strategy for tumor therapy [55].

Characteristics of the TME

There are many differences between the TME and the normal tissue microenvironment, notably the former's characteristically low oxygen tension, low pH and high pressure [56]. Tumor cells proliferate and migrate to distant locations because of their adaptive mechanisms to the low pH environment. Consequently, the TME's acidity favors both local spread and metastatic dissemination [43, 56]. However, the acidic TME itself appears to play only a minor role in fatty acid uptake by tumor cells.

In addition to the poorly vascularized nature of the TME and a reduced ability to dispose of CO_2, tumor cells contribute to TME acidity via several other cooperating and non-mutually-exclusive mechanisms. Among the most important of these is the tumor's reliance on anaerobic metabolism (the Warburg effect), which produces large amounts of lactic acid. Another mechanism is the tumor cell's reliance on a variety of membrane-localized ion exchange pumps, such as typical V-ATPases, that transport excess protons generated during metabolism to the outside of the cell in order to maintain the relative pH neutrality or alkalinity of the cytoplasm [57]. Finally, the low pH of the TME can form a positive feedback loop with some tumor cells, which promotes the secretion of TGF-β2. This stimulates PCK-Zeta-mediated CD36 translocation to promote fatty acid uptake [58], a much needed substrate under these conditions where both glucose and glutamine concentrations may be exceedingly low [59].

Fatty acids can be stored for extended periods of time in lipid droplets in the form of triglycerides through diacylglycerol O-acyltransferase 1 (DGAT1). This allows for their rapid mobilization and oxidation to generate ATP during times of energetic stress and/or when other nutrients are limiting [60]. Like the metabolic changes themselves, cancer cells' interactions with the TME are complex and dynamic. Unsupervised clustering of gene expression changes involving fatty acid metabolism has shown that fatty acid biosynthesis pathways are often significantly up-regulated in tumor samples compared with adjacent normal samples [61].

While seemingly disorganized, a tumor is actually a complex, metabolically well-organized and unique tissue. Indeed, in addition to providing nutrients and maintaining the extratumoral environment, the TME also contains stromal cells, immune cells, vasculature and extracellular matrix (ECM) components, all of which are dependent on lipid metabolism [62, 63]. How these non-tumor cell types affect lipid disposition in tumor cells and how lipids in turn affect these components of the TME are of significant importance.

Tumor-associated macrophages (TAMs)

TAMs regulate many processes associated with tumor progression, such as growth, drug resistance, metastasis, angiogenesis and immunosuppression. Tumors and the TME play important roles in polarizing macrophages, and intracellular lipid accumulation by these cells is key to this process [64]. In colorectal cancer, TAMs enhance lipid absorption through the CD36 cell surface receptor and derive energy in the form of ATP from the oxidation of fatty acids. Higher oxidative stress induced by fatty acid oxidation increases de-phosphorylation of STAT6-specific tyrosine phosphatase (SHP1) and Phos-tyr641-STAT6, which correlate with and presumably support the immunosuppressive and tumor-promoting functions of macrophages [65].

Zhu *et al. Journal of Hematology & Oncology* (2022) 15:120

Page 5 of 18

Cancer-associated fibroblasts (CAFs)

CAFs are mainly derived from the tumor microenvironment [66]. Inhibition of arachidonic lipoxygenase 15 (ALOX15) by miR-522 in CAFs derived from gastric cancers reduced lipid-derived ROS and decreased chemotherapeutic sensitivity [67]. Heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) was found to mediate the accumulation of miR-522 into CAF exosomes, and ubiquitin-specific protease 7 (USP7) stabilized hnRNPA1 by de-ubiquitination [67].

Mesenchymal stem cells (MSCs)

MSCs can affect drug resistance of gastric cancer cells in the TME. MSC co-culture improved drug resistance of gastric cancer (GC) cells. LncRNA histocompatibility leukocyte antigen complex P5 (HCP5) was induced in GC cells by MSC co-culture, contributing to drug resistance. Mechanistically, HCP5 sequestered miR-3619-5p and up-regulated PPARG coactivator 1 alpha (PPARGC1A), increasing transcription complex peroxisome proliferator-activated receptor (PPAR) coactivator 1α (PGC1α)/CEBPB and transcriptionally inducing carnitine CPT1, which prompted the fatty acid oxidation (FAO) in GC cells. These findings indicate that targeting HCP5 was a novel approach to enhancing the efficacy of chemotherapy in GC [68].

Tumor-infiltrating dendritic cells (TIDCs)

Gene knockout or pharmacological inhibition of PPARα effectively removes immunologically dysfunctional TIDCs induced by fatty acid-carrying tumor-derived exosomes (TDEs), and characterized by increasing intracellular lipid content and mitochondrial respiration. Mechanically, TDE-derived fatty acids activate PPARα, which leads to excessive lipid drop biogenesis and enhanced FAO, metabolic transition to mitochondrial oxidative phosphorylation and dendritic cells immune dysfunction [69].

T cells

T cells, which are effectors of anti-tumor immunity in certain solid tumors, compete with both tumor cells and non-malignant cellular components of the TME for limited nutrients. However, the TME in which lipids accumulate inhibits their ability to control tumor progression [70]. Pancreatic ductal adenocarcinoma (PDAC)-associated CD8^{+} T cells exhibit specific down-regulation of very long-chain acyl coenzyme A dehydrogenase (VLCAD), which leads to their accumulation of very long-chain fatty acids (VLCFAs) that mediate lipo-toxicity [71]. Tumor immunotherapy-activated CD8^{+} T cells mediate cell death mainly by inducing perforin–granzyme and the Fas–Fas ligand pathway [72].

Interferon-γ (IFN-γ) released from CD8^{+} T cells down-regulates the expression of SLC3A2 and SLC7A11, two subunits of the glutamate-cysteine antiporter system, thereby impairing the uptake of cysteine by tumor cells. IFN-γ also promotes lipid peroxidation and ferroptosis of tumor cells [73]. Effector memory CD4^{+} T cells respond differently to restricted supplies of glucose than other T cell subsets and maintain high levels of IFN-γ production in a malnourished environment [74].

Regulatory T cells (Treg cells) negatively regulate the immune system and play an important role in maintaining immune tolerance homeostasis. However, the accumulation of Tregs in the TME can hinder the anti-tumor immune response [75]. Generalized therapeutic targeting of Tregs leads to a systemic autoimmune responses and inflammation. Consequently, more specific and focused ways of specifically destroying Treg cells in tumors are needed for cancer immunotherapy. Enzymes and transcriptional factors of lipid metabolism including SREBPs, SCAP, FASN and FABP5 are potential targets in Treg cells whose inhibition might be associated with a more restricted anti-tumor response [76]. Gene enrichment analysis has shown lipid metabolism pathways to be enriched in Tregs from tumors compared to those from peripheral lymph nodes, with SREBP-target genes being particularly enriched. Tregs in tumor tissues maintain the functional status of TME-associated Tregs through the SREBP-dependent lipid synthesis pathway [77]. Specific inhibition of lipid synthesis and metabolic signaling of SREBPs in Tregs can release an effective anti-tumor immune response while sparing autoimmune toxicity [77, 78].

Immune checkpoint inhibitors (ICIs) have dramatically altered the prognosis of some advanced cancers, yet many patients still do not respond to treatment or relapse after relatively short responses or remissions [79]. If combined with ICIs, targeting tumor cell metabolism to regulate the immunosuppressive tumor microenvironment may achieve better effects. The loss of SCAP in tumor Tregs has been shown to increase the proportion of CD8^{+} T cells and Foxp3-CD4^{+} T cells in the TME, to inhibit tumor growth and to enhance anti-PD-1 immunotherapy. The proportion of Tregs and IFN-γ^{+} Tregs also decreased in tumor tissues but did not change in peripheral lymph nodes [80].

Fatty acid-binding proteins (FABPs) are a class of lipid chaperones that are required for intracellular lipid uptake and transport [81]. FABP5 inhibition in Tregs can cause mitochondrial DNA release and cGAS/STING-dependent type I IFN signaling, thereby increasing the production of regulatory cytokine IL-10 and promoting Treg inhibitory activity [82]. As a central metabolic regulator, CD36 is selectively up-regulated in intratumoral

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 6 of 18

Tregs. CD36 fine-tunes mitochondrial fitness through the PPAR-β signaling pathway, enabling Tregs to adapt to the lactate-rich and acidic TME. CD36 silencing in Tregs inhibited tumor growth, decreased tumor-associated Tregs and enhanced the anti-tumor activity of tumor-infiltrating lymphocytes without significantly impacting immune homeostasis [83]. Targeting sphingosine kinase 1 (SK1) significantly enhanced the ICI response in mouse models of melanoma, breast cancer and colon cancer. Mechanistically, SK1 silencing was shown to reduce the expression of various immunosuppressive factors in the TME, thereby limiting the infiltration of Tregs [84].

T cells shape the immune responses in cancer, autoimmune diseases and infection via CD4$^+$ T helper (Th) and CD8$^+$ T cells. These responses are in turn suppressed by Treg cells [85]. Tregs inhibit the secretion of IFN-γ by CD8$^+$ T cells, which can block the immunosuppressive (M2-like) TAMs-mediated activation of fatty acid synthesis [86]. Dysregulation of invariant natural killer T (INKT) cells in the tumor microenvironment hinders their anti-tumor effects. High levels of lactate in the TME reduced the anti-tumor immune response of INKT cells in the tumor [87]. PPARγ expression was inhibited in INKT cells, thereby reducing cholesterol (the substrate of IFN-γ) synthesis and IFN-γ production. After pharmacological activation of INKT cells, lipid biosynthesis was increased, and PPARγ and PLZF were synergistically promoted by enhancing the transcription of SREBF1. Hence, to promote lipid biosynthesis of INKT cells enhances the anti-tumor efficacy of immunotherapy [88].

Tumor-associated myeloid cells (TAMs)

Although TAMS maintain an immunosuppressive microenvironment within tumors [89], identifying the myeloid specific receptors that modulate this function and that myeloid-derived suppressor cells (MDSC) remains a challenge. Members of the leukocyte immunoglobulin-like receptor B (LILRB) family are negative regulators of myeloid cell activation. LILRB2 antagonizes SHP1/2 receptor-mediated activation and enhances pro-inflammatory responses. In the presence of M-CSF and IL-4, LILRB2 antagonism inhibits the activation of Akt and STAT6 [90]. LIlRB2 blockers effectively inhibited granulocyte MDSC and Treg infiltration and significantly promoted the anti-tumor effect of T cell immune checkpoint inhibitors in vivo [91].

Polynucleate granulocytic MDSCs (PMN-MDSCs) are pathologically activated neutrophils that affect the anti-tumor immune response, thereby altering the efficacy of some tumor therapies. Fatty acid transporter 2 (FATP2) expression is specifically up-regulated in mouse and human PMN-MDSCs and plays a role by regulating arachidonic acid accumulation and the downstream

synthesis of prostaglandin E2 (PGE2). Inhibition of FATP2 has recently been shown to reduce the growth of multiple tumor types, including lymphoma and lung, colorectal and pancreatic carcinomas [92].
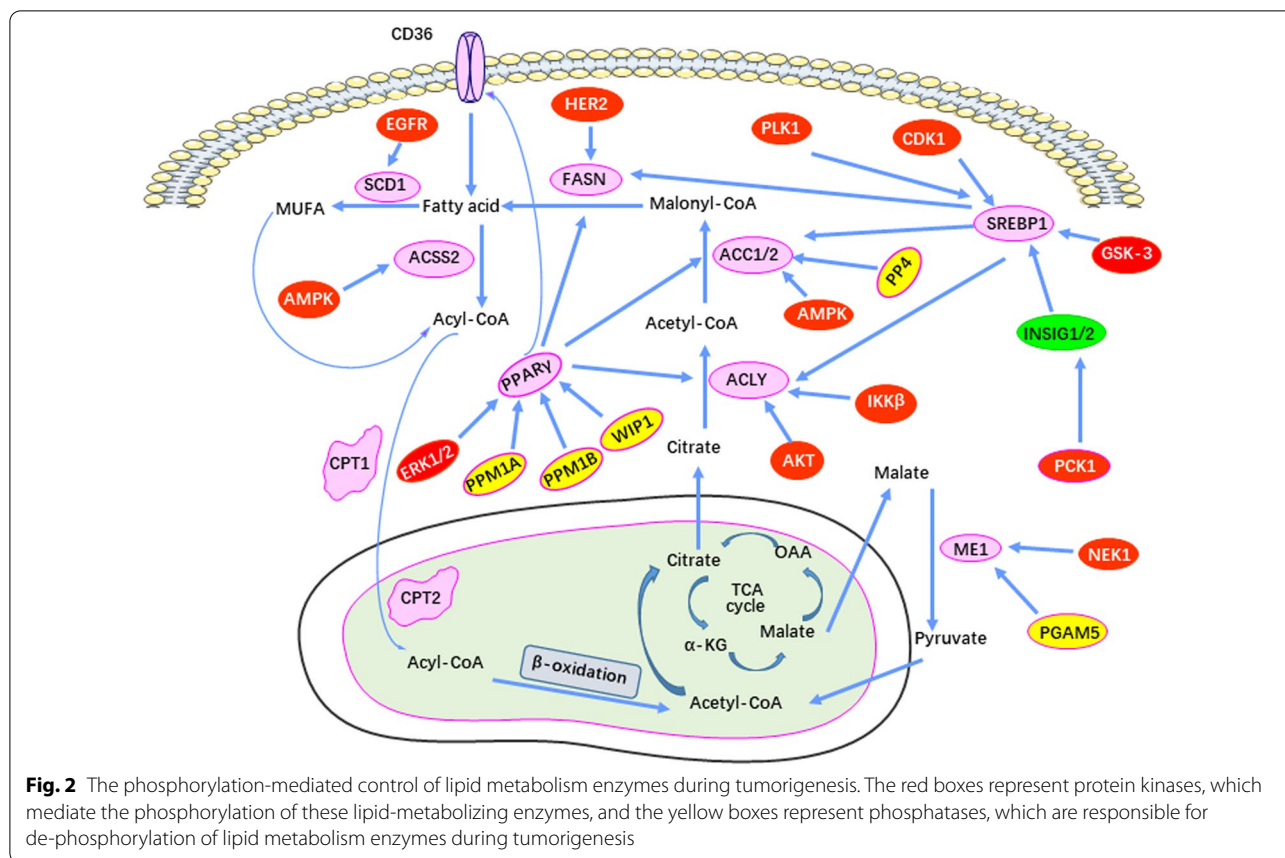
Single-target therapies rarely take into account the immense molecular, biochemical and metabolic heterogeneity of most tumors, let alone that of the TME. Moreover, the TME often hinders the sensitization of effector lymphocytes, which reduces their infiltrative ability along with that of other effector cells, leading to impaired anti-tumor activity and the generation of so-called immunologically "cold tumors" [93]. More global multi-target drug design should thus consider not only the tumor cells themselves, but also the TME and its contents so as to achieve better therapeutic effects and fewer toxicities. The challenge is further complicated by the marked differences in intratumoral TME contents of regions within close geographical proximity of one another and by the rapidity with which the TME environment can adapt to environmental alterations [94, 95].

Posttranslational modifications (PTMs) in cancer lipid metabolism

PTMs at specific amino acid residues of proteins are necessary for and mediate almost all dynamic processes within cellular signaling networks [96–100]. Protein PTMs include, but are not limited to, phosphorylation, acetylation, ubiquitination, SUMOylation, succinylation and methylation [99–104]. These alterations, which are often transient in nature, affect the structure, function, stability and localization of many proteins [96, 100, 105, 106]. PTMs may be differ considerably between tumors and their normal tissue counterparts and often serve as driving forces for tumorigenesis [107–110].

Phosphorylation and de-phosphorylation in cancer lipid metabolism

Phosphorylation is among the most widely studied PTMs involved in lipid metabolism reprogramming in tumors (Fig. 2). In response to aberrant oncogenic signaling, protein kinases may either activate or inhibit the activities of their target proteins while also affecting subcellular localization and the interaction with other proteins in ways that are not necessarily mutually exclusive. Collectively, these various PTMs serve to regulate cell growth, differentiation, apoptosis, metabolism and cell signal transduction in both normal or transformed cells [111–113]. The most frequently phosphorylated amino acids are threonine, serine and tyrosine [114]. Phosphatases, which reverse the PTMs mediated by their attendant kinases, normally function in tandem to maintain the proper balance between the phosphorylated and un-phosphorylated state. This balance is often altered by the aberrant

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 7 of 18

Fig. 2 The phosphorylation-mediated control of lipid metabolism enzymes during tumorigenesis. The red boxes represent protein kinases, which mediate the phosphorylation of these lipid-metabolizing enzymes, and the yellow boxes represent phosphatases, which are responsible for de-phosphorylation of lipid metabolism enzymes during tumorigenesis

signaling pathways that are activated in many tumors [115–119].

Protein kinases are one of the largest gene families [120]. Although tyrosine kinases are the most important class of kinases that regulate cell growth and differentiation, the serine/threonine kinases are actually more numerous [109]. Altered phosphorylation patterns can lead to serious consequences, such as the development of cancer. Indeed, the first identified function of an oncogene was the constitutively active tyrosine kinase activity of the transforming avian retroviral protein v-src [121]. Therefore, drugs targeting phosphorylation pathways, particularly kinases themselves, have long been a promising area for cancer therapy [122].

The AMPK complex senses intracellular ATP levels and plays an important role in maintaining cellular energy supplies. Under low-energy conditions, AMPK phosphorylates specific enzymes and growth control nodes, thereby increasing ATP production and reducing ATP consumption. As might be expected, functions that are stimulated by AMPK activation include the major energy-generating pathways of glycolysis, OXPHOS and FAO, whereas energy-consuming functions such as those centered around protein translation and proliferation are

inhibited. Collectively, the re-wiring of these pathways allows the energy-depleted cell to regain a normal energy balance and which point AMPK signaling is mitigated [123, 124].

AMPK depletes liver lipid content by reducing the activity of mTORC and inhibiting the expression of SREBP1c. In mice, AMPK also phosphorylates SREBP1c at Ser372, decreased SREBP1c nuclear localization and inhibition of the diet-induced hepatic steatosis of insulin resistance [125]. mTORC is an important medium for regulating cell metabolism and growth and promoting SREBP-dependent fatty acid synthesis [126, 127].

ACC is phosphorylated and inactivated by AMPK and many other kinases [128]. AMPK phosphorylates functionally homologous sites on ACC1 and ACC2 (Ser79 and Ser219, respectively) thereby inhibiting their activities. Phospho-ACC1 Ser79 thus serves as a general indicator of AMPK activity [129, 130]. TGF-activated kinase 1 (TAK1) mediates ACC1 inhibitory phosphorylation, which promotes an increase in cell acetylated coenzyme A, thereby promoting the acetylation and activation of Smad2 transcription factor and ultimately inducing epithelial–mesenchymal transformation and metastasis [131].

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 8 of 18

Phosphorylation and de-phosphorylation play important roles in de novo fatty acid biosynthesis. Mice maintained on high-fat diets contain high levels of USP30, which de-ubiquitinates and stabilizes ACLY and FASN. IKK-beta directly phosphorylates ACLY and promotes its interaction with USP30, thereby increasing USP30-mediated de-ubiquitination of ACLY and fatty acid biosynthesis [132].

Phosphorylation and de-phosphorylation reactions are also important for cholesterol synthesis. In the liver, the rate-limiting enzyme of the pathway, hydroxymethyl glutaryl coenzyme A reductase (HMGCR), has been shown to be significantly up-regulated after feeding via a mechanism involving its interaction with USP20. Elevated postprandial glucose and insulin levels stimulate mTORC1 to phosphorylate S132 and S134 in USP20. This licenses USP20's recruitment into the HMGCR complex and antagonizes its degradation, thereby stabilizing HMGCR and promoting cholesterol synthesis [133]. In contrast to this positive control, the phosphorylation of HMGCR at Ser872 can inhibit AMPK-mediated activation of HMGCR, which may be a potential mechanism of hypercholesterolemia and related cancers [134].

Phosphorylation/de-phosphorylation also plays an important role in FAO. In colon cancer cells, PKC Zeta interacts with SIRT6 following their exposure to palmitic acid. PKC Zeta phosphorylate T294 of SIRT6, which facilitates SIRT6's interaction with chromatin. T294 phosphorylation is required for SIRT6's localization to and deacetylation of chromatin, particularly around the promoters of genes such as acyl-CoA synthetase long-chain family member 1 (ACSL1), CPT1, carnitine–acyl-carnitine translocase (CACT) and HADHB and then induces the expression of these genes to mediate FAO [135]. In conclusion, the balance between phosphorylation and de-phosphorylation is normally responsible for maintaining proper levels of lipid metabolism. Reprogramming of several of these pathways is important for maintaining the growth of certain tumors and represents potential points of therapeutic intervention.

Acetylation and deacetylation in cancer lipid metabolism

Acetylation is a key posttranslational modification that coordinates metabolic flow with circadian rhythms, cell cycle and energy production. Lysine acetyltransferases (KATS) and lysine deacetylases (KDACs) are responsible for regulating reversible protein acetylation [136].

Acetylation and deacetylation affect de novo lipid synthesis (Fig. 3). For example, lipin 1 is a phospholipid acid phosphorylase that plays an important role in lipid metabolism. In growth factor-deficient mammalian cells, GSK-3 kinase activates the acetyltransferase TIP60 (TIP60-Ser86) and catalyzes the acetylation of ULK1 (Atg1), thereby activating autophagy [137]. TIP60's direct acetylation of lipin 1 promotes the latter's translocation to the endoplasmic reticulum, thereby promoting triglyceride synthesis. SIRT1 deacetylates lipin 1 and inhibits the synthesis of triglycerides [138]. ACAT1-mediated acetylation of dihydroxyacetone phosphate acyltransferase (GNPAT) plays a key role in FASN stabilization to increase lipid synthesis in hepatocellular carcinoma. ACAT1 is up-regulated by excess palmitic acid and acetylates GNPAT K128, which in turn inhibits TRIM21-mediated ubiquitination and degradation of GNPAT. In contrast, SIRT4 antagonizes the function of ACAT1 by antagonizing deacetylation of GNPAT. Acetylated GNPAT competes with FASN to bind TRIM21, which inhibits TRIM21-mediated FASN degradation to enhance lipid synthesis [139]. DHA (Docosahexaenoic acid), an omega-3 polyunsaturated fatty acid, down-regulates SREBP1. DHA induces SIRT1 expression in CCD-841CON human colon epithelial cells. SIRT1 deacetylates SREBP1 to inhibit intracellular signal transduction mediated by SREBP1, including downstream lipid synthesis pathways and COX_2-involved angiogenesis [140].

Acetylation and deacetylation can affect FAO. Low levels of palmitate activate the CDK1-SITR3-CPT2 cascade in liver. SIRT3 catalyzes the deacetylation and dimerization of CPT2, promoting mitochondrial FAO and protecting the liver from lipid toxicity [141]. In hepatic stellate cells (HSC), SIRT1 can deacetylate PPAR-γ to prevent activation of hepatic stellate cells (HSC), thus protecting the liver from fibrosis and sclerosis [142].

Ubiquitylation and de-ubiquitination in cancer lipid metabolism

Ubiquitylation is an important PTM that plays a crucial role in regulating the levels and activities of numerous metabolic enzymes and ensures proper control over intracellular homeostasis. The regulation of ubiquitination itself is multifaceted, not only at the transcriptional and posttranslational levels (phosphorylation, acetylation, methylation, etc.), but also at the translational level [143].

Ubiquitylation is an ATP-dependent cascade that links ubiquitin oligomers of variable length to proteins. Ubiquitin (Ub) is a highly conserved regulatory protein containing 76 amino acids whose covalent attachment to its targets occurs via a cascade of step-wise enzymatic reactions that mediate Ub activation (E1), Ub binding (E2) and Ub linking (E3). Ub's sites of attachment include seven of its lysine residues (K6, K11, K27, K29, K33, K48 and K63). Different Ub chain lengths and different sites of attachment (both on Ub and its targets) lead to different fates of its substrates. K48 polyubiquitination is one of the most widely studied types and is primarily used
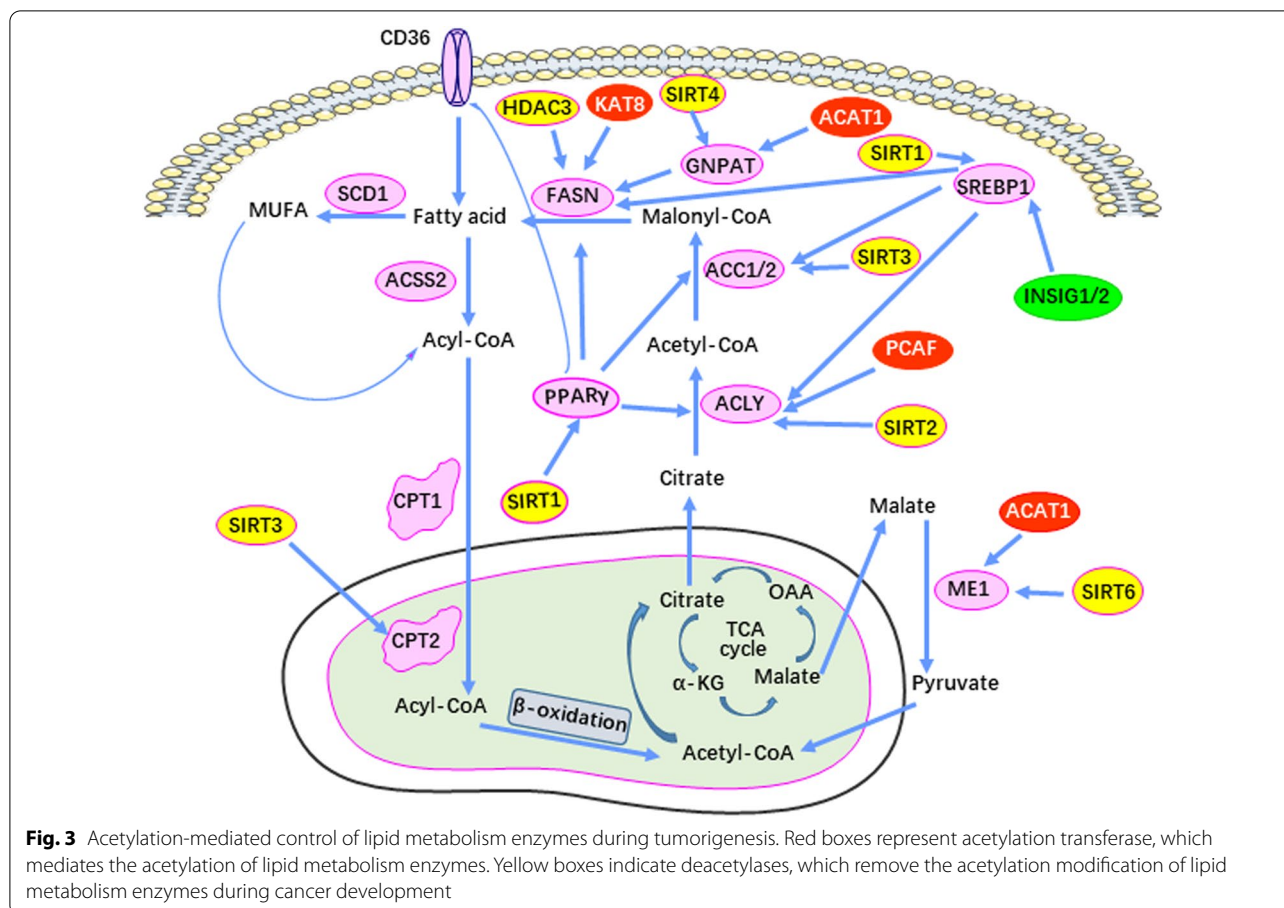
Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 9 of 18

Fig. 3 Acetylation-mediated control of lipid metabolism enzymes during tumorigenesis. Red boxes represent acetylation transferase, which mediates the acetylation of lipid metabolism enzymes. Yellow boxes indicate deacetylases, which remove the acetylation modification of lipid metabolism enzymes during cancer development

to label proteins that are recognized and degraded by the 26S proteasome [132, 133]. The E3 reaction involves a large number of Ub ligases whose sites of targeting on their protein substrates are associated with different outcomes. Collectively, the lysine substrate attachment sites on Ub, the site(s) of its attachment on its substrates and the number of Ub molecules at these sites exert highly sensitive and specific control over the fate and function of the modified substrate. Abnormalities in each of these regulatory process may lead to serious human diseases, including cancer (Fig. 4) [144].
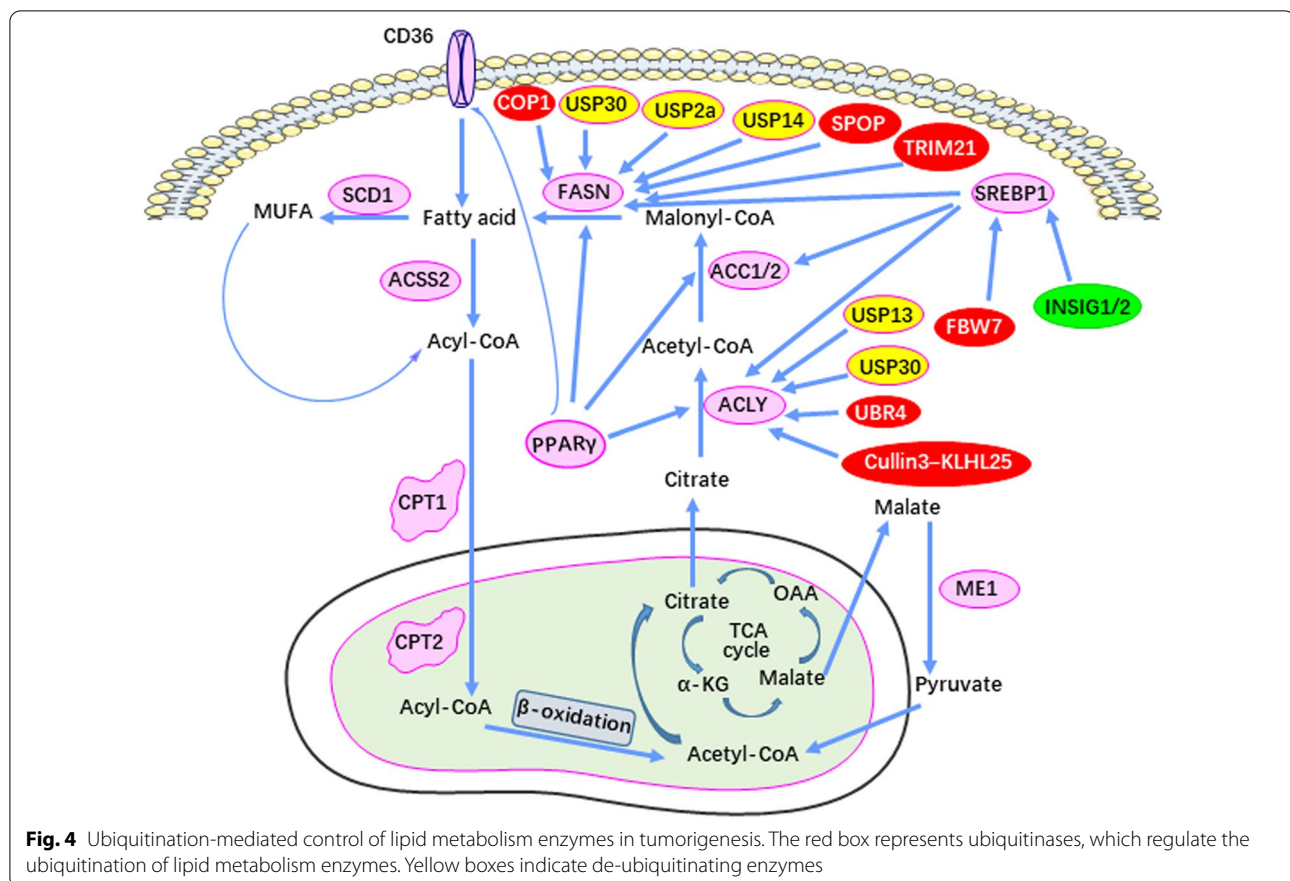
In contrast to the ubiquitinating enzymes, those involved in de-ubiquitination (DUBs) catalyze the removal of Ub and are relatively few in number. However, they also exhibit targeted specificity and have a decisive effect on cellular functions such as cell cycle progression, apoptosis, receptor regulation and gene transcription [145, 146].

Ubiquitylation/de-ubiquitination also affects lipid synthesis. For example, the de-ubiquitination enzyme USP30 is highly expressed in HCC. IKK-beta phosphorylates USP30 S210/S364. This stabilizes USP30, which in turn de-ubiquitinates and stabilizes ACLY and FASN to

increase lipid synthesis [132]. As an adaptor, TRB3 binds the E3 ubiquitin ligase COP1 to ACC1/2 and thereby mediates the proteolysis of ACC1/2 in a UB-dependent manner while inhibiting fatty acid synthesis and stimulating lipolysis [147]. COP1 also ubiquitinates FASN and uses as an adapter protein SH2-tyrosine phosphatase (SHP2) whose SH2 domain is critical for the interaction [148]. Activated Akt inhibits FASN ubiquitination through the de-ubiquitination enzyme USP2A, thereby promoting lipid synthesis in HCC [149].

Ubiquitylation and de-ubiquitination also affect cholesterol metabolism. High sterol concentrations can induce HMGCR degradation. Ring finger protein 145 (RNF145) is a UB ligase that interacts with the ER protein Insig-1/2. RNF145 and gp78, each acting as sterol responsive ER-resident E3 ligases, independently coordinate the ubiquitination-mediated degradation of HMGCR. The UBE2G2-dependent E3 ligase HRD1 partially regulates the stability of HMGCR. UBXD, also an E3 ligase, can mediate steroid-induced ubiquitination and degradation of HMGCR [150–152].

Cholesterol synthesis is very sensitive to oxygen levels. In response to hypoxia, hypoxia-inducible factor 1

Zhu *et al. Journal of Hematology & Oncology* (2022) 15:120

Page 10 of 18

Fig. 4 Ubiquitination-mediated control of lipid metabolism enzymes in tumorigenesis. The red box represents ubiquitinases, which regulate the ubiquitination of lipid metabolism enzymes. Yellow boxes indicate de-ubiquitinating enzymes

alpha (HIF-1α) activates INSIG-2 transcription, leading to the accumulation of INSIG-2 protein, which binds to HMGCR and accelerates its ubiquitination and degradation, thus contributing to proliferative inhibition [153]. Abnormal cholesterol metabolism in multidrug-resistant cancer cells leads to decreased E3 ligase Trc8, up-regulation of HMGCR and enhanced cholesterol synthesis [154].

Squalene mono-oxygenase is an important control point in the pathway of cholesterol synthesis and is regulated at the posttranslational level by accelerated cholesterol-dependent ubiquitination, thereby leading to proteasomal degradation and squalene accumulation [155]. The E3 UB ligase DOA10/TEB4 promotes the degradation of squalene mono-oxygenase [156]. LXR transcriptionally induces the IDOL E3 Ub ligase, and IDOL ubiquitinates the cytoplasmic domain of the low-density lipoprotein receptor (LDLR), thus targeting its degradation and inhibiting the LDL uptake [157].

SUMOylation and de-SUMOylation in cancer lipid metabolism

Many studies have shown that ubiquitination/de-ubiquitination imbalance is an important cause of tumorigenesis.

Small ubiquitin-like modifier (SUMO) is similar to ubiquitin in its three-dimensional structure, despite differing in its amino acid sequence and surface charge distribution. There are four types of SUMO subtypes: SUMO1-4, with SUMO2 and 3 being the most closely related. With the exception of SUMO4, they are widely distributed in human tissues [158].

Unlike ubiquitination, which tends to promote proteolysis, SUMOylation more commonly reduces the degradation of modified proteins by regulating protein–protein interactions as well as subcellular localization and function. By analogy to ubiquitination reactions, the reversible binding of SUMO molecules to their substrates is catalyzed by a cascade of enzymes (E1 activators, E2-binding enzymes, E3 ligases and SENPs) that mediate maturation, activation, conjugation, ligation and de-SUMOylation [159].

SUMOylation and de-SUMOylation significantly impact the transcriptional regulation of lipid metabolism. In HCC, up-regulation of SUMO1 induces ubiquitin-like modification of K751 of large tumor suppressor (LATS1), resulting in instability of its phospho-T1079 site and attenuation of LATS1 kinase activity. SUMO1 up-regulation also SUMOylates CPAP K921 and K975, which are

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 11 of 18

necessary for CPAP to act as a coactivator of NF-κB [160, 161]. SUMO2 up-regulation catalyzes ubiquitination of liver kinase B1 (LKB1) K178 and impedes nuclear-to-cytoplasmic transport [162].

SUMO-specific protease I (SENP1) enhances HIF-1α stability and transcriptional activity in hypoxic HCC cells by de-SUMOylating the K391 or K477 residues of HIF-1α. On the other hand, without affecting HIF-1α protein levels, CBX4 promotes HIF-1α-K391/K477 SUMOylation and enhances HIF-1α transcriptional activity to promote lipid metabolism and angiogenesis in tumors [163, 164]. SUMO1 up-regulation also induces a variety of other effects, including the disintegration of TBL1-TBLR1 from the NCOR complex and increased transcriptional activity [165], as well as increased nuclear transport of KLF5 [166].

Methylation and de-methylation in cancer lipid metabolism

Arginine methylation affects many biological processes in mammalian cells, including transcription, metabolism, signal transduction, mRNA translation, receptor transport and protein stability [167]. The protein arginine methyltransferases (PRMTs) are a family of nine enzymes that regulate the stability, cellular localization and activity of substrates that include histones, transcription factors and other proteins [168]. PRMTs transfer one or two methyl groups from S-adenosylmethionine (SAM) to the guanidine nitrogen atom of arginine to form methylarginine and the metabolite S-adenosylhomocysteine (SAH) [169].

Methylation/de-methylation reactions regulate lipid metabolism in many tumor types. For example, PRMT5-mediated symmetric di-methylation of SREBP1a at R321 is associated with HCC progression and poor prognosis. This methylation excludes the phosphorylation of S430 of SREBP1a by GSK-3β resulting in the dissociation of SREBP1a from FBXW7 and its inability to be ubiquitinylated and proteasomally degraded. In this manner, the now stabilized SREBP1a can participate in de novo lipid synthesis, thus contributing to tumor growth and proliferation [170].

Cross talk between different posttranslational modifications in cancer lipid metabolism

Although cross talk among different PTMs is common, it has been poorly studied. The interactions among PTMs are complex and likely reflect variations in charge, steric hindrance, the resulting conformational changes mediated by each PTM and the different environments in which they reside. Interactions between the known PTMs that affect cancer lipid metabolism-related enzymes are summarized in Fig. 5.
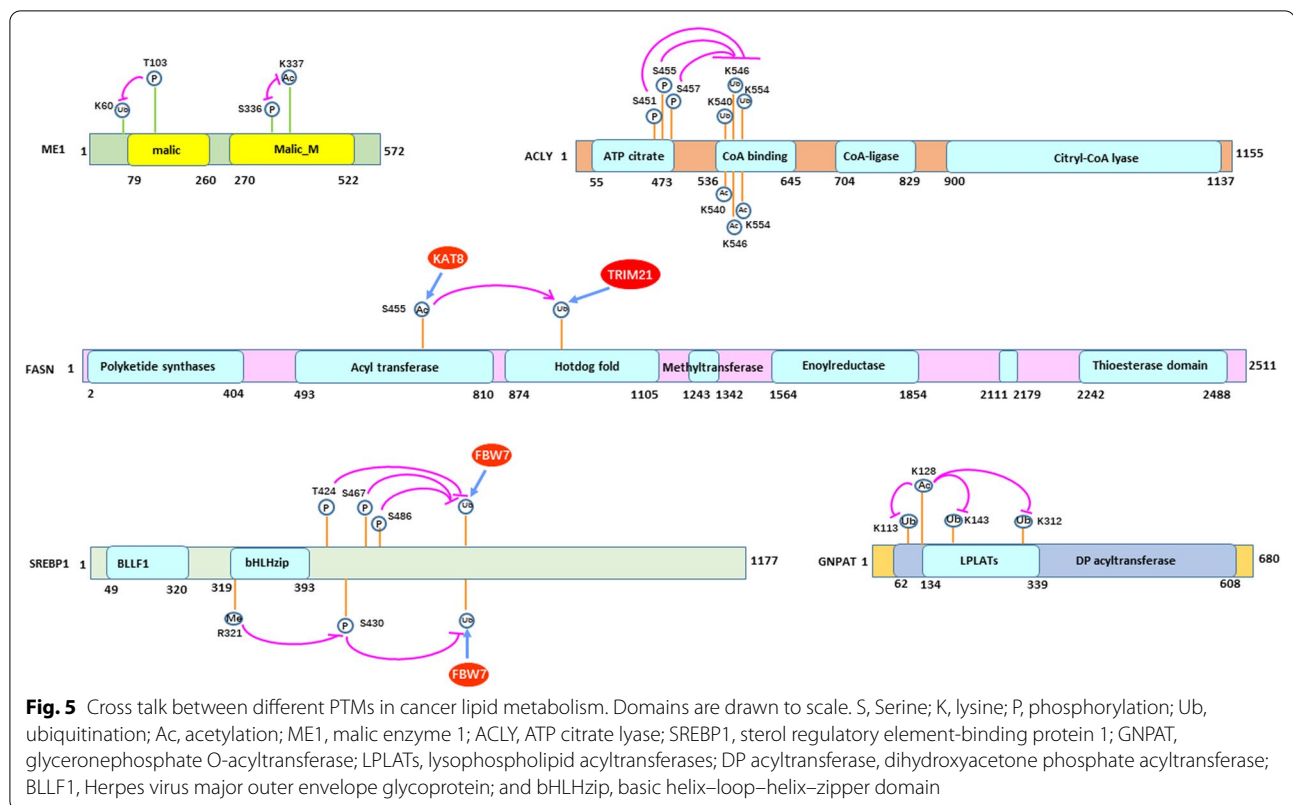
Malic enzyme 1 (ME1) generates NADPH for fatty acid biosynthesis via the reversible oxidative decarboxylation of malate and the production of pyruvate. S336 phosphorylation and K337 acetylation are mutually exclusive PTMs at adjacent sites in ME1. NEK1 kinase-mediated phosphorylation of S336 antagonizes acetylation at K337. In contrast, de-phosphorylation of this site by the PGAM phosphatase increases ACAT1-mediated acetylation of K337. This event licenses ME1 dimerization and activation, thus enhancing NADPH generation, lipogenesis and the promotion of colorectal tumorigenesis. In contrast, SIRT6-mediated deacetylation of K337 antagonizes ACAT1 by restoring inhibitory S336 phosphorylation and inhibiting ME1 homo-dimerization [171].

Competition between acetylation and ubiquitination for the same lysine residues in ACLY regulates fatty acid synthesis and cell growth responses to glucose [172]. In HCC, and in the presence of glucose, the P300-related factor acetyltransferase acetylates the 540, 546 and 554 (3 K) lysine residues of ACLY by blocking ubiquitination and degradation thereby stabilizing the protein and promoting lipid biosynthesis. In contrast, Sirtuin2 deacetylates and de-stabilizes ACLY by allowing for ubiquitination of the same sites and proteasome-mediated degradation. Importantly, 3 K acetylation of ACLY is increased in human lung cancer [173].

In HCC, IKK-β can phosphorylate S451, S455 and S457 of ACLY, which mediates an association between ACLY and USP30 and promotes the latter's de-ubiquitination at K540, K546 and K554, its stabilization and a resulting increase in fatty acid synthesis [132]. Also in HCC, ACAT1 mediates GNPAT acetylation at K128, which inhibits TRIM21-mediated ubiquitination of GNPAT at K113, K146 and K312 thereby stabilizing GNPAT by excluding the ubiquitylation of these resides and slowing proteasomal degradation [139].

PRMT5 binds SREBP1a and catalyzes its symmetric di-methylation of R321. This prevents the GSK-3β mediated phosphorylation of SREBP1a S430, resulting in the dissociation of SREBP1a from the F-Box protein FBXW7 and the failure to degrade SREBP1a via the proteasome [170].

The Polo-like kinase Plk1 mediates the phosphorylation of T424, S467 and S486 of nuclear SREBP1, which abrogates its degradation by disrupting its association with FBXW7 in cervical cancer [174]. There FBXW7 also interacts with nuclear SREBP1a and enhances its ubiquitination and degradation in a manner that is also dependent on the GSK-3β-mediated phosphorylation of T426 and S430 [175]. Finally, in colorectal cancer, KAT8-mediated acetylation of FASN promotes its association with the E3 ubiquitin ligase TRIM21, which enhances its proteasome-mediated degradation [176].

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 12 of 18

Fig. 5 Cross talk between different PTMs in cancer lipid metabolism. Domains are drawn to scale. S, Serine; K, lysine; P, phosphorylation; Ub, ubiquitination; Ac, acetylation; ME1, malic enzyme 1; ACLY, ATP citrate lyase; SREBP1, sterol regulatory element-binding protein 1; GNPAT, glyceronephosphate O-acyltransferase; LPLATs, lysophospholipid acyltransferases; DP acyltransferase, dihydroxyacetone phosphate acyltransferase; BLLF1, Herpes virus major outer envelope glycoprotein; and bHLHzip, basic helix–loop–helix–zipper domain

Targeting reprogramed lipid metabolism and PTMs of cancer lipid metabolism enzymes for cancer treatment

A variety of approaches have been proposed for capitalizing on the differences in lipid metabolism between normal and malignant cells for the purpose of achieving therapeutic benefit. Many inhibitors of fatty acid metabolic enzymes have been designed toward this goal. Targeting FASN effective inhibits the growth of most cancers including liver, colorectal and pancreatic cancers, largely by inducing tumor cell death [177]. FASN inhibitors that repress tumor growth both in vitro and in mouse models include cerulenin, orlistat, C57, C93, IPI-9119 and TVB-2640 [178, 179]. We recently showed that combining the ACLY inhibitor ETC1002 and anti-PD-L1 antibody therapy significantly inhibited the incidence and growth of DEN-induced HCC [132]. Similarly, the SOAT1 inhibitor avasimibe has effectively inhibited the growth of high-cholesterol/high-fat diet (HCHFD)-induced HCC and colorectal cancer by inhibiting cholesterol esterification [180, 181]. Both the HMGCR inhibitor simvastatin and the squalene epoxidase inhibitor terbinafine repress the induction of HCC by blocking de novo cholesterol synthesis [182, 183]. The ACC1 inhibitors soraphen A, 5-tetradecyl-oxy-2-furoic acid and ND-646 block the growth of many cancer cell types by inhibiting de novo

fatty acid synthesis and enhancing FAO [184, 185]. Sulfo-N-succinimidyl oleate, a CD36 inhibitor, reduced cancer cell migration and growth by repressing fatty acid uptake [186]. The SREBPs inhibitors fatostatin and betulin decreased invasion and progression of many cancer types by reducing lipogenesis [187, 188]. Active ongoing or completed clinical trials on targeted agents for the cancer lipogenesis enzymes/pathways are summarized (Table 1). These studies suggest that targeting fatty acid metabolism showed potential anti-tumor effects in many cancer types.

To this end, targeting the enzymes responsible for the PTMs of cancer lipid metabolism enzymes has thus rightfully attracted much attention (Table 2). In mammals, cholesterol biosynthesis increases after feeding but is inhibited during fasting. In response to feeding, USP20 stabilizes HMGCR. The small molecule GSK2643943A targets USP20 and de-stabilizes HMGCR, without affecting the total of phosphorylated levels of USP20. As a result, GSK2643943A significantly decreases diet-induced weight gain and serum and liver lipid levels while improving insulin sensitivity and increasing energy consumption [133]. Non-alcoholic steatohepatitis (NASH) and cirrhosis are predisposing factors for HCC development [189]. Thus, the prevention or reversal of hepatic inflammation and the ensuing hepatic fibrosis should

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 13 of 18

Table 1 Active ongoing or completed clinical trials on targeted agents for the cancer lipogenesis enzymes/pathways

Drugs	Targeted protein	Cancer type	Function	ClinicalTrial. gov identifier	Status
TVB-2640	FASN	Advanced tumors	To inhibit FASN	NCT02223247	Completed
TVB-2640	FASN	Breast and colon cancer	To inhibit FASN	NCT03179904	Recruiting
CLA	FASN	Breast cancer	To inhibit FASN	NCT00908791	Completed
Statins	HMGCR	Solid tumors	To inhibit HMGCR	NCT02285738	Completed
Metformin	AMPK	Acute lymphoblastic leukemia	To activate AMPK	NCT03118128	Recruiting
Metformin	AMPK	Breast, endometrial, Prostate cancer	To activate AMPK	NCT01620593	Completed
Lapatinib	AMPK	Metastatic breast cancer	To activate AMPK	NCT01477060	Terminated
RGX-104	LXRs	Lung and endometrial cancer	To activate LXRs	NCT02922764	Recruiting
NRX194204	RXR	Non-small cell lung cancer	agonist of RXR	NCT01540071	Active
Bexarotene	RXR	Cutaneous T-cell lymphoma	To activate RXR	NCT01007448	recruiting
Pioglitazone	PPARa	Bladder cancer	agonist of PPARa	NCT01637935	Completed
TPST-1120	PPARa	Hepatocellular carcinoma	antagonist of PPARα	NCT03829436	Active

Table 2 Targeting posttranslational modification of cancer lipid metabolism enzymes for cancer treatment

Protein	Targeting PTMs	Drugs	Function	References
HMGCR	De-ubiquitination	GSK2643943A	To de-stabilize HMGCR	[133]
FXR	SUMOylation	SP/GA	To enhance FXR protein levels	[190–192]
ME1	Phosphorylation	Ulixertinib	To repress ME1 de-ubiquitination and promote it degradation	[193]
GNPAT	Acetylation	AH	Mediated GNPAT ubiquitination and degradation	[139]
SREBP1	Phosphorylation	Sorafenib	Reduction SREBP1 protein levels	[194]
SREBP1	Phosphorylation	Silibinin	To block SREBP1 nuclear translocation	[195]

reduce the incidence of this deadly neoplasm. The FXR-Plin1 cascade could thus be an important target for drug discovery and treatment in liver fibrosis. However, activated HSCs show only a limited response to some FXR agonists due to enhanced FXR SUMOylation, possibly due to enhanced FXR SUMOylation and decreased FXR protein levels in the process of liver fibrosis. SUMOylation of FXR in HSCs is mainly mediated by SUMO1 at K122, K275 and E277, which could be a potential target for inhibition of FXR degradation. In various models of NASH and hepatic fibrosis, the combination of SUMOylation inhibitors such as SP (a natural product aminocyclitol produced by *Streptomyces spectabilis*) and GA (anacardic acid isolated from the seed coat of *Ginkgo biloba*) together with OCA (obeticholic acid, a potent FXR agonist) inhibited HSC activation and fibrogenesis. Such combination of FXR agonists and SUMOylation inhibitors represents potentially promising strategies for reversing or preventing hepatic fibrosis in response to a variety of etiologies, including toxins, cholestasis and NASH [190–192]. Ulixertinib reduced ME1 T103 phosphorylation and promoted ME1 protein degradation, which dramatically inhibited spontaneous and chemically induced colorectal cancer through decreasing lipid

synthesis and NADPH production [193]. The ACAT1 inhibitor AH also significantly induced GNPAT ubiquitination and degradation through targeting its acetylation, which markedly inhibited hepatocarcinogenesis in mice [139]. Sorafenib is a modestly effective multi-kinase inhibitor that has been approved for the treatment of advanced HCC. Sorafenib-induced tumor cell killing is mediated by the AMPK-mTOR-SREBP1 signaling pathway [172]. Mono-unsaturated fatty acids, such as oleic acid, are significantly reduced following sorafenib treatment. In HCC cells, sorafenib also inhibits ATP production, leading to phosphorylation-mediated AMPK activation, a reduction of SREBP1 levels and phosphorylation of mTOR [194]. Silibinin inhibited SREBP1 nuclear translocation via activating AMPK-mediated SREBP1 phosphorylation, and ultimately inhibiting cancer cell proliferation [195]. Based on the above results, targeting the posttranslational modification of lipid metabolism enzyme brought new opportunities for cancer therapy.

Conclusion
Lipid metabolism in cancer cells and the TME is complex and highly subject to PTMs of many of its key and/or rate-limiting enzymes. Understanding these

Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 14 of 18

modifications in greater detail is likely to provide reasonable target candidates for cancer treatments.

Recently, metabolomics and RNA-seq have been used to show that, in some cases, lipid metabolism can be used to assess the prognosis and risk factors for cancer patients, thereby providing a novel molecular diagnostic approach [196, 197]. Targeting lipid metabolism directly using agents such as statins has also demonstrated promising results [198, 199]. Metabolomics and protein "PTM-omics" potentially provide additional unbiased methods to assess lipid metabolism in cancers and could potentially also be used for diagnostic purposes. Cancers might potentially be classifiable into different stages based on their metabolomics profiles just as they currently are using transcriptomic-based approaches. This in turn could allow for more precise individualization of various therapies. More specific, tumor classification and therapeutic option selection might be achievable using lipid metabolomics profiling, thus allowing additional diagnostic therapeutic and prognostic personalization and refinement.

Future work will likely reveal additional levels of metabolic control. The study of PTMs that modulate enzymatic activity, particularly those that prove mutually antagonistic, is likely to provide therapies that, together with more traditional ones, will prove additive or synergistic.

Abbreviations

ACAT1: Acetyl-CoA acetyltransferase 1; ACC: Acetyl-CoA carboxylase; ACLY: ATP-citrate synthase; ALOX15: Arachidonic lipoxygenase 15; AMPK: 5'-AMP-activated protein kinase; AR: Androgen receptor; ATP: Adenosine triphosphate; CAFs: Cancer-associated fibroblasts; CBX4: Chromobox4; CCRK: Cell cycle-associated kinase; CEBPB: CCAAT/enhancer-binding protein beta, C/EBP beta; COP1: E3 ubiquitin-protein ligase COP1; COX2: Cyclooxygenase-2; CPT1: Carnitine palmityl transferase 1; DC: Dendritic cells; DGAT1: Diacylglycerol O-acyltransferase 1; ECM: Extracellular matrix; FA: Fatty acids; FABPs: Fatty acid-binding proteins; FAO: Fatty acid oxidation; FASN: Fatty acid synthase; FATP2: Fatty acid transporter 2; FBXW7: F-box/WD repeat-containing protein 7; GNPAT: Dihydroxyacetone phosphate acyltransferase; HCC: Hepatocellular carcinoma; HCP5: Histocompatibility leukocyte antigen complex P5; HIF-1α: Hypoxia-inducible factor 1-alpha; HMGCR: HMG-CoA reductase; hnRNPA1: Heterogeneous nuclear ribonucleoprotein A1; HRD1: E3 ubiquitin-protein ligase HRD1; HSC: Hepatic stellate cells; ICIs: Immune checkpoint inhibitors; IDOL: E3 ubiquitin-protein ligase MYLIP; IFN-γ: Interferon-γ; IGF2BP1/IGF2BP3: Insulin-like growth factor-2 mRNB-binding proteins 1/3; IKK-beta: Inhibitor of nuclear factor kappa-B kinase subunit beta; IL-4: Interleukin-4; INKT: Invariant natural killer T cells; LATS1: Large tumor suppressor; LCFAs: Long-chain fatty acids; LDLR: Low-density lipoprotein receptor; LIHC: Liver hepatocellular carcinoma; LILRB: Leukocyte immunoglobulin-like receptor B; LILRB2: Leukocyte immunoglobulin-like receptor subfamily B member 2; LKB1: Liver kinase B1; LTA: Lipoteichoic acid; LXR: Liver X receptor; M-CSF: Macrophage colony-stimulating factor; MDR: Multidrug-resistant cancer cells; MDSC: Myeloid-derived suppressor cells; ME1: Malic enzyme 1; MSDC: Mesenchymal stem cell; NASH: Non-alcoholic steatohepatitis; NEK1: Serine/threonine-protein kinase Nek1; NPC: Nuclear pore complex; PCAF: P300/Calc-binding protein (CBP)-related factor; PCK: Phosphoenolpyruvate carboxy-kinase; PDA: Pancreatic ductal adenocarcinoma; PGAM5: Serine/threonine-protein phosphatase; PGE2: Prostaglandin E2; PI3K: Phosphatidylinositol 3-kinase; PPAR: Peroxisome proliferator-activated receptor; PPARGC1α: PPARG coactivator 1α; PRAD: Prostate adenocarcinoma; PRMTs: Protein arginine methyltransferases; PTM: Posttranslational modification; ROS: Reactive oxygen species; S1P: Sphingosin-1-phosphate; SAE1: SUMO-activating enzyme subunit 1; SAE2: SUMO-activating enzyme subunit 2; SAH: S-adenosylhomocysteine; SAM: S-adenosylmethionine; SASP: Senior-related secretion phenotype; SDMA: Symmetric di-methylated arginine; SENP1: SUMO-specific protease I; SHP1: Protein-tyrosine phosphatase SHP-1; SHP2: SH2-tyrosine phosphatase; SIRT6: NAD-dependent protein deacetylase Sirt6; spHK1: Sphingosine kinase 1; spHK2: Sphingosine kinase 2; SREBPs: Sterol-regulation-element-binding proteins; STAT6: Signal transducer and activator of transcription 6; TAMs: Tumor-associated macrophages; TDEs: Tumor-derived exosomes; TGF-β2: Transforming growth factor beta-2 proprotein; TIDCs: Tumor-infiltrating dendritic cells; TME: Tumor microenvironment; Treg cells: Regulatory T cells; TRIM21: E3 ubiquitin-protein ligase TRIM21; UBC9: SUMO-conjugating enzyme UBC9; UBXD: UBX domain-containing protein; USP30: Ubiquitin carboxyl-terminal hydrolase 30; USP7: Ubiquitin-specific protease 7; VLCAD: Very long-chain acyl coenzyme A dehydrogenase; VLCFAs: Very long-chain fatty acids; ZNF451: E3 SUMO-protein ligase ZNF451.

Declarations

Ethical Approval and Consent to participate
No ethics approval was required for this review.

Consent for publication
All authors consent to publication.

Competing interests
The authors declare that they have no conflict of interest.

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Zhu *et al. Journal of Hematology & Oncology*   (2022) 15:120

Page 15 of 18

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Zhu *et al. Journal of Hematology & Oncology*　　　(2022) 15:120

Page 17 of 18

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Page 18 of 18

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