The role of ubiquitination and deubiquitination in cancer metabolism

Tianshui Sun, Zhuonan Liu and Qing Yang

Abstract
Metabolic reprogramming, including enhanced biosynthesis of macromolecules, altered energy metabolism, and maintenance of redox homeostasis, is considered a hallmark of cancer, sustaining cancer cell growth. Multiple signaling pathways, transcription factors and metabolic enzymes participate in the modulation of cancer metabolism and thus, metabolic reprogramming is a highly complex process. Recent studies have observed that ubiquitination and deubiquitination are involved in the regulation of metabolic reprogramming in cancer cells. As one of the most important type of post-translational modifications, ubiquitination is a multistep enzymatic process, involved in diverse cellular biological activities. Dysregulation of ubiquitination and deubiquitination contributes to various disease, including cancer. Here, we discuss the role of ubiquitination and deubiquitination in the regulation of cancer metabolism, which is aimed at highlighting the importance of this post-translational modification in metabolic reprogramming and supporting the development of new therapeutic approaches for cancer treatment.

Keywords: Ubiquitination, Deubiquitination, Cancer, Metabolic reprogramming

Background
Metabolic pathways are of vital importance in proliferating cells to meet their demands of various macromolecules and energy [1]. Compared with normal cells, cancer cells own malignant properties, such as increased proliferation rate, and reside in environments short of oxygen and nutrient. Correspondingly, metabolic activities are altered in cancer cells to support their malignant biological behaviors and to adapt to stressful conditions, such as nutrient limitation and hypoxia [1]. Cancer metabolism is an old field of research. Warburg effect observed in the 1920s provides a classical example of metabolic reprogramming in cancer [2]. In the past few decades, enhanced biosynthesis of macromolecules, altered energy metabolism, and maintenance of redox homeostasis have been observed to be essential features of cancer metabolism. Altered metabolism in cancer cells have aroused increasing attention and interest [3]. Because of the generality of metabolic alterations in cancer cells, metabolic reprogramming is thought as hallmark of cancer, providing basis for tumor diagnosis and treatment [1]. For instance, the application of 18F-deoxyglucose positron emission tomography is based on tumors’ characteristic of increased glucose consumption [4]. Inhibition of some metabolic enzymes, such as L-lactate dehydrogenase A chain (LDH-A), have been observed to regress established tumors [5, 6]. Therefore, research of metabolic reprogramming is of critical importance, which might provide new opportunities for cancer diagnosis and treatment.

Amongst multiple post-translational modification, protein ubiquitination is a common and important process in cells [7, 8]. Ubiquitination and deubiquitination have been observed to be dysregulated in various types of cancers. Genetic and epigenetic aberrations, such as mutation, amplification and deletion, can be the common causes of dysregulated ubiquitination and deubiquitination in cancer cells [9]. Ubiquitination and deubiquitination can also...
be abnormally regulated by transcriptional, translational or posttranslational mechanisms in cancer cells, exerting oncogenic or anti-cancer roles in carcinogenesis [7, 8, 10]. In recent years, the involvement of ubiquitination and deubiquitination in the regulation of metabolic reprogramming in cancer cells has received a growing body of attention [11]. Given the complexity and importance of both cancer metabolism and protein ubiquitination, the exact roles of protein ubiquitination and deubiquitination in metabolic reprogramming are worth further studies and analyses. The present review will highlight the ubiquitination and deubiquitination system as a regulator of cancer metabolism and discuss future directions focusing on the strategies to improve cancer therapy.

Cancer metabolism
To satisfy nutrient and energy requirements for cells’ survival and growth, metabolic pathways are altered in cancer cells, which is called metabolic reprogramming [1]. Metabolic reprogramming is a highly regulated process [12]. Aberrant activation of mechanistic target of rapamycin complex 1 (mTORC1) is one of the most common alterations in proliferating cancer cells, playing a key role in metabolic reprogramming [12]. Under the stimulation of amino acids, mTORC1 can be activated, which subsequently exerts various biological effects by activation of different downstream targets, such as hypoxia-inducible factor 1 (HIF-1) and sterol regulatory element-binding protein (SREBP) [12, 13]. Proliferating cancer cells require elevated synthesis of protein, lipid and nucleotide. Glycolysis can be upregulated by mTORC1 activation, providing more glycolytic intermediates for biosynthesis of these macromolecules [14]. Moreover, mTORC1 activation promotes glutamine uptake to maintain mitochondrial ATP production [15]. Fatty acids can also supply carbon to the tricarboxylic acid (TCA) cycle to sustain mitochondrial function [16]. PI3K-AKT signaling is the most well-known mechanism for activating mTORC1 [17]. Besides, mTORC1 can be activated or inhibited by various signaling pathways directly or indirectly. For instance, 5′-AMP-activated protein kinase (AMPK) activated by energy shortage is a crucial inhibitor of mTORC1 [18]. What’s more, transcription factor c-Myc and p53 also take part in metabolic reprogramming through transcriptional regulation of metabolism-related genes [19, 20]. Based on multiple regulatory mechanisms, expression or activity of the enzymes involved in glucose, amino acids and fatty acids metabolism are altered, directly contributing to metabolic reprogramming [21]. What’s more, the up-regulation of various metabolic processes in cancer cells triggers accumulation of reactive oxygen species (ROS) [22]. Transcription factors nuclear factor erythroid 2-related factor 2 (NRF2) and HIF-1 play key roles in maintenance of redox homeostasis, keeping ROS in an appropriate level to promote tumor growth rather than inducing damage [23, 24].

Under nutrient rich conditions, activation of mTORC1 supports cancer cells growth. In periods of cellular stress, low levels of amino acids or absent ATP induces mTORC1 inhibition, which subsequently activates a compensatory mechanism named autophagy [25]. Autophagy is a highly regulated pathway essential for cell survival in nutrient-deprived conditions, complementing the classical pathways like glycolysis. Autophagy supplies amino acids by inducing degradation of macromolecules and organelles in lysosome, thereby providing intracellular amino acids supply to fuel the TCA cycle, gluconeogenesis and protein synthesis [26]. However, the interplay between autophagy and glycolysis seems to be complex. Activation of autophagy has been observed to enhance glycolysis [27]. Deficiency of mitophagy can induce mitochondrial dysfunctions, enhancing glycolysis and Warburg effect [28]. Additionally, studies have found that oxidative stress induced by cancer cells can promote aerobic glycolysis and autophagy in cancer associated fibroblasts to obtain recycled nutrients from cancer associated fibroblasts. This phenomenon is called “Reverse Warburg Effect” [29]. Therefore, both the anabolic pathways, such as glycolysis, and the catabolic pathways, such as autophagy, interplay with each other, together contribute to cancer metabolism and supporting cellular growth. Taken together, abnormal alterations of multiple signaling pathways, transcription factors and metabolic pathways synergistically lead to metabolic reprogramming in cancer cells.

Ubiquitination and deubiquitination
Ubiquitination is an ATP-dependent cascade process ligating ubiquitin, a ubiquitously expressed protein consisting of 76 amino acids, to a substrate protein [30]. Ubiquitin-activating enzymes (E1s) initially bind to ubiquitin for activation, and then transfer activated ubiquitin to ubiquitin-conjugating enzymes (E2s). Ubiquitin ligases (E3s) finally transfer ubiquitin from E2 to substrates [30]. According to the number of ubiquitin attaching to one lysine residue in protein, ubiquitination is divided into monoubiquitination (single ubiquitin) and polyubiquitination (a chain of ubiquitin) [31]. In the polyubiquitination chain, ubiquitin can be attached via 7 lysine residues (K6, K11, K27, K29, K33, K48, and K63) or the first methionine (M1) [32]. Different types of ubiquitination lead to disparate fates of substrate proteins. K48-linked polyubiquitination is the most widely studied type, which mainly labels proteins for 26S proteasome-mediated recognition and degradation [32]. K48-linked polyubiquitination also has proteasome independent functions, including regulation of signaling events and...
transcription, which are possibly determined by the length of the ubiquitin chain [33–35]. K11-linked polyubiquitination is also associated with proteolysis [32]. Ubiquitin-proteasome system is involved in the degradation of more than 80% of proteins in cells [36]. K63-linked polyubiquitination is involved in signaling assemblies [32]. E3 ligases play a key role in the whole process of ubiquitination because of their specificity for substrates. In human genome, there are approximately 1000 E3 ligases, which can be divided into the homology to E6AP C terminus (HECT) domain-containing E3s, the RING-between-RING (RBR) family E3s and the really interesting new gene (RING) finger domain-containing E3s [37]. Deubiquitination is catalyzed by deubiquitinating enzymes (DUBs) to remove ubiquitin from ubiquitinated proteins, thus reversing the ubiquitination process [7]. About 100 DUBs fall into seven subgroups: the ubiquitin-specific proteases (USPs), the ubiquitin C-terminal hydrolases (UCHs), the ovarian tumor proteases (OTUs), the Machado-Josephin domain proteases (MJDS), the JAB1/MPN+/ MOV34 (JAMM) domain proteases, the monocyte chemotactic protein-induced proteins (MCPIPs), and the motif interacting with ubiquitin-containing DUB family (MINDY) [10]. Dynamic conversion between ubiquitination and deubiquitination is closely related to various cellular functions and thus, its dysregulation results in multiple disease, such as neurodegenerative diseases and cancer [38]. Understanding of ubiquitination and deubiquitination may provide novel insights into the treatment of these diseases.

**Ubiquitination and metabolic signaling pathways**

**Ubiquitination of mTOR**

Aberrant activation of mTORC1 is considered as a key feature of metabolic reprogramming. mTORC1 is a complex consisting of mTOR, Raptor, mLST8, PRAS40 and DEPTOR [39]. mTOR is an evolutionarily conserved serine/threonine protein kinase in the PI3K-related kinase superfamily, responsible for the catalytic activity of mTORC1 [40]. Translocation of mTORC1 to lysosome is the premise for its subsequent activation, identified as a critical step in the activation of mTORC1 signaling [41]. Activated RagA is thought to be the main participant in the re-localization of mTORC1 to the lysosomes in amino acid-stimulated cells [41]. Studies have found that E3 ligase TRAF6, which is upregulated in cancer cells, can mediate K63-linked polyubiquitination of mTOR by interacting with p62 under the stimulation of amino acids, promoting the translocation of mTORC1 to the lysosomes and subsequent activation (Fig. 1) [42]. In addition, decreased K48-linked ubiquitination of mTOR by E3 ligase FBX8 and FBXW7 alleviates proteasome-dependent degradation of mTOR, exerting an oncogenic effect in cancer as well [43, 44]. Reduced mTOR ubiquitination is also linked to therapy resistance in cancer. Everolimus is a mTOR inhibitor used in breast cancer patients. Following downregulated phosphorylation of mTOR induced by depletion of dual specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2), ubiquitination and degradation of mTOR diminish, resulting in everolimus resistance [45]. Non-thermal plasma exerts anti-tumor effect by inducing RNF126 mediated K48-linked polyubiquitination and degradation of mTOR [46]. However, when faced with mitochondrial stress, E3 ligase PARKIN targets mTOR for ubiquitination, which maintains mTORC1 activity instead of affecting mTOR stability, thereby enhancing cell survival [47]. DUB USP9X can negatively modulate mTOR function and mTORC1 activity without changing mTOR protein level [48]. Therefore, different types of ubiquitination and deubiquitination play diverse roles in the regulation of mTOR function.

**Ubiquitination of raptor**

Raptor is the regulatory protein of mTORC1, maintaining the correct subcellular localization of mTORC1 and allowing the binding of mTORC1 with substrates [49]. DDB1-CUL4 E3 ligase complex is essential for maintaining mTORC1 stability by ubiquitinating Raptor. Displacement of DDB1-CUL4 complex by DUB UCH-L1 can remove K63-linked poly-ubiquitin chains on Raptor, bringing about reduced mTORC1 [49].

**Ubiquitination of mLST8**

mLST8, also called GβL, is a component of both mTORC1 and mTORC2. mLST8 is associated with the catalytic domain of mTOR and stabilizes its kinase activation loop [50]. mLST8 can be ubiquitinated by TRAF2 through K63-mediated linkage, which breaks the interaction between mLST8 and SIN1 in mTORC2, giving rise to elevated formation of mTORC1. This process can be reversed by DUB OTUD7B, leading to increased mTORC2 formation [50]. The study highlighted the role of ubiquitination and deubiquitination in the balance and competence between mTORC1 and mTORC2 signaling under various conditions.

**Ubiquitination of DEPTOR**

DEPTOR is an inhibitor of both mTORC1 and mTORC2. mTORC2 activation can phosphorylate DEPTOR and promote its recognition by SCFβ-TrCP ubiquitin ligase, targeting DEPTOR for polyubiquitination and proteolytic degradation [51, 52]. In tumors with isocitrate dehydrogenase1/2 (IDH1/2) mutations, oncometabolite 2-hydroxyglutarate indirectly promotes DEPTOR polyubiquitination by SCFβ-TrCP, thus activating mTOR [51]. E3 ligase RNF7 exerts oncogenic effect in prostate tumorigenesis by promoting ubiquitination and degradation of DEPTOR [53]. DUB OTUB1 specifically stabilizes DEPTOR via deubiquitination, thereby playing an...
anticancer role [54]. CUL5 also targets DEPTOR for degradation, which is inhibited during autophagy activation [55]. Autophagy triggered by decreased ubiquitination and degradation of DEPTOR is related to drug resistance in cancer. Anticancer agent MLN4924 causes protective autophagy via inactivation of the CUL E3 ligase and accumulation of DEPTOR, which suppresses its effectiveness [56]. Enhancement of DEPTOR degradation can attenuate autophagy, which has been found to be an effective target in Temozolomide-resistant glioblastoma cells [57].

Ubiquitination of RagA

As we mentioned above, activated RagA plays a key role in the re-localization of mTORC1 to the lysosomes and subsequent activation of mTORC1 [41]. Study found that downregulation of lysosomal E3 ligase RNF152 protected cells from autophagy [58]. RNF152 modifies RagA by K63-linked polyubiquitination and promotes recruitment of RagA inhibitor GATOR1, thus inducing RagA inactivation. Then mTORC1 is released from the lysosomal surface, giving rise to blockade of mTORC1 signaling pathway [58]. Moreover, K63-linked polyubiquitination of RagA can also be mediated by E3 ligase SKP2, which exerts a similar effect with RNF152 [59].

Ubiquitination of GATORs

GATOR1 is a complex consisting of DEPDC5, NPRL2 and NPRL3, while GATOR2 consists of Mios, WDR24, WDR59, Seh1L and sec13. GATOR2 negatively regulates DEPDC5 in GATOR1, which acts as an inhibitor of RagA. Thus, GATOR2 exerts a promoting effect on RagA. Oncogenic E3 ligase CUL3-KLHL22 was observed to mediate K48-linked polyubiquitination of DEPDC5 and target DEPDC5 for degradation under the stimulation of amino acids and promote mTORC1 activation in tumor [60].

Ubiquitination of Rheb

GTP-bound Rheb is the activator of mTORC1 after translocation of mTORC1 to the lysosome. Monoubiquitination of Rheb by the lysosomal E3 ligase RNF152 can enhance its interaction with the tuberous sclerosis complex (TSC) complex, the major inhibitor of Rheb, and can decrease mTORC1 activation [61]. Following
phosphorylation by AKT, USP4 can deubiquitinate Rheb to reverse the action of RNF152. Therefore, the dynamic change of ubiquitinating state of Rheb is associated with mTORC1 activation and tumor growth [61].

**Ubiquitination of TSC complex**
TSC complex, composed of TSC1, TSC2, and TBC1D7, is identified as a major upstream regulator of Rheb, converting GTP-bound Rheb to GDP-bound Rheb, thus inhibiting mTORC1 activation. TRIM31 mediated K48-linked ubiquitination of TSC1-TSC2 complex induces its degradation and promotes growth of hepatocellular carcinoma cells [62]. FBXW5 recruits TSC2 protein to DDB1-CUL4-ROC1 E3 ligase complex, promoting its ubiquitination and degradation [63]. Moreover, E3 ligase Pam, HERC1 and UBE3A were also observed to mediate TSC2 protein ubiquitination and to enhance its degradation [64–66]. Interaction of TSC2 with TSC1 can prevent TSC2 from HERC1 ubiquitin ligase mediated degradation [66], while VPS34 can competitively bind to TSC1, resulting in TSC2 degradation [67]. E3 ubiquitin ligase SCFβTrCP can ubiquitinate free TBC1D7 for degradation. Binding to TSC or AKT dependent phosphorylation of free TBC1D7 can prevent TBC1D7 from interaction with SCFβTrCP, stabilizing the pool of TBC1D7 [68].

**Ubiquitination of PI3K**
PI3K-mTORC1 signaling is the crucial signaling pathway that governs metabolic reprogramming and tumor cell growth. PI3K can be activated under the stimulation of growth factors. Activated PI3K phosphorylates PIP2, converting PIP2 to PIP3, which recruits 3-phosphoinositide-dependent protein kinase 1 (PDK1) and Akt to the membrane. PDK1 subsequently activates AKT, a negative regulator of TSC complex, and subsequently activating mTORC1 [69]. Activation of PI3K-mTORC1 signaling can exert various effects on metabolic process and play a key role in the regulation of tumor metabolism [69]. PI3K is a dimeric enzyme composed of a catalytic subunit (p110α, p110β, or p110γ) and a regulatory subunit (p85α, p85β, p55α, p55γ, or p50α) [70]. A dynamic cycle of proteasome-dependent degradation and re-synthesis of PI3Kp110α were observed in activation of PI3K signaling. NEDD4 E3 ligase catalyzes free PI3Kp110α for ubiquitination, leading to its proteasome-dependent degradation and maintenance of PI3K signaling [70]. TRAF6 E3 ligase promotes activation of PI3K pathway in cancer by nonproteolytic polyubiquitination of PI3K catalytic subunit p110α [70]. TRAF6 also directs PI3K recruitment via K63-linked polyubiquitination of PI3Kp85α, which is essential for TGF-β-induced activation of PI3K signaling [71]. What’s more, PI3K regulatory subunit p85α can be ubiquitinated by E3 ligase MKRN2 and E3 ligase complex HSP70-CHIP through K48-mediated linkage, bringing about proteolysis of PI3Kp85α and downregulation of PI3K signaling in cancer [72, 73]. Dephosphorylated free p85β is ubiquitinated by FBXL2 for proteolysis. Decreased free p85β reduces its competition with p85-p110 heterodimers for docking sites on cell membrane, thus upregulating PI3K signaling [74]. Therefore, both the catalytic subunit and the regulatory subunit can be ubiquitinated, exerting various effects on PI3K signaling.

**Ubiquitination of PDK1**
PDK1 phosphorylates and activates AKT, transducing signal from activated PI3K to AKT. Attenuated ubiquitination and degradation of PDK1 are related to chemoresistance in ovarian cancer [75]. Monoubiquitination of PDK1 in cancer cell lines can be reversed by USP4 catalyzation, the function of which still remains unclear [76].

**Ubiquitination of AKT**
AKT, a negative regulator of TSC complex, can be activated by PI3K signaling, exerting oncogenic effect by promoting mTORC1 signaling. K63-linked polyubiquitination of AKT catalyzed by TRAF6, NEDD4, SCF-SKP2, FBXL18, RSP5 or TRAF4 E3 ligase is required for cell membrane localization of AKT and is essential in activation of PI3K-AKT-mTOR pathway and subsequent up-regulation of glycolysis [77–82]. SETDB1 catalyzed methylation of AKT enhances its K63-linked ubiquitination and activation [83]. After interaction with KDM4B, TRAF6 promotes its ubiquitination of AKT in colorectal cancer, facilitating glucose metabolism and tumor growth [84]. DUB CYLD, OTUD5 and USP1 can reverse K63-linked polyubiquitination of AKT and inhibit its activation [85–87]. Bisdemethoxycurcumin can inhibit hepatocellular carcinoma cell growth by promoting CYLD-mediated deubiquitination of AKT [88]. Enhanced AKT ubiquitination and activation caused by downregulation of DUB OTUD5 give rise to radioresistance in cervical cancer [86]. pAKT ubiquitinated by NEDD4 can regulate its nuclear trafficking to promote tumorigenesis [79]. What’s more, E3 ligases CHIP, BRCA1, TTC3, TRIM13, ZNF1, MUL1 can modify AKT by K48-linked ubiquitination and promote degradation of AKT to suppress its activation [89–94]. Anticancer agents Rhus coriaria, SC66 and Vitamin C can stimulate ubiquitination and degradation of AKT in cancer cells [95, 96]. When proteasome impairs in cellular stress, E3 ligase MUL1 catalyzes K48-linked ubiquitination of AKT, which subsequently undergoes lysosomal degradation, playing
Ubiquitination of PTEN
As a negative regulator of PI3K/AKT signaling pathway, phosphatase and tensin homolog (PTEN) converts PIP3 back to PIP2, playing tumor suppressive functions in various cancers. Identified as the E3-ligase of PTEN, NEDD4 not only contributes to monoubiquitination of PTEN for its nuclear transport but also mediates polyubiquitination of PTEN for its proteasomal degradation to activate AKT signaling transduction [98]. Up-regulation of LINC00152 enhances NEDD4 mediated ubiquitination and degradation of PTEN in breast cancer [99]. E3 ligase WWP2, TRIM10, TRIM14, TRIM25, TRIM27, TRIM59 and XIAP can target PTEN for ubiquitination and degradation as well [100–106]. AKT-activated MKRN1 E3 ligase also mediates ubiquitination and degradation of PTEN, thus positively regulating PI3K/AKT signaling axis [107]. The E3 ligase WWP1 mediated polyubiquitination can suppress the membrane recruitment and function of PTEN [108]. Ubiquitination via E3 ligase RFP can downregulate PTEN phosphatase activity rather than altering its stability or localization [109]. As for the deubiquitination of PTEN, USP10, USP11, USP13, USP49, and OTUD3 catalyze removal of K48-linked ubiquitin chain on PTEN to enhance protein stability of PTEN and attenuate AKT signaling pathway [110–114]. USP7-induced deubiquitination of PTEN results in its nuclear exclusion rather than regulating its protein stability [115, 116]. DUB ATXN3 suppress PTEN expression by reducing its transcription rather than altering its protein level [117].

Ubiquitination of AMPK
AMPK is an inhibitor of mTORC1 by phosphorylating Raptor and activating TSC2. As an energy sensor, AMPK is crucial in maintenance of NADPH and ATP homeostasis [118]. E3 ligase complex MAGE-A3/6-TRIM28 and E3 ligase CRL4A catalyze ubiquitination of AMPKα and target it for degradation, thus reducing autophagy and altering cancer metabolism [118, 119]. UBE2O, an atypical ubiquitin enzyme with both E2 and E3 activities, ubiquitinates AMPKα2 for degradation [120]. CRL4A catalyzed ubiquitination also directs AMPKγ proteolysis [121]. GID ubiquitin ligase mediates ubiquitination and degradation of AMPK as well, leading to decreased autophagy and increased mTOR activity [122]. Ubiquitination of AMPKα can be reversed by USP10 to remove the ubiquitin chain from AMPKα and promote AMPK activation [122].

Ubiquitination of KRAS
As a common mutated oncogene driving tumorigenicity in pancreatic, colon and lung cancers, KRAS enhances expression of glucose transporter type 1 (GLUT1) and controls glycolysis and glutamine metabolism in cancer cells, which is considered to be associated with metabolic reprogramming in primary invasive cancers [123]. Monoubiquitination and diubiquitination of KRAS elevate its GTP loading ability [124]. CUL3-based E3 ligase complex can mediate polyubiquitination and degradation of KRAS [125]. KRAS4B, an alternative splicing of KRAS gene, is targeted by E3 ligase NEDD4 for ubiquitination and proteolysis. However, activated KRAS signaling upregulates NEDD4 expression and prevents NEDD4-mediated KRAS ubiquitination. This in return promotes NEDD4 catalyzed degradation of PTEN to trigger tumor growth [126]. Therefore, modification of signaling molecules by ubiquitination can exert various effects in signaling pathways, thereby regulating metabolic reprogramming in cancer cells.

Ubiquitination and transcription factors
Ubiquitination of HIF-1
HIF-1 is a metabolic-associated transcription factor which can be activated by mTORC1, accumulation of ROS and accumulation of TCA cycle metabolites. Activation of HIF-1 enhances expression of various glycolytic genes including hexokinase 1 (HK1), HK2, LDHA, and pyruvate dehydrogenase kinase isoenzyme 1 (PDK1), strengthening glycolytic flux and maintaining redox homeostasis [127]. HIF-1 consists of α and β subunits. Compared with HIF-1β, HIF-1α is unstable and susceptible to ubiquitination. E3 ligase VHL can mediate degradation of HIF-1α under normoxic conditions. Loss of VHL in cancer cells stabilizes HIF-1α, contributing to aerobic glycolysis [128, 129]. E3 ligase MDM2, PARKIN and HUWE1 can catalyze ubiquitination of HIF-1α and targets it for degradation, thus exerting an anti-tumor effect [130–132]. Tumor suppressors PTEN and p53 can enhance MDM2-mediated ubiquitination and degradation of HIF-1α to inhibit tumorigenesis [133–135]. Following phosphorylation by GSK3β, HIF-1α ubiquitination via FBXW7 is increased, which promotes proteolysis of HIF-1α and inhibits tumor growth [136]. Anticancer drug glycoollins and thymoquinone can inhibit tumor growth by elevating ubiquitination and degradation of HIF-1α [137, 138]. E3 ligase FBX11 can reduce the mRNA stability rather than protein stability of HIF-1α [139]. DUB USP28 can antagonize the ubiquitination of HIF-1α by FBXW7 [136]. TRIM44, USP20 and USP7 also stabilizes HIF-1α by deubiquitination, leading to tumor progression under hypoxia [140–143]. DUB OTUD7B can suppress degradation of HIF-1α via proteasome-independent manner [144]. USP8 mediated
deubiquitination of HIF-1α was to maintain its expression level in normal conditions [145]. K63-linked polyubiquitination of HIF-1α catalyzed by TRAF6 can protect it from degradation [146]. XIAP modifies HIF-1α by K63-linked polyubiquitination to promote its nuclear retention and enhance HIF-dependent gene expression [147]. In conclusion, ubiquitination is an important regulatory mechanism of HIF-1.

**Ubiquitination of c-Myc**

Transcription factor c-Myc contributes to metabolic reprogramming through transcriptional regulation of genes participating in metabolism, such as LDHA [148]. c-Myc is an unstable protein susceptible to ubiquitination and proteolysis. E3 ligase SKP2, HUWE1, FBX29, TRUSS, RCHY1, CHIP, FBXW7, VHL, SPOP, TRIM32, NEDD4 and FBXL14 can target c-Myc for ubiquitination and degradation [149–160]. Decreased ubiquitination of c-Myc by VHL is observed to drive aerobic glycolysis in breast cancer cells [159]. Mutation or deletion of these E3 ligase genes induces carcinogenesis by attenuating c-Myc degradation. Anticancer drugs, including lanatoside C, diminish cancer cell growth by upregulating ubiquitination and degradation of c-Myc in cancer [161–163]. Ubiquitination of c-Myc can also be regulated by interaction with other molecules. FBXL16 can competitively bind with c-Myc without inducing ubiquitination of c-Myc, thereby rescuing c-Myc from FBXW7-mediated degradation [164]. Interaction with Ev5 also antagonizes FBXW7-mediated ubiquitination of c-Myc protein in laryngeal squamous cell carcinoma [165]. Phosphorylated ANXA2 interacts with MYC and inhibits ubiquitin-dependent proteasomal degradation of MYC protein in esophageal cancer [166]. LncRNA XLOC_006390, GLCC1 and LINCO1638 also block ubiquitination of c-Myc [156, 167, 168]. What’s more, E3 ligase FBX28 mediated non-proteolytic ubiquitination of c-Myc can enhance c-Myc dependent transcription [169]. Ubiquitination of c-Myc by E3 ligase SCFβ-TrCP in G2 phase can stabilize c-Myc to facilitate recovery from an S-phase arrest [170]. Moreover, the DUB USP7, USP13, USP22, USP28, USP36 and USP37 stabilize c-Myc, thereby stimulating tumor growth [155, 157, 171–174].

**Ubiquitination of p53**

As a critical tumor suppressor participating in cell cycle regulation and apoptosis, p53 was also clarified by recent studies of its participation in metabolic reprogramming. Loss of p53 induces enhancement of glycolysis and maintenance of redox homeostasis in cancer cells [175]. Monoubiquitination, K48-linked and K63-linked polyubiquitination were observed to be common post-translational modification of p53 protein. MDM2/MDMX complex is the major E3 ligases and the main negative regulator of p53, degrading p53 and decreasing transcription of p53 target genes [176]. At the same time, MDM2 is targeted by p53 to form a negative feedback loop for the dynamic regulation of p53 under stressed and unstressed conditions [177]. RCHY1, COP1, CHIP, HUWE1, RING1, FBXW7, Synoviolin, MKRN1, TOPORS, CARP1/2, CUL4a-DBD1-ROC, CUL5, RNF115, TRIM23, TRIM24, TRIM28, TRIM39, TRIM69, TRIM71 can also target p53 for K48-linked polyubiquitination and degradation [178–185]. K48-linked polyubiquitination of p53 can be regulated by various molecules. For instance, MAVS and ATF3 can stabilize p53 by preventing p53 from MDM2-mediated ubiquitination [186, 187]. ACP5 mediated p53 phosphorylation enhanced the ubiquitination and degradation of p53 [188]. p53 protein can be deubiquitinated by DUB OTUD1, OTUD3, OTUD5, ATXN3, USP10, USP11, USP15, USP24, USP29 and USP42 to enhance its function as tumor suppressor under the conditions of high carcinogenicity and genotoxicity [117, 189–198]. DUB USP7 can catalyze deubiquitination of p53 and regulate level of p53 protein as well [199]. On the other hand, USP7 mediates deubiquitination and stabilization of MDM2 and MDMX, the major E3 ligase of p53 protein, thereby reducing the protein level of p53 [200, 201]. Studies have found that the binding of USP7 with MDM2 is much stronger than that with p53 [200]. USP7 is highly expressed in most cancers, such as breast cancer and colorectal cancer, and plays carcinogenic role by deubiquitinating MDM2 and MDMX [202, 203]. Application of USP7 inhibitors can activate the p53 signaling in cancer cells and play anti-cancer functions [204]. However, USP7 is downregulated in some tumors, such as pulmonary adenocarcinoma, and plays a tumor suppressive role in p53-dependent mechanism [205]. Therefore, USP7 acts in a content-dependent manner and has a paradoxical action on p53 according to different tissues. What’s more, CUL7-mediated K63-linked polyubiquitination of p53 and MDM2 or MSL2-mediated monoubiquitination of p53 are associated with its translocation to the cytoplasm [206]. Anticancer drug HLI98 inhibits p53 degradation via MDM2 to enhance its tumor suppressive function [207]. Therefore, it’s likely for p53 ubiquitination regulation to act as an effective therapeutic method for cancers.

**Ubiquitination of NRF2**

Accumulation of ROS can also activate NRF2, another essential transcriptional factor for the maintenance of redox homeostasis. KEAP1, a substrate-specific adapter of a CUL3-RBX1 E3 ligase complex, is the binding partner of NRF2 and it negatively controls NRF2 stability. Under normal conditions, the CUL3-RBX1 mediates ubiquitination and degradation of NRF2. Electrophile
metabolites formed in oxidative stress prevents CUL3-RBX1-KEAP1 complex from ubiquitinating NRF2, thereby stabilizing NRF2. NRF2 subsequently activates transcription of antioxidant proteins, such as GPXs and TXNs as well as enzymes involved in glutathione and NADPH synthesis [208]. p62, RMP and CDK20 can competitively bind with KEAP1 [209–211]. TRIM25 targets KEAP1 for ubiquitination and degradation [212]. DUB USP15 can stabilize KEAP1 [212]. These events will change the level of NRF2 and affect the transcriptional activity of NRF2 targeted genes. In non-small cell lung cancer, phosphorylation by BMP8A or interaction with PAQR4 can prevent ubiquitination of NRF2 by KEAP1 and stabilize NRF2, resulting in chemotherapy resistance [213, 214]. Besides CUL3-RBX1-KEAP1 complex, E3 ligase SCFβ-TrCP, CUL4-DDB1-WDR23, HRD1 can also ubiquitinate NRF2 and regulate its stability [215–217]. DUB Dub3 removes ubiquitin chain on NRF2 and stabilize NRF2, leading to chemoresistance in colorectal cancer [218].

Ubiquitination of SREBP1
SREBP1 is a transcription factor associated with lipogenic genes [219]. mTORC1 signaling induces enhanced activity of SREBP1 to meet the requirements for fatty acid in proliferating cancer cells [220]. Activation of SREBP1 upregulates fatty acid synthesis as well as lipid import from extracellular space [220]. After phosphorylated by GSK-3, SREBP1 is prone to ubiquitination by E3 ligase FBXW7 and degradation via the ubiquitin-proteasome system [221, 222]. Deacetylation of SREBP by SIRT1 also enhances its ubiquitination and proteolysis [223]. RNF139 can ubiquitinate precursor forms of SREBP1, thereby preventing SREBP1 synthesis [224].

Ubiquitination and autophagy
Ubiquitination of ULK1
In nutrient-deprived conditions, inhibition of mTORC1 subsequently activates autophagy, a highly regulated pathway essential for cell survival [25]. Autophagy complements amino acids by inducing degradation of macromolecules and organelles in lysosomes [26]. ULK1 complex, composed of the ULK1, ATG13 and FIP200, is directly regulated by mTORC1 and is required for autophagy induction. TRAF6 catalyzed K63-linked polyubiquitination of ULK1 can stabilize ULK1 to promote activation of autophagy, which is related to drug resistance in chronic myeloid leukemia patients [225]. Activating molecule in BECN1-regulated autophagy protein 1 (AMBRA1) is a cofactor that interacts with Beclin-1 to regulate autophagy. Decreased phosphorylation of AMBRA1 caused by mTORC1 inactivation will promote its interaction with TRAF6 to upregulate polyubiquitination of ULK1, thereby potentiating autophagy initiation [226]. TRIM16 and TRIM32 also target ULK1 for K63-linked polyubiquitination, which stabilizes ULK1 and increases its phosphorylating activity, respectively [227, 228]. DUB USP1 hydrolyzes the K63-linked ubiquitin chain on ULK1 [229]. Downregulation of USP24 also enhances ULK1 ubiquitination, thereby increasing protein stability and kinase activity of ULK1 [230]. These studies indicate the shift between ubiquitinated ULK1 and deubiquitinated ULK1 is essential for autophagy initiation.

Ubiquitination was also observed to be essential in the regulation of autophagy threshold during autophagy progression. NEDD4L-mediated ULK1 ubiquitination via K27 and K29-linkage assembly induces its proteolysis [231]. Decreased level of ULK1 activates transcription of ULK1 to maintain its basal protein level. Newly synthesized ULK1 will be deactivated by mTOR to ensure a safe threshold of autophagy [231]. CUL3-KLHL20 complex can also downregulate autophagy by targeting activated ULK1 for ubiquitination and proteolysis [232]. ULK1 can be deubiquitinated by USP20, which prevents it from degradation, maintaining its basal level required for the initiation of autophagy [233]. In prolonged starvation, the interaction between USP20 and ULK1 reduces to terminate autophagy [233]. In conclusion, ubiquitination and deubiquitination play essential functions in both autophagy initiation and autophagy progression. Modulating ubiquitination might be an effective treatment for chemoresistant patients with enhanced autophagy in cancer cells.

Ubiquitination of class III PI3K complex
Class III PI3K complex is composed of Beclin-1, ATG14, VPS34 and AMBRA1, essential for the nucleation of the phagophore. Various factors interact with Beclin-1 to regulate autophagy signaling. BCL2 can suppress autophagy by inhibiting Beclin-1 [234]. Starvation induced K63-linked ubiquitination of Beclin-1 by TRAF6 or AMBRA1 can block its interaction with BCL2, thus activating autophagy [235, 236]. AMBRA1 targeted polyubiquitination of Beclin-1 can enhance its association with VPS34 to activate of VPS34 [236]. TRIM50 mediated K63-linked polyubiquitination of Beclin-1 promotes its activation by ULK1 and induces autophagy in starvation [237]. DUB A20 and USP14 limit autophagy by reversing K63-linked ubiquitination of Beclin-1 [235, 238]. NEDD4 and RNF216 ubiquitinate Beclin-1 through K11- and K48-mediated linkage, respectively, which promote its degradation [239, 240]. DUB including USP19, ATXN3, USP10 and USP13 can reverse K11- or K48-ubiquitination of Beclin-1 to rescue it from degradation [241–243]. Beclin-1 also increases deubiquitinating
activities of USP10 and USP13, further enhancing autophagy by positive feedback [241]. FBXL20 mediates ubiquitination and proteasome degradation of VPS34 to inhibit autophagy [244]. ATG14 was observed to be ubiquitinated by ZBTB16-CUL3-ROC1 E3 ubiquitin ligase complex for degradation [245]. AMBRA1 is degraded via the action of E3 ligase CUL4 under normal conditions. Activation ofULK1 dissociates CUL4 from AMBRA1, causing stabilization of AMBRA1 to promote autophagy. Disassociation of AMBRA1 with CUL4 can promote AMBRA1 binding to CUL5 to inhibit CUL5-mediated DEPTOR degradation, thereby inducing autophagy [55]. CUL4 can re-associate with AMBRA1 to promote its proteolysis when autophagy terminates, thus regulating autophagy response [55]. What's more, E3 ligase RNF2 can also catalyze K48-linked ubiquitination and proteolysis of AMBRA1, thus downregulating autophagy [246]. Therefore, all the components of the Class III PI3K complex can be regulated by ubiquitination, which exerts important effects on autophagy.

**Ubiquitination of WIPI2**

WIPI2 is involved in an early step of the formation of preautophagosomal structures. mTORC1 can mediate phosphorylation of WIPI2. E3 ligase HUWE1 interacts with phosphorylated WIPI2 and catalyzes ubiquitination of phosphorylated WIPI2, which is subsequently targeted for proteolysis, thus inhibiting autophagy flux [247].

**Ubiquitination of ATG4**

ATG4 contributes to LC3 processing, playing an essential role in the phagophore expansion and autophagosome completion. E3 ligase RNF5 targets ubiquitination and degradation of ATG4B, thus limiting autophagy flux. When cell starves, RNF5 de-associates with ATG4B to induce autophagy [248].

**Ubiquitination and metabolic enzymes**

**Ubiquitination and glucose metabolism**

Increased glucose uptake and enhanced glycolytic flux are metabolic characteristics of cancer cells, supplying subsidiary pathways to provide substrates for macro-molecule synthesis. Activated AKT was observed to inhibit ubiquitination of HK1, the first rate-limiting enzyme in the glucose metabolism pathway, promoting glycolysis and glioblastoma progression [249]. HUWE1 mediated K63-linked ubiquitination of HK2 promotes its re-localization and activation, enhancing glycolysis and tumor growth (Fig. 2) [250]. TRAF6 mediated K63-linked ubiquitination of HK2 directs HK2 degradation by autophagy, thereby negatively regulating glycolysis [251]. Deubiquitination of HK2 catalyzed by CSN5 can rescue it from degradation and enhance glycolytic flux during hepatocellular cancer metastasis [252]. Mitochondrial HK can also be ubiquitinated by PARKIN, inducing its proteasomal degradation [253].

Phosphofructokinase (PFK), the second rate-limiting enzyme in glycolysis, is a key regulator of glycolytic flux in cancer cells. Decreased A20 mediated ubiquitination and degradation of PFK liver type (PFKL) are related to increased glycolysis during hepatocellular carcinoma progression [254]. Phosphorylation of PFK1 platelet isoform (PFKP) by AKT can prevent it from TRIM21-mediated ubiquitination and degradation, promoting aerobic glycolysis in glioblastoma cells [255].

Pyruvate kinase M2 (PKM2) is the third rate-limiting enzyme of glycolysis. Decreased CHIP catalyzed ubiquitination and degradation of PKM2 are associated with Warburg effect in ovarian cancer cells [256]. Downregulated ubiquitination of PKM2 by TRIM58 is related to progression of osteosarcoma [257]. E3 ligase PARKIN modifies PKM2 by ubiquitination to decrease its enzymatic activity without affecting its stability [258]. PKM2 deubiquitinated by USP7 can strengthen the protein stability of PKM2 [259], USP20 can also hydrolyze the ubiquitin chain on PKM2, but the detailed function of this deubiquitination is unclear [260].

Other enzymes in glucose metabolism can be also modified by ubiquitination. Glucose-6-phosphate isomerase (GPI), which catalyzes the conversion of glucose-6-phosphate to fructose-6-phosphate, can be ubiquitinated and degraded by E3 ligase RNF45 and TRIM25 [261]. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) is a glycolysis-promoting enzyme catalyzing the conversion between fructose 2,6-bisphosphate and fructose 6-phosphate. ROCK2 interacts with PFKFB3 and attenuates its ubiquitination and degradation in osteosarcoma cells [262]. What's more, glycolysis during different stages of cell cycle in Hela cells is regulated by E3 ligases. Decreased E3 ligase APC/C-CDH1 can attenuate proteasomal degradation of PFKFB3, promoting glycolysis and transition of late G1 phase into S phase. E3 ligase SCFβ-TrCP activated during S phase can target PFKFB3 for degradation [263]. Similarly, decreased ubiquitination and increased stability of glutaminase 1 (GLS1) were also observed to be mediated by decreased APC/C-CDH1 in mid-to-late G1 [264]. Phosphoglycerate kinase 1 (PGK1) catalyzes the conversion of 1,3-diphosphoglycerate to 3-phosphoglycerate. Decreased ubiquitination of PGK1 leads to chemotherapy resistance in gallbladder cancer cells [265]. Interaction between MetaLnc9 and PGK1 blocks ubiquitin-mediated degradation of PGK1, promoting lung cancer metastasis [266]. Following phosphorylation, phosphoglycerate mutase (PGAM), which converts 3-phosphoglycerate to 2-phosphoglycerate, can be ubiquitinated by MDM2 for degradation [267]. Decreased ubiquitination of PGAM...
by MDM2 contributes to neoplastic transformation [267]. PDK can be ubiquitinated by RNF126, which targets them for proteasomal degradation, enhancing conversion of pyruvate to acetyl-CoA by pyruvate dehydrogenase (PDH) in cancer cells [268].

Ubiquitination of enzymes involved in the TCA cycle is also associated with cancer progression. Decreased UBR5-mediated ubiquitination of citrate synthase leads to citrate accumulation in hypoxia breast cancer cells, promoting cell migration, invasion, and metastasis [269]. HIF-1 activation under hypoxia condition can promote α-ketoglutarate dehydrogenase (α-KGDH) complex ubiquitination and proteolysis by SIAH2. Decreased α-KGDH activity inhibits glutamine oxidation and promotes glutamine-dependent lipid synthesis for tumor growth [270]. USP13 promotes ovarian cancer progression by debiquitinating and upregulating α-KGDH [271].

Glucose-6-phosphate dehydrogenase (G6PD) catalyzes the oxidative pentose phosphate pathway, an essential process producing ribose-5-phosphate and NADPH from G6P. G6PD was observed to be ubiquitinated and degraded by VHL E3 ubiquitin ligase in podocytes [272]. VHL is tumor-suppressor protein [273]. But whether this regulation exists in cancer cells is unclear. Fructose-1,6-biphosphatase (FBP1) is a rate-limiting enzyme of gluconeogenesis. MAGE-TRIM28 mediated ubiquitination and degradation of FBP1 in hepatocellular carcinoma promotes Warburg effect and cancer progression [274]. Phosphoenolpyruvate carboxykinase 1 (PEPCK1)
is another rate-limiting enzyme in gluconeogenesis. High glucose in diabetes stimulates PEPCK1 acetylation, which promotes UBR5 mediated ubiquitination and degradation of PEPCK1 [275]. Studies have found that GLUT1 can be ubiquitinated for degradation in diabetes [276]. E3 ubiquitin ligase Malin mediated ubiquitination of glycogen debranching enzyme (AGL) is associated with Lafora and Cori’s disease [277]. But whether ubiquitination of GLUT1, PEPCK1 and AGL participates in tumor progression is still unknown. What’s more, ubiquitination and deubiquitination of other cancer associated metabolic enzymes is still unknown, such as enolase in glycolysis, isocitrate dehydrogenase in the TCA cycle, glycogen phosphorylase in glycogen metabolic process, and pyruvate carboxylase in gluconeogenesis. The relationship between their specific E3 ligases and DUBs and oncogenesis still need exploration.

Ubiquitination and fatty acid metabolism

Fatty acids synthesis is necessary for membrane biosynthesis in proliferating tumor cells. CUL3-KLHL25 E3 ligase can inhibit lipid synthesis and tumor growth by targeting ATP citrate lyase (ACLY) for ubiquitination and proteolysis [278]. However, USP13 and USP30 can mediate deubiquitination of ACLY, increasing the stability of ACLY to promote development of ovarian cancer and hepatocellular carcinoma, respectively [271, 279]. TRB3-COP1 mediates proteolysis of acetyl-coenzyme A carboxylase (ACC) in ubiquitin-dependent manner, inhibiting fatty acid synthesis and stimulating lipolysis [280]. But in breast cancer cells, ACC-alpha (ACCA) interacts with AKR1B10, which prevents ACCA from ubiquitination and proteolysis, thereby promoting de novo fatty acid synthesis and enhancing tumor growth [281]. E3 ligase COP1 can ubiquitinate fatty acid synthase (FASN) with SHP2 as an adapter [282]. E3 ligase SPOP mutation, which is common in prostate cancer, inhibits its ubiquitination of FASN. Increased FASN triggers lipid accumulation and promotes prostate cancer progression [283]. AKT activation promotes deubiquitination of FASN by the USP2a and increased lipogenesis, which promotes hepatocarcinogenesis [284, 285].

3-hydroxy-3-methyl glutaryl-coenzyme A reductase (HMGCR) is a rate-limiting enzyme in cholesterol biosynthesis. E3 ligases UBXD, RNF145 and RNF45 can mediate sterol-induced ubiquitination and degradation of HMGCR, attenuating cholesterol biosynthesis [286–288]. Hypoxia triggered upregulation of insulin-induced gene 2 can interact with HMGCR and promote its ubiquitination and degradation to avoid unnecessary oxygen consumption [289]. Dysregulated cholesterol metabolism is observed in multidrug resistant cancer cells (MDR), in which decreased E3 ligase RNF139 upregulates HMGCR and induces enhanced cholesterol synthesis [290]. Squalene epoxidase (SQLE), which catalyzes the first oxygenation reaction of cholesterol biosynthesis, can be ubiquitinated and degraded by E3 ligase MARCH6 under stimulation of sterol [291]. Additionally, E3 ligase MYLIP can modulate cellular cholesterol uptake by ubiquitinating LDL receptor which is responsible for cholesterol import [292]. But whether ubiquitination of SQLE and LDL receptor participate in cancer progression is unknown. In addition, ubiquitination and deubiquitination of other enzymes participating in fatty acid metabolism, such as Carnitine O-palmitoyltransferase 1 (CPT1), and their relationship with cancer progression have not been studied yet.

Ubiquitination and amino acid metabolism

In cancer cells, glutamine serves as another important carbon source for the TCA cycle to sustain mitochondrial ATP production [1]. Glutamine uptake increases dramatically in cancer cells. NEDD4L-depleted cancer cells have enhanced neutral amino acid transporter B (ASCT2) stability and glutamine uptake to fuel the mitochondrial metabolism [293]. Promotion of RNF5-targeted ubiquitination and degradation of glutamine carrier proteins ASCT2 and SLC38A2 can improve responsiveness of breast cancer cells to Paclitaxel treatment [294]. Glutamine can be converted via GLS to glutamate, which can subsequently be converted to α-ketoglutarate to fuel the TCA cycle. Succinylation of GLS suppresses its K48-linked ubiquitination and degradation, stabilizing GLS and promoting glutaminolysis in cancer cells [295]. Study also found the function of supranutritional dose of selenite in suppressing tumor progression by promoting APC/C-CDH1 mediated GLS1 ubiquitination and degradation [296]. Ubiquitination of other enzymes involved in glutamine metabolism, such as glutamate dehydrogenase 1 (GLUD1), hasn’t been studied.

3-phosphoglycerate, an intermediate product of glycolysis, can be converted to serine by D-3-phosphoglycerate dehydrogenase (PHGDH). This conversion is subsequently associated with formate production for nucleotide synthesis. Downregulated PARKIN in cancer suppresses ubiquitination of PHGDH and enhances its stability and protein level, thereby activating serine synthesis and promoting cancer progression [297]. Serine hydroxymethyltransferase 1 (SHMT1) is involved in the conversion of serine to glycine. K48-linked ubiquitination of SHMT1 mediates its degradation in the cytoplasm. K63-linked ubiquitination of SHMT1 by UBC13 in the nucleus promotes its nuclear export and prevents it from degradation, promoting tumor progression [298]. What’s more, dysregulation of aspartate and arginine metabolism is also associated with cancer progression [299]. However, ubiquitination and
deubiquitination of the enzymes participating in asparagine and arginine metabolism haven’t been studied and are worth attention in the future.

Conclusions
In the past decades, extensive efforts have been made to clarify the molecular mechanisms associated with metabolic reprogramming in cancer. In this review, we highlight the roles of ubiquitination and deubiquitination as modulators of cancer metabolism. Facing metabolic stresses, such as hypoxia, ubiquitination and deubiquitination in cancer cells can be abnormally regulated [10, 270]. On the other hand, dysregulated ubiquitination and deubiquitination play nonnegligible roles in cancer metabolism by involving in the regulation of metabolic reprogramming related signaling pathways, transcription factors as well as metabolic enzymes. For instance, hypoxia induces E3 ubiquitin ligase SIAH2 mediated ubiquitination and proteolysis of α-KGDH, inhibiting glutamine oxidation and promoting glutamine-dependent lipid synthesis to promote tumor growth [270]. Therefore, the interactions between ubiquitination/deubiquitination and cancer metabolism are complex and require more studies. Most studies have focused on the involvement of ubiquitination and deubiquitination in the regulation of signaling pathways and transcription factors, while ubiquitination and deubiquitination of the enzymes involved in glucose, fatty acid and amino acid metabolism are worth more attention in the future.

In the regulation of cancer metabolism and tumor progression, the E3 ubiquitin ligases/DUBs-substrates network is of high complexity. Single E3 ubiquitin ligase or DUB can target numerous substrates, and one molecule can be regulated by multiple E3 ubiquitin ligases or DUBs. For example, FBXW7 acts as a tumor suppressor by targeting mTOR, HIF-1α, c-Myc and SREBP1 for degradation [43, 136, 160, 222]. However, when facing DNA damage, elevated FBXW7 mediates proteasomal degradation of p53, leading to radiotherapy resistance [300]. Amino acids can stimulate subcellular localization of TRAF6 to lysosomes for subsequent K63-linked polyubiquitination and activation of mTOR signaling [42]. However, in starvation induced autophagy, TRAF6 mediates K63-linked polyubiquitination of ULK1, which leads to stabilization of ULK1 and activation of autophagy [225]. Therefore, E3 ligases and DUBs act in a context-dependent manner. Their exact roles in cancer may vary according to their substrates, tissues types, tumor stages, or different metabolic conditions. The study of ubiquitination and deubiquitination in cancer still has a long way to go. For example, whether metabolite levels within cancer cells act as modulators of ubiquitination is ambiguous. Importantly, development of specific drugs that disrupt or enhance specific E3 ligases/DUBs-substrates interactions holds promise for more efficient and less toxic therapeutics. What’s more, we have observed that decreased ubiquitination and increased stability of the metabolic related molecules, such as PDK1, NRF2, ULK1 and phosphoglycerate kinase 1, are associated with chemoresistance in various cancers. Thereby, modulating the activity of E3 ligases or DUBs could be exploited as a potential strategy for controlling chemoresistance in cancer treatment. Furthermore, various E3 ligases and DUBs have been already identified as potential targets for cancer therapy. Actually, many E3 ligases serve as tumor suppressors by catalyzing ubiquitination and degradation of metabolic related proteins which play oncogenic roles in cancers, indicating that drugs enhancing activities or expression of these E3 ligases should also be emphasized in further researches.

In conclusion, ubiquitination and deubiquitination are suggested to be essential regulators of metabolic reprogramming in cancer cells, demanding more studies in the future with the aim of improving cancer therapy.

Abbreviations
LDHA: L-lactate dehydrogenase A chain; mTORC1: Mechanistic target of rapamycin complex 1; HIF-1: Hypoxia-inducible factor 1; SREBP: Sterol regulatory element-binding protein; TCA: Tricarboxylic acid; AMPK: 5′-AMP-activated protein kinase; ROS: Reactive oxygen species; NRF2: Nuclear factor erythroid 2-related factor 2; HECT: Homology to E6AP C terminus; RING: RING-between-RING; RING: Really interesting new gene; DUB: Deubiquitinating enzyme; USP: Ub-specific protease; UCH: Ub C-terminal hydrolase; OUT: Ovarian tumor protease; MJD: Machado-Joseph domain protease; JAMM: LAB1/MPN+/MOV34; DYRK2: Dual specificity tyrosine-phosphorylation-regulated kinase 2; IDH1/2: Isocitrate dehydrogenase 1/2; TSC: Tuberculous sclerosis complex; PDK1: 3-phosphoinositide-dependent protein kinase 1; PTEN: Phosphatase and tensin homolog; GLUT1: Glucose transporter type 1; HR1: Hexokinase 1; PDK: Pyruvate dehydrogenase kinase; AMBRA1: Activating molecule in BECN1-regulated autophagy protein 1; PFK: Phosphofructokinase; PFKL: PFK liver type; PKP: PKI platelet isozyme; PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; GLS1: Glutaminase 1; PKM2: Pyruvate kinase M2; PKG1: Phosphoglycerate kinase 1; PGAMS: Phosphoglycerate mutase 5; α-KGDH: α-ketoglutarate dehydrogenase; G6PD: Glucose-6-phosphate dehydrogenase; PEPCK: Phosphoenolpyruvate carboxykinase 1; PDH: Pyruvate dehydrogenase; FBP1: Fructose-1,6-bisphosphatase; AGL: Glycogen debranching enzyme; ACLY: ATP citrate lyase; ACC: Acetyl-coenzyme A carboxylase; FASN: Fatty acid synthase; HMGCR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SGLT: Squalene epoxidase; CPT1: Carnitine O-palmitoyltransferase 1; MDR: Multidrug resistant; ASCT2: Neutral amino acid transporter B; PHGD H: D-3-phosphoglycerate dehydrogenase; SHMT1: Serine hydroxymethyltransferase 1

Acknowledgements
Not applicable.

Authors’ contributions
T.S., Z.L. and Q.Y. conceived the review. T.S. and Z.L. wrote the first version of the manuscript. Q.Y. revised the manuscript. All of the authors approved the final version of the manuscript.

Funding
This research was supported by National Natural Science Foundation of China (Grant/Award Numbers: 81872125).
Availability of data and materials
All the data obtained and/or analyzed during the current study were available from the corresponding authors on reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors give consent for the publication of manuscript in Molecular Cancer.

Competing interests
The authors declare that there is no potential competing interest.

Author details
1Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Heping District, Shenyang 110004, China. 2Department of Urology, First Hospital of China Medical University, Shenyang, China.

Received: 15 July 2020 Accepted: 23 September 2020
Published online: 01 October 2020

References
1. DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. Sci Adv. 2016;2:e1600200.
2. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. Annu Rev Cell Dev Biol. 2011;27:441–64.
3. Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, Yang C, Do QN, Moreau P, Attal M, Caillot D,Macro M, Karlin L, Garderet L, Facon T, Duffy KJ, Raasi S, Zhang H, Yen JL, Kaiser P. A ubiquitin-interacting motif K11/K48-branched ubiquitin chains. Structure. 2020;28:1
4. Xie H, Hanai J, Ren JG, Kats L, Burgess K, Bhargava P, Signoretti S, Billiard J, Moreau P, Attal M, Caillot D, Macro M, Karlin L, Garderet L, Facon T, Benboubker L, Escoffre-Barbe M, Stoppa AM, et al. Prospective evaluation of magnetic resonance imaging and [(18)F]fluorodeoxyglucose positron emission tomography-computed tomography at diagnosis and before maintenance therapy in symptomatic patients with multiple myeloma included in the IFM/DFCI 2009 trial: results of the IMA/JEM study. J Clin Oncol. 2017;35:2991–8.
5. Xie H, Hanai J, Ren JG, Kats L, Burgess K, Bhargava P, Signoretti S, Billiard J, Duffy KJ, Grant A, et al. Targeting lactate dehydrogenase—a inhibits tumorigenesis and tumor progression in mouse models of lung cancer and impacts tumor-initiating cell. Cell Metab. 2014;19:795–809.
6. Wang YH, Israelsen WJ, Lee D, Yu VWC, Jeanson NT, Clish CB, Cantley LC, Deberardinis RJ, Yu Y, Tu BP. Loss of a negative regulator of mTORC1 input with biosynthetic output. Nat Cell Biol. 2013;15:555–64.
7. Lack R, Roy S, Kenfic CM, Su JS, Salas E, Ronen SM, Debnath J. Autophagy facilitates glycolysis during Ras-mediated oncogenic transformation. Mol Biol Cell. 2011;22:165–78.
8. Zhang C, Lin M, Wu R, Wang X, Yang B, Levine AJ, Hu W, Feng Z, Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect. Proc Natl Acad Sci U S A. 2011;108:16259–64.
9. Martinez-Outschoorn UE, Pavlides S, Howell A, Pestell RG, Tanowitz HB, Sotgia F, Lisanti MP. Stromal epithelial metabolic coupling in cancer: integrating autophagy and metabolism in the tumor microenvironment. Int J Cancer. 2011;143:1045–51.
10. Hendrick A, Chechanover A. The ubiquitin system. Annu Rev Biochem. 1998;67:425–79.
11. Sewduth RN, Baete MF, Sabrina AA. Cracking the monoubiquitin code of genetic diseases. Int J Mol Sci. 2020;21.
12. Baur R, Raper M. Getting closer: insight into the structure and function of K11/K48-branched ubiquitin chains. Structure. 2020;28:1–3.
13. Yao T, N’djoua A. Regulation of gene expression by the ubiquitin-proteasome system. Semin Cell Dev Biol. 2012;23:523–9.
14. Flick K, Raaii S, Zhang H, Yen JL, Kaiser P. A ubiquitin-interacting motif protects polyubiquitinated Met4 from degradation by the 26S proteasome. Nat Cell Biol. 2006;8:509–64.
15. Le Cam L, Linaire LK, Paul C, Julien E, Lacroix M, Hatchi E, Triboulet R, Bossis G, Shamuella A, Rodriguez MS, et al. EAF1 is an atypical ubiquitin ligase that modulates p53 effector functions independently of degradation. Cell. 2006;127:775–88.
16. Glickman MH, Chechanover A. The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. Physiol Rev. 2002;82:373–428.
17. Tang R, Langdon WY, Zhang J. Regulation of immune responses by E3 ubiquitin ligase Cbl-b. Cell Immunol. 2019;340.
rapalogues and dual kinase inhibitors on mTORC1 and mTORC2 stoichiometry. Int J Mol Med. 2019;43:47–56.
40. Wang P, Zhang Q, Tan L, Xu YN, Xie XB, Zhao Y. The regulatory effects of mTOR complexes in the differentiation and function of CD4(+) T cell subsets. J Immunol Res. 2020;2020.
41. Rogala KB, Gu X, Kedar JF, Abu-Ramahi M, Bianchi LF, Bottino AMS, Dueholm R, Niehaus A, Overwijn D, Fils ACP, et al. Structural basis for the docking of mTORC1 on the lysosomal surface. Science. 2019;366:468–+.
42. Linares JF, Duran A, Yajima T, Pasparakis M, Moscat J, Diaz-Meco MT. K63 polyubiquitination and activation of mTOR by the p62-TRAF6 complex in nutrient-activated cells. Mol Cell. 2013;51:283–96.
43. Mao JH, Kim IJ, Wu D, Climent J, Kang HC, DellRosario R, Balmain A. FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression. Science. 2008;321:499–502.
44. Wang FF, Zhang XJ, Yan YR, Zhu XH, Yu J, Ding Y, Hu JL, Zhou WJ, Zeng ZC, Liao WT, et al. FBX8 is a metastasis suppressor downstream of miR-223 and targeting mTOR for degradation in colorectal cancer. Cancer Lett. 2017;386:85–95.
45. Mimoto R, Nihira NT, Hirooka S, Takeyama H, Yoshida K. Diminished YRDK2 sensitizes hormone receptor-positive breast cancer to everolimus by the escape from degradation mTOR. Cancer Lett. 2017;384:27–38.
46. Kim SY, Kim HJ, Kim HJ, Kim CH. Non-thermal plasma induces antileukemic effect through mTOR ubiquitination. Cells. 2020;9.
47. Park D, Lee MN, Jeong H, Koh A, Yang YR, Suh PG, Ryu SH. Parkin ubiquitinates mTOR to regulate mTORC1 activity under mitochondrial stress. Cell Signal. 2014;26:2122–30.
48. Agrawal P, Chen YT, Schilling B, Gibson BW, Hughes RE. Ubiquitin-specific peptidase 9, X-linked (USP9X) modulates activity of mammalian target of rapamycin (mTOR). J Biol Chem. 2012;287:21164–75.
49. Hussain S, Feldman AL, Da C, Ziesmer SC, Ansell SM, Galardy PJ. Ubiquitin hydrolase UCH-L1 destabilizes mTORC1 complex 1 by antagonizing DDB1-CUL4mediated ubiquitination of raptor. Mol Cell Biol. 2013;33:1188–97.
50. Wang B, Jie ZL, Joo DH, Ordureau A, Liu P, Gan WJ, Guo JP, Zhang JF, North BJ, Dai XP, et al. TRAF2 and OTUD7B govern a ubiquitin-dependent switch that regulates mTORC2 signalling. Nature. 2017;545:365–+.
51. Carbonneau M, Gabrie LM, Lalonde ME, Germain MA, Motorina A, Guoit MC, Secco B, Vincent EE, Tumber A, Hulea L, et al. The oncometabolite 2-hydroxyglutarate activates the mTORC1 signalling pathway. Nat Commun. 2016;7.
52. Chen L, Liu TY, Tu YH, Rong DY, Gao Y. Cul1 promotes melanoma cell proliferation by promoting DEPTOR degradation and enhancing capdependent translation. Oncol Rep. 2016;35:1049–56.
53. Tan MJ, Xu J, Siddiqui J, Feng FL, Sun Y. Depletion of SAG/RBX2 E3 ubiquitin ligase suppresses prostate tumorigenesis via inactivation of the PI3K/AKT/mTOR axis. Mol Cancer. 2016;15.
54. Zhao LL, Wang XB, Yu Y, Deng L, Chen L, Peng XP, Jiao CC, Gao GL, Tan X, Sun Y, Moon JH, et al. TRAF2 and OTUD7B govern a ubiquitin-dependent switch that regulates mTORC2 signalling. Oncogene. 2018;37:1084–91.
55. Zheng L, Ding HR, Lu ZM, Li Y, Pan YQ, Ning T, Ye J, E3 ubiquitin ligase E6AP-mediated mTORC2 turnover in the presence and absence of HPV16 E6. Genes Cells. 2008;13:285–94.
56. Chong-Kopera H, Inoki K, Li Y, Zhu TQ, Garcia-Gonzalo FR, Rosa JL, Guan KL. TSC2 stabilizes TSC2 by inhibiting the interaction between TSC2 and the HERC1 ubiquitin ligase. J Biol Chem. 2006;281:7831–6.
57. Mohan N, Shen Y, Dokmanovic M, Endo Y, Hirsch DS, Wu WJ, VPS34 regulates TSC1/TSC2 heterodimer to mediate Rheb and mTORC1/S6K1 activation and cellular transformation. Oncotarget. 2016;7:52239–54.
58. Madigan JP, Hou F, Ye LL, Hu JC, Dong AP, Tempel W, Yohe ME, Randazzo PA, Jenkins LMM, Gottesman MM, Tong YF. The tuberous sclerosis complex subunit TBC1D7 is stabilized by Akt phosphorylation-mediated 14–3–3 binding. J Biol Chem. 2018;293:16142–59.
59. Rodríguez-Escudero I, Redelants FM, Thorner J, Nombela C, Molina M, Cid VJ. Reconstitution of the mammalian PI3K/PTEN/Akt pathway in yeast. Biochemistry. 2005;39:6013–23.
60. Wang XZ, Dang TT, Liu TT, Chen S, Li L, Huang S, Fang M. NEDD4L4 protein catalyzes ubiquitination of PIK3CA protein and regulates PI3K-AKT signaling. J Biol Chem. 2016;291:17467–77.
61. Hanmi A, Song J, Thakur S, Martinson R, Niihara S, Marcusson A, Bergh A, Heldin CH, Sandstrom M. TGF-beta promotes PI3K-AKT signalling and prostate cancer cell migration through the TRAF6-mediated ubiquitylation of p85 alpha. Sci Signal. 2017;10.
62. Jiang J, Xu YT, Ren HJ, Wudu M, Wang GZ, Song X, Su HB, Jiang XZ, Jiang LH, Quo XS. MKRN2 inhibits migration and invasion of non-small-cell lung cancer by negatively regulating the PI3K/Akt pathway. J Exp Clin Cancer Res. 2018;37.
63. Ko HR, Kim CK, Lee SB, Song J, Lee KH, Kim KK, Park KW, Cho SW, Ahn JY, P42 Ebp1 regulates the proteasomal degradation of the p85 regulatory subunit of PI3K by recruiting a chaperone-E3 ligase complex HSP70/CHIP. Cell Death Dis. 2014;5.
64. Kuchay S, Duan SS, Schenkein E, Peschiaroli A, Saraf A, Flores L, Washburn MP, Pagano M. FBXL2- and PTP1-mediated degradation of p110 alpha/p85 beta regulatory subunit controls the PI3K signaling cascade. Nat Cell Biol. 2013;15:472–8+.
65. Wu YH, Chang TH, Huang YF, Chen CC, Chou CY. COL11A1 confers chemoresistance on ovarian cancer cells through the activation of Akt/c/EBP beta regulatory subunit. FEBS Lett. 2017;591:145–52.
66. Zhang JD, Yang ZF, Ou JY, Xia XJ, Zhi F, Cui J. The F-box protein FBXL18 inhibits prolactin-induced EGFR phosphorylation and Akt activation in colorectal carcinoma. Cancer Lett. 2017;386:741–50.
67. Zhao LL, Wang XB, Yu Y, Deng L, Chen L, Peng XP, Jiao CC, Gao GL, Tan X, Sun Y, Moon JH, et al. TRAF4 is a critical molecule for Akt activation in lung cancer. Cancer Lett. 2017;384:741–50.
68. Madigan JP, Hou F, Ye LL, Hu JC, Dong AP, Tempel W, Yohe ME, Randazzo PA, Jenkins LMM, Gottesman MM, Tong YF. The tuberous sclerosis complex subunit TBC1D7 is stabilized by Akt phosphorylation-mediated 14–3–3 binding. J Biol Chem. 2018;293:16142–59.
69. Rodríguez-Escudero I, Redelants FM, Thorner J, Nombela C, Molina M, Cid VJ. Reconstitution of the mammalian PI3K/PTEN/Akt pathway in yeast. Biochemistry. 2005;39:6013–23.
70. Ko HR, Kim CK, Lee SB, Song J, Lee KH, Kim KK, Park KW, Cho SW, Ahn JY. P42 Ebp1 regulates the proteasomal degradation of the p85 regulatory subunit of PI3K by recruiting a chaperone-E3 ligase complex HSP70/CHIP. Cell Death Dis. 2014;5.
71. Kuchay S, Duan SS, Schenkein E, Peschiaroli A, Saraf A, Flores L, Washburn MP, Pagano M. FBXL2- and PTP1-mediated degradation of p110 alpha/p85 beta regulatory subunit controls the PI3K signaling cascade. Nat Cell Biol. 2013;15:472–8+.
72. Wu YH, Chang TH, Huang YF, Chen CC, Chou CY. COL11A1 confers chemoresistance on ovarian cancer cells through the activation of Akt/c/EBP beta regulatory subunit. FEBS Lett. 2017;591:145–52.
73. Zhang JD, Yang ZF, Ou JY, Xia XJ, Zhi F, Cui J. The F-box protein FBXL18 inhibits prolactin-induced EGFR phosphorylation and Akt activation in colorectal carcinoma. Cancer Lett. 2017;386:741–50.
74. Madigan JP, Hou F, Ye LL, Hu JC, Dong AP, Tempel W, Yohe ME, Randazzo PA, Jenkins LMM, Gottesman MM, Tong YF. The tuberous sclerosis complex subunit TBC1D7 is stabilized by Akt phosphorylation-mediated 14–3–3 binding. J Biol Chem. 2018;293:16142–59.
75. Rodríguez-Escudero I, Redelants FM, Thorner J, Nombela C, Molina M, Cid VJ. Reconstitution of the mammalian PI3K/PTEN/Akt pathway in yeast. Biochemistry. 2005;39:6013–23.
82. Liang CX, Liang GY, Zheng XQ, Huang YX, Huang SH, Yin D. RPS2 positively regulates the osteogenic differentiation of mesenchymal stem cells by activating the K36-linked ubiquitination of Akt. Stem Cells Int. 2020;202020.

83. Wang GH, Long J, Gao Y, Zhang WN, Han F, Xu C, Sun L, Yang SC, Lan QJ, Hou ZL, et al. SETDB1-mediated methylation of Akt promotes its K36-linked ubiquitination and activation leading to tumorgenesis. Nat Cell Biol. 2019;21:214.

84. Li HJ, Lan QJ, Wang GH, Guo KK, Han CS, Li XL, Hu JB, Cao ZX, Luo XL. KDM4B facilitates colorectal cancer growth and glucose metabolism by stimulating TRAF6-mediated AKT activation. J Exp Clin Cancer Res. 2020;39.

85. Lim JH, Jono H, Komatsu K, Woo CH, Lee J, Miyata M, Matsuno T, Xu XB, Huang YX, Zhang WH, et al. CYLD negatively regulates transforming growth factor-beta-signalization via deubiquitinating. Nat Commun. 2012;3.

86. Yang FL, He HG, Zhang B, Zheng JH, Wang M, Zhang M, Cui HX. Effect of deubiquitinaing ovarian tumor domain-containing protein 5 (OTUD5) on radiosensitivities of cervical cancer by regulating the ubiquitination of Akt and its mechanism. Med Sci Monit. 2019;25:3469–75.

87. Goldbräedh D, Neufeld D, Eid-Mutläk V, Lassy I, Gilda JE, Parnis A, Cohen S. USP1 deubiquitimates Akt to inhibit PI3K-Akt-FoxO signaling in muscle during prolonged starvation. EMBO Rep. 2020;21.

88. Qiu CJ, Liu KR, Zhang S, Gao SM, Chen WR, Li DT, Huang YX. Bisdemethoxycurcumin inhibits hepatocellular carcinoma proliferation through Akt inactivation via CYLD-mediated deubiquitination. Drug Des Deliv Ther. 2020;14:993–1001.

89. Xiang T, Ohashi A, Huang YP, Pandita TK, Ludwig T, Powell SN, Yang Q. Negative regulation of Akt activation by BRCA1. Cancer Res. 2008;68:10040–4.

90. Su X, Shen Z, Yang Q, Sui F, Pu J, Ma JJ, Ma SR, Yao DM, Ji MJ, Hou P. BCR-ABL disrupts PTEN nuclear-cytoplasmic shuttling through phosphorylation-dependent activation of HAUSP. Leukemia. 2014;28:1256–3.

91. Bae SH, Kim SY, Jeong JH, Park D, Magis AT, Zhang J, Zhou W, Sica GL, Ramalingam SS, Curran T. Dephosphorylation of AKT by a cancer-specific ubiquitin ligase. Mol Cell. 2013;50:420–7.

92. Macheja M, Liu YJ, Li JY, Lee XX, Yang H, Tian CC, Chen J, An IS, Kim JH, Jeong JB, Seong KM, Nam SY, Yang KH, Kim CS, Kim HS, Sun JT, Huang WC, et al. USP10 inhibits lung cancer cell growth and invasion by upregulating PTEN. Mol Cell. 2015;61.

93. Lee JT, Shan J, Zhang JY, Li MY, Zhou B, Zhou A, Parsons R, Gu W. RFP-mediated ubiquitination of PTEN modulates its effect on AKT activation. Cell Res. 2013;23:562–64.

94. Sun J, Li TX, Zhao YY, Huang LR, Sun H, Wu H, Jiang XF. USP10 inhibits lung cancer cell growth and invasion by upregulating PTEN. Mol Cell. 2018;44:1–7.

95. Zhang JS, Zhang PJ, Wei YK, Piao HL, Wang WQ, Maddika S, Wang M, Chen DH, Sun YT, Hung MC, et al. Deubiquitylation and stabilization of PTEN by USP13. Nat Cell Biol. 2013;15:13486.

96. Yuan L, Li YR, Li HC, Gao HD, Song SS, Zhang Y, Xing GC, Kong XZ, Wang LJ, Li Y, et al. Deubiquitylase OTUD3 regulates PTEN stability and suppresses tumorigenesis (vol 17, pg 1169, 2015). Nat Cell Biol. 2015;17.

97. Shen WM, Yin JN, Xu RJ, Xu DF, Zheng SY. Ubiquitin specific peptidase 49 inhibits non-small cell lung cancer cell growth by suppressing PI3K/AKT signaling. Kaohsiung J Med Sci. 2019;35:401–7.

98. Zhang H, Wei PT, Liu WV, Han XT, Yang JH, Qin SF. Long noncoding RNA Inc-DILC stabilizes PTEN and suppresses clear cell renal cell carcinoma progression. Cell Biosci. 2019.

99. Morotti A, Panuzzo C, Crivellaro S, Pergolizzi B, Familiari U, Berger AH, Saglio G, Pandolfi PP. BCR-ABL disrupts PTEN nuclear-cytoplasmic shuttling through phosphorylation-dependent activation of HAUSP. Leukemia. 2014;28:1256–33.

100. Wu Y, Zhou H, Wu K, Lee J, Li S, Liu X. PTEN phosphorylation and nuclear export mediate free fatty acid-induced oxidative stress. Antioxid Redox Signal. 2014;60:1382–95.

101. Sacco JJ, Yau TY, Darling S, Patel V, Liu H, Urbe S, Clague MJ, Coulson JM. The deubiquitylase Ataxin-3 restricts PTEN transcription in lung cancer cells. Oncogene. 2014;33:4265–72.

102. Pineda CT, Ramanathan S, Tzoker KF, Weon JL, Potts MB, Ou YH, White MA, Potts PR. Dephosphorylation of AMPK by a cancer-specific ubiquitin ligase. Cell. 2015;160:715–28.

103. Kwon E, Li X, Deng Y, Chang HW, Kim DY. AMPK is down-regulated by the CROLA-CBNN axis through the polyubiquitination of AMPKalpha isoforms. FASEB J. 2019;33:36539–50.

104. Wla IK, Song SJ, Song MS. A new duet in cancer biology: AMPK the typical and UBE2O the atypical. Mol Cell Oncol. 2017;4:1034864.

105. Yang SJ, Sejon NJ, Nguyen TV, Deshaies RJ, Park CS, Lee KM. Ubiquitin-dependent proteasomal degradation of AMPK controls metabolism and cell cycle progression. Mol Cell. 2019;70:1675–28.

106. Sun J, Li TX, Zhao YY, Huang LR, Sun H, Wu H, Jiang XF. USP10 inhibits lung cancer cell growth and invasion by upregulating PTEN. Mol Cell. 2018;44:1–7.

107. Lee MS, Jeong MH, Lee HW, Han HJ, Ko A, Hewitt SN, Kim JH, Chun KH, Chung JY, Lee C, et al. PI3K/AKT activation induces PTEN ubiquitination and destabilization accelerating tumorigenesis. Nat Commun. 2015;6.

108. Lee YR, Chen M, Lee JD, Zhang JY, Lin SY, Fu TM, Chen H, Ishikawa T, Chang SY, Katon J, et al. Reactivation of PTEN tumor suppressor for cancer treatment through inhibition of a MYC-WWP1 inhibitory pathway. Science. 2019;364.

109. Lee JT, Shan J, Zhang JY, Li MY, Zhou B, Zhou A, Parsons R, Gu W. RFP-mediated ubiquitination of PTEN modulates its effect on AKT activation. Cell Res. 2013;23:562–64.

110. Sun J, Li TX, Zhao YY, Huang LR, Sun H, Wu H, Jiang XF. USP10 inhibits lung cancer cell growth and invasion by upregulating PTEN. Mol Cell. 2018;44:1–7.

111. Kim SY, Jeong SY, Jung JH, Park D, Magis AT, Zhang J, Zhou W, Sica GL, Ramalingam SS, Curran T. Dephosphorylation of AMPK by a cancer-specific ubiquitin ligase. Cell. 2015;160:715–28.

112. Kwon E, Li X, Deng Y, Chang HW, Kim DY. AMPK is down-regulated by the CROLA-CBNN axis through the polyubiquitination of AMPKalpha isoforms. FASEB J. 2019;33:36539–50.

113. Wla IK, Song SJ, Song MS. A new duet in cancer biology: AMPK the typical and UBE2O the atypical. Mol Cell Oncol. 2017;4:1034864.

114. Yang SJ, Sejon NJ, Nguyen TV, Deshaies RJ, Park CS, Lee KM. Ubiquitin-dependent proteasomal degradation of AMPK controls metabolism and cell cycle progression. Mol Cell. 2019;70:1675–28.
126. Zeng TL, Wang Q, Fu J, Lin Q, Bi J, Ding WC, Qiao YK, Zhang S, Zhao WX, Lin HY, et al. Impeded Nedd4–1-mediated Ras degradation underlies Ras-driven tumorigenesis. Cell Rep. 2017;4:871–82.

127. Dang CV. The interplay between MYC and HIF in the Warburg effect. Ernst Schering Found Symp Proc. 2007:35–53.

128. Buckley DL, Van Mole I, Garreis PC, Tae HS, Michel J, Nobljin DJ, Jorgensen WL, Colli A, Crews CM. Targeting the von Hippel-Lindau E3 ubiquitin ligase using small molecules to disrupt the VHL/HIF-1α interaction. J Am Chem Soc. 2012;134:4466–8.

129. Guo Y, Meng X, Ma J, Zheng Y, Wang Q, Wang Y, Shang H. Human papillomavirus 16 E6 contributes to HIF-1α-mediated induced Warburg effect by attenuating the VHL/HIF-1 interaction. Int J Mol Sci. 2014;15:7974–86.

130. Liu J, Zhang C, Zhao YH, Yue XT, Wu H, Huang S, Chen J, Tomisky K, Ye HY, Kehla CA, et al. Parkin targets HIF-1 α for ubiquitination and degradation to inhibit breast tumor progression. Nat Commun. 2017;8.

131. Zhang L, Cao J, Dong L, Lin H. Tiparp forms nuclear condensates to degrade HIF-1α and suppress tumorigenesis. Proc Nat Acad Sci U S A. 2020;117:13447–56.

132. Thiiruang P, Vigneshwaran V, Prasanth T, Vijay Arv BR, Malojao VA, Rakesh H, Khanan SA, Mahmood R, Prabhakar BT, BP-1T, an antiangiogenic benzenopheno-thiazole pharmacophore, counteracts HIF-1-1 signaling through p53/MDM2-mediated HIF-1α pro teaseosomal degradation. Angiogenesis. 2017;20:55–71.

133. Joshi S, Singh AR, Durden DL. MDM2 regulates hypoxic hypoxia-inducible factor 1α stability in an E3 ligase, proteasome, and FEN1-phosphatidylinositol 3-kinase-AKT-dependent manner. J Biol Chem. 2014;289:22785–95.

134. Chowdhury AR, Fuchs SY, Rustgi A, Avadhani NG. Mitochondrial stress-induced p53 regulates HIF-1α activity by physical association and enhanced ubiquitination. Oncogene. 2017;36:397–409.

135. Amelio I, Inoue S, Markert EK, Levine AJ, Knight RA, Mak TW, Melino G. TAp73 opposes tumor angiogenesis by promoting hypoxia-inducible factor 1α degradation. Proc Natl Acad Sci U S A. 2015;112:226–31.

136. Flugel D, Gorlach A, Kietzmann T. GSK-3β regulates cell growth, migration, and angiogenesis via Fbw7 and USP28-dependent degradation of HIF-1α. Blood. 2012;119:1292–301.

137. Lee SH, Lee JG, Bae JS, Liu KH, Lee YM. A group of novel HIF-1α inhibitors, glycolins, blocks HIF-1α synthesis and decreases its stability via inhibition of the PDK1/akt/mTOR pathway and Hsp90 binding. J Cell Physiol. 2015;230:853–62.

138. Lee YM, Kim GH, Park EI, Oh TI, Lee S, Kan SY, Kang H, Kim BM, Kim JH, Lim JH. Thymoquinone selectively kills hypoxic renal cancer cells by suppressing HIF-1α-mediated glycolysis. Int J Mol Sci. 2019;20.

139. Ju UI, Park JW, Park HS, Kim SJ, Chun YS. FXB0112 represses cellular response to hypoxia by destabilizing hypoxia-inducible-factor-1α mRNA. Biochem Biophys Res Commun. 2015;464:1008–15.

140. Chen Z, Lin TC, Bi X, Lu G, Dawson BC, Miranda R, Medeiros LJ, McIlmeie I, McCarty N. TRIM44 promotes quiescent multiple myeloma cell occupancy of HIF-1α and dictates H3K56 acetylation promoting hypoxia-induced HIF-1α degradation. Blood. 2012;119:1292–301.

141. Wang SQ, Wang N, Zheng YF, Yang BW, Liu PX, Zhang FX, Li M, Song JX, Chang XW, ZYL. Caveolin-1 inhibits breast cancer stem cells via c-Myc mediated metabolic reprogramming. Cell Death Dis. 2020;11:40.

142. Gonzalez-Pecchi V, Kwan AK, Doyle S, Ivanov AA, Du Y, Fu H. Nsd2Is stabilized Myc through hindering its interaction with FBXW7. J Mol Cell Biol. 2020;12:438–47.

143. Sriratanasak N, Pettri K, Laobuthese A, Wattanathana W, Vinayawanuakkit C, Luarpitpong S, Chanvorachote P. Novel c-Myc targeting compound N, N-Bis (5-Ethyl-2-Hydroxybenzyl) methanimine for mediated c-Myc ubiquitously-proteasomal degradation in lung cancer cells. Mol Pharmacol. 2020;98:130–42.

144. Fiore D, Piscopo C, Proto MC, Vasaturo M, Dal Piaz F, Fusco BM, Pagano C, Laeeza C, Bifusco M, Gazzero P. N6-Isopentenyladenosine inhibits colorectal cancer and improves sensitivity to 5-fluorouracil targeting FBXW7 tumor suppressor. Cancers. 2019;11.

145. Hu Y, Yu K, Wang G, Zhang D, Shi C, Ding Y, Hong D, Zhang D, He H, Sun L, et al. Laronotide C inhibits cell proliferation and induces apoptosis through attenuating Wnt/beta-catenin/c-Myc signaling pathway in human gastric cancer cell. Biochem Pharmacol. 2018;150:280–92.

146. Morel M, Shah KN, Long WW. The F-box protein FBXL16 up-regulates the stability of c-Myc oncoprotein by antagonizing the activity of the F-box protein FBW7. J Biol Chem. 2020;295:7970–80.

147. Hao CC, Zhou XC, Jiang YD, Wang JJ, Tao ZZ, Guo J. The Epv5 oncogene promotes lymphatic cancer cell proliferation by stabilizing c-Myc protein. Cancer Cell. 2020;20:20.

148. Ma S, Lu CC, Yang LY, Wang JJ, Wang BS, Cai HQ, Hao JJ, Xu X, Cai Y, Zhang Y, Wang MR. ANXA2 promotes esophageal cancer progression by activating MYC-HIF1A-VEGF axis. J Exp Clin Cancer Res. 2018;37.

149. He J, Li FZ, Zhou Y, Hou XY, Liu SS, Li XC, Zhang YW, Jing XQ, Yang LP, LncRNA XLOC_006390 promotes pancreatic carcinogenesis and glucose metabolism by stabilizing c-Myc. Cancers. 2020;12:419–29.

150. Tang JY, Yan TT, Bao YJ, Shen CQ, Yu CY, Zhu XQ, Tian XL, Guo FF, Liang Q, Liu Q, et al. LncRNA GLCC1 promotes colorectal carcinogenesis and glucose metabolism by stabilizing c-Myc. Nat Commun. 2019;10.
Cepeda D, Ng HF, Sharifi HR, Mahmoudi S, Cerrato VS, Fredlund E, Magnusson K, Nilsson H, Malyskova A, Rantala J, et al. CDK-mediated activation of the SCFβTrCP ubiquitin ligase promotes MYC-driven transcription and tumourigenesis and predicts poor survival in breast cancer. Embo Mol Med. 2013;5:1067–86.

Popov N, Schulein C, Jaenicke LA, Eilers M. Ubiquitylation of the amino terminus of MYC by SCF beta-TRCP antagonizes SCFFBW7-mediated turnover. Nat Cell Biol. 2010;12:973–81.

Sun X, He X, Yin L, Sears R, Dai MS. The nuclear ubiquitin-specific protease USP36 deubiquitinates and stabilizes c-Myc. Cancer Res. 2015;75.

Pan J, Deng Q, Jiang C, Wang X, Ni T, Li H, Chen T, Jj, Pan W, Cai X, et al. USP7 directly deubiquitinates and stabilizes c-Myc in lung cancer. Oncogene. 2015;34:3987–67.

Zhang WL, Liu ZK, Wang JM, Tian QB. Knockdown of USP28 enhances the radiosensitivity of esophageal cancer cells via the c-Myc-hypoxia-inducible-factor-1 alpha pathway. J Cell Biochem. 2019;120:201–12.

Kim D, Hong A, Park H, Shin WH, Yoo L, Jeon SJ, Chung KC. Deubiquitinating enzyme USP22 positively regulates c-Myc stability and tumorigenic activity in mammalian and breast cancer cells. J Cell Physiol. 2017;232:3664–76.

Li X, Wu LM, Zopp M, Kopelow S, Du W. p33-TP53-induced glycolysis regulator mediated glycolytic suppression attenuates DNA damage and genomic instability in fanconi anemia hematopoietic stem cells. Stem Cells. 2019;37:937–47.

Wade M, Wang YV, Wahl GM. The p53 orchestra: Mdm2 and Mdmx set the tone. Trends Cell Biol. 2008;28:309–19.

Barak Y, Juven T, Haffner R, Oren M. mdm2 expression is induced by wild type p53 activity. EMBO J. 1993;12:461–7.

Bang S, Xue S, Kurokawa M. Regulation of the p53 family proteins by the ubiquitin proteasomal pathway. Int J Mol Sci. 2020;8:2179–92.

Luo X, Ehrlich E, Xiao ZW, Zhang WY, Xie X, Yu XF. Adenovirus E4orF6 assembles with Cullin5-ElonginB-ElonginC E3 ubiquitin ligase through an HIV/SIV Vif-like BC-box to regulate p53. FASEB J. 2007;21:1742–50.

Luo Z, Ye X, Shou F, Cheng Y, Li F, Wang G. NRF1-mediated ubiquitination of p53 regulates lung adenocarcinoma proliferation. Biochem Biophys Res Commun. 2020.

Alfton K, Jain AK, Herz HM, Tsai WW, Qin J, Bergmann A, Johnson RL, Barton MC. Trim24 targets endogenous p53 for degradation. Proc Natl Acad Sci U S A. 2010;107:16116–6.

Banks D, Wu M, Higa LA, Gavrilova N, Quan JM, Ye T, Kobayashi R, Sun H, et al. TRIM24 signaling pathway in clear cell renal cell carcinoma. Cancer Sci. 2019;111:1555–63.

Chen D, Hong A, Park HI, Shin WH, Yoo L, Jeon SJ, Chung KC. Cell Cycle. 2009;8:3093–105.

Popov N, Schulein C, Jaenicke LA, Eilers M. Ubiquitylation of the amino terminus of MYC by SCF beta-TRCP antagonizes SCFFBW7-mediated turnover. Nat Cell Biol. 2010;12:973–81.

Sun X, He X, Yin L, Sears R, Dai MS. The nuclear ubiquitin-specific protease USP36 deubiquitinates and stabilizes c-Myc. Cancer Res. 2015;75.

Pan J, Deng Q, Jiang C, Wang X, Ni T, Li H, Chen T, Jin J, Pan W, Cai X, et al. USP7 directly deubiquitinates and stabilizes c-Myc in lung cancer. Oncogene. 2015;34:3987–67.

Zhang WL, Liu ZK, Wang JM, Tian QB. Knockdown of USP28 enhances the radiosensitivity of esophageal cancer cells via the c-Myc-hypoxia-inducible-factor-1 alpha pathway. J Cell Biochem. 2019;120:201–12.

Kim D, Hong A, Park H, Shin WH, Yoo L, Jeon SJ, Chung KC. Deubiquitinating enzyme USP22 positively regulates c-Myc stability and tumorigenic activity in mammalian and breast cancer cells. J Cell Physiol. 2017;232:3664–76.

Li X, Wu LM, Zopp M, Kopelow S, Du W. p33-TP53-induced glycolysis regulator mediated glycolytic suppression attenuates DNA damage and genomic instability in fanconi anemia hematopoietic stem cells. Stem Cells. 2019;37:937–47.

Wade M, Wang YV, Wahl GM. The p53 orchestra: Mdm2 and Mdmx set the tone. Trends Cell Biol. 2008;28:309–19.

Barak Y, Juven T, Haffner R, Oren M. mdm2 expression is induced by wild type p53 activity. EMBO J. 1993;12:461–7.

Bang S, Xue S, Kurokawa M. Regulation of the p53 family proteins by the ubiquitin proteasomal pathway. Int J Mol Sci. 2020;21.

Alfton K, Jain AK, Herz HM, Tsai WW, Qin J, Bergmann A, Johnson RL, Barton MC. Trim24 targets endogenous p53 for degradation. Proc Natl Acad Sci U S A. 2010;107:16116–6.

Banks D, Wu M, Higa LA, Gavrilova N, Quan JM, Ye T, Kobayashi R, Sun H, et al. TRIM24 signaling pathway in clear cell renal cell carcinoma. Cancer Sci. 2019;111:1555–63.

Chen D, Hong A, Park HI, Shin WH, Yoo L, Jeon SJ, Chung KC. Cell Cycle. 2009;8:3093–105.

Popov N, Schulein C, Jaenicke LA, Eilers M. Ubiquitylation of the amino terminus of MYC by SCF beta-TRCP antagonizes SCFFBW7-mediated turnover. Nat Cell Biol. 2010;12:973–81.
239. Piatta HW, Abrahamson H, Thoresen SB, Stenmark H. Nedd4-dependent lysine-11-linked polyubiquitination of the tumour suppressor Beclin 1. Biochem J. 2012;441:399–406.

240. Xu CF, Feng K, Zhao XN, Huang SQ, Cheng YJ, Qian L, Wang YN, Sun HX, Jin M, Chuang TH, Zhang YJ. Regulation of autophagy by E3 ubiquitin ligase RNF26 through BECN1 ubiquitination. Autophagy. 2014;10:2239–50.

241. Liu JL, Xia HG, Kim M, Xu LH, Li Y, Zhang LH, Cai Y, Norberg HV, Zhang T, Furuya T, et al. Beclin1 controls the levels of p53 by regulating the deubiquitination activity of USP10 and USP13. Cell. 2011;147:223–34.

242. Jin SH, Tian S, Yang YM, Chou XH, Xia XJ, Cui J, Wang RF. USP19 modulates autophagy and antiviral immune responses by deubiquitinating beclin-1. EMBO J. 2016;35:866–80.

243. Ashkenazi A, Bento CF, Rickets T, Vicinanza M, Siddiqi F, Pavel M, Squitieri F, Hardenberg MC, Imarisio S, Menzies FM, Rubinsztein DC. Polyglutamate tracts regulate beclin 1-dependent autophagy. Nature. 2017;545:108.

244. Xiao J, Zhang T, Xu DC, Wang HB, Cai Y, Jin TJ, Liu M, Jin MZ, Wu KJ, Yuan JY. FBXL20-mediated Vps34 ubiquitination as a p33 controlled checkpoint in regulating autophagy and receptor degradation. Genes Dev. 2015;29:184–97.

245. Wang T, Zhang D, Liang W, Xu DC, Xia HG, Geng JF, Najafov A, Liu M, Li YX, Han XR, et al. G-protein-coupled receptors regulate autophagy by ZBTB16-mediated ubiquitination and proteasomal degradation of Atg14L. Elife. 2015;4.

246. Morel E, Dupont N, Codogno P. Autophagy regulation: RNF2 targets AMBRA1. Cell Res. 2014;24:1029–30.

247. Wang W, You YZ, Zhou L, Xu YF, Feng C, Zhou TH, Yi C, Shi Y, Liu W. mTORC1-regulated and HUWE1-mediated WD2 degradation controls autophagy flux. Mol Cell. 2018;72:303.

248. Kuang E, Okumura CY, Shelly-Levin S, Varsano T, Shu VW, Qi JF, Niesman IR, Yang HJ, Lopez-Otin C, Yang WY, et al. Regulation of ATG4B stability by RNF5 limits basal levels of autophagy and influences susceptibility to bacterial infection (vol 8, e1003007, 2012). PLoS Genet. 2020;16.

249. Liu CH, Zhang Y, She XL, Fan L, Li PY, Feng, F, Bu HJ, Liu Q, Liu Q, Zhao CH, et al. A cytoplasmic long noncoding RNA LINCO0470 as a new AKT activator to mediate globastoma cell autophagy. J Hematol Oncol. 2018;11.

250. Lee HJ, Li CF, Ruan D, He J, Montal ED, Lorenz S, Gimmn GD, Chan CH. Non- proteolytic ubiquitination of hexokinase 2 by HectH9 controls tumor metabolism and cancer stem cell expansion. Nat Commun. 2019;10.

251. Jiao L, Zhang HL, Li DD, Yang KL, Tang J, Li K, Jy, Yu Y, Wu RY, Ravichandran S, et al. Regulation of glycolytic metabolism by autophagy in liver cancer involves selective autophagic degradation of HK2 (hexokinase 2). Autophagy. 2018;14:671–84.

252. Huang MW, Xiong H, Liu DL, Xu BR, Liu HJ. CSNS upregulates glycolysis to promote hepatocellular carcinoma metastasis via stabilizing the HK2 protein. Exp Cell Res. 2020;388.

253. Okoniewski M, Jermušek S, Koyano F, Go E, Kimura M, Natsume T, Tanaka K, Matsuda N. Mitochondrial hexokinase HK1 is a novel substrate of the Parkin ubiquitin ligase. Biochem Biophys Res Commun. 2012;428:197–202.

254. Feng YL, Zhang Y, Cai Y, Liu RJ, Ml, Li TMZ, Yu F, Guo M, Huang HC, Ou YF, Chen YH. A20 targets PFKL and glycoalisis to inhibit the progression of hepatocellular carcinoma. Cell Death Dis. 2020;11.

255. Lee JH, Liu RJ, Li ZH, Zhang CB, Wang YG, Cai QS, Qian X, Xia Y, Zhang YH, Piao YJ, et al. Stabilization of phosphofructokinase 1 platelet isoform by AKT promotes tumorogenesis. Nat Commun. 2017;8:200.

256. Shang Y, He J, Wang Y, Feng Q, Zhang Y, Guo J, Li J, Li S, Wang Y, Yan G, et al. CHIP/Stub1 regulates the Warburg effect by promoting degradation of PINK1 in ovarian carcinoma. Oncogene. 2017;36:4191–200.

257. Yuan P, Zhou YW, Wang R, Chen SY, Wang QQ, Xu ZJ, Liu Y, Yang WY, et al. Regulation of ATG4B stability by RNF5 limits basal levels of autophagy and influences susceptibility to bacterial infection (vol 8, e1003007, 2012). PLoS Genet. 2020;16.

258. Liu CH, Zhang Y, She XL, Fan L, Li PY, Feng, F, Bu HJ, Liu Q, Liu Q, Zhao CH, et al. A cytoplasmic long noncoding RNA LINCO0470 as a new AKT activator to mediate globastoma cell autophagy. J Hematol Oncol. 2018;11.

259. Lee HJ, Li CF, Ruan D, He J, Montal ED, Lorenz S, Gimmn GD, Chan CH. Non- proteolytic ubiquitination of hexokinase 2 by HectH9 controls tumor metabolism and cancer stem cell expansion. Nat Commun. 2019;10.

260. Jiao L, Zhang HL, Li DD, Yang KL, Tang J, Li K, Jy, Yu Y, Wu RY, Ravichandran S, et al. Regulation of glycolytic metabolism by autophagy in liver cancer involves selective autophagic degradation of HK2 (hexokinase 2). Autophagy. 2018;14:671–84.

261. Huang MW, Xiong H, Liu DL, Xu BR, Liu HJ. CSNS upregulates glycolysis to promote hepatocellular carcinoma metastasis via stabilizing the HK2 protein. Exp Cell Res. 2020;388.

262. Okoniewski M, Jermušek S, Koyano F, Go E, Kimura M, Natsume T, Tanaka K, Matsuda N. Mitochondrial hexokinase HK1 is a novel substrate of the Parkin ubiquitin ligase. Biochem Biophys Res Commun. 2012;428:197–202.

263. Feng YL, Zhang Y, Cai Y, Liu RJ, Ml, Li TMZ, Yu F, Guo M, Huang HC, Ou YF, Chen YH. A20 targets PFKL and glycoalisis to inhibit the progression of hepatocellular carcinoma. Cell Death Dis. 2020;11.
262. Deng XQ, Yi X, Deng JY, Zou YQ, Wang SS, Shan WH, Liu P, Zhang ZB, Chen LF, Hao L. ROCK2 promotes osteosarcoma growth and metastasis by modifying PFKFB3 ubiquitination and degradation. Exp Cell Res. 2019;385.

263. Tudzava V, Colombo SL, Strober K, Carcino S, Williams GH, Moncada S. Two ubiquitin ligases, NPC1/CC1 and SKP1/CLUL1 (SCT)-beta-TrCP, sequentially regulate glycolysis during the cell cycle. Proc Natl Acad Sci U S A. 2011;108:2728-83.

264. Colombo SL, Palacios-Callender M, Frakich N, Carcino S, Kovacs I, Tudzava V, Moncada S. Molecular basis for the differential use of glucose and glutamine in cell proliferation as revealed by synchronized HeLa cells. Proc Natl Acad Sci U S A. 2011;108:20697-74.

265. Cai Q, Wang SH, Jin LY, Weng MZ, Zhou D, Wang JD, Tang ZH, Quan ZW. Long non-coding RNA GBCDR1c induces chemoresistance of gallbladder cancer cells by activating autophagy. Mol Cancer. 2019;18.

266. Yu T, Zhao YJ, Hu ZX, Li J, Chu DD, Zhang JW, Li Z, Chen B, Zhang X, Pan HY, et al. MalATc9 facilitates lung cancer metastasis via a PKG1-activated AKT/mTOR pathway. Cancer Res. 2017;77:7582-94.

267. Mikawa T, Murayama T, Okamoto K, Nakagama H, Leonart ME, Tsusaka T, Han C. Amplification of Usp13 drives ovarian cancer metabolism. Clin Cancer Res. 2013;19:2248-56.

268. Deng XQ, Yi X, Deng JY, Zou YQ, Wang SS, Shan WH, Liu P, Zhang ZB, Chen LF, Hao L. ROCK2 promotes osteosarcoma growth and metastasis by modifying PFKFB3 ubiquitination and degradation. Exp Cell Res. 2019;385.

269. Hwang S, Nguyen AD, Jo Y, Engelking LJ, Brugarolas J, DeBoese-Boyd RA. Hypoxia-inducible factor 1alpha activates insulin-induced gene 2 (insig-2) transcription for degradation of 3-Hydroxy-3-methylglutaryl (HMG-CoA) reductase in the liver. J Biol Chem. 2017;292:9582-93.

270. Jeon YJ, Khelifa S, Ratnikov B, Scott DA, Feng YM, Parisi F, Ruller C, Liao DF, Cao DL. Aldo-keto reductase family 1B10 affects fatty acid synthesis by regulating the stability of acetyl-CoA carboxylase-alpha in breast cancer cells. J Biol Chem. 2008;283:3418-23.

271. Liu J, Zhang C, Wu H, Hu J, Zhou Y, Hu B, Wang Q, Lin J, Zhang H, Hu Y, Li Y. The IKKbeta-USP30-ACLY axis controls Lipogenesis and tumorigenesis. Hepatology. 2020.

272. Gu L, Zhu Y, Lin X, Lu B, Zhou X, Zhu F, Zhao Q, Prochownik EV, Li Y. The IKKbeta-USP30-ACLY axis controls Lipogenesis and tumorigenesis. Hepatology. 2020.

273. Yang C, Zhang M, Gentry MS, Worby CA, Dixon JE, Saltiel AR. A role for Jiang WQ, Wang SW, Xiao MT, Lin Y, Zhou LS, Lei QY, Xiong Y, Guan KL, Zhao Y, Jin X, Pan Y, Wang L, Zhang L, Ravichandran R, Potts PR, Jiang J, Wu H, Sun J, Xiao ML, Li F, Wang Y, Wang GX. Speckle-type POZ protein suppresses lipid accumulation and prostate cancer growth by stabilizing fatty acid synthase. Prostate. 2019;79:864-71.

274. Calvisi DF, Wang CM, Ho C, Ladu S, Lee SA, Mattu S, Destefanis G, Delogu S, Mazzieri A, Ericsson J, et al. Increased lipogenesis, induced by AKT-mTORC1-RPS6 signaling, promotes development of human hepatocellular carcinoma. Gastroenterology. 2011;140:1U51-U1542.

275. Grant E, Tang D, Rossi S, Baron A, Migita T, Weinstein J, Lechpammer M, Huesken D, Zimmermann J, Signoretti S, Loda M. The isopeptidase USP2a regulates the stability of fatty acid synthase in prostate cancer. Cancer Cell. 2004;5:253-61.

276. Menzies SA, Volkmar N, van den Boomen DJ, Timms RT, Dickson AS, Nathan JA, Lehr PJ. The sterol-responsive NRF145 E3 ubiquitin ligase mediates the degradation of HMG-CoA reductase together with gp78 and Hrd1. Elife. 2018;7.

277. Jiang LY, Jiang W, Tian N, Xiong YN, Liu J, Wei J, Wu KY, Luo J, Shi XJ, Song BL. Ring finger protein 145 (NRF145) is a ubiquitin ligase for sterol-induced degradation of HMG-CoA reductase. J Biol Chem. 2018;293:4047-55.

278. Llorente C, Raaben M, Moreno E, Castilla B, Gazzano E, Ghigo D, Rizzo AM, Riganti C. Omega 3 fatty acids chemosensitize multidrug resistant colon cancer cells by down-regulating cholesterol synthesis and altering detergent resistant membranes composition. Mol Cancer. 2013;12.

279. Foresti O, Ruggiano A, Hannibal-Bach HK, Ejsing CS, Carvalho P. Sterol homeostasis requires regulated degradation of squalene monooxygenase by the ubiquitin ligase Doo1/Teb4. Elife. 2013;2:e00953.

280. Zelcer N, Hong C, Boyadjian R, Tontonoz P. LXR regulates cholesterol uptake through idol-dependent ubiquitination of the LDL receptor. Science. 2009;325:4040-9.

281. Lee DE, Yoo JE, Kim J, Kim S, Kim S, Lee H, Cheong HS, NEDD4L downregulates autophagy and cell growth by modulating ULK1 and a glutamine transporter. Cell Death Dis. 2020;11:1-11.

282. Ito J, Khelifa S, Ratnikov B, Scott DA, Feng YM, Parisi F, Ruller C, Liao DF, Cao DL. Aldo-keto reductase family 1B10 affects fatty acid synthesis by regulating the stability of acetyl-CoA carboxylase-alpha in breast cancer cells. J Biol Chem. 2008;283:3418-23.

283. Yu XJ, Deng R, Zhu HH, Zhang SS, Zhu CH, Montmigny M, Davis R, Feng GS. Modulation of fatty acid synthase degradation by concerted action of p38 MAP kinase, E3 ligase COP1, and SH2-tyrosine phosphatase Shp2. J Biol Chem. 2013;288:3823-30.

284. Gang XK, Xuan LL, Zhao X, Lv Y, Li F, Wang Y, Wang GX. Speckle-type POZ protein suppresses lipid accumulation and prostate cancer growth by stabilizing fatty acid synthase. Prostate. 2019;79:864-71.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and photos.