Gonidas *et al. J Biol Res-Thessalon (2022) 29:1*
https://doi.org/10.26262/jbrt.v29i0.8380

e-ISSN 2241-5793

RESEARCH

Open Access

Deubiquitinating enzymes at the crossroads of lipid metabolism and cancer

Christos Gonidas, Paul Hadweh and George Mosialos*

Abstract

Deregulated lipid metabolism has been recognized as a critical alteration that supports the development and growth of various types of tumors. Changes in lipid metabolism enable reprogramming of energetics and availability of synthetic intermediates and signaling mediators that can have pleiotropic effects in cellular physiology. The identification of critical factors that reshape lipid metabolism during oncogenesis can provide targets for the development of novel therapeutic protocols. Enzymes are an attractive class of molecules for the development of therapeutic compounds. This review focuses on deubiquitinating enzymes (DUBs) that have been implicated both in lipid and cellular homeostatic processes. In certain cases, a causative link between the two processes is mediated by the deubiquitinating enzyme whereas in other cases we present evidence that support a possible role for the DUB as the underlying linker of lipid content and cell growth deregulation. Collectively, our report highlights critical nodes of deubiquitination-dependent metabolic and growth regulatory processes that can be interrogated further for a detailed understanding of cancer promoting mechanisms and therapeutic exploitation.

Keywords: cancer, lipid metabolism, ubiquitin, deubiquitinating enzymes

Introduction

Metabolic rewiring has been recognized as a hallmark of cancer [1]. Although the identification of changes in cancer cell metabolism date many decades back to the pioneering work of Otto Warburg in the beginning of the twentieth century [2], the introduction of sophisticated genetic and biochemical tools permitted the detailed dissection of cellular and molecular mechanisms underlying the metabolic changes that accompany the development of malignancies [3]. The identification and characterization of metabolic steps that constitute major dependencies for cancer cells dictated the development of successful anticancer drugs and reemerges as an area of highly active investigation [4]. In this report we focus on aspects of lipid metabolism in cancer that are affected by deubiquitinating enzymes. This is an area that has attracted recent attention and has the potential to reveal possibilities of therapeutic interventions for cancer and metabolic diseases. Following an overview of cancer associated alterations in lipid metabolism we introduce a brief overview of protein ubiquitination to focus in the end on specific deubiquitinating enzymes that have roles in both cellular homeostasis and lipid metabolism.

Lipid metabolism and cancer

Lipids play pleiotropic roles in animal cellular physiology. Fatty acids are a major source of energy production under aerobic conditions and in the form of glycerol esters they

***Corresponding Author**
George Mosialos, School of Biology, Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece, Tel: +302310998907, Email: gmosialo@bio.auth.gr

provide an efficient means for energy storage. Phospholipids and sphingolipids are fundamental components of membranes. Finally, various types of lipids play critical roles in signal transduction processes that orchestrate responses to extracellular stimuli. The broad range of structural and functional effects that are mediated by lipids explain the deregulation of multiple aspects of their homeostasis in cancer. Malignant cells have increased demands for membrane synthesis and energy due to their enhanced proliferation rates [5]. Therefore, it comes as no surprise that they reorganize several processes associated with the availability and use of different types of lipids [6]. These processes include enhanced fatty acid synthesis and modifications in fatty acid liberation from endogenous sources, increased uptake of fatty acids from the environment, increased fatty acid oxidation and deregulation of cholesterol metabolism.

Specific changes in gene expression and protein function underlie the metabolic changes associated with lipid homeostasis deregulation in cancer. Fatty acid synthase which is the principal fatty acid biosynthetic enzyme is upregulated in various types of cancer [7, 8]. In addition, inhibition of ATP citrate lyase and acetyl-coA carboxylases that catalyze early steps in fatty acid synthesis have tumoricidal effects [9]. Similar effects have been associated with the use of statins that inhibit cholesterol biosynthesis [10]. Notably, aberrant activation of the transcription factors SREBP1 and SREBP2, which orchestrate fatty acid and cholesterol biosynthesis, has been observed in different types of cancer [11, 12, 13]. These findings highlight the importance of *de novo* fatty acid and cholesterol biosynthesis for the growth of cancer cells. In addition to *de novo* biosynthesis of lipids, cancer cells acquire survival benefits if they can facilitate import of lipids from their microenvironment. This is based on the enhanced expression of molecules implicated in lipid binding and import and include CD36, fatty acid binding proteins and proteins involved in lipoprotein import and processing [14, 15, 16]. Fatty acids constitute a rich energy source that is alternative to glucose. Gene expression mediated enhancement of processes that mediate fatty acid oxidation in mitochondria has been observed in breast cancers, pancreatic cancers and glioblastomas [17, 18, 19, 20]. In addition to energy production, fatty acid oxidation can support the antioxidant armamentarium of the cell by increasing the levels of NADPH [21]. Nevertheless, unregulated accumulation of lipids can lead to toxic effects and cancer cells develop mechanisms of lipid storage and metabolism reorganization to avoid lipotoxicity effects. These include the formation of lipid droplets and the activation of a specialized autophagy mechanism for lipids called lipophagy [22, 23]. In addition, enzymes involved in lipolysis are regulated appropriately to establish fatty acid homeostasis [24]. Finally, cancer cells must balance the levels of saturated and unsaturated fatty acids depending on the environmental conditions in which they grow [25]. Polyunsaturated fatty acids can undergo peroxidation by reactive oxygen species and lead to cell death by an iron-dependent mechanism called ferroptosis. Cells with polyunsaturated fatty acids in membranes are more vulnerable to ferroptosis and they develop mechanisms to reduce membrane polyunsaturated fatty acid content. These include *de novo* lipogenesis and redistribution of polyunsaturated fatty acids between phospholipids and triacyl glycerols [26, 27]. On the other hand, increased levels of saturated fatty acids in membranes can have toxic effects. In order to balance this situation, cancer cells rely on elevated levels of fatty acid desaturating enzymes such as stearoyl-CoA desaturase 1 to increase the levels of unsaturated fatty acids [28, 29]. In summary, lipid metabolism reprograming in cancer is pleiotropic to allow for the optimal adaptation, survival, growth, and dissemination of cancer cells in their changing microenvironment. Identifying molecules that mediate such a metabolic plasticity is of paramount importance for the development of effective therapeutic approaches.

Protein ubiquitination deubiquitination and cancer

Ubiquitination constitutes an evolutionarily conserved posttranslational modification of proteins that mediates the regulation of a broad range of processes that are tightly associated with cellular homeostatic mechanisms (reviewed in [30]). Typically, it involves the attachment of ubiquitin, a 76-amino acid protein, to the side chain of a lysine residue on the target protein. The attachment is mediated by an isopeptide bond between the ubiquitin carboxyl terminal group and the e-amino group of the lysine residue. Proteins can be modified by monoubiquitination (attachment of one ubiquitin moiety) or polyubiquitination (attachment of multiple linked ubiquitin moieties) to one or multiple lysine residues. Polyubiquitin chains can be formed by conjugating the carboxyl terminus of one ubiquitin to one of the seven lysine residues (termed KX-linked chains, where X is the respective lysine residue number) or the amino terminal methionine (termed M1-linked chains) of the neighboring ubiquitin molecule. Structurally and functionally distinct types of

polyubiquitin chains can be formed depending on which ubiquitin lysine residue is used to form the isopeptide linkage with the neighboring ubiquitin molecule. For example, K48-linked polyubiquitin chains mediate proteasome-dependent protein degradation whereas K63- and M1-linked polyubiquitin chains are used in the assembly of signaling complexes. The repertoire of ubiquitin-based recognition codes is further expanded by the formation of mixed-linkage chains, conjugation of ubiquitin with ubiquitin-like molecules and ubiquitin modifications such as phosphorylation and acetylation.

Protein ubiquitination is an enzymatic process that is typically carried out by the cooperation of a ubiquitin activating enzyme (E1), a ubiquitin conjugating enzyme (E2) and a ubiquitin ligase (E3) [31]. E3s usually confer the specificity of target selection, thus they represent the largest group of cooperating enzymes for protein ubiquitination. Importantly, protein ubiquitination can be reversed by proteolytic enzymes known as deubiquitinating enzymes (DUBs), which can hydrolyze the isopeptide bond that links ubiquitin moieties to each other and the target protein [32]. They fall in different classes based on the structural characteristics of their ubiquitin-protease domain and they can be selective or specific towards different types of polyubiquitin chains. Protein ubiquitination and deubiquitination are tightly regulated in accordance with the broad range of cellular functions that mediate and control. Interestingly, multiple enzymes involved in protein ubiquitination have been implicated in cellular homeostatic processes including cancer-preventing checkpoint bypass [33]. Frequently, such checkpoints involve the rewiring of metabolic processes that can fuel the growth of cancer cells. Deubiquitinating enzymes that have been associated with cancer development and lipid metabolism will be the focus of the following sections.

DUBs implicated in cellular homeostasis and lipid metabolism

Gene expression and genetic analyses have highlighted the association or involvement of several DUBs in tumor development [34]. Oncogenic and tumor suppressing activities have been ascribed to these enzymes but the full spectrum of molecular mechanisms that underlie these activities is incompletely understood in many cases.

A20, which is also known as TNFAIP3, is a ubiquitin-editing enzyme encoded by a gene that is frequently inactivated by mutations in B-cell lymphomas including multiple myeloma, diffuse large B cell lymphoma, Hodgkin's lymphoma, and follicular lymphoma [35]. Tumor promoting activities have been ascribed to A20 by virtue of its upregulation in glioblastoma and certain types of breast cancer. Interestingly, A20 is a critical regulator of lipid homeostasis in hepatocytes and its genetic inactivation exacerbates non-alcoholic steatohepatitis, a condition that can lead to hepatocellular carcinoma [36]. Consistent with these findings is the suppression of free fatty acid-mediated triglyceride accumulation in HepG2 cells by A20 overexpression, whereas its downregulation had the opposite effect [37]. A20 contains an amino terminal deubiquitinating domain and seven carboxyl terminal zinc-finger domains that include an E3 ligase domain. It has a well-established inhibitory activity towards NF-kappaB activation which plays a central role in its anti-inflammatory function. Furthermore, A20 has a profound anti-apoptotic role which may underlie its tumor promoting properties. Its NF-kappaB inhibitory activity has been linked to its ability to hydrolyze K63-inked polyubiquitin chains from various NF-kappaB activation mediators such as RIPK1 or NEMO, followed at least in some cases by their degradative ubiquitination by its E3 ligase activity. Furthermore, the seventh zinc finger domain of A20 can bind linear polyubiquitin chains and modulate their stability and accessibility by other proteins to regulate NF-kappaB activation by TNF. The anti-inflammatory and death-preventing activities of A20 have been associated with conditions that can promote oncogenesis. Interestingly, its effects on lipid homeostasis have recently emerged as an additional factor that can promote tumorigenesis particularly in the liver. The ability of A20 to prevent lipid accumulation in hepatocytes has been linked to its ability to deubiquitinate and inactivate the ASK1 kinase and limit the downstream activation of p38 and JNK1/2 as well as its ability to promote fatty acid oxidation and decrease fatty acid and cholesterol uptake involving among other mechanisms the induction of PPARalpha levels [36]. It would be interesting to investigate whether A20 affects lipid homeostasis in other cell types in a manner that affects their growth and survival.

The tumor suppressor CYLD is a deubiquitinating enzyme that was originally identified as a gene mutated in familial cylindromatosis and its loss in various tumor types results in enhanced cell survival or cell proliferation (reviewed in [38]). The human CYLD protein consists of 956 amino acids and contains three cytoskeletal-associated protein-glycine-conserved (CAP-Gly) repeats, two conserved proline-rich segments, and a carboxyl terminal deubiquitinating domain (reviewed in [39]). The two amino terminal CAP-Gly domains mediate the interaction of CYLD

with microtubules, which affects microtubule dynamics. Depending on the cell type and stimulus, CYLD can inhibit several growth and antiapoptotic signaling pathways that include the NF-kappaB, JNK and p38 pathways (reviewed in [40]). The inhibition of these pathways by CYLD is mediated by the deubiquitination of critical signaling molecules and the apparent disruption of multisubunit complexes that are assembled on K63- and M1-linked polyubiquitin chains. Targets of CYLD that play a critical role in the inhibition of the aforementioned pathways include the kinases RIPK1 and TAK1, the E3-ubiquitin ligases TRAF2 and TRAF6 and the transcription factor Bcl3 (reviewed in [40]. CYLD expression can be modulated by transcription regulation as well as via posttranslational modifications. Interestingly, several pieces of evidence have indicated a role for CYLD in lipid homeostasis with direct implications for cellular homeostasis. CYLD downregulation has been associated with steatosis and non-alcoholic steatohepatitis in humans [41]. Furthermore, genetic inactivation of the *CYLD* gene in mouse hepatocytes enhances lipid accumulation upon high-fat diet conditions whereas overexpression of CYLD in hepatocytes ameliorates the effects of high fat diet. The detrimental effects of CYLD-deficiency in hepatocytes are also associated with exacerbation of inflammation. The protective effect of CYLD towards non-alcoholic steatohepatitis has been linked to its ability to inhibit hyperactivation of the TAK1 kinase and its downstream effector JNK [41, 42]. Based on these findings it has been suggested that upregulation of CYLD may have beneficial effects for non-alcoholic steatohepatitis. Interestingly pioglitazone, which is a PPARgamma activator is recommended for the treatment of a subset of non-alcoholic steatohepatitis patients and we have demonstrated that PPARgamma activation can induce the expression of CYLD mRNA and protein [43]. It is conceivable that the beneficial effect of pioglitazone in non-alcoholic steatohepatitis patients may be mediated at least partly through the induction of CYLD. Finally, it is worth noting that the effects of CYLD on lipid homeostasis may be evolutionarily conserved since downregulation of the *Drosophila melanogaster* CYLD ortholog resulted in altered fat body morphology, increased triglyceride levels and increased survival under starvation conditions [44].

BAP1 is a deubiquitinating enzyme with broad tumor suppressing activities that include mesothelioma, renal cell carcinoma, uveal melanoma and hepatocellular carcinoma [45]. BAP1 participates in multiple chromatin -associated complexes and plays a critical role in the regulation of gene expression, DNA replication and repair by inducing the deubiquitination of specific targets. A notable BAP1 target is histone H2A, the deubiquitination of which is involved in the control of gene expression. Liver specific inactivation of the BAP1 gene resulted in hypercholesterolemia and marked reduction of lipid accumulation in the liver [46]. These phenotypic effects were associated with elevated levels of enzymes involved in cholesterol biosynthesis and downregulation of genes involved in lipid uptake and/or storage. Furthermore, inactivation of BAP1 by cytoplasmic retention, which is mediated by its ubiquitination, promotes adipocyte differentiation [47]. The link between the tumor suppressing and metabolic regulatory activities of BAP1 is conceivable but additional studies are required to firmly establish such an association.

Several DUBs with predominantly oncogenic activities have been associated with lipid homeostatic mechanisms. The oncogenic activities of USP2a have been primarily linked to its ability to deubiquitinate and stabilize growth regulatory proteins including cyclins, MDM2 and beta-catenin [48]. Interestingly, USP2a can deubiquitinate and stabilize fatty acid synthase to promote fatty acid synthesis which can presumably fuel the growth of tumor cells [49-51]. Consistent with this notion is the ability of the oncogenic and prolipogenic activity of the Akt kinase to induce the expression of USP2a in hepatocellular carcinoma [51]. Furthermore, the lipogenic ability of USP2a to deubiquitinate and stabilize fatty acid synthase was associated with the growth transforming properties of Epstein-Barr virus and its principal oncoprotein LMP1 in B cells [52]. USP7 promotes cell survival and proliferation by various mechanisms involving the deubiquitination and stabilization of critical regulators. Its role in stabilizing preferentially the p53 E3 ligase MDM2 is well established and prompted he development of USP7 inhibitors for the treatment of relevant tumors. USP7 enhances insulin sensitivity by deubiquitinating and stabilizing PPARgamma and IRS1 [53, 54]. The potential effects of these metabolic reprogramming activities on the promotion of tumorigenesis remain to be established. USP14 expression has been correlated with the development or progression of several malignancies including prostate cancer, hepatocellular carcinomas, lung cancers and multiple myeloma (reviewed in [55]). Notable direct or indirect targets of USP14 are the androgen receptor and beta-catenin. Interestingly, USP14 deubiquitinates and stabilizes the fatty acid synthase to promote de novo lipogenesis which may promote the growth tumor cells at least in some cases [56]. Clearly, further studies are need to establish the broader significance of lipid metabolism regulation by USP14 and its tumor

promoting activities. USP18 has cell growth promoting effects by positively regulating EGF receptor expression (reviewed in [57]). Notably, USP18 was downregulated in the livers of non-alcoholic steatohepatitis patients and mice treated with high fat diet [58]. Furthermore, its exogenous expression in hepatocytes was shown to protect mice from high fat diet induced liver steatosis whereas its genetic inactivation exacerbated hepatic steatosis. The protective effects of USP18 towards high fat diet induced liver steatosis were associated with its ability to inhibit hyperactivation of TAK1, similarly to the function of CYLD. These findings highlight the critical role of TAK1 activity regulation for the metabolic homeostasis of hepatocytes. USP34 is a deubiqutinating enzyme that can promote cell growth by positively regulating Wnt signaling [59]. USP34 plays an important role in liver homeostasis by deubiquitinating and stabilizing gp78, a well-established regulator of lipid biogenesis in the liver [60]. Given the fact that genetic inactivation of gp78 causes obesity and non-alcoholic steatohepatitis in mice it would be important to explore the potential involvement of USP34 in steatohepatitis cases and associated pathologies in humans.

Conclusion

Deubiquitination has emerged as a critical posttranslational regulatory mechanism for a broad spectrum of cellular processes with important pathophysiological roles including cell and tissue homeostasis and its disruption in tumorigenesis. Many efforts during the recent years have been focusing on understanding the metabolic deviations that fuel the development of cancer with the ultimate goal to design innovative and effective therapeutic schemes. In this review, functional relations between the tumor inhibiting or promoting role of DUBs and their involvement in lipid metabolism have been highlighted to reveal novel concepts of combinatorial therapeutic interventions that may be beneficial in a clinical setting. Towards this goal, DUBs with oncogenic activities could be targeted with small molecule inhibitors [61] whereas the downregulation of DUBs with tumor suppressing activity could be reversed by molecules that target transcriptional or posttranscriptional regulatory mechanisms. These interventions could be combined with drugs that modulate lipid homeostasis and standard chemotherapeutic agents.

Acknowledgments

The authors would like to thank Drs Sofia Gargani and Dimitris L. Kontoyiannis for critically reading the manuscript.

Funding

Work related to this report has been co-financed by Greece and the European Union (European Social Fund - ESF) through the Operational Programme ΄Human Resources Development, Education and Lifelong Learning 2014-2020΄ in the context of the project "The role of tumor suppressor protein CYLD in mammary epithelial cell differentiation to adipocytes." (MIS 5047914).

Authors' contributions

CG, PH and GM conceived the initial idea and searched the relevant literature. GM wrote the initial draft. CG, PH and GM edited and proof read the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece

Authors affiliations

*Department of Genetics, Development and Molecular Biology, School of Biology, Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece

Received: 10 September 2021 **Accepted: 21 September 2021**

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000; 100:57-70.
2. Warburg O, Posener K, Negelein E. Uber den Stoffwechsel der Carcinomzelle. Biochem Zeitschrift. 1924;152:309-344.
3. Schmidt DR, Patel R, Kirsch DG, Lewis CA, Vander Heiden MG, Locasale JW. Metabolomics in cancer research and emerging applications in clinical oncology. CA Cancer J Clin. 2021;71:333-358.
4. Luengo A, Gui DY, Vander Heiden MG. Targeting Metabolism for Cancer Therapy. Cell Chem Biol. 2017;24:1161-1180.
5. Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. Cell Metab. 2016;23:27-47.
6. Broadfield LA, Pane AA, Talebi A, Swinnen JV, Fendt SM. Lipid metabolism in cancer: New perspectives and emerging mechanisms. Dev Cell. 2021;56:1363-1393.
7. Menendez JA, Vellon L, Espinoza I, Lupu R. The metastasis inducer CCN1 (CYR61) activates the fatty acid synthase (FASN)-driven lipogenic phenotype in breast cancer cells. Oncoscience. 2016;3:242-257.
8. Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer. 2007;7:763-777.
9. Menendez JA, Vellon L, Colomer R, Lupu R. Pharmacological and small interference RNA-mediated inhibition of breast cancer-associated fatty acid synthase (oncogenic antigen-519) synergistically enhances Taxol (paclitaxel)-induced cytotoxicity.

Int J Cancer. 2005;115:19-35.
10. Rao S, Lowe M, Herliczek TW, Keyomarsi K. Lovastatin mediated G1 arrest in normal and tumor breast cells is through inhibition of CDK2 activity and redistribution of p21 and p27, independent of p53. Oncogene. 1998;17:2393-2402.
11. Zhang N, Zhang H, Liu Y, Su P, Zhang J, Wang X, et al. SREBP1, targeted by miR-18a-5p, modulates epithelial-mesenchymal transition in breast cancer via forming a co-repressor complex with Snail and HDAC1/2. Cell Death Differ. 2019;26:843-859.
12. Kanagasabai T, Li G, Shen TH, Gladoun N, Castillo-Martin M, Celada SI, et al. MicroRNA-21 deficiency suppresses prostate cancer progression through downregulation of the IRS1-SREBP-1 signaling pathway. Cancer Lett. 2021.
13. Sharma B, Gupta V, Dahiya D, Kumar H, Vaiphei K, Agnihotri N. Clinical relevance of cholesterol homeostasis genes in colorectal cancer. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;1864: 1314-1327.
14. Bensaad K, Favaro E, Lewis CA, Peck B, Lord S, Collins JM, et al. Fatty acid uptake and lipid storage induced by HIF-1alpha contribute to cell growth and survival after hypoxia-reoxygenation. Cell Rep. 2014;9:349-365.
15. Lupien LE, Bloch K, Dehairs J, Traphagen NA, Feng WW, Davis WL, et al. Endocytosis of very low-density lipoproteins: an unexpected mechanism for lipid acquisition by breast cancer cells. J Lipid Res. 2020;61:205-218.
16. Wang J, Li Y. CD36 tango in cancer: signaling pathways and functions. Theranostics. 2019;9:4893-4908.
17. Lin H, Patel S, Affleck VS, Wilson I, Turnbull DM, Joshi AR, et al. Fatty acid oxidation is required for the respiration and proliferation of malignant glioma cells. Neuro Oncol. 2017;19:43-54.
18. Park JH, Vithayathil S, Kumar S, Sung PL, Dobrolecki LE, Putluri V, et al. Fatty Acid Oxidation-Driven Src Links Mitochondrial Energy Reprogramming and Oncogenic Properties in Triple-Negative Breast Cancer. Cell Rep. 2016;14:2154-2165.
19. Li S, Zhou T, Li C, Dai Z, Che D, Yao Y, et al. High metastaticgastric and breast cancer cells consume oleic acid in an AMPK dependent manner. PLoS One. 2014;9:e97330.
20. Khasawneh J, Schulz MD, Walch A, Rozman J, Hrabe de Angelis M, Klingenspor M, et al. Inflammation and mitochondrial fatty acid beta-oxidation link obesity to early tumor promotion. Proc Natl Acad Sci USA. 2009;106:3354-3359.
21. Ludtmann MH, Angelova PR, Zhang Y, Abramov AY, Dinkova-Kostova AT. Nrf2 affects the efficiency of mitochondrial fatty acid oxidation. Biochem J. 2014;457:415-424.
22. Geng F, Guo D. Lipid droplets, potential biomarker and metabolic target in glioblastoma. Intern Med Rev (Wash D C). 2017;3: 10.18103/imr.v3i5.443.
23. Maan M, Peters JM, Dutta M, Patterson AD. Lipid metabolism and lipophagy in cancer. Biochem Biophys Res Commun. 2018;504:582-589.
24. Nomura DK, Long JZ, Niessen S, Hoover HS, Ng SW, Cravatt BF. Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. Cell. 2010;140:49-61.
25. Ackerman D, Simon MC. Hypoxia, lipids, and cancer: surviving the harsh tumor microenvironment. Trends Cell Biol. 2014;24: 472-478.
26. Rysman E, Brusselmans K, Scheys K, Timmermans L, Derua R, Munck S, et al. De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. Cancer Res. 2010;70:8117-8126.
27. Ackerman D, Tumanov S, Qiu B, Michalopoulou E, Spata M, Azzam A, et al. Triglycerides Promote Lipid Homeostasis during Hypoxic Stress by Balancing Fatty Acid Saturation. Cell Rep. 2018;24:2596-2605 e5.
28. Tracz-Gaszewska Z, Dobrzyn P. Stearoyl-CoA Desaturase 1 as a Therapeutic Target for the Treatment of Cancer. Cancers (Basel). 2019;11:948.
29. Peck B, Schulze A. Lipid desaturation - the next step in targeting lipogenesis in cancer? FEBS J. 2016;283:2767-2778.
30. Kwon YT, Ciechanover A. The Ubiquitin Code in the Ubiquitin-Proteasome System and Autophagy. Trends Biochem Sci. 2017;42:873-886.
31. Zheng N, Shabek N. Ubiquitin Ligases: Structure, Function, and Regulation. Annu Rev Biochem. 2017;86:129-157.
32. Mevissen TET, Komander D. Mechanisms of Deubiquitinase Specificity and Regulation. Annu Rev Biochem. 2017;86:159-192.
33. Ge Z, Leighton JS, Wang Y, Peng X, Chen Z, Chen H, et al. Integrated Genomic Analysis of the Ubiquitin Pathway across Cancer Types. Cell Rep. 2018;23:213-226 e213.
34. Lai KP, Chen J, Tse WKF. Role of Deubiquitinases in Human Cancers: Potential Targeted Therapy. Int J Mol Sci. 2020;21.
35. Martens A, van Loo G. A20 at the Crossroads of Cell Death, Inflammation, and Autoimmunity. Cold Spring Harb Perspect Biol. 2020;12:a036418.
36. Zhang P, Wang PX, Zhao LP, Zhang X, Ji YX, Zhang XJ, et al. The deubiquitinating enzyme TNFAIP3 mediates inactivation of hepatic ASK1 and ameliorates nonalcoholic steatohepatitis. Nat Med. 2018;24:84-94.
37. Ai L, Xu Q, Wu C, Wang X, Chen Z, Su D, et al. A20 Attenuates FFAs-induced Lipid Accumulation in Nonalcoholic Steatohepatitis. Int J Biol Sci. 2015;11:1436-1446.
38. Sun SC. CYLD: a tumor suppressor deubiquitinase regulating NF-kappaB activation and diverse biological processes. Cell Death Differ. 2010;17:25-34.
39. Massoumi R. Ubiquitin chain cleavage: CYLD at work. Trends Biochem Sci. 2010;35:392-399.
40. Rajan N, Ashworth A. Inherited cylindromas: lessons from a rare tumour. Lancet Oncol. 2015;16:e460-469.
41. Ji YX, Huang Z, Yang X, Wang X, Zhao LP, Wang PX, et al. The deubiquitinating enzyme cylindromatosis mitigates nonalcoholic steatohepatitis. Nat Med. 2018;24:213-223.
42. Nikolaou K, Tsagaratou A, Eftychi C, Kollias G, Mosialos G, Talianidis I. Inactivation of the deubiquitinase CYLD in hepatocytes causes apoptosis, inflammation, fibrosis, and cancer. Cancer Cell. 2012;21:738-750.
43. Pseftogas A, Gonidas C, Mosialos G. Activation of peroxisome proliferator-activated receptor gamma in mammary epithelial cells upregulates the expression of tumor suppressor Cyld to mediate growth inhibition and anti-inflammatory effects. Int J Biochem Cell Biol. 2017;82:49-56.
44. Tsichritzis T, Gaentzsch PC, Kosmidis S, Brown AE, Skoulakis EM, Ligoxygakis P, et al. A Drosophila ortholog of the human cylindromatosis tumor suppressor gene regulates triglyceride content and antibacterial defense. Development. 2007;134: 2605-2614.
45. Masclef L, Ahmed O, Estavoyer B, Larrivee B, Labrecque N, Nijnik A, et al. Roles and mechanisms of BAP1 deubiquitinase in tumor suppression. Cell Death Differ. 2021;28:606-625.
46. Baughman JM, Rose CM, Kolumam G, Webster JD, Wilkerson EM, Merrill AE, et al. NeuCode Proteomics Reveals Bap1 Reg-

ulation of Metabolism. Cell Rep. 2016;16:583-595.
47. Mashtalir N, Daou S, Barbour H, Sen NN, Gagnon J, Hammond-Martel I, et al. Autodeubiquitination protects the tumor suppressor BAP1 from cytoplasmic sequestration mediated by the atypical ubiquitin ligase UBE2O. Mol Cell. 2014;54:392-406.
48. Kitamura H, Hashimoto M. USP2-Related Cellular Signaling and Consequent Pathophysiological Outcomes. Int J Mol Sci. 2021;22.
49. Graner E, Tang D, Rossi S, Baron A, Migita T, Weinstein LJ, et al. The isopeptidase USP2a regulates the stability of fatty acid synthase in prostate cancer. Cancer Cell. 2004;5:253-261.
50. Tao BB, He H, Shi XH, Wang CL, Li WQ, Li B, et al. Up-regulation of USP2a and FASN in gliomas correlates strongly with glioma grade. J Clin Neurosci. 2013;20:717-720.
51. Calvisi DF, Wang C, Ho C, Ladu S, Lee SA, Mattu S, et al. Increased lipogenesis, induced by AKT-mTORC1-RPS6 signaling, promotes development of human hepatocellular carcinoma. Gastroenterology. 2011;140:1071-1083.
52. Hulse M, Johnson SM, Boyle S, Caruso LB, Tempera I. Epstein-Barr Virus-Encoded Latent Membrane Protein 1 and B-Cell Growth Transformation Induce Lipogenesis through Fatty Acid Synthase. J Virol. 2021;95:e01857-01820.
53. Forand A, Koumakis E, Rousseau A, Sassier Y, Journe C, Merlin JF, et al. Disruption of the Phosphate Transporter Pit1 in Hepatocytes Improves Glucose Metabolism and Insulin Signaling by Modulating the USP7/IRS1 Interaction. Cell Rep. 2016;16:2736-2748.
54. Lee KW, Cho JG, Kim CM, Kang AY, Kim M, Ahn BY, et al. Herpesvirus-associated ubiquitin-specific protease (HAUSP) modulates peroxisome proliferator-activated receptor g (PPARg) stability through its deubiquitinating activity. J Biol Chem. 2013;288:32886-32896.
55. Wang D, Ma H, Zhao Y, Zhao J. Ubiquitin-specific protease 14 is a new therapeutic target for the treatment of diseases. J Cell Physiol. 2021;236:3396-3405.
56. Liu B, Jiang S, Li M, Xiong X, Zhu M, Li D, et al. Proteome-wide analysis of USP14 substrates revealed its role in hepatosteatosis via stabilization of FASN. Nat Commun. 2018;9:4770.
57. Kang JA, Jeon YJ. Emerging Roles of USP18: From Biology to Pathophysiology. Int J Mol Sci. 2020;21.
58. An S, Zhao LP, Shen LJ, Wang S, Zhang K, Qi Y, et al. USP18 protects against hepatic steatosis and insulin resistance through its deubiquitinating activity. Hepatology. 2017;66:1866-1884.
59. Lui TT, Lacroix C, Ahmed SM, Goldenberg SJ, Leach CA, Daulat AM, et al. The ubiquitin-specific protease USP34 regulates axin stability and Wnt/beta-catenin signaling. Mol Cell Biol. 2011;31:2053-2065.
60. Wang H, Ju D, Kho DH, Yang H, Li L, Raz A, et al. The ubiquitin specific protease USP34 protects the ubiquitin ligase gp78 from proteasomal degradation. Biochem Biophys Res Commun. 2019;509:348-353.
61. Harrigan JA, Jacq X, Martin NM, Jackson SP. Deubiquitylating enzymes and drug discovery: emerging opportunities. Nat Rev Drug Discov. 2018;17:57-78.