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EDITORIAL

Progress in therapeutic strategies based on cancer lipid metabolism

Lipids are widely distributed in cellular organelles and comprise thousands of different types of molecules, including fatty acids, phospholipids, triglycerides, sphingolipids, cholesterol, etc. Normal cells acquire lipids through de novo synthesis and uptake. In order to satisfy the demands of growth and proliferation, cancer cells must rewire their metabolism,[1,2] especially lipid metabolism.[3] Indeed, lipid synthesis is strongly upregulated in cancers to satisfy the demands of increased membrane biogenesis[4] and even acquire therapeutic resistance.[5] Lipid uptake and storage are also elevated in cancer cells.[6,7] Targeting lipid metabolism has become a novel anti-cancer strategy.

Past strategy: Blocking lipid synthesis

Accumulating evidence has demonstrated that increased de novo fatty acid (FA) synthesis is a hallmark of cancer.[3,8] The expression levels of enzymes responsible for FA synthesis are usually upregulated in many types of cancer.[9,10] Previous studies revealed that pharmacologically inhibition of the key enzymes of FA synthesis decreases cancer cell proliferation.[11,12] Fatty acid synthase (FASN) was the first molecular discovery linking lipid metabolism to cancer.[13] Many studies have since shown increased FASN expression in various cancers,[14] while inhibiting FASN by its inhibitors, such as TVB-3166 and C93, significantly reduces FA synthesis and suppresses tumor growth in the xenograft models of lung cancer.[15,16] Additionally, the acetyl-CoA carboxylase (ACC) catalyzes ATP-dependent carboxylation of acetyl-CoA, generating malonyl-CoA for fatty acid synthesis following the conversion of citrate and acetate to acetyl-CoA. The ACC inhibitors TOFA, soraphen A and ND646 have also shown significant anti-tumor effects in xenograft models of lung and breast cancer.[17–19] ATP citrate lyase (ACLY) converts cytoplasmic citrate to acetyl-CoA, a precursor of lipid synthesis and a substrate for protein acetylation. Inhibiting ACLY at the genetic level or pharmacologically significantly suppresses tumor growth.[20,21]

Current progress: Blocking lipid uptake, intracellular lipolysis and utilization of lipids

Recent studies have shown that blocking lipid uptake, intracellular lipolysis and utilization of lipids are potential approaches to inhibit tumor growth. Compared to normal cell, cancer cells require more lipids than normal cells, therefore, they obtain lipids by upregulating cell surface receptors for plasma lipids.[3] Cluster of differentiation 36 (CD36) is a cell surface receptor that facilitates lipid uptake.[22] It has been established as a functional driver of metastasis in a lipid metabolism-dependent manner.[23] In addition, the uptake of extracellular fatty acids in breast cancer and glioblastoma cell lines is promoted under hypoxia via the upregulation of heart-type fatty-acid-binding protein 3 and 7 (FABP3 and FABP7), thereby leading to elevated lipid droplet (LD) formation.[24] These findings expand our knowledge of lipid metabolism in cancer progression and add promising new targets for the development of novel anti-cancer therapeutics.

Cytoplasmic fatty acids are usually stored as triglycerides (TGs) in LDs and are released through intracellular lipolysis.[11,25] Adipose triglyceride lipase (ATGL)[26,27] and monoacyl glycerol lipase (MAGL)[28] provide a stream of intracellular free FA that play important and critical roles in cancer cells proliferation and tumor progression by de-esterification. Therefore, inhibiting intracellular lipolysis shows promise as a therapeutic strategy for cancer.

Abundant lipids in cancer cells provide essential substrates for signaling molecules, and mitochondrial oxidative metabolic fuels to support the rapid growth and proliferation of cancer cells.[29,30] Signaling lipids, for example, phosphoinositides, eicosanoids and sphingolipids, control important cellular processes and dysfunction of their metabolism has been implicated in cancer.[31] As the critical roles of lipid signaling pathways in cancer have been established, compounds targeting lipid signaling pathways, such as Rapamycin,[32] Curcumin,[33] Tetracycline,[34] ICI182780,[35] etc., are becoming available for clinical use. Lipids also supply energy to cancer cells through fatty acid β-oxidation. Oxidative mitochondrial pathways such as fatty acid β-oxidation and oxidative phosphorylation (OXPHOS) have been implicated in cancer cell survival, and inhibiting fatty acid β-oxidation reduces the tumor-initiating potential.[36] This evidence suggests the possibility of the fatty acid β-oxidation pathway as a potential therapeutic target for cancer.

Future perspectives: Blocking lipid storage while limiting lipid synthesis and utilization

In addition to limiting lipid synthesis and utilization, how to block lipid storage is the future therapeutic direction in cancer. LDs are key organelles that function as storage of cellular surplus of lipid molecules in esterified form. Cancer cells contain more lipid droplets than normal cells. The upregulation of LD-decorating proteins, such as hypoxia-inducible protein 2 (HIG2), Perilipin, adipose differentiation -related protein (ADRP) and Tip47 exhibited in multiple cancer cells have been shown to promote formation and accumulation of LDs.[37] Moreover, Savkovic and colleagues reported that stimulation of LD density promoted proliferation in colon cancer, whereas silencing perilipin 2 (PLIN2) or overexpression of forkhead box O3 (FOXO3) inhibited proliferation. Thus, they suggested that FOXO3 and LDs might serve as new targets for therapeutic intervention of colon cancer.[38] Furthermore, Penrose *et al.* demonstrated that LD-depletion, through the inhibition of lipid synthesis or silencing of PLIN2, significantly attenuated proliferation of colon cancer cells.[39] These studies support LD-associated proteins as potential targets for cancer treatment. However, the molecular mechanisms underlying LD-associated stress responses need to be further elucidated.

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References

1 Wang Y, Xia Y, Lu Z. Metabolic features of cancer cells. *Cancer Commun* 2018; **38** (1): 65. https://doi.org/10.1186/s40880-018-0335-7.
2 Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell* 2011; **144** (5): 646–74. https://doi.org/10.1016/j.cell.2011.02.013.
3 Cheng C, Geng F, Cheng X, Guo D. Lipid metabolism reprogramming and its potential targets in cancer. *Cancer Commun* 2018; **38** (1): 27. https://doi.org/10.1186/s40880-018-0301-4.
4 Rohrig F, Schulze A. The multifaceted roles of fatty acid synthesis in cancer. *Nat Rev Cancer* 2016; **16** (11): 732–49. https://doi.org/10.1038/nrc.2016.89.
5 Kuo CY, Ann DK. When fats commit crimes: Fatty acid metabolism, cancer stemness and therapeutic resistance. *Cancer Commun* 2018; **38** (1): 47. https://doi.org/10.1186/s40880-018-0317-9.
6 Zhao J, Zhi Z, Wang C *et al.* Exogenous lipids promote the growth of breast cancer cells via CD36. *Oncol Rep* 2017; **38** (4): 2105–15. https://doi.org/10.3892/or.2017.5864.
7 Pascual G, Avgustinova A, Mejetta S *et al.* Targeting metastasis-initiating cells through the fatty acid receptor CD36. *Nature* 2017; **541** (7635): 41–5. https://doi.org/10.1038/nature20791.
8 Santos CR, Schulze A. Lipid metabolism in cancer. *FEBS J* 2012; **279** (15): 2610–23. https://doi.org/10.1111/j.1742-4658.2012.08644.x.
9 Mashima T, Seimiya H, Tsuruo T. De novo fatty-acid synthesis and related pathways as molecular targets for cancer therapy. *Br J Cancer* 2009; **100** (9): 1369–72. https://doi.org/10.1038/sj.bjc.6605007.
10 Esslimani-Sahla M, Thezenas S, Simony-Lafontaine J *et al.* Increased expression of fatty acid synthase and progesterone receptor in early steps of human mammary carcinogenesis. *Int J Cancer* 2007; **120** (2): 224–9. https://doi.org/10.1002/ijc.22202.
11 Young SG, Zechner R. Biochemistry and pathophysiology of intravascular and intracellular lipolysis. *Genes Dev* 2013; **27** (5): 459–84. https://doi.org/10.1101/gad.209296.112.
12 Mullen GE, Yet L. Progress in the development of fatty acid synthase inhibitors as anticancer targets. *Bioorg Med Chem Lett* 2015; **25** (20): 4363–9. https://doi.org/10.1016/j.bmcl.2015.08.087.
13 Kuhajda FP, Jenner K, Wood FD *et al.* Fatty acid synthesis: A potential selective target for antineoplastic therapy. *Proc Natl Acad Sci U S A* 1994; **91** (14): 6379–83. https://doi.org/10.1073/pnas.91.14.6379.
14 Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer* 2007; **7** (10): 763–77. https://doi.org/10.1038/nrc2222.
15 Ventura R, Mordec K, Waszczuk J *et al.* Inhibition of de novo palmitate synthesis by fatty acid synthase induces apoptosis in tumor cells by remodeling cell membranes, inhibiting signaling pathways, and reprogramming gene expression. *EBioMedicine* 2015; **2** (8): 808–24. https://doi.org/10.1016/j.ebiom.2015.06.020.
16 Orita H, Coulter J, Lemmon C *et al.* Selective inhibition of fatty acid synthase for lung cancer treatment. *Clin Cancer Res: Off J Am Assoc Cancer Res* 2007; **13** (23): 7139–45. https://doi.org/10.1158/1078-0432.CCR-07-1186.
17 Svensson RU, Parker SJ, Eichner LJ *et al.* Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. *Nat Med* 2016; **22** (10): 1108–19. https://doi.org/10.1038/nm.4181.
18 Wang C, Xu C, Sun M, Luo D, Liao DF, Cao D. Acetyl-CoA carboxylase-alpha inhibitor TOFA induces human cancer cell apoptosis. *Biochem Biophys Res Commun* 2009; **385** (3): 302–6. https://doi.org/10.1016/j.bbrc.2009.05.045.
19 Tan W, Zhong Z, Wang S *et al.* Berberine regulated lipid metabolism in the presence of C75, compound C, and TOFA in breast cancer cell line MCF-7. *Evidence-Based Complementary Altern Med: eCAM* 2015; **2015**: 396035. https://doi.org/10.1155/2015/396035.

20 Lee JH, Jang H, Lee SM *et al.* ATP-citrate lyase regulates cellular senescence via an AMPK- and p53-dependent pathway. *FEBS J* 2015; **282** (2): 361–71. https://doi.org/10.1111/febs.13139.
21 Hanai JI, Doro N, Seth P, Sukhatme VP. ATP citrate lyase knockdown impacts cancer stem cells in vitro. *Cell Death Dis* 2013; **4**: e696. https://doi.org/10.1038/cddis.2013.215.
22 Kuemmerle NB, Rysman E, Lombardo PS *et al.* Lipoprotein lipase links dietary fat to solid tumor cell proliferation. *Mol Cancer Ther* 2011; **10** (3): 427–36. https://doi.org/10.1158/1535-7163.MCT-10-0802.
23 Li Z, Kang Y. Lipid metabolism fuels Cancer's spread. *Cell Metab* 2017; **25** (2): 228–30. https://doi.org/10.1016/j.cmet.2017.01.016.
24 Bensaad K, Favaro E, Lewis CA *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** (1): 349–65. https://doi.org/10.1016/j.celrep.2014.08.056.
25 Zechner R, Zimmermann R, Eichmann TO *et al.* FAT SIGNALS--lipases and lipolysis in lipid metabolism and signaling. *Cell Metab* 2012; **15** (3): 279–91. https://doi.org/10.1016/j.cmet.2011.12.018.
26 Yang X, Lu X, Lombes M *et al.* The G(0)/G(1) switch gene 2 regulates adipose lipolysis through association with adipose triglyceride lipase. *Cell Metab* 2010; **11** (3): 194–205. https://doi.org/10.1016/j.cmet.2010.02.003.
27 Welch C, Santra MK, El-Assaad W *et al.* Identification of a protein, G0S2, that lacks Bcl-2 homology domains and interacts with and antagonizes Bcl-2. *Cancer Res* 2009; **69** (17): 6782–9. https://doi.org/10.1158/0008-5472.CAN-09-0128.
28 Nomura DK, Lombardi DP, Chang JW *et al.* Monoacylglycerol lipase exerts dual control over endocannabinoid and fatty acid pathways to support prostate cancer. *Chem Biol* 2011; **18** (7): 846–56. https://doi.org/10.1016/j.chembiol.2011.05.009.
29 Boroughs LK, DeBerardinis RJ. Metabolic pathways promoting cancer cell survival and growth. *Nat Cell Biol* 2015; **17** (4): 351–9. https://doi.org/10.1038/ncb3124.
30 Zaidi N, Lupien L, Kuemmerle NB, Kinlaw WB, Swinnen JV, Smans K. Lipogenesis and lipolysis: The pathways exploited by the cancer cells to acquire fatty acids. *Prog Lipid Res* 2013; **52** (4): 585–9. https://doi.org/10.1016/j.plipres.2013.08.005.
31 Wymann MP, Schneiter R. Lipid signalling in disease. *Nat Rev Mol Cell Biol* 2008; **9** (2): 162–76. https://doi.org/10.1038/nrm2335.
32 Neshat MS, Mellinghoff IK, Tran C *et al.* Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. *Proc Natl Acad Sci U S A* 2001; **98** (18): 10314–9. https://doi.org/10.1073/pnas.171076798.
33 Koeberle A, Northoff H, Werz O. Curcumin blocks prostaglandin E2 biosynthesis through direct inhibition of the microsomal prostaglandin E2 synthase-1. *Mol Cancer Ther* 2009; **8** (8): 2348–55. https://doi.org/10.1158/1535-7163.MCT-09-0290.
34 Sala G, Dituri F, Raimondi C *et al.* Phospholipase Cγ1 is required for metastasis development and progression. *Cancer Res* 2008; **68** (24): 10187–96. https://doi.org/10.1158/0008-5472.CAN-08-1181.
35 Nava VE, Hobson JP, Murthy S, Milstien S, Spiegel S. Sphingosine kinase type 1 promotes estrogen-dependent tumorigenesis of breast cancer MCF-7 cells. *Exp Cell Res* 2002; **281** (1): 115–27.
36 Viale A, Pettazzoni P, Lyssiotis CA *et al.* Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature* 2014; **514** (7524): 628–32. https://doi.org/10.1038/nature13611.
37 Togashi A, Katagiri T, Ashida S *et al.* Hypoxia-inducible protein 2 (HIG2), a novel diagnostic marker for renal cell carcinoma and potential target for molecular therapy. *Cancer Res* 2005; **65** (11): 4817–26. https://doi.org/10.1158/0008-5472.CAN-05-0120.
38 Qi W, Fitchev PS, Cornwell ML *et al.* FOXO3 growth inhibition of colonic cells is dependent on intraepithelial lipid droplet density. *J Biol Chem* 2013; **288** (23): 16274–81. https://doi.org/10.1074/jbc.M113.470617.
39 Penrose H, Heller S, Cable C *et al.* Epidermal growth factor receptor mediated proliferation depends on increased lipid droplet density regulated via a negative regulatory loop with FOXO3/Sirtuin6. *Biochem Biophys Res Commun* 2016; **469** (3): 370–6. https://doi.org/10.1016/j.bbrc.2015.11.119.

