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Chapter

Fatty Acid Metabolism as a Tumor Marker

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Abstract

Cancer cells tend to make metabolism changes in the human body for their growth and survival. One of the most interesting changes is the alteration of fatty acid metabolism in order for the high rate of fatty acid synthesis required to increase the level of fatty acids needed for cancer cell proliferation. Thus, the reprogramming of fatty acid metabolism is needed for cancer cell survival. Fatty acid metabolic reprogramming is one of the hallmarks of the cancer condition since it can affect cellular functions. The reprogramming of fatty acid synthesis includes increased exogenous fatty acid uptake, de novo fatty acid synthesis, and oxidation of fatty acids. Identifying biochemical targets in fatty acid metabolism is useful for diagnosing and predicting the therapeutic efficiency in tumor treatment.

Keywords: fatty acids, cancer, metabolic reprogramming, tumor marker, fatty acid targeting

1. Introduction

Cancer cells need to control their environment to survive. Under a nutrient-limited microenvironment, they compete for oxygen and micronutrients with normal cells to survive and maintain their malignancy potential. Thus, oncogene-directed metabolic reprogramming is needed for cancer cell survival. Since lipids are essential molecules for cancer cells, understanding lipid metabolism reprogramming might be a useful hallmark for cancer. Those hallmarks include sustaining growth signaling, evading growth suppressors, resisting apoptosis programs, inducing angiogenesis, and activating invasion and metastasis.

In this chapter, we will focus on changes in fatty acid metabolism. Fatty acids are essential building blocks for some lipids with numerous essential roles in the human body. The body usually gains fatty acids from the diet, known as exogenous fatty acids. However, fatty acids can also be obtained endogenously through de novo fatty acid synthesis. In cancer conditions, a large number of fatty acids are needed. Changes in fatty acid metabolism are common to provide the needs of fatty acids for cancer cells.

A high rate of fatty acid metabolism must be followed by activating several enzymes involved in fatty acid metabolism. Overexpression of those enzymes might be useful as a marker for a cancer condition. Another benefit of understanding how a tumor cell influences the environment around it is also essential for developing new targeted therapies.
2. Fatty acids

Lipids are molecules that have numerous essential roles in the human body. In intracellular activity, lipids act as a ligand and second messenger. Lipids are composed of water-insoluble molecules such as fatty acids, triacylglycerides, phospholipids, or cholesterol. Fatty acids are molecules consisting of a carboxylic acid group and a hydrocarbon chain. Fatty acids are classified based on their hydrocarbon chain length: short-chain fatty acids (less than six carbon atoms), medium-chain fatty acids (6–12 carbon atoms), long-chain fatty acids (12–21 carbon atoms), and very-long-chain fatty acids (22 or more carbon atoms) [1–3].

Fatty acids are essential building blocks for lipids such as phospholipids, sphingolipids, and more complex lipids such as diacylglycerides (DAGs) and triacylglycerides (TAGs), which are important in regulating biochemical processes in a normal cell. In mammals, the main source of fatty acids is gained from the microenvironment (exogenous) through some transporter: fatty acid translocase (FAT) or cluster of differentiation 36 (CD36), fatty acid transport protein family (FATPs), and plasma membrane fatty-acid-binding proteins (FABPpm). In some conditions, fatty acids can be synthesized through de novo synthesis inside the body [3].

3. Synthesis and regulation of fatty acids

In order to build some essential lipids, fatty acids are obtained from direct uptake from the microenvironment. Exogenous fatty acids are taken up to the plasma membrane by some transporters: CD36, FATPs, and FABPpm. Those fatty acids are then stored as lipid droplets, which can convert to nicotinamide-adenine dinucleotide phosphate (NADPH) and acetyl CoA via β-oxidation, or known as fatty acid oxidation (FAO) [1, 3, 4].

NADPH is then used as energy fuel for metabolism activity, meanwhile acetyl-CoA is used as a material for the tricarboxylic acid (TCA) cycle. Acetyl-CoA is not only produced by β-oxidation, but is also generated from glucose and acetate metabolism. In the TCA cycle, acetyl-CoA is converted into citrate. When de novo fatty acid synthesis (FAS) is activated, those mitochondria-derived citrate together with glucose and amino acids then enter de novo FAS to produce fatty acids [3, 4].

De novo FAS is the formation of fatty acids from carbon atoms derived from carbohydrates such as glucose and amino acids, including glutamine. De novo synthesis occurs mainly in the liver and adipose tissue and is highly responsive to changes in dietary regimen. This pathway contributes to triacylglycerol's homeostasis, where most of the TAG is obtained from the diet. A high-carbohydrate diet activates a lipogenic response in liver tissue to increase the synthesis and secretion of very-low-density lipoprotein (VLDL) and increase hepatic de novo synthesis contributing to hypertriglyceridemia [1, 2].

De novo FAS requires some catalyst enzymes, such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN). ACLY bridges glucose and FA metabolism by converting six-carbon citrate to oxaloacetate and two-carbon acetyl-CoA. The acetyl-CoA transforms into malonyl-CoA by ACC, which is regulated by citrate and glutamate. The next step produces 16-carbon palmitate from malonyl-CoA by FASN. Acetyl-CoA synthetase 2 (ACSS2) also plays a role in de novo FAS by converting acetate to acetyl-CoA before entering the TCA cycle [3, 5].
One of TCA products is mitochondria-derived citrate, which converts to acetyl-CoA by ACLY in the cytosol. This acetyl-CoA is fuel for de novo FAS as it converts into malonyl-CoA by ACC. Finally, malonyl-CoA converts into palmitate by FASN (Figure 1). Subsequently palmitate is then esterified to form triglycerides or cholesterol esters. Palmitate may also form new fatty acids by elongation of very-long-chain fatty acid protein (ELOVLs) [1, 3, 4].

The regulation of de novo lipogenesis occurs through the activation of sterol regulatory element-binding proteins (SREBPs). There are three main transcription factors: SREBP1a and SREBP1c, and SREBP2. SREBPs are inactive 125-kDa precursors bound to the endoplasmic reticulum (ER). When the concentration of intracellular cholesterol is high, insulin-induced genes (INSIGs) will bind to SREBP-cleavage-activating proteins (SCAPs) and localize the SREBP precursors to the ER. But, when the cholesterol concentration is low, SCAPs will facilitate the translocation of ER-bound SREBPs to the Golgi and then release the active N terminus. This N-terminal fragment translocates to the nucleus and induces the transcription of genes containing sterol regulatory elements (SREs), such as FASN, ACLY, and ACC. Some growth factors and estrogen receptors also regulate FASN expressions, such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), estrogen receptor, and progesterone receptor [3].
4. Fatty acid oxidation (FAO)

Fatty acid oxidation, known as fatty acid β-oxidation, is the degradation of long-chain fatty acids in mitochondria. The balance between exogenous fatty acid uptake, FAO, and de novo FAS depends on dietary intake and metabolic rate in mitochondria [4, 6].

Carnitine palmitoyl transferase (CPT) 1, CPT2, and carnitine-acylcarnitine translocase (CACT) are enzymes needed to catalyze the FAO (Figure 2). CPT1 is an outer membrane enzyme and has a role in translocating long-chain fatty acids into acyl-CoA across the membrane. In this process, acyl-CoA is converted into acylcarnitine. After successfully penetrating the membrane, the CPT2 as an inner membrane enzyme converts acylcarnitine back into acyl-CoA for oxidation [4, 6].

![Figure 2. Role of CPT1 and CPT2 in FAO [6]. LACS: long-chain acyl-coenzyme A (CoA) synthetases, CPT1: carnitine palmitoyl transferase 1, CPT2: carnitine palmitoyl transferase 2, CACT: carnitine-acylcarnitine translocase.](image)

5. Reprogramming of fatty acid metabolism in cancer

Tumor cells need to control their environment to survive. Under a nutrient-limited microenvironment, they compete for oxygen and micronutrients with normal cells to survive and even maintain their malignancy potential. Changes in lipid metabolism are common to provide the needs of fatty acids for cancer cells. Cancer cells require fatty acids to build the membrane and molecule signaling. Thus, fatty acid metabolism reprogramming is one of the hallmarks of the cancer condition. This reprogramming includes alteration of fatty acid uptake, de novo fatty acid synthesis, and fatty acid oxidation (FAO) [3–5].
5.1 Increased exogenous fatty acid uptake

Overexpression of CD36 has been correlated with breast cancer survival and leads to elevation of exogenous fatty acid uptake. This elevated exogenous fatty acid uptake is implicated in enhancing tumor growth and metastasis and providing the cancer cell with chemoresistance. Elevated lipid droplets resulting from excess fatty acids are used by cancer cells for various vital roles, such as maintaining lipid homeostasis and preventing cancer cells from death under metabolic stress [3–5].

5.2 Increased de novo fatty acid synthesis

The body usually uses exogenous fatty acids to maintain homeostasis in normal conditions. De novo FAS is present when the diet is not adequate. But in the presence of cancer cells, increased de novo fatty acid synthesis usually occurs to meet the demand for high fatty acids. This is thought to be part of the general metabolic shift from a nonproliferative catabolic phenotype to a proliferative anabolic phenotype [2, 4].

Cancer cells upregulate some critical enzymes, such as ACC, ACLY, and FASN, to enhance the rate of de novo FAS (Figure 3). ACLY has a role in glucose metabolism and FA metabolism by converting six-carbon citrate to oxaloacetate and two-carbon acetyl-CoA. ACLY overexpression and activity have been represented in some cancers: in the lung, prostate, bladder, breast, and liver. This overexpression was correlated with a poorer prognosis in lung adenocarcinoma. Thus, inhibiting ACLY may induce activation of p53, which plays a role in suppressing cancer cell proliferation [3, 7].

FASN is a 270-kDa dimeric enzyme responsible for producing fatty acids from malonyl-CoA and acetyl-CoA. In breast cancer, HER2/neu increased FASN transcription and lipogenesis. In addition, a study found that HER2/neu directly phosphorylates FASN, and this phosphorylation increases FASN synthesis activity [2, 5, 8].

Overexpression of FASN has been known as a hallmark of phenotypic alteration for most human malignancies. This elevation of FASN leads to increase fatty

Figure 3.
De novo FA synthesis alteration. GLUT1: glucose transporter 1, FASN: fatty acid synthase, ACLY: ATP citrate lyase, ACC: acetyl-CoA carboxylase, TCA: tricarboxylic acid.
acid synthesis and correlates with poor prognosis for many cancer types. FASN also promotes tumor angiogenesis since it correlates with vascular endothelial growth factor (VEGF).

The level of fatty acids is also correlated with gynecological outcomes in epithelial ovarian cancer. A study reports that a higher level of fatty acids is correlated with suboptimal debulking in epithelial ovarian cancer patients. Increased FASN expression and activity were also found in early oncogenesis and correlated with cancer development. A study in ovarian cancer showed that overexpression of FASN is more correlated with tumor proliferation than tumor metastasis. Conversely, FASN inhibition leads to accumulating malonyl-CoA, which induces apoptosis [3, 5, 9, 10].

Cancer cells tend to upregulate ACC under metabolic stress or lipid depletion. These ACC then convert acetyl-CoA to malonyl-CoA to meet the high demand for fatty acids. On the other hand, ACC inhibition decreases palmitic acid and induces an apoptosis program. In a breast cancer cell, apoptosis triggered by depletion of ACC only occurs in the nonmalignant cell [3, 10].

5.3 Increased fatty acid oxidation

Another reprogramming of fatty acid metabolism is increased fatty acid oxidation. The products of fatty acid oxidation such as NADH, NADPH, FADH2, and ATP are used for cancer cells as energy-carrying molecules, which are important for their survival. High levels of ATP from FAO are correlated with the proliferation of triple-negative breast cancer. Acetyl-CoA from the FAO also can be used by cancer cells to gain fatty acids through de novo FAS. An increase in CPT1 is common in cancer cells. CPT1 also provides neovascularization for the tumor microenvironment [4, 6].

CPT1C is one of the subtypes of CPTC, which is upregulated in some cancers and protects the cancer cells from metabolic stress such as hypoxia or glucose depletion. Elevation of CPT1C in cancer cells provides FAO and adaptation to metabolic stress and resistance to mTOR complex 1 (mTORC1) inhibitor. Thus, increased FAO is essential not only for tumor growth but also for cancer chemoresistance [4, 6].

6. The role of fatty acids for tumorigenesis

As mentioned above, fatty acid metabolism has some essential roles in helping the cancer cell to survive. Interestingly, fatty acids are involved in signaling pathways to regulate cellular homeostasis and create an appropriate microenvironment for tumor progression and metastasis. Those signaling pathways include phosphoinositide 3 kinase (PI3K), protein kinase B (Akt), and mTOR signaling pathways [3, 11].

Synthesis of saturated and monounsaturated fatty acids is increased due to the high rate of de novo FAS in cancer cells. Interestingly, a rigid and stable cell membrane is formed from de novo FAS products. This high cholesterol structure protects the cell from peroxidation and limits its ability to spread (Figure 4A). To reduce the rigidity and increase the fluidity of cell membranes, the cancer cell needs to release intracellular cholesterol. After decreasing cholesterol levels, the cell membrane is less rigid and more flexible in changing its shape, and epithelial-to-mesenchymal transition (EMT) can occur [3, 11].

EMT is an important mode for cancer cells to spread. As an enzyme involved in de novo FAS, FASN correlates with EMT. The level of FASN is increased in EMT cells. FASN can regulate the Wnt or (transforming growth factor β) TGF-β signaling
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pathways to alter cell membrane rigidity and increase the mobility of cancer cells. This opportunity gives the cancer cell ability to spread. But conversely, high cholesterol levels in cell membrane lead to cholesterol-rich lipid rafts formation and induce onco-
genic signaling via PI3K-AKT (Figure 4B). With this contradictive theory, inhibiting cholesterol synthesis still can be considered as a therapy for early-stage cancer [3, 11].

Another signaling molecule, which contributes in tumorigenesis, is phosphati-
dylinositol (PtdIns). PtdIns is composed of two fatty acid chains bound to an inositol ring and glycerol. Some phosphoinositide species, such as phosphatidylinositol (3,4)-biphosphate or PI(3,4), phosphatidylinositol (4,5)-biphosphate or PI(4,5), phosphatidylinositol 3-phosphate or PI(3)P, and phosphatidylinositol (3,4,5)-tri-
sphosphate or PIP3, are generated from hydroxyl group of inositol ring. PIP3 activates oncogenic AKT and induces activation of mammalian target of rapamycin complex 2 (mTORC2), leading to tumorigenesis. On the other hand, PI(3)P induces tumorigen-
esis via serum- and glucocorticoid-induced protein kinase-3 (SGK3) activation.

7. Targeting fatty acid metabolism for cancer treatment

Considering reprogramming fatty acid metabolism is an important hallmark for cancer development; targeting key enzymes involved in fatty acid metabolism is a
promising strategy. Not only de novo FAS and FAO, but lipid uptake is also a potential target for cancer treatment.

7.1 Targeting lipid uptake

CD36 inhibition might be useful for tumors with lipoprotein lipase (LPL) and CD36 overexpression. Anti-CD36 use implicates complete inhibition of metastasis in immunodeficient mice without any adverse effect. In prostate cancer, CD36 monoclonal antibody use can reduce exogenous fatty acid uptake and several oncogenic signaling lipids. Further study is still needed to reveal the side effects of long-term inhibition of CD36. Decreased lipid uptake into the cell using orlistat may also be used for targeted therapy. Orlistat is used to inhibit LPL in order to decrease exogenous fatty acid uptake [4].

7.2 Targeting enzymes involved in de novo FAS

Since the role of FASN is important in supporting both anabolic metabolism and oncogenic signaling, targeting FASN for cancer therapy might be promising. Inhibition of FASN leads to toxic accumulation of malonyl-CoA in inducing cell death. In cells derived from a lymph node metastasis of prostate carcinoma (LNCaP), RNA interference (RNAi) activity against FASN implicates cancer cell growth inhibition. First-line chemical inhibitors of FASN such as C75, orlistat, and cerulenin are shown to reduce and inhibit tumor growth by inducing cell-cycle arrest. Orlistat provides antitumor properties for some cancers such as breast cancer and melanoma. FASN inhibition was also sensitive for ovarian cancer cells by C75 and G28UCM. Using this first generation of FASN inhibitors had some adverse effects such as increased energy expenditure, loss of adipose tissue, and decreased body weight [3–5].

The next generation of FASN inhibitors, such as TVB-3166 and TVB-2640, has shown antitumor potential, higher specificity for FASN, and limited systemic toxicity in a preclinical study. Antitumor activity has been shown in breast cancer and colorectal cancer by TVB-3166 and TVB-3664 use in preclinical study. In a clinical trial, TVB-3166 and TVB-2640 showed limiting systemic toxicity in early phase. The significant difference between the first and next generations is that the newer generation does not implicate indirect CPT1 in peripheral tissue. Omeprazole may also be used for FASN inhibitors and has entered clinical trials in triple-negative breast cancer patients [3, 4].

Some ACLY inhibitors have shown high efficacy in lowering LDL cholesterol. ETC-1002 has entered clinical trial in phase 2/3, and hydroxy citrate has already entered randomized control trials. Thus, ACLY inhibitors can be considered as a therapeutic strategy for cancer therapy and have been demonstrated to reduce tumor proliferation in some cancers, such as breast cancer, lung cancer, and prostate cancer [4].

SCD1 inhibitors such as CVT11127, MF-483 also have potential as an anticancer therapeutic target. The combination of SCD1 inhibitor with other drugs shows potency against cancer cell chemoresistance and enhances therapeutic efficacy. Commonly used drugs in combination with SCD1 are gefitinib, temozolomide, and temsirolimus [4].

AKT/mTOR/SREBP-1 pathway is also interesting to point out as targeted therapy. The activity of fatty acid synthase may be reduced by reducing its transcription levels. Inhibiting SREBP-1 in cancer cells could decrease fatty acid synthase gene expression and prevent cancer cell growth. Among SREBP-1 inhibitors, betulin has
increased the sensitivity of hepatocellular carcinoma cells to their first-line anti-tumor agent, sorafenib. On the other hand, a combination of the mTOR inhibitor everolimus and metformin can inhibit the proliferation of breast cancer cells [4].

7.3 Targeting fatty acid catabolism

Limiting excess fatty acids by increasing fatty acid degradation by mitochondria β-oxidation can be beneficial in reducing the proliferation of cancer cells. Otherwise, the high rate of fatty acid oxidation could prevent cancer cells from metabolic stress by providing abundant ATP as an energy fuel. Thus, decreasing fatty acid oxidation might be a promising strategy against cancer cells [4, 5].

CPT1 is the first and rate-limiting step of fatty acid oxidation. The use of CPT1 inhibitors such as etomoxir may inhibit tumor cell proliferation. Perhexiline, αβ-oxidation inhibitor has also shown to be beneficial by inhibiting fatty acid

![Diagram of Therapeutic targets in fatty acid metabolism](image-url)
utilization and tumor cell proliferation. In addition to perhexiline, sensitivity in gastrointestinal cancer for its first-line regimen therapy has increased (Figure 5) [4].

8. Conclusions

Fatty acids are essential building blocks for lipids, which have numerous essential roles in the human body. Fatty acids are needed for cell survival, not only in healthy cells but also in cancer cells. Thus, fatty acid reprogramming is a useful hallmark for cancer conditions. Understanding several enzymes involved in fatty acid metabolism, such as FASN, ACC, and ACLY, is also helpful in developing therapeutic targets for cancer.

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Conflict of interest

The author declares no conflict of interest.

Pictures

The author declares all the figures as original and not published elsewhere.

Other declarations

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