Chapter

An Important Component of Tumor Progression: Fatty Acids

Jin Wang, Qifei Wang and Guangzhen Wu

Abstract

Fatty acids (FAs) are complex and essential biomolecules in the human body and are critical to the formation of cell membranes, energy metabolism, and signaling. FAs are the major components of several lipids including phospholipids, sphingolipids, and triglycerides, and consist of carboxylic acid groups and hydrocarbon chains of different carbon lengths and degrees of desaturation. They can synthesize more complex lipids, including acylglycerides (DAG) and triacylglycerides (TAG). Saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA), and monounsaturated fatty acids (MUFA) can be classified according to whether the hydrocarbon chain is saturated or not. Normal cells are commonly supplied with energy by the tricarboxylic acid cycle. On the contrary, to obtain energy, tumor cells usually use aerobic glycolysis (Warburg effect) and produce large amounts of FAs to maintain membrane structure to support cell proliferation. In addition, cancer migration, immune escape, development of drug resistance, and fatty acids are very closely related. In conclusion, a deeper understanding of the molecular mechanisms of fatty acid metabolism could provide a more plausible explanation for the progression of cancer cells and provide new potential targets for therapy.

Keywords: fat acids, tumor progression, cancer, lipid mediators, fatty acid metabolism

1. Introduction

FAs are important for human health and nutrition and are characterized by a wide variety and functional complexity. We have summarized some of the main functions of FAs as follows.

1. Provision of energy: Fatty acids are a major component of triglyceride synthesis. On the one hand, fatty acids can be esterified with glycerol for efficient energy storage [1], and on the other hand, it can also produce ATP through fatty acid oxidation (FAO, also known as β-oxidation) to supply energy to the body. FAO is a multistep catabolic process. Long-chain fatty acids are first converted to acetyl-CoA, which is then fully oxidized by the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC), producing ATP. Several studies have shown that abnormal activity of FAO is associated with multiple aspects of tumorigenesis. Many cancer cells are FAO-dependent for proliferation, survival, drug resis-

tance, or metastasis. So, the study of key enzymes and regulatory mechanisms in the FAO process is helpful for cancer treatment [2].

2. Constituting biological membranes: Acetyl-CoA is recycled back to fatty acyl CoA, then converted to fatty acids via fatty acid synthase (FAS) [3]. Fatty acids are prolonged and desaturated by stearoyl coenzyme A desaturase (SCD1) to produce some of the unsaturated fatty acids, triglycerides, and phospholipids required for the synthesis of biological membranes [4]. Both these and cholesterol are essential components of biological membranes. The biofilm is a functionally complex structure composed of thousands of different lipids, and all communication inside and outside the cell is controlled by it [5].

3. Synthesis of signaling molecules as lipid mediators. For example, arachidonic acid (AA) is an omega-6-derived PUFA that can synthesize eicosanoids, including prostaglandins and thromboxanes, and can also serve as a substrate for leukotriene synthesis via the lipoxygenase pathway. Prostaglandins play a role in inhibiting inflammation and promoting a tumorigenic environment [6].

2. De novo synthesis of fatty acids

Most adult mammalian cells obtain lipids from the blood, which are partly derived from the diet and partly from hepatic synthesis. Still, cancer reactivates de novo lipogenesis, making them more independent of externally supplied lipids themselves. Numerous research results have verified that the growth and survival of cancer cells depend on the de novo synthesis of FA [1, 7]. De novo fatty acid biosynthesis in the adult organism occurs primarily in the liver, adipose tissue, and lactating breast [8]. In cells, glucose, glutamine, or acetate produce acetyl-CoA, which synthesizes FAs [9]. Acetyl-CoA is activated by acetyl-CoA carboxylase (ACC) to form malonyl CoA; it is then condensed with the participation of FAS to form the 16 carbon saturated fatty acid palmitate. Next, palmitate undergoes elongation and desaturation to create a cellular pool of nonessential FAs, which include the 18 carbon monounsaturated fatty acid oleate (C18:1). Multiple oncogenic signaling pathways are focused on FA synthesis. For example, the PI3K/Akt signaling pathway, on the one hand, promotes the expression of enzymes required for FA synthesis. On the other hand, it increases the phosphorylation and activation of ATP citrate lyase (ACLY). ACLY is a key enzyme linking glucose metabolism and lipid synthesis and can catalyze cytoplasmic citrate to acetyl-CoA [10, 11]. In contrast, under the STK11/LKB1 tumor suppressor pathway control, AMP-activated protein kinase (AMPK) blocks FA synthesis by phosphorylating ACC [12]. Because increased de novo FA synthesis in cancer cells alters cellular lipid composition, it can be used for diagnosis [13]. Also, FA uptake is essential for cancer, and reducing fatty acid uptake of prostate cancer cells by silencing CD36 has been reported for use in preclinical models for the treatment of prostate cancer [14].

3. Function of fatty acids in cancer cells

The tumor tissue must also acquire some lipids from the extracellular environment. The uptake and function of FAs require the involvement of fatty acid-binding protein (FABP). FABPs are a family of proteins involved in FA uptake and transport,

and nine FABP factors have been identified in mammalian cells and are numbered in the order of their discovery (FABP1, FABP2, FABP3, FABP4, FABP5, FABP6, FABP7, FABP8 and FABP9) (**Table 1**).

3.1 Promotes tumor growth

Due to the active proliferative characteristics of tumor cells, FA is required to provide the lipids and energy necessary to form cellular structures, so cell growth must be closely related to the induction of lipid synthesis. Moreover, a common feature of cancer is the conversion to a glucose-dependent form of metabolism. Once the glucose metabolism of tumor cells exceeds the bioenergetic requirements, the excess metabolites are combined into lipids. For example, inhibition of ACLY with small molecules can impair the development of immortalized hematopoietic stem cells stimulated by the corresponding growth factors [26]. There are other studies showing that ACLY overexpression promotes tumor cell growth, while inhibition of ACLY inhibits tumor cell growth [27–29].

3.2 Changing the composition of membrane lipids

It is also possible to change the composition of lipids in biological membranes to affect the function of organelles in membrane-containing cells, thereby altering FA synthesis and modification. Cardiolipids (CLs) are structurally specialized phospholipids located mainly in the inner mitochondrial membrane, where they control mitochondrial respiration and can signal the induction of apoptotic processes [30]. Regulation of FA biosynthesis and uptake in cancer cells can directly influence

FABPS	Characteristics	Refs
FABP1	FABP1 is also known as liver-FABP, is widely distributed in the cytoplasm of hepatocytes and is less distributed in the nucleus and the outer mitochondrial membrane.	[15]
FABP2	FABP2 is also known as intestinal-FABP, is expressed in the epithelium of the small intestine.	[16]
FABP3	FABP3, which preferentially binds to n-6 PUFAs such as AA, is expressed in the brain, heart, skeletal muscle, lactating mammary glands, and placenta.	[17]
FABP4	FABP4 may be secreted from adipocyte cells and transferred to tumor cells. In breast and prostate cancer, FABP4 promotes cell growth and metastasis.	[18, 19]
FABP5	FABP5 is upregulated in a variety of cancers, including triple-negative breast cancer, bladder cancer, pancreatic cancer, and oral squamous cell carcinoma.	[20]
FABP6	FABP6 is mainly expressed in ileal epithelial cells, which plays an extremely important role in the intracellular transporter of bile acids and the metabolism of cholesterol.	[21, 22]
FABP7	FABP7 is well known for its significant expression in brain tissue and its function has been extensively studied in glioblastoma cell lines.	[23]
FABP8	FABP8 is a major cytosolic protein constituent of myelin in the peripheral nervous system.	[24]
FABP9	FABP9 is a member of the FABPs family and is mainly expressed in testis tissue.	[25]

Table 1.
Characteristics of FABP family proteins.

cellular bioenergetics by modulating the electron transport chain (ETC) activity. It was shown that the CL profile of mouse brain tissue, both in mitochondria separated from tumor tissue and normal tissue, was significantly different and correlated with impaired ETC enzyme activity [31]. Therefore, we can assume that interfering with CL synthesis, and thus mitochondrial function, has the potential to have a therapeutic effect on cancer.

3.3 Protein acylation

The abundance and degree of saturation of cellular FA also dictate that signaling protein activity requires acylation to function. For example, WNT (wingless-related MMTV integration site) proteins are a family of proteins that regulate development, and its dysregulation is closely associated with many disease-related processes and cancers [32]. Disruption of epithelial cell polarity due to aberrant activation of the WNT-β-catenin pathway leads to loss of cell–cell adhesion [33]. SRC and RAS oncoproteins are also cancer-associated acylated proteins modified mainly through thioesterification of saturated palmitoyl residues [34].

3.4 Lipid mediators

Lipid mediators are bioactive molecules derived from PUFAs, such as AA, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), through enzymatic or non-enzymatic oxidative metabolism [35]. For example, these compounds include sphingosine-1-phosphate (S1P) [36] and lysophosphatidic acid (LPA) [37], which are biologically active lipids. Diacylglycerol (DAG) [38], inositol-1,4,5-trisphosphate (IP3) and phosphatidylinositol-3,4,5-trisphosphate (PIP3) [39], can act as lipid second messengers. S1P is a member of the sphingolipid family and is involved in the regulation of various physiological responses, including cell growth, transformation, migration, and cell death [40]. LPA is signaled through autocrine and paracrine mechanisms and has multiple effects on cell proliferation, differentiation and intracellular messaging, stimulating cell migration, inflammation, and angiogenesis [37]. Targeting lipid mediators in the tumor microenvironment or within the tumor may be a new therapeutic approach for treating cancer patients.

4. Role of fatty acids in cancer progression

Although cancers are a series of distinct diseases, there are common features among cancers such as proliferation, apoptosis resistance, metabolic adaptation, migration, and invasion, and these features contribute to cancer progression. Fatty acids not only have an essential factor in the development of cancer but also play a crucial role in tumor development and metastasis, and even become a major cause of cancer death.

4.1 Cell migration

Usually, epithelial-mesenchymal transition (EMT) leads to increased motility of cancer cells [41]. EMT consists of multiple dynamic transition states between epithelial and mesenchymal phenotypes that can regulate tumor progression and metastasis [42]. Induction of EMT can promote changes in membrane fluidity required for cell

migration by remodeling the composition of cellular lipids. After tail vein injection in mice, breast cancer cells can be treated with compounds that disrupt the gene expression profile associated with EMT to reduce membrane fluidity and block cancer cell migration and lung metastasis formation [43]. Cancer cells may change from a state of proliferation to a state of migration in such a way that FA uptake or selective release of specific FA species from membrane lipids creates a signaling molecule that promotes cell migration and invasion.

4.2 Angiogenesis

Normally, angiogenesis occurs only during embryonic development, the female reproductive cycle, and wound repair. While aberrant angiogenesis is a key mediator and major process in cancer development [44]. The induction of angiogenesis determines the proliferation of metastasis and the growth of primary and metastatic tumors [45]. Lipid signaling, including prostaglandin E2 (PGE2), lysophosphatidic acid (LPA), and sphingosine-1-phosphate (S1P), can stimulate blood vessel growth while recruiting immune cells (especially macrophages), promoting tumor angiogenesis [46, 47]. As the possibilities of anti-angiogenic therapy are continually explored, it will become possible to target cancer with angiogenesis.

4.3 Immune escape

Immune editing refers to how cancer cells escape immune surveillance through evolution. Cancer cells can suppress the cytotoxic function of T cells by expressing checkpoint proteins and changing macrophages into a pre-tumorigenic phenotype by reprogramming them. The interactions between cancer and stromal cells involved in immune editing are complex and these interactions may be regulated by lipid-derived factors [48], such as PEG2.

5. Utilization of fatty acid metabolism

In countries around the world, cancer is the leading cause of death. The burden of cancer incidence and mortality is rapidly increasing worldwide, so the treatment of cancer has been a focus of clinical development [49, 50]. There is growing evidence that lipid metabolic reprogramming is present in a variety of cancers [7, 51]. Because of the close relationship between FA metabolism and cancer pathogenesis, it is clinically significant to develop therapeutic approaches that target FA metabolic reprogramming. Not surprisingly, FAS has received the most attention in tumor-targeted therapies associated with dysregulated lipid metabolism, due to its multifaceted functions in supporting anabolic and oncogenic signaling. It has been shown that when comparing normal tissues with malignant ovarian cancer models, the expression of FAS mainly reflects the proliferation and growth status of cells rather than the degree of malignancy [52]. Therefore, FAS inhibitors are widely concerned with cancer therapy, such as the natural product cerulenin and the new compound C75, which selectively kill cancer cells by inducing apoptosis [53]. Despite these encouraging results, the issue of potential side effects of targeted FAS remains serious. Another validated target is ACLY. Previous studies have observed increased ACLY expression and activity in glioblastoma, colorectal, breast, and hepatocellular carcinomas [26]. There is substantial preclinical evidence to support the overall role of ACLY in

tumorigenesis, not only for its genetic targeting but also for its pharmacological targeting that significantly reduces the growth of xenografts in lung and prostate tumors and this antitumor effect is more pronounced in highly glycolytic cells [26].

6. Conclusion

Past studies have shown that lipid metabolism, especially FA synthesis, plays an important role in the normal human body. Alterations in FAs not only affect cancer cell migration but also induce angiogenesis, metabolic symbiosis, immune evasion, and drug resistance. FA is similarly important in the progression of cancer cells and FA synthesis has received much attention as a potential target for cancer therapy. However, it seems that clinical practice is still scarce. The reason for this may be that it is difficult for us to inhibit lipid metabolism in cancer cells in a highly selective manner without affecting other tissues throughout the body. Moreover, cellular lipids are diverse, complex in function, and also closely related to other metabolisms, so targeting this aspect of cancer cell metabolism remains challenging. Therefore, the link between FA and tumors requires further research. The development of drug resistance has been one of the main reasons for high cancer-related mortality, and alterations in lipid metabolism can also affect drug resistance. This also provides new strategies to explore cancer treatment.

Author details

Jin Wang, Qifei Wang* and Guangzhen Wu*
Department of Urology, The First Affiliated Hospital of Dalian Medical University, Dalian, China

*Address all correspondence to: wuguang0613@hotmail.com
and wangqifei6008@hotmail.com

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