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The Role of Fatty Acids in Cancer Cell Growth and Metastasis

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ABSTRACT

Cancer cells have metabolic processes that are distinct from normal cells. Even under oxygen-sufficient conditions, cancer cells undergo lactate fermentation to produce only two ATPs through aerobic glycolysis. The reason cancer cells use this inefficient metabolism is to produce nucleic acids, amino acids, lipids, etc. necessary for rapid cell growth by using metabolic intermediates of glycolysis and TCA cycle. All cancers require fatty acids for the production of cell membranes and signaling molecules during cell growth and metastasis. Here, we aim to investigate fatty acid synthesis (FAS) metabolism and understand the role of fatty acids in cancer cell proliferation and metastasis. In addition, it is intended to present an understanding of cancer treatment methods that target fatty acids as molecular targets.

Keywords: Cancer Cell; Fatty Acid Synthesis; Metastasis

Abbreviations: FATPs: Fatty Acid Transport Proteins; IDH: Isocitrate Dehydrogenase; ACC: Acetyl-Coa Carboxylase; FASN: Fatty Acid Synthase; ACLY: ATP-Citrate Lyase; TG: Triacylglycerol; LD: Lipid Droplets; SREBP-1: Regulatory Element Binding Protein-1; ER: Endoplasmic Reticulum; SCD: Stearoyl-CoA Desaturase; SCAP: SREBP-Cleavage Activating Protein

Introduction

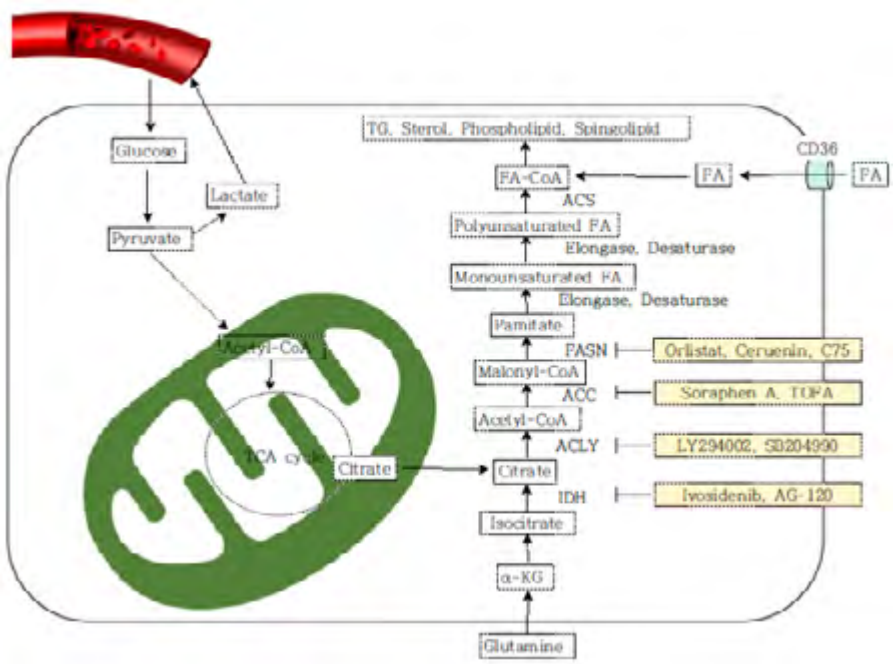
Fatty Acid Synthesis (FAS) Metabolism

Fatty acid is widely used in the growth and metastasis of cancer cells. Fatty acids are obtained through two pathways: absorbing fatty acids from outside the cell or synthesizing de nove within the cell [1,2]. Cancer cells absorb fatty acids secreted from adjacent adipocytes using fatty acid transporters such as CD36, fatty acid transport proteins (FATPs), fatty acid binding proteins (FABPs), and low-density lipoprotein receptors [3-6]. The substrate used in the first step of FAS is citrate. In general, citrate is produced by pyruvate through the TCA cycle. However, in the case of cancer cells, the mitochondrial function is suppressed because they are growing in a hypoxic environment, so the TCA cycle has low operating efficiency. Therefore, cancer cells absorb glutamine as an alternative nutrient to produce α-ketoglutarate (α-KG), which is converted to citrate by isocitrate dehydrogenase (IDH) [7]. Cancer cells then activate ATP-citrate lyase (ACLY) through Akt activation to convert citrate to acetyl-CoA [8]. Acetyl-CoA is then converted to malonyl-CoA by acetyl-CoA carboxylase (ACC). Malonyl-CoA is finally produced as a saturated fatty acid, palmitate, by fatty acid synthase (FASN). Palmitate is elongated or converted to unsaturated fatty acids by various elongases and desaturases. The produced fatty acids are processed into fatty acid-CoA by acyl-CoA synthetase and converted into phospholipids or sphingolipids in cell membranes, or converted to triacylglycerol (TG) or sterols in the lipid droplets (LD). Key enzymes involved in FAS, such as

ACLY, ACC, and FASN, are expressed by regulatory element binding protein-1 (SREBP-1), a transcriptional activator which is activated by PI3K/Akt/mTORC signaling pathway. The ratio of saturated and unsaturated fatty acids in the cell must be kept constant. Excessive accumulation of saturated fatty acids could induce cancer cell death through mitochondrial dysfunction, ROS production, and induction of endoplasmic reticulum (ER) stress. Therefore, maintaining the activity of stearoyl-CoA desaturase (SCD), which synthesizes unsaturated fatty acids, is essential for fatty acid balance in cancer cells.

Fatty Acid and Cancer Cell Proliferation

Treatment with an antibody against CD36, which is responsible for the intracellular uptake of exogenous fatty acids, inhibited the proliferation of prostate cancer [2]. In addition, it has been confirmed that cancer proliferation can be effectively reduced through inhibitors against FATP and FABP [3,9]. In addition to the development of drugs that inhibit fatty acid absorption, studies to inhibit the de nove synthesis of fatty acids in cancer cells are being actively conducted. Cancer cells have more active fatty acid synthesis than normal cells, so they are attracting a lot of attention as an attractive anticancer strategy. Among the enzymes that act in the fatty acid synthesis process, studies on inhibitors of FASN have been extensively conducted. FASN inhibitors such as orlistat, cerulenin, C75, IPI-9119, and EGCG inhibited the proliferation of cancer cells by inducing apoptosis in various cancer cells [10-13]. In addition to FASN, inhibitors targeting ACLY and ACC also inhibited the proliferation of cancer cells by inhibiting the cell cycle and inducing apoptosis in various cancer cells [14-16]. In addition, treatment with BPTES, an inhibitor of isocitrate dehydrogenase (IDH), which converts glutamine to α-ketoglutarate, has been reported to inhibit head and neck cancer cells growth [17]. SREBP-1 is a transcription factor that regulates the expression of ACLY, ACC, and FASN acting on the fatty acid synthesis pathway. Direct inhibitors of SREBP-1 have not yet been developed, but inhibitor that represses binding SREBP-1 to SREBP-cleavage activating protein (SCAP) has been developed. Such inhibitors include fatostatin and betulin, which have shown effective cell proliferation inhibition in prostate cancer [18,19]. Palmitate produced through fatty acid synthesis is converted to monounsaturated fatty acids and polyunsaturated fatty acids through the action of several elongation and desaturase enzymes to supply energy. In a recent study, inhibitors of the unsaturated fatty acid synthase SCD (betulinic acid, SSI-4, MF-438) were reported to inhibit the proliferation and growth of cancer [20, 21]. Fatty acid synthesis metabolism and inhibitors are shown in (Figure 1).



Note: α-KG: α-ketoglutarate, IDH: isocitrate dehydrogenase, ACLY: ATP-citrate lyase, ACC: acetyl-CoA carboxylase, FASN: fatty acid synthase, ACS: acyl-CoA synthetase, TCA: tricarboxylic acid, TG: triacylglycerol, FA: fatty acid, FA-CoA: fatty acid-CoA.

Figure 1: Overview of cancer cell fatty acid metabolism and inhibitor.

Fatty Acid and Cancer Cell Metastasis

Metastasis is the movement of cancer cells from the primary organ to other organs. Cancer metastasis involves the growth of cancerous tissue, infiltrating surrounding organs, and moving to distant organs along blood vessels or lymphatic vessels. The degree of cancer lymph node metastasis predicts the survival rate of cancer patients and determines the direction of treatment. The mechanism of metastasis and survival of cancer cells to lymph nodes is still not well understood. It was reported that most cancer cells use glucose as their main energy source, but a recent study revealed that cancer cells that reached the lymph nodes use fatty acids as their main energy source [22]. Treatment that suppress fatty acid biosynthesis metabolism could inhibit cancer cell metastasis and decrease cancer cell survival [22,23].

Conclusion

Cancer cells operate separately from glycolysis and the TCA cycle even in an oxygen-rich environment. This avoids maximal ATP production from carbohydrates, but instead obtains the material needed for cancer cell growth. In addition, cancer cells store extra energy by synthesizing fatty acids, and use them for cell membrane synthesis and the production of signaling substances. Since fatty acid metabolism plays an important role in the growth and metastasis of cancer cells, it is important to develop new drugs that inhibit fatty acid synthesis and oxidation.

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