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Review

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Fatty acid metabolism and cancer development

Yuanying Chen · Peng Li

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Abstract Although the type and etiology of cancers are different, pathways in glucose metabolism, pentose phosphate pathway (PPP) and glutamine metabolism have been reprogrammed in cancer cells to adapt to their rapid growth and proliferation. Recent research has also shown that multiple lipid metabolic pathways are altered in cancer cells. Here, we provide a brief review for the role of fatty acid metabolism in cancer development with a special focus on fatty acid uptake and de novo synthesis, triglycerides synthesis, storage and degradation. Reprogramming in fatty acid metabolism plays important roles in providing energy, macromolecules for membrane synthesis and lipid signals during cancer development. Understanding the mechanism of deregulated lipid metabolic pathways in cancer cells would reveal novel therapeutic approaches to combat cancer.

Keywords Lipid metabolism · TAG · Fatty acids · Cancer development

1 Introduction

Cancer cells are known to have alterations in metabolic pathways. The most well understood metabolic reprogramming is the Warburg effect as cancer cells limit their energy production to glycolysis and produce lactate in the presence of oxygen [1]. Another commonly observed metabolic alteration is the increased glutamine metabolism that results in the generation of higher levels of α-ketoglutarate and citrate in the Krebs cycle [2]. Recently, reprogramming in fatty acid metabolism in cancer cells and its functional role in promoting tumor progression has received increasing attention.

Lipids include fatty acids (FAs), phosphlipids, cholesterol and neutral triglycerides (TAG) are important macromolecules responsible for membrane structure and energy supply. Lipids can also serve as signaling molecules to regulate various biological processes such as cell growth, differentiation and apoptosis. Lipid metabolism includes lipid synthesis, uptake, trafficking, storage and degradation. Most mammalian cells acquire lipids from the blood stream either as free FAs (FFA) or lipoproteins. Theses lipids are obtained from dietary sources or by de novo synthesis in the liver, adipose tissue and the lactating breast. Extracellular FAs are then untaken into the cells and transported to various subcellular organelles by fatty acid binding proteins (FABPs) [3, 4]. The de novo FA synthesis pathway converts citrate to FA through multiple enzymatic reactions that are catalyzed by enzymes including ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN). The expression levels of these enzymes are controlled by transcription factor sterol regulatory element-binding proteins (SREBPs) [5]. Exogenous or de novo synthesized FAs require its activation via fatty acyl-CoA synthetase (ACS) that converts free FAs to FA-CoA. FA-CoA can enter into the TAG synthesis pathway through the chain reactions catalyzed by glycerol-3-phosphate acyltransferase (GPAT), acylglycerolphosphate acyltransferase (AGPAT), phosphatidic acid phosphohydrolase (lipin or PAP) and diacylglycerol acyltransferase (DGAT). TAG is then stored in a special subcellular organelles lipid droplets (LD) as energy source that can be degraded by specific lipases to release FAs [6]. The

SPECIAL TOPIC: Lipid metabolism and human metabolic disorder

Y. Chen · P. Li (✉)
MOE Key Laboratory of Bioinformatics and Tsinghua-Peking Center for Life Sciences, School of Life Sciences, Tsinghua University, Beijing 100084, China
e-mail: li-peng@mail.tsinghua.edu.cn

hydrolysis of TAG is catalyzed by adipose triglyceride lipase (ATGL), hormone sensitive lipase (HSL) and monoacylglycerol lipase (MAGL), sequentially [7]. Released FAs will be uptaken by other tissues like muscle, heart and liver and convert into FA-CoA for oxidation through TCA cycles in mitochondria (Fig. 1). FA metabolism can also be influenced by cholesterol and phospholipid metabolism [8, 9].

2 Fatty acid metabolism in cancer

2.1 Deregulation of fatty acid metabolism in cancer development

There is increasing evidence that cancer cells have specific alterations in different aspects of fatty acid metabolism and these data were summarized extensively by Currie et al. [10]. Besides fatty acid metabolism, altered cholesterol and phospholipid metabolism are also discovered in cancer cells and may play important roles in tumor progression. Here, we summarized the most updated information in fatty acid metabolism with special focus on proteins and enzymes in FA and TAG metabolic pathways that are dysregulated in cancer cells.

2.2 Fatty acid uptake

FA uptake and Intracellular trafficking mediated by FABPs are shown to be associated with cancer development. For example, gene profiling analysis demonstrated that FABP5, one of the FA transporting protein that has high affinity to long chain FAs, is preferentially expressed in estrogen

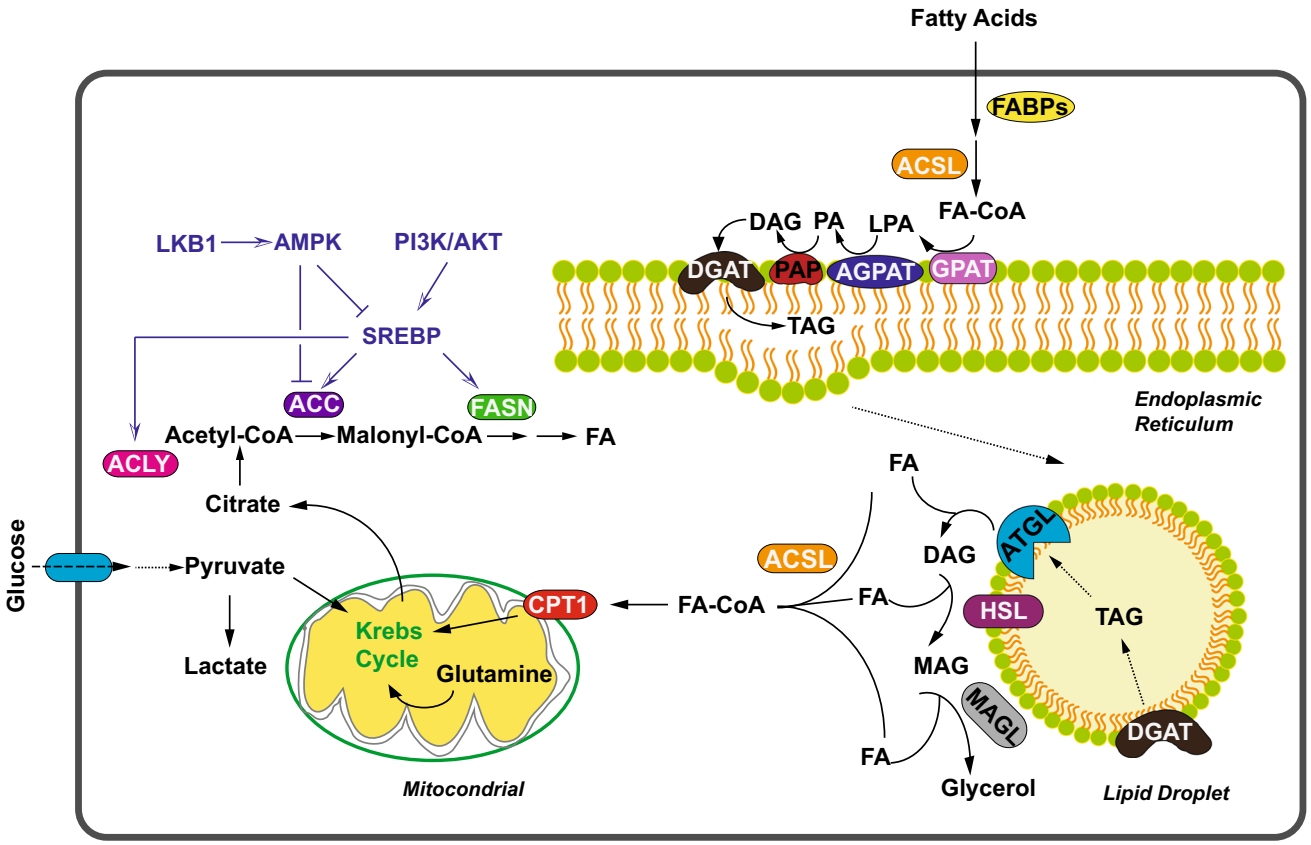

Fig. 1 (Color online) Schematic diagram of lipid metabolism regulation. Extracellular FAs are untaken into the cells and transported by FABPs. The de novo FA synthesis contains multiple enzymatic reactions that are catalyzed by ACLY, ACC and FASN to convert citrate to FA. The expression levels of these enzymes are controlled by transcription factor SREBPs. Exogenous or de novo synthesized FAs requires the activation via ACSL that converts free FAs to FA-CoA. FA-CoA can enter into the TAG synthesis pathway through the chain reactions catalyzed by GPAT, AGPAT, lipin and DGAT. TAG is stored in LD as energy source that can be degraded by specific lipases to release FAs. The hydrolysis of TAG is catalyzed by ATGL, HSL and MAGL, sequentially. Released FAs will be uptaken by other tissues such as muscle, heart and liver and are converted into FA-CoA that can be transported by CPT1 and oxidized in mitochondria. FABPs, fatty acid binding proteins; ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; SREBPs, sterol regulatory element-binding proteins; ACSL, fatty acyl-CoA synthetase; GPAT, glycerol-3-phosphate acyltransferase; AGPAT, acylglycerolphosphate acyltransferase; lipin, phosphatidic acid phosphohydrolase; DGAT, diacylglycerol acyltransferase; LD, lipid droplets; ATGL, adipose triglyceride lipase; HSL, hormone sensitive lipase; MAGL, monoacylglycerol lipase; CPT1, carnitine palmitoyltransferase