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Review

Nuclear localization of metabolic enzymes in immunity and metastasis

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ABSTRACT

Metabolism is essential to all living organisms that provide cells with energy, regulators, building blocks, enzyme cofactors and signaling molecules, and is in tune with nutritional conditions and the function of cells to make the appropriate developmental decisions or maintain homeostasis. As a fundamental biological process, metabolism state affects the production of multiple metabolites and the activation of various enzymes that participate in regulating gene expression, cell apoptosis, cancer progression and immunoreactions. Previous studies generally focus on the function played by the metabolic enzymes in the cytoplasm and mitochondrion. In this review, we conclude the role of them in the nucleus and their implications for cancer progression, immunity and metastasis.

1. Introduction

Metabolism is the total of all chemical reactions in cells and organisms that provide energy and biomolecules and maintain life. Metabolism consists of catabolic processes and anabolic processes. Catabolic process refers to the breakdown of molecules generally to produce energy. While the anabolic process is the synthesis of components such as proteins, lipids, and nucleic acids, which costs energy to provide building blocks or energy storage medium [1]. Though involving different types of metabolic pathways, both atabolic processes and anabolic processes require numerous enzymes to catalyze biochemical reactions. For example, amylase, pyruvate dehydrogenase complex (PDC) and ATP hydrolase are crucial enzymes in the catabolic processes, breaking down amylum, pyruvate and ATP respectively to generate energy. While Adenosine triphosphate (ATP)-citrate lyase (ACL), pyruvate kinase (pklr, pkm2) and fatty acid synthase participate in anabolic processes to synthetize acetyl-CoA, pyruvate and ATP, and fatty acid, providing precursor molecules for other reactions and storing energy. Cellular metabolism is complicated, involving various chemical pathways linking each other by enzymatic reactions in which the product of one step is the substrate for the next.

Metabolism is not machine-parsable. Instead, it varies frequently to keep in consonance with the environmental change and cell function that is more obvious in inflammatory response and tumorigenesis [2]. As the intracellular or extracellular changes happen, such as stress reaction, oxygen or alimentary deficiency, metabolism state or metabolism pathways varies, altering either the signal transduction pathways or the post-translational modifications (PTMs) of chromatin [3,4]. As a result, energy conversion, information transfer, gene expression and protein production changes. The reprogramming of metabolic pathways is particularly common in cancer cells [5], which require vast energy and macromolecules to meet the increasing needs of the rapid cell division and propagation [6,7]. During inflammatory responses, reprogramming is crucial for the transformation of the lymphocyte types and the production of specific antibodies [8].

Inflammation is the body's basic response to a variety of external or internal insults, such as infectious agents, physical injury, hypoxia, or disease processes [9]. The activation, growth, and proliferation, engagement of effector functions and return to homeostasis of immune cell are closely linked to energy metabolism and that cross-talk between these processes is fundamental to the pathogenesis of many human diseases [10] particularly diabetes, cancer, and sepsis.

Cancer is one of the most devastating diseases that threats global human public health and life quality [11]. In 1924, Otto Warburg pointed one universal feature of malignant tumors as they have increased glucose uptake and are in a state of high aerobic glycolysis instead of oxidative phosphorylation that is named as the Warburg effect [12,13]. Cancer cells alter their metabolic pathways to generate

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more fatty acids from lipogenesis to meet the increasing needs of the rapid cell division and propagation and the demand for energy [14]. This reprogramming of metabolic pathways is one of the most important features of cancer that have potential utility as prognostic markers as well as therapeutic targets [15].

Several metabolic enzymes participate in this regulating pathway as both regulators and sensors of the changes. Here in this review, we mainly discuss the main metabolic enzymes, including adenosine triphosphate (ATP)-citrate lyase (ACLY), pyruvate dehydrogenase complex(PDC), and pyruvate kinase (pklr, pkm2).

2. Adenosine triphosphate (ATP)-citrate lyase (ACLY)

Adenosine triphosphate (ATP)-citrate lyase (ACLY) is a crucial cytosolic enzyme which play an important role in the synthesis of acetyl-CoA [16]. ACLY catalyzes the formation of acetyl-CoA and oxaloacetate in the cytoplasm using citrate and CoA as precursor substance coupled with the hydrolysis of ATP to ADP and phosphate [17]. The synthesized acetyl-CoA is then translocated in different organelles and participates in several important biosynthetic pathways. Since acetyl-CoA is a central metabolic intermediate in lipogenesis, oxidation of glucose to produce ATP, cholesterogenesis and the acetylation reactions of histone protein, the function of ACLY is rather crucial in maintaining the homeostasis.

2.1. Location

ACLY can be detected primarily expressed in liver and white adipose tissue [18,19] while less in brain, heart, small intestine and muscles [18,20]. In pancreatic beta cells, ACLY expresses and plays a functional activity in the secretion of insulin [19,21]. ACLY is generally accepted as a cytosolic enzyme which bounds to endoplasmic reticulum in mammalian cells [22]. However, ACLY also represents to nuclei of different mammalian cells for example, mouse embryonic fibroblasts, murine pro-B-cell lymphoid cells, human glioblastoma cells and colon carcinoma cells [23]. These results indicate that the production of acetyl-CoA may be achieved in both the cytoplasm and nuclear compartments in mammalian cells, influencing both metabolism and the global regulation of the gene expression. Nevertheless, whether ACLY is constitutively expressed in the nucleus or is translocated from the cytoplasm in special condition is still unclear.

2.2. Metastasis

ACLY is thought to be a cross-link between glucose and glutamine metabolism and fatty acid synthesis and mevalonate pathways by converting citrate into acetyl CoA in the cytoplasm. And the produced acetyl CoA is further used mainly in three aspects, including mevalonate pathway, fatty acid synthesis pathway and acetylation reactions [24]. The synthetic fatty acids and cholesterols can be utilized for membrane composition, protein modification and signal transduction as a second messenger, all of which are especially crucial for cancer cells in cell survival, proliferation and transformation in [25] (Fig. 1).

In the fatty acid synthesis pathway, ACLY is regarded as the first rate-limiting enzyme involved in de novo lipogenesis. ACLY-catalysed acetyl CoA is carboxylated to malonyl CoA by acetyl-CoA carboxylase (ACACA). Then, the condensation of acetyl CoA and malonyl CoA is induced by the main lipogenic enzyme, fatty acid synthase (FASN), to produce the long-chain fatty acid palmitate [26]. Thus, inhibiting the activity of ACLY is a potential way for the treatment of dyslipidemia [27,28].

In the mevalonate pathway, the synthesis of farnesyl-pyrophosphate (FPP) is achieved using acetyl CoA as a precursor. FPP is the branch point for several pathways such as cholesterol biosynthesis and geranylgeranyl-pyrophosphate (GG-PP) synthesis. Both FPP and GG-PP participate in farnesylation and geranylgeranylation of multiple proteins, regulating their functions as well as the level of the cell metabolism. Farnesylation and geranylgeranylation, together termed as prenylation, are required for the ability of Ras and Rho proteins to induce malignant transformation, invasion, and metastasis [29].

As for acetylation reactions, ACLY-catalysed acetyl CoA is a key determinant of protein acetylation, affecting the vast the expression of majority of human proteins and determining their stability, localization, and function [30,31]. The most important part involving the acetylation of histone proteins, which influence the structure of the chromosome and the expression of the gene [23].

Apart from the three aspects illustrated above, ACLY can also influence cell metabolism by affecting glucose-induced insulin secretion [32]. Patients with type-2 diabetes shows a decrease of expression and activity of ACLY by 55% in pancreatic islets compared with non-diabetic donors [19]. In addition, elevated levels of circulating fatty acids suppress ACLY activity leading to pancreatic cell stress and apoptosis [33]. Insulin is the primary enzyme responsible for the uptaken and utilization of glucose. And the dis-secretion cannot only affect the energy production through anaerobic glycolysis and aerobic metabolism such as TCA, but also interfere many other pathways that acquire the metabolite of glycose.

In short, ACLY influcing metastasis via directly regulating the production of acetyl CoA which subsequently affects the generation of fatty acid, farnesyl-pyrophosphate, and the level of protein acetylation, and indirectly upregulating the metastasis by promoting the glucose-induced insulin secretion.

2.3. Cancer progression

Fatty acids have crucial functions in a variety of cellular processes. De novo lipogenesis (DNL) is an endogenous pathway that occurs at low rates in most non-dividing cells of normal tissues but enhanced in almost every kind of cancer cells [6]. In DNL, carbohydrates are converted to fatty acids to either produce energy or support cell growth as building blocks which is especially important for these rapidly proliferating cancer cells [34]. Citrate generated by the tricarboxylic acid cycle(TCA) is preferentially exported from the mitochondria to the cytosol and then cleaved by ATP citrate lyase (ACLY) to produce cytosolic acetyl coenzyme A, which is the precursor for DNL [35].

Upregulation of ACLY is generally seen in various cancer cell whose distinctive elevation of expression and activity has been reported in pancrea [36], lung, prostate [37], bladder [38], breast [39], liver [40], stomach [41], and colon tumors [42]. In these tumor cells, ACLY can be phosphorylated and activated through different kinds of ways [38]. For instance, ACLY expression is mainly regulated by the transcription factor SREBP-1 (sterol regulatory element binding protein-1) [43] which up-regulates ACLY at mRNA level via Akt signaling [44]. However, ACLY protein levels are independent of SREBP-1 [45] but closely related to PI3K/Akt pathway which stimulates ACLY activity predominantly through phosphorylation of ACLY rather than transcriptional up-regulation. The phosphorylation of ACLY contributes to its protein stabilization [45]. Thr446, Ser450 and Ser454 residues of ACLY are shown to be phosphorylated in vitro [46]. ACLY can be phosphorylated at other sites by other kinases, such as nucleoside diphosphate kinase [47] and cyclic AMP-dependent protein kinase [48]. Phosphorylation of ACLY is enhanced by glucagon, insulin, vasopressin and transforming growth factor b1 [49]. Elevated ACLY promotes cancer cell survival and growth and enhances aggressive biological behaviors such as migration and invasion [50], leading to a poor prognosis. However, inhibition of ACLY, cancer cells undergo a proliferation arrest both in vivo and in vitro and show decreased lactate secretion, glucose consumption, and reduced expression of glycolytic enzymes indicating that this enzyme plays an important role in cancer cell growth and progression [51] (Fig. 1). Though the exact mechanism is yet unclear, it is believed that ACLY accomplishes its function by regulating the synthesis of acetyl CoA, whose cell content variation is in