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REVIEW

Roles of Long-chain Acyl Coenzyme A Synthetase in Absorption and Transport of Fatty Acid[△]

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Abstract Long-chain acyl coenzyme A synthetase (ACSL) is a member of the synthetase family encoded by a multigene family; it plays an important role in the absorption and transport of fatty acid. Here we review the roles of ACSL in the regulating absorption and transport of fatty acid, as well as the connection between ACSL and some metabolic diseases.

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AS is known to all, fatty acid, is not only a major source of energy for mammals, but also a vital participant in normal growth and metabolism of cells. Long-chain acyl coenzyme A synthetase (ACSL) is considered to be a vital synthetase acting on absorption and transport of fatty acid. The increasing evidences have indicated that ACSLs are the crucial enzymes responsible for fatty acid metabolism throughout the body.¹ ACSLs have been confirmed to carry out anabolism of triglycerides, phospholipids, and cholesterol ester, as well as oxidation of fatty acid. They can activate the breakdown of endogenous and exogenous fatty acids by catalyzing free fatty acid to form acyl coenzyme A

(acyl-CoA).^{1, 2} This process occurs in the rough endoplasmic reticulum and mitochondrial outer membrane. Each ACSL isoform has a unique effect on different tissues and organs. We discuss the functions of ACSL in the absorption and transport of fatty acid and the relationship of ACSL and metabolic diseases.

CHARACTERISTICS OF ACSL

ACSL is a kind of synthetase encoded by a multigene family, consisting of at least 25 members.^{3, 4} In mammal, ACSL family includes 5 isoforms: ACSL1, ACSL3, ACSL4, ACSL5, and ACSL6, and each unique isoform is generated by alternatively spliced transcript variants that are encoded by a member of the gene family.

Although 5 isoforms of ACSL exhibit highly amino acid homology,^{4, 5} they reveal the considerable differences concerning organ distribution,⁶ subcellular localization, enzyme kinetics, gene expression, and substrate specificity,

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and so on.⁵ N-terminal amino acid sequence of each ACSL isoform that is different from each other may contribute to the different subcellular locations. ACSL1 and ACSL6 have been revealed to locate on the plasma membrane, indicating that they might involve in the assimilation of cellular fatty acid.^{7, 8} ACSL4 has been found in the endoplasmic reticulum and peroxisomes.⁹ ACSL5 isoform encoded by ACSL5 gene that lies on chromosome 10q25.1-q25.2,⁹ is localized on the inner mitochondrial membrane and appears to exert a regulatory role in the mitochondrial energy metabolism. Moreover, ACSL5 is highly expressed in the jejunum, which may indicate its special role in fatty acid absorption.¹⁰

ROLE OF ACSL IN FATTY ACIDS ABSORPTION AND TRANSPORT

The absorption and transport of fatty acids is important in the physiological activities of cells.¹¹ Free fatty acid, the substrate of ACSL, can transport across plasma membranes, however its product, acyl-CoA, can not to do so. Hence, esterification of free fatty acids by ACSL results in trapping the non-membrane permeant acyl-CoA inside the cells.¹² A series of animal experiments have proved that changing the expression of ACSL genes can regulate the absorption and transport of fatty acids, and even in some cases the absorption of fatty acids is mainly dependent on the activity of ACSL gene, rather than the subcellular structure of ACSL.¹³

The increasing evidences suggest that ACSL alone or ACSL binding proteins are involved in modulating the absorption and transport of fatty acids.

ACSLs have been recognized as important intracellular mediators of long-chain fatty acids absorption by increasing the conversion rate of fatty acyl-CoA and accelerating the metabolism of fatty acyl-CoA.^{1, 14} The uptake of fatty acids has been considered to be a passive process, involving ACSL molecule sited into the plasma membrane. However, ACSL1, ACSL4, and ACSL5 isoforms have been demonstrated to be located only on the intracellular organelles, and their over-expression can promote the absorption of fatty acids.¹⁵ This situation indicates the presence of other fat acid-binding proteins to take part in the uptake and intracellular transport of fat acid molecules.

Fatty acid transport proteins (FATPs) identified as fat acid-binding proteins, selectively facilitate the preferential transport of free fatty acids outside cells across the lipid bilayer of the plasma membrane. ACSL1 has been found to interact with the fatty acid transporter FATP1 to regulate absorption and transport of fatty acids in the adipocytes.^{15, 16} The studies on specific yeast cell lines confirmed that

decreased expression of ACSL can increase FATP expression, thus improving ASCL activity; complete silence of ACSL expression induce FATP overexpression.^{2, 17} The underlying biochemical mechanisms of FATPs' association with ASCL controlling absorption and transport of fatty acids require to be fully clarified.

ACSL AND METABOLIC DISEASES

Because of the fundamental role of ACSL as modulators of absorption and transport of fatty acids, it has been hypothesized that they link to several metabolic diseases,¹⁸ such as non-alcohol fatty liver disease (NAFLD), obesity, atherosclerosis, and diabetes, and so on.

Liver is the center of the lipid metabolism. Excessive fatty acid deposition can produce reactive oxygen species by lipid peroxidation. NAFLD, a clinicopathological syndrome, is characterized by excessive fat deposition in the hepatocytes. Except ACSL6, other members of ACSL family are expressed in the liver. ACSL3 and ACSL5 involve the *de novo* synthesis of fatty acids, and regulate the subsequent reaction to produce triglycerides and phospholipids.^{14, 19} As the main isoform in the liver, ACSL1 can catalyze oleic acid into triglycerides and phospholipids acid, to reduce lipotoxicity in the hepatocyte.²⁰

Obesity, a chronic metabolic disease, mainly characterized by increased fat cell volume and excessive lipid deposition in some areas. Li *et al*²¹ found ACSL inactivation can substantially impact on lipid metabolism, resulting in obesity. Through regulating activation and absorption of fatty acids in the intestine, thereby adjusting the amount of fatty acids in circulation, ACSL can radically reduce absorption of exogenous fatty acids.²²

Atherosclerosis usually caused by fat metabolism disorder, is characterized by lipid deposition in the major artery intima. The increasing evidences have indicated that through activating inflammatory signaling pathways, saturated fatty acids injure vascular cells, including vascular smooth muscle cells, macrophages, and endothelial cells.^{23, 24} By reducing the absorption of saturated fatty acid in the intestine, ACSL can reduce the occurrence rate of atherosclerosis.²⁵ Moreover, ACSL4 can stimulate vascular smooth muscle to release prostaglandin E2, which can promote the formation of atherosclerosis.^{26, 27}

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia, accompanied with defects of insulin secretion or insulin function. The increased ACSL1 expression has been demonstrated in the mononuclear cells of type 1 diabetes mellitus patients, indicating that ACSL1 may involve in the pathogenesis of diabetes.²⁸ In

addition, free fatty acids in the blood circulation increase the risk for individuals attacked by obesity as well as developing diabetes.²⁹

As highlighted in this review, a complete understanding of the pathogenic role of ACSL playing in NAFLD, obesity, atherosclerosis, and diabetes is still lacking.

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