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Review

SLC27 fatty acid transport proteins ☆

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ABSTRACT

The uptake and metabolism of long chain fatty acids (LCFA) are critical to many physiological and cellular processes. Aberrant accumulation or depletion of LCFA underlie the pathology of numerous metabolic diseases. Protein-mediated transport of LCFA has been proposed as the major mode of LCFA uptake and activation. Several proteins have been identified to be involved in LCFA uptake. This review focuses on the SLC27 family of fatty acid transport proteins, also known as FATPs, with an emphasis on the gain- and loss-of-function animal models that elucidate the functions of FATPs *in vivo* and how these transport proteins play a role in physiological and pathological situations.

Contents

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1. Introduction

One of the primary sources of energy for a cell is long-chain fatty acids (LCFA). Uptake and activation of LCFA is integral to many cellular processes, including membrane synthesis, intracellular signal transduction, energy metabolism, posttranslational modifications, and transcriptional regulation of metabolic genes (Kazantzis and Stahl, 2011). Many obesity-related diseases are due to an abnormal influx of LCFA from adipose stores into highly metabolic tissues such as heart, liver, and muscle, where the aberrant accumulation of lipids leads to insulin resistance, endoplasmic reticulum (ER) stress, and cell death (Kazantzis and Stahl, 2011). Therefore, studying the molecules responsible for cellular uptake of LCFA is key to identifying potential therapies for metabolic diseases.

When LCFA are released from their stores in adipose tissue or from the breakdown of triacylglycerides into the circulation they are bound to albumin, while in the intestine they form mixed micelles with bile acids (Schwenk et al., 2010). Upon crossing of the plasma membrane into the cytoplasm, LCFA become bound to cytoplasmic fatty acid binding proteins (FABPc) (Schwenk et al., 2010). While albumin-bound LCFA do have the ability to passively diffuse through the plasma membrane, the majority of LCFA uptake appears to be protein-mediated (Stahl et al., 2002). Several membrane proteins have been implicated in LCFA uptake, including fatty acid translocase (FAT)/CD36 (Coburn et al., 2000), plasma membrane fatty acid binding proteins (FABPpm) (Huang et al., 2002), long-chain fatty acyl-coenzyme A (CoA) synthetase (ACSL), and fatty acid transport proteins (FATP). This review will focus on the FATP family, also known as solute carrier family 27, which contains members A1 through 6 (SLC27A1-6) family (Table 1), and how they function *in vivo* in normal and pathological situations.

2. The SLC27 family

The SLC27 gene family is comprised of six members, *SLC27A1-6*, which encode FATP1-6 (Table 1). *SLC27A1*, encoding FATP1, was the first member of this gene family to be identified through screening of a cDNA library from 3T3-L1 adipocytes for cDNAs that augment LCFA uptake (Schaffer and Lodish, 1994). Three FATPs have been listed in the transporter classification database: FATP1 (TC# 4.C.1.1.9.), FATP4 (TC# 4.C.1.1.1.) and FATP5 (TC# 4.C.1.1.8.). FATPs range from 63–80 kilodaltons (kDa) in size and are integral membrane proteins with at least one transmembrane domain (Fig. 1) (Lewis et al., 2001; Schaffer and Lodish, 1994). The N-terminus is located on the extracellular/luminal side and the C-terminus on the cytosolic side (Fig. 1) (Lewis et al., 2001; Schaffer and Lodish, 1994). All FATP members have a highly conserved, 311-amino acid signature sequence known as the FATP sequence, as well as an AMP binding domain, located on the C-terminus (Fig. 1). This region is responsible for the binding and uptake of LCFA and is commonly found in members of the ACSL family (Faergeman et al., 1997; Hirsch et al., 1998; Milger et al., 2006). A lipocalin motif, which is present in several proteins that are carriers of small hydrophobic molecules, has been identified near the N-terminus of FATP1 (Fig. 1) (Ordovás et al., 2006). Interestingly, FATP4 has been shown to have an ER localization signal domain, which aids in bringing the transport protein into the ER (Fig. 1) (Milger et al., 2006). While FATPs have sequence similarities, the proteins are differentially expressed in a wide variety of tissues and cell types, including adipose tissue, liver, skeletal muscle, heart, intestine, skin, and endothelial cells (Fig. 2).

3. Fatty acid transport and activation by FATP family members

Gain- and loss-of-function studies have demonstrated a categorical role for FATPs in mediating LCFA uptake (summarized in Tables 2 and 3). However, the precise mechanism by which FATPs function in LCFA uptake is still debatable. It has been proposed that FATPs can function as direct transporters of LCFA, as enzymes that activate LCFA through inherent acyl-CoA synthetase (ACS) activity, or as bifunctional proteins with independent transport and enzymatic activity.

3.1. Fatty acid uptake function of FATPs

FATP1 was the first FATP to be identified based on its ability to increase LCFA uptake upon overexpression in cells (Schaffer and Lodish, 1994). Since then, many studies have demonstrated the direct role FATPs play in LCFA uptake in a variety of tissues and cell types (Doege et al., 2006; Falcon et al., 2010; Stahl et al., 1999). In order for FATP1 to function in the uptake of LCFA dimerization is required, but the ability of other FATPs to form homodimers remains to be determined (Richards et al., 2003).

3.2. ACS activity of FATPs

In addition to a role in fatty acid uptake, FATPs have also been shown to display ACS activity. ACS enzymes catalyze the conversion of LCFA to acyl-CoA thioesters in order to activate LCFA. Activated LCFA can then be used by the cell in many metabolic processes, such as fatty acid synthesis and oxidation and phospholipid synthesis (Black and DiRusso, 2007b). Mutations in the yeast homolog of FATP1, Fat1p, resulted in reduced very-long-chain ACS (VLACS) activity (Watkins et al., 1998). Overexpression of wild-type FATP1 in COS1 cells led to increased ACS activity, while mutation of a domain within FATP1 that is highly conserved in ACS proteins abolished ACS activity (Coe et al., 1999). Concomitant with reduced ACS