Molecular Aspects of Medicine 34 (2013) 586–589

Contents lists available at SciVerse ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

The acetyl-CoA transporter family SLC33 ☆

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Guest Editor Matthias A. Hediger
Transporters in health and disease (SLC series)

ARTICLE INFO

Article history:
Received 21 February 2012
Accepted 29 March 2012

Keywords:
SLC33
Acetyl-CoA transporter
Glycoconjugate
Lysine-acetylation
Endoplasmic reticulum
Autosomal dominant hereditary spastic paraplegias (SPG42)
Motor neuron

ABSTRACT

The acetyl-CoA (Ac-CoA) transporter, ACATN is a multiple (11 or 12) transmembrane protein in the endoplasmic reticulum. Ac-CoA is transported into the lumen of the endoplasmic reticulum/Golgi apparatus, where it serves as the substrate of acetyltransferases that modify a variety of molecules including the sialic acid residues of gangliosides and lysine residues of membrane proteins. The ACATN gene, assigned as SLC33A1, was cloned from human melanoma cells and encodes the ACATN/ACATN1 (Acetyl-CoA Transporter 1) protein. Although homologs of this family of proteins have been identified in lower organisms such as *Escherichia coli*, *Drosophila melanogaster* and *Caenorhabditis elegans*, only one member of this SLC33A1 family has been identified. Although acetylated gangliosides are synthesized in the luminal Golgi membrane and show a highly tissue-specific distribution, ACATN1 is enriched in the ER membrane and is ubiquitously expressed. Phylogenetically, the *SLC33A1* gene is highly conserved, suggesting that it is particularly significant. In fact, ACATN1 is essential for motor neuron viability. *SLC33A1* is associated with neurodegenerative disorders such as sporadic amyotrophic lateral sclerosis (ALS) and Spastic Paraplegia 42, in the Chinese population.

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1. Introduction

The terminal sialic acids of glycoproteins and gangliosides are often modified by *O*-acetylation, frequently at the 9-position (Butor et al., 1993). *O*-Acetylation of sialic acids is remarkably tissue specific and developmentally regulated in a variety

☆ Publication in part sponsored by the Swiss National Science Foundation through the National Center of Competence in Research (NCCR) TransCure, University of Bern, Switzerland; Director Matthias A. Hediger; Web: http://www.transcure.ch.

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http://dx.doi.org/10.1016/j.mam.2012.05.009

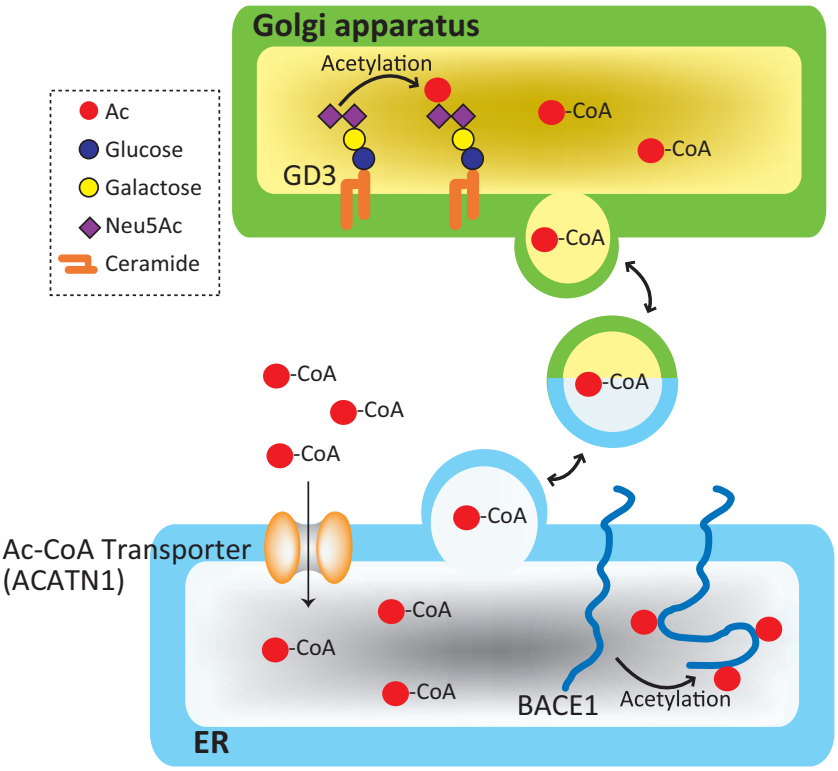

Fig. 1. Roles of ACATN1. Cytosolic Ac-CoA is transported into the lumen of the ER by the membrane transporter ACATN1. Ac-CoA is then utilized for acetylation of membrane proteins, BACE1 (Costantini et al., 2007), APP, etc. (Jonas et al., 2010). The acetylation is catalyzed by the membrane-bound lysine acetyltransferases, ATase1 and ATase2 (Ko and Puglielli, 2009). Acetylation also occurs in the Golgi membrane with gangliosides such as GD3 and GT3 being synthesized in the lumen of the Golgi apparatus via a reaction catalyzed by the sialyltransferase STSia8-I. Terminal sialic acids are further modified by acetylation at the 9-position by an *O*-acetyltransferase in the Golgi membranes. GD3, NeuAcα2-8NeuAcα2-3Galβ1-4GlcβCer; GT3, NeuAcα2-8NeuAcα2-8NeuAcα2-3Galβ1-4GlcβCer.

Table 1
SLC33-acetyl-CoA transporter family. For detailed information about the SLC gene tables, please visit: http://www.bioparadigms.org.

Human gene name	Protein name	Aliases	Predominant substrates	Transport type/ coupling ions*	Tissue distribution and cellular/ subcellular expression	Link to disease#	Human gene locus	Sequence Accession ID
SLC33A1	ACATN1	AT-1	Acetyl-CoA	F	Brain, spinal cord, prostate, placenta, uterus, testis, thymus, trachea/ endoplasmic reticulum	Autosomal dominant spastic paraplegia (SPG42)	3q25.3	NM_004733

F: facilitated transporter.

of biological systems. Recently, the *O*-acetylated glyco-glycerophospholipid, 6-*O*-Ac-phosphatidylglucoside was isolated from fetal rodent brains and its expression was also shown to be developmentally regulated (Nagatsuka et al., 2006). The exact physiological roles of *O*-acetylation of sialic acid and glucose, however, remain to be elucidated (Varki et al., 1991; Malisan et al., 2002). Moreover, *O*-acetylation occurs on membrane proteins such as BACE1 (Costantini et al., 2007) and amyloid precursor protein (APP) in the endoplasmic reticulum (ER) membranes (Jonas et al., 2010).

Acetylation of sugars and lysine residues on proteins occurs in the lumen of the Golgi apparatus and the ER, respectively (Fig. 1) (Jonas et al., 2010; Varki and Diaz, 1985). The acetate donor is acetyl CoA (Ac-CoA) which is synthesized in the cytosol and then transported into the lumen of ER/Golgi apparatus for the subsequent acetylation reaction (Varki and Diaz, 1985; Kanamori et al., 1997). The molecular cloning of the gene encoding the Ac-CoA transporter and recent discovery of a mutated gene in patients affected by autosomal dominant spastic paraplegia-42 (SPG42) (Lin et al., 2008) demonstrate the physiological significance of the ACATN1 dependent modifications with acetate (see Table 1).

According to the "Transporter Classification Data Base" (TCDB) operated by the Saier Lab Bioinformatics Group, ACATN1 belongs to the first member of the Peptide-Acetyl-Coenzyme A Transporter (PAT) Family (2.A.1.25.1: http://www.tcdb.org/search/result.php?tc=2.A.1.25.1).