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MINI-REVIEW

Membrane-bound *O*-acyltransferases (MBOATs)

Catherine C. Y. CHANG (✉), Jie SUN, Ta-Yuan CHANG (✉)

Department of Biochemistry, Dartmouth Medical School, Hanover, NH 03755 USA

Abstract **The MBOAT enzyme family, identified in 2000, comprises 11 genes in the human genome that participate in a variety of biological processes. MBOAT enzymes contain multiple transmembrane domains and share two active site residues, histidine and asparagine. Several MBOAT members are drug targets for major human diseases, including atherosclerosis, obesity, Alzheimer disease, and viral infections. Here we review the historical aspects of MBOAT enzymes, classify them biochemically into 3 subgroups, and describe the essential features of each member.**

Keywords cholesterol metabolism, neutral lipid biosynthesis, protein acylation, membrane phospholipid remodeling, atherosclerosis, diabetes, obesity, cancer, nutrient sensing

Introduction to MBOAT

Enzymes in the membrane-bound *O*-acyltransferase (MBOAT) family contain multiple transmembrane domains and share two common active site residues, histidine (His) and asparagines (Asn). The active histidine is embedded within a long stretch of hydrophobic residues, while the active asparagine is located within a hydrophilic region (Fig. 1). Based on biochemical reactions, the MBOAT family can be categorized into 3 subgroups: the first acylates the –OH moiety of cholesterol or diacylglycerol; the second acylates an amino acid residue within a protein or a peptide hormone; and the third acylates a lysophopholipid to reform a phospholipid. MBOAT members participate in diverse biological processes, including neutral lipid biosynthesis, embryogenesis, normal development, nutrient sensing, and membrane lipid remodeling. Here we provide a brief account of the history of MBOAT and the essential features of each MBOAT member. For each member, key reviews are cited for further reading.

History of MBOAT

The identification of MBOAT was based on the discovery of two genes: acyl-coenzyme A:cholesterol acyltransferase 1 (ACAT1) and Porcupine. ACAT acylates the –OH group of cholesterol with a long- chain fatty acid, and Porcupine acylates the protein Wingless with a long-chain fatty acid. In 1958, Alfinslater and colleagues detected ACAT enzyme activity in rat liver homogenates (Mukherjee et al., 1958). In1964, Goodman and colleagues showed that ACAT is a membrane-bound enzyme. However, the molecular identity of ACAT remained elusive until 1993, when Chang and colleagues identified the first ACAT gene (*Acat1*) by functional complementation of mutant Chinese hamster ovary cells lacking ACAT activity (Chang et al., 1993). Knowledge of the ACAT1 sequence led to the discovery of its homologs ACAT2 (Yang et al., 1996; Yu et al., 1996; Anderson et al., 1998; Cases et al., 1998a; Oelkers et al., 1998) and diacylglycerol *O*-acyltransferase 1 (DGAT1), an enzyme that attaches long-chain fatty acids to the –OH group of diacylglycerol (Cases et al., 1998b). Still, the recognition of MBOAT required the sequencing of a seemingly unrelated protein, Porcupine, which is required for the normal functioning of Wingless, the *Drosophila* homolog of Wnt in mammalian cells. Wnt proteins are involved in embryogenesis, normal physiological processes, and carcinogenesis. The human genome contains more than 10 similar but distinct Wnt proteins, each of which plays a key role in the Wnt-mediated signal transduction pathway (Logan and Nusse, 2004). Perrimon and colleagues showed in 1996 that processing of Wingless requires a multispan membrane protein, Porcupine, with unknown function (Kadowaki et al., 1996). In 2000, Hofmann analyzed the amino acid sequence of Porcupine and discovered that it contains a conserved

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Correspondence: [a]Catherine C. Y. CHANG; [b]Ta-Yuan CHANG
E-mail: [a]Catherine.Chang@Dartmouth.Edu;
[b]Ta.Yuan.Chang@Dartmouth.Edu

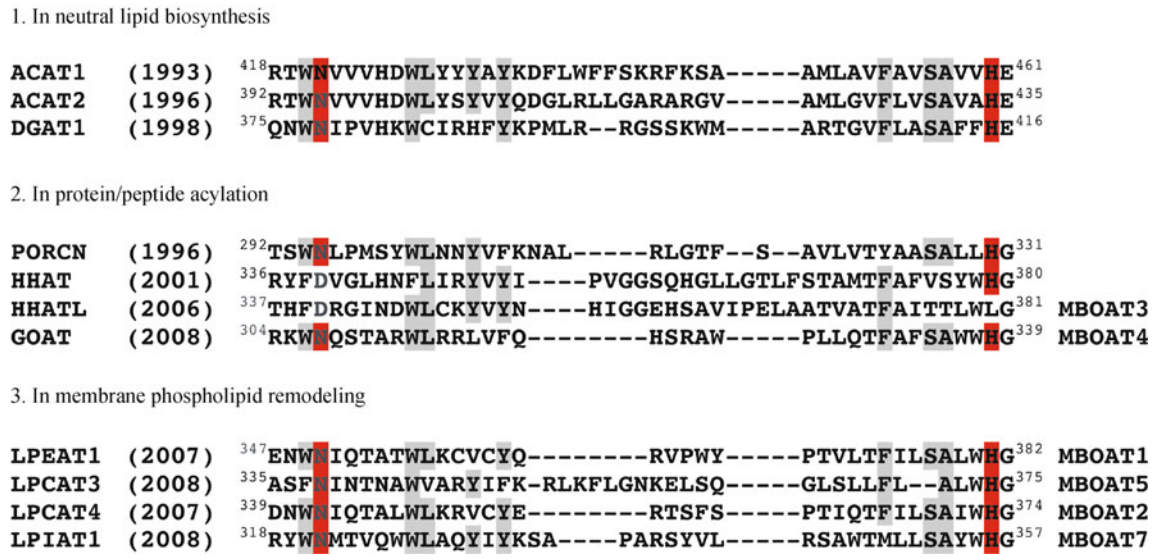

Figure 1 Alignment of the most highly conserved region of 11 MBOATs in the human genome. Based on biochemical reactions, the MBOAT family can be categorized into 3 subgroups. Amino acid residues conserved in more than 50% of the sequences are shaded in gray color. The putative catalytic asparagines and histidine residues are shaded in red. The accession numbers for all the MBOATs are as follows:
ACAT1, Sterol *O*-acyltransferase 1 (NP_003092.4); ACAT2, Sterol *O*-acyltransferase 2 (NP_003569.1); DGAT1, Diacylglycerol *O*-acyltransferase 1 (NP_036211.2); PORCN, Porcupine (NP_073736.2); HHAT, hedgehog acyltransferase (NP_001116306.1); HHATL, MBOAT3 (NP_065758.3); GOAT, Ghrelin *O*-acyltransferase, MBOAT4 (NP_001094386.1); LPEAT1, MBOAT1 (NP_001073949.1); LPCAT3, MBOAT5 (NP_005759.4); LPCAT4, MBOAT2 (NP_620154.2); LPIAT1, MBOAT7, (NP_001139528.1).

region shared by ACAT1, ACAT2, and DGAT1: thus, he hypothesized that Porcupine may be a putative acyltransferase. Unlike ACAT or DGAT, however, Porcupine may have a protein substrate rather than a small hydrophobic molecule. Additional analysis of the entire genome led Hofmann to identify an enzyme family, MBOAT (Hofmann, 2000). This work facilitated the subsequent identification of several MBOAT members at the biochemical level, including at least 11 members in the human genome. Here we classify them into 3 subgroups, as shown in Fig. 1. The shaded amino acids are the most highly conserved within all MBOATs.

Subgroup 1: enzymes involved in neutral lipid biosynthesis

ACAT1

ACAT1 is present ubiquitously in various cell types. Its main function, which it performs by converting cholesterol to its storage form, cholesteryl ester, is to protect excess cholesterol from building up in the membranes of the endoplasmic reticulum (ER). The recombinant human ACAT1 protein has been purified to homogeneity with full biological activity (Chang et al., 1998). This work demonstrates that a single polypeptide is sufficient to catalyze the acylation reaction. ACAT1 is homotetrameric, with 9 transmembrane domains (TMD). The first active site, His-460, is located within the 7th TMD; the second active site, Asn-421, is located within the 3rd large cytosolic loop (Guo et al., 2007). His-460 may be involved in catalysis, while Asn-421 may be involved in binding the long-chain fatty acyl-coenzyme A. ACAT1 directly binds to cholesterol in a stereospecific manner and prefers to use oleoyl coenzyme A as its substrate (Chang et al., 2010). The enzyme activity is allosterically regulated by its substrate cholesterol (Chang et al., 2009). ACAT1 is a potential drug target for atherosclerosis (Chang et al., 2009) and Alzheimer disease (Bryleva et al., 2010).

ACAT2

ACAT2 is mainly expressed in intestines and plays an important role in producing cholesteryl esters in the chylomicron, the lipoprotein that carries dietary fat (Buhman et al., 2000; Repa et al., 2004), making it a potential drug target for atherosclerosis (Willner et al., 2003; Bell et al., 2006). Like ACAT1, ACAT2 is also a multi-span membrane protein regulated allosterically by cholesterol. Further investigation is required to clarify its membrane topography (Chang et al., 2009).

DGAT1

DGAT1 is an MBOAT member, while DGAT2, a different enzyme that catalyzes the same biochemical reaction, is the founding member of the DGAT2/Acyl coenzyme A:

monoacylglycerol acyltransferase family (Yen et al., 2008; Turkish and Sturley, 2009). DGAT1, but not DGAT2, is a multifunctional acyltransferase, and catalyzes the biosynthesis of retinyl esters, wax esters, and triacylglycerol (Yen et al., 2005). DGAT1 resides in the ER, is homotetrameric (Cheng et al., 2001), and contains 3 TMDs (McFie et al., 2010). In mice, DGAT1 and DGAT2 are responsible for the bulk of triacylglycerol biosynthesis and lipid droplet formation in adipocytes, but not in all cell types (Hartmann, 2006). DGAT1 is a drug target for obesity and type II diabetes (Harris et al., 2011; Birch et al., 2010; Lee et al., 2010). Recently, Herker and colleagues showed that DGAT1 is required to form infectious hepatitis C virus (HCV) particles in living cells (Herker et al., 2010).

Subgroup 2: enzymes involved in protein/peptide acylation

Porcupine

Porcupine probably catalyzes the acylation of the serine and cysteine residues in the protein Wingless; the attached lipid is either the saturated fatty acid palmitate or the monounsaturated fatty acid palmitoleate (Willert et al., 2003; Takada et al., 2006). Acylation by Porcupine targets Wnt-1 to a specialized microdomain at the cell surface for secretion (Zhai et al., 2004). The Porcupine cDNAs have multiple isoforms; whether all forms can be acylated are currently unknown.

Sonic hedgehog acyltransferase (HHAT)

Sonic hedgehog (SHH) was originally designated as one of the mutations that affect segment number and polarity in *Drosophila* (Nüsslein-Volhard and Wieschaus, 1980); the gene was identified by three different groups in 1992 (Lee et al., 1992; Tabata et al., 1992; Mohler and Vani, 1992). Similar to the Wnt-signaling pathway, the hedgehog-signaling pathway plays an important role in the development of a variety of tissues in animals ranging from *Drosophila* to humans. SHH is the best-studied ligand of the hedgehog-signaling pathway. The C-terminal domain of SHH catalyzes auto-processing, producing a 19 kDa N-terminal signaling domain (HnN). The C-terminal of HnN is modified by cholesterol (Porter et al., 1996). The N-terminal (cysteine) of HnN is modified by palmitate via an amide linkage; the palmitoylation reaction is catalyzed by hedgehog palmitoylacyltransferase (Chamoun et al., 2001; Buglino and Resh, 2008), and is essential for SHH signaling activity. Cholesterol attachment to the C-terminal of HnN also contributes to its signaling activity, but is not required for HHAT activity. The full-length recombinant HHAT expressed in H293 cells has been purified to homogeneity with retention of biological activity (Buglino and Resh, 2008). HHAT prefers to utilize palmitoyl CoA as its substrate. Porcupine, HHAT, and GOAT (see description below) all perform acylation reactions within the lumen of the ER/secretory vesicles. A second MBOAT homology region (196–234) required for HHAT activity has been reported; these residues are highly conserved within MBOAT members that transfer fatty acids onto protein substrates (Buglino and Resh, 2010). In eukaryotes, the major protein palmitoylation reactions are carried out not by MBOAT members, but by various protein acyltransferases (PAT) that catalyze thioester bond formation between a long-chain fatty acid and the –SH moiety of a cysteine residue within certain proteins (Smotrys and Linder, 2004). These PATs have a signature “DHHC cysteine-rich domain” . In mammals, at least 23 different PATs have been identified.

GOAT (MBOAT4)

Ghrelin is an octanoylated, 28-amino-acid peptide hormone, produced as a proteolytic cleavage fragment of 117-amino-acid pre-proghrelin in endocrine cells. Ghrelin is secreted by the stomach. Ghrelin was identified by Kojima and colleagues (1999) through its ability to stimulate the release of growth hormone from pituitary cells. Acylation occurs at serine-3 of proghrelin and is carried out by the enzyme ghrelin *O*-acyltransferase (GOAT), which prefers to use octanoyl coenzyme A as its substrate (Gutierrez et al., 2008; Yang et al., 2008). Both ghrelin and GOAT are drug targets for obesity treatment (Lim et al., 2011).

HHATL/GUPI

Gup1p was discovered in yeast (Bosson et al., 2006) (see below). Interestingly, the mammalian homolog of Gup1p, Hedgehog acyltransferase-like (HHATL; MBOAT3), performs a different function than Gup1p. HHATL interacts directly with SHH. However, in HHATL, the conserved histidine present in the MBOAT motif has been replaced with leucine; in addition, the conserved asparagine has been replaced with aspartic acid. Thus, HHATL cannot act as an acyltransferase. The authors propose that HHATL acts as a negative regulator for N-terminal palmitoylation of SHH (Abe et al., 2008).

Subgroup 3: enzymes involved in phospholipid remodeling

GUP1

Several proteins use the covalent glycosylphosphatidylinositol (GPI) linkage to anchor at the extracellular leaflet of the plasma membrane. The GPI moiety is first attached to proteins newly synthesized at the ER. While these proteins are transported *en route* to the PM, the GPI moieties are remodeled by deacylation/reacylation reactions. In yeast, the

gene *PERI* is required to produce lyso-GPI; PERI may possess phospholipase A2 activity (Fujita et al., 2006). Gup1p was shown to be essential to complete the remodeling of GPI by producing the C26:0-containing diacylglycerol anchors (Bosson et al., 2006). Gup1p is involved in virulence and drug resistance of the opportunistic yeast *Candida albicans* (Ferreira et al., 2010).

LPATs (LPEAT1, LPCAT3, LPCAT4, and LPIAT1)

Lysophospholipid acyltransferases (LPATs) are involved in membrane phospholipid remodeling. Phospholipids play important structural and functional roles in membranes and serve as precursors for various cellular lipid mediators. All glycerophospholipids contain fatty acyl moieties as ester linkages with the –OH moieties at C1 and C2 of the glycerol backbone. Saturated and monounsaturated fatty acids usually occupy the C1 position, while polyunsaturated fatty acids usually occupy the C2 position. To modify the fatty acid composition of a given phospholipid, the fatty acid at C2 can be cleaved by a phospholipase A2 to produce lysophospholipid (LP). LP can then be reacylated by various LPATs to form phospholipid that contains a different fatty acid at C2. A few LPATs belong to the 1-acylglycerol-3-phosphate *O*-acyltransferase (AGPAT) family (Lewin et al., 1999; Cao et al., 2004), while lyso-PE acyltransferase 1 (LPEAT1; MBOAT1) (Benghezal et al., 2007; Jain et al., 2007; Riekhof et al., 2007), lyso-PC acyltransferase 3 (LPCAT3; MBOAT5) (Hishikawa et al., 2008; Zhao et al., 2008), lyso-PC acyltransferase 4 (LPCAT4; MBOAT2) (Tamaki et al., 2007; Hishikawa et al., 2008), and lyso-PI acyltransferase 1 (LPIAT1; MBOAT7) (Gijón et al., 2008; Lee et al., 2008) belong to the MBOAT family (Shindou and Shimizu, 2009). Both MBOAT5 and MBOAT7 prefer to use arachidonoyl CoA as their substrates and are involved in arachidonate recycling to regulate leukotriene levels in neutrophils (Gijón et al., 2008). MBOAT5 plays an important role in preventing the unfolded protein response caused by the saturated fatty acid accumulation in membranes (Ariyama et al., 2010), and is a direct target of the ligand-induced transcription factor LXR (Demeure et al., 2011). Four novel motifs within the MBOAT protein sequences, essential for LPAT activity, have been identified by site-specific mutagenesis experiments (Shindou et al., 2009). Three of these motifs may be involved in binding lysophospholipids as the substrates.

Conclusions

Today, the biochemical reactions carried out by each known MBOAT member were all essentially revealed. The next challenge will be to enhance our understanding of their physiologic functions *in vivo*. Several MBOAT members are potential drug targets for treating major human diseases, including atherosclerosis, obesity, Alzheimer disease, viral infections, and cancer. Solving the protein structures of these enzymes at high resolution will be important to enable the rational design of specific inhibitors.

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