Lipin proteins and metabolic homeostasis

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Abstract **The lipin protein family, consisting of three members, was first identified early this century. In the last few years, the lipin proteins have been shown to have important roles in glycerolipid biosynthesis and gene regulation, and mutations in the corresponding genes cause lipodystrophy, myoglobinuria, and inflammatory disorders. Here, we review some of the progress toward elucidating the molecular and physiological functions of the lipin proteins.—**Reue, K., and J. R. Dwyer. **Lipin proteins and metabolic homeostasis.** ***J. Lipid Res.*** **2009.** 50: **S109–S114.**

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THE LIPIN PROTEIN FAMILY

The lipin protein family consists of three members, lipin-1, lipin-2, and lipin-3. The founding member of the family, lipin-1, was identified via positional cloning as the mutated gene product in the fatty liver dystrophy (*fld*) mouse (1). The name of the mutation refers to the occurrence of fatty liver and hypertriglyceridemia during the neonatal period, and peripheral neuropathy, which progresses throughout adulthood (2, 3). In addition, these mice are lipodystrophic, develop insulin resistance, and have increased susceptibility to atherosclerosis (4). Lipin-1 is expressed in a variety of tissues, with the most prominent expression in adipose tissue, skeletal muscle, and testis (1). Two lipin-1 protein isoforms are generated by alternative mRNA splicing, giving rise to proteins with predicted sizes of ~98 and 102 kDa (5, 6). Interestingly, lipin-1 protein can localize to either the cytoplasm or the nucleus (6), which may be related to the dual roles of the protein (described below).

The genes for lipin-2 and lipin-3 were identified by similarity of their predicted protein sequence to lipin-1 (1). In addition, single lipin orthologs were identified in invertebrates, plasmodia, and yeast, and two lipin orthologs are present in plants. All lipin proteins exhibit two regions of especially high sequence conservation located in the N- and C-terminal protein regions, known as the N-LIP and C-LIP domains, respectively. This review will principally focus on lipin-1, about which the most is known, with information about the other two lipin family members provided where available.

MOLECULAR FUNCTION OF LIPIN PROTEINS

Lipin-1 has two recently discovered molecular functions. First, lipin-1 acts as a phosphatidate phosphatase (PAP) enzyme, which converts phosphatidate to diacylglycerol during triglyceride, phosphatidylcholine, and phosphatidylethanolamine biosynthesis (reviewed in Refs. 7, 8 and Brindley, this issue). Although PAP enzyme activity had been studied for more than 50 years, the molecular identity was a mystery until Han, Wu, and Carman (9) purified the enzyme from the yeast *Saccharomyces cerevisiae* and obtained peptide sequence that identified it as the yeast lipin ortholog. The PAP enzyme activity requires a DxDxT motif located in the C-LIP domain (see **Fig. 1**).

After identification of the yeast PAP enzyme, PAP activity was subsequently demonstrated for all three mammalian lipin proteins, with lipin-1 having the highest specific activity (10, 11). In the presence of elevated fatty acid levels within the cell, lipin proteins translocate from the cytosol to the endoplasmic reticulum membrane, where they encounter phosphatidic acid and catalyze its conversion to diacylglycerol (8). The three lipin genes have a distinct, but overlapping, tissue distribution (10), suggesting that each may be responsible for the PAP activity in a specific set of tissues. As determined in tissues from the *fld* mouse, lipin-1 accounts for all of the PAP activity in adipose tissue and skeletal muscle, but only part of the activity in liver, heart, kidney, and brain (10, 11), and lipin-2 and/or lipin-3 may be active in these tissues.

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Abbreviations: *fld*, fatty liver dystrophy; PAP, phosphatidate phosphatase; PPARα, peroxisome proliferator-activated receptor α.

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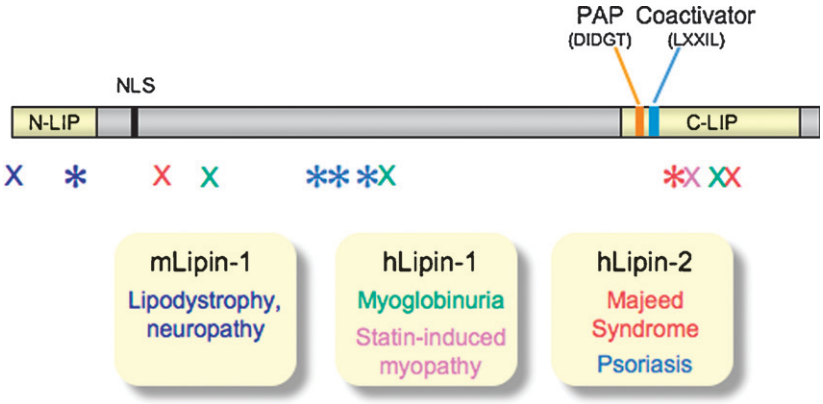

Fig. 1. Lipin protein domains and disease-related mutations. At top is shown a schematic diagram of lipin protein domain structure, with N-LIP and C-LIP domains indicated with yellow shading and other functional motifs labeled. NLS, nuclear localization signal; PAP, PAP active site; coactivator, nuclear receptor interaction motif. Below is shown the position relative to protein domains of nonsense (X) and missense (*) mutations related to disease. mlipin-1, mouse lipin-1; hLipin-1, human lipin-1; hLipin-2, human lipin-2. See text for primary references.

In addition to cytosolic localization, all of the mammalian lipin proteins possess a putative nuclear localization signal. It has been demonstrated that lipin-1 can localize to the nucleus in adipocytes (6) and hepatocytes (12), and subcellular localization may be influenced by protein phosphorylation (11). The role of nuclear lipin-1 may be related to its function as a transcriptional coactivator. Finck et al. (13) have shown that lipin-1 is required for the activation of hepatic fatty acid oxidation genes during fasting conditions. Lipin-1 directly interacts with the nuclear receptor peroxisome proliferator-activated receptor α (PPARα) and PPARγ coactivator 1α (PGC-1α) in a complex that modulates fatty acid oxidation gene expression. Lipin-1 coactivator activity requires an LxxIL sequence motif within the C-LIP domain (Fig. 1). These studies established a key role for lipin-1 in hepatic gene expression during fasting, but it is not clear whether lipin-1 coactivator activity has a physiological role in other tissues nor whether the other lipin family members exhibit similar activity.

The recent elucidation of lipin-1 PAP and coactivator activities has provided new insight into the biological functions of lipin-1. One approach to understanding lipin-1 physiological function has been to study the effects of lipin-1 deficiency or enhanced lipin-1 expression using mouse models. As summarized below and in **Fig. 2**, lipin-1 has a unique physiological role in lipid homeostasis in tissues, including adipose tissue, skeletal muscle, liver, and peripheral nerve.

LIPIN PROTEINS AND ADIPOGENESIS

The lipodystrophy in lipin-1-deficient mice is characterized by the presence of immature adipocytes that fail to store lipid or express mature adipocyte markers (4). The lack of triglyceride storage in adipocytes from these mice can be attributed in large part to the deficiency in PAP activity, which is responsible for lipid synthesis in mature adipocytes. However, lipin-1-deficient cells exhibit additional defects in adipocyte differentiation. Lipin-1-deficient cells and adipose tissue fail to induce the key adipogenic transcription factor, PPARγ, and its target genes and instead express high levels of preadipocyte factor-1, an inhibitor of adipogenesis (14). Complementation of lipin-1-deficient preadipocytes with a retroviral vector expressing PPARγ partially rescues differentiation, suggesting that there is a requirement for lipin-1 at early stages of adipogenesis to facilitate PPARγ expression.

Lipin-2 may also have a role in adipogenesis. Whereas lipin-1 is the predominant lipin in adipose tissue and its expression increases during differentiation of the 3T3-L1 adipocyte cell line, lipin-2 protein can be detected in preadipocytes but diminishes during differentiation (15). The fact that lipin-2 cannot compensate for lipin-1 function in adipose tissue of *fld* mice indicates that the two proteins serve different roles and may suggest that lipin-2 provides a regulatory function during adipogenesis.

LIPIN-1, OBESITY, AND INSULIN SENSITIVITY

While lipin-1 deficiency produces lipodystrophy in the mouse, enhanced lipin-1 expression in either adipose tissue or skeletal muscle promotes obesity (16). On a high-fat diet, both adipose tissue and muscle-specific lipin-1 transgene expression induce more rapid weight gain than in nontransgenic mice by 2-fold (adipose transgenic) or 4-fold (muscle transgenic), despite equivalent food intake. However, the mechanism for the obesity and the resulting effects on glucose homeostasis differ depending on whether lipin-1 expression is enhanced in adipose tissue or in muscle.

The muscle-specific lipin-1 transgenic mice exhibit reduced energy expenditure and develop insulin resistance

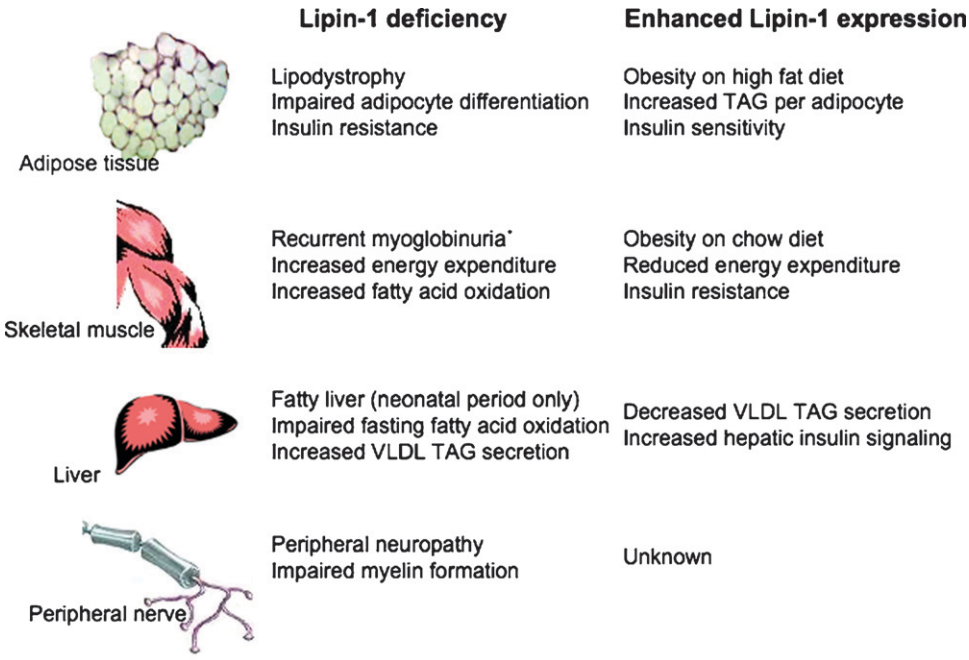

Fig. 2. Physiological effects of lipin-1 deficiency or enhanced expression. Summary of lipin-1 effects on metabolism in tissues shown. Characteristics shown in the left column are derived from studies in the lipin-1-deficient *fld* mouse or lipin-1-deficient human subjects (denoted by *). Characteristics shown in the right column are derived from studies of adipose-specific lipin-1 transgenic mice (adipose), muscle-specific lipin-1 transgenic mice (muscle), or from lipin-1 overexpression in liver via adenovirus (liver). See text for primary references.

(16). The insulin resistance in these mice is presumably secondary to the obesity and/or increased PAP activity leading to triglyceride accumulation and altered metabolism in muscle. In contrast, enhanced lipin-1 levels in adipose tissue lead to increased adipocyte triglyceride content but lower glucose and insulin levels than wild-type mice on both chow and high-fat diets (16). Importantly, studies in humans have revealed a similar positive correlation between lipin-1 expression levels in adipose tissue and insulin sensitivity. This is true in both obese subjects with normal or impaired glucose tolerance (17, 18) and in healthy young men (19). It is possible that lipin-1 may promote efficient incorporation of fatty acids into adipocyte triglycerides, thereby preventing lipid deposition in other tissues where they could compromise insulin action (20). Additionally, in human adipocytes, lipin-1 expression levels are correlated with glucose transporter 4 expression, which may increase glucose uptake (21), and with expression of PPARα and fatty acid oxidation genes, which may prevent fatty acid accumulation (19). Interestingly, lipin-1 expression is induced in adipocytes by insulin-sensitizing drugs such as thiazolidinediones and harmine (18, 22).

In addition to the connection between lipin-1 and insulin sensitivity discussed above, insulin induces phosphorylation of lipin-1 at multiple sites (5, 11). Phosphorylation does not appear to alter the PAP-specific activity but rather to shift the localization toward the cytosolic rather than microsomal compartment (11), potentially altering the proportion of lipin-1 that is available to catalyze the PAP reaction at the microsomal membrane. Studies in yeast have identified a specific phosphatase that acts on yeast lipin, and the mammalian counterpart of this phosphatase, known as Dullard, acts on mammalian lipin-1 (23, 24). Although the physiological significance of lipin protein phosphorylation is not yet fully understood, it is likely to represent an important mechanism for rapid modulation of lipin-1 compartmentalization and/or activity in response to insulin and other metabolic stimuli.

LIPIN-1 AND PERIPHERAL NERVE FUNCTION

The lipodystrophy in lipin-1-deficient mice is accompanied by severe peripheral neuropathy (3). It is now clear that lipin-1 deficiency causes a lack of PAP activity in the fat pads that constitute the bulk of the epineurium in adult nerve, as well as in Schwann cells themselves (25). Elegant studies of a Schwann cell-specific, lipin-1-deficient mouse demonstrated that lack of PAP activity in these cells is sufficient to cause peripheral neuropathy associated with myelin degradation and attenuated nerve conduction velocity (26). Furthermore, the accumulation of phosphatidate, the substrate for PAP, is responsible for eliciting aberrant signaling through the MEK/Extracellular signal-related kinase pathway, leading to dedifferentiation and proliferation of Schwann cells. These results raise the intriguing possibility that other symptoms of lipin deficiency are related not only to the loss of PAP enzyme function, but also to the

deleterious effects of phosphatidate accumulation within the cell (reviewed in Ref. 8).

LIPIN-1 AND HEPATIC LIPOPROTEIN SECRETION

It has been known for decades that PAP activity in the liver is regulated in response to changing metabolic conditions. For example, hepatic PAP activity is diminished in diabetes and starvation conditions and is increased with glucocorticoids (reviewed in Ref. (8). All three lipin family members are expressed in hepatocytes, but their expression is regulated independently. Glucocorticoids specifically increase mRNA and protein levels of lipin-1, but not lipin-2 or lipin-3 (27, 28). The effect of glucocorticoids on lipin-1 is enhanced by glucagon or cAMP and antagonized by insulin (27).

Recent studies have implicated lipin-1 in the synthesis and secretion of VLDL in liver. This function of lipin-1 has been investigated by modulating lipin-1 levels in cultured hepatocytes and in the mouse. Enhanced expression of lipin-1 in a rat hepatocyte cell line led to stimulation of triglyceride synthesis and secretion, while knockdown of endogenous lipin-1 expression decreased the secretion of newly synthesized triglycerides (12). Interestingly, deletion of the lipin-1 nuclear localization signal led to impaired association with the microsomal membranes and less effective induction of triglyceride synthesis. These results suggest that lipin-1 compartmentalization within hepatocytes may be a determinant of triglyceride synthesis and VLDL secretion.

However, studies performed in vivo indicate that the relationship between lipin-1 and VLDL secretion is more complex than observed in a hepatocyte cell line. Hepatocytes isolated from adult *fld* mice were shown to secrete VLDL at increased rates compared with wild-type hepatocytes (29), suggesting that lipin-2 and/or lipin-3 are capable of promoting VLDL synthesis and secretion. On the other hand, mice treated with an adenovirus to increase lipin-1 expression in the liver exhibited reduced rates of VLDL secretion (29), in direct contrast to results obtained in vitro (12). Through the use of mutant lipin-1 molecules, this effect was shown to require lipin-1 transcriptional coactivator but not PAP enzyme function. Consistent with the results of lipin-1 adenovirus overexpression in the mouse, hepatic lipin-1 expression levels and VLDL secretion both increased in obese individuals following gastric bypass surgery (30). Taken together, it appears that lipin proteins influence hepatic triglyceride synthesis and VLDL secretion, but at present, it is difficult to attribute effects solely to specific lipin family members and to distinguish the contributions of PAP versus coactivator activities.

LIPIN-1 GENE MUTATIONS AND POLYMORPHISMS ASSOCIATED WITH DISEASE

Mutations affecting lipin-1 and lipin-2 cause human disease. While two distinct mutations in mouse *Lpin1* cause lipodystrophy (1) (Fig. 1), analysis of human lipodystrophic subjects has failed to detect causative mutations in the *LPIN1* gene (31, 32). However, mutations in *LPIN1* have been identified in patients with recurrent acute myoglobinuria in childhood (33). Distinct inactivating mutations were detected in patients from several ethnic backgrounds and occur at dispersed locations throughout the lipin-1 protein structure (see Fig. 1). Unlike mice with lipin-1 deficiency, the patients were reported to have normal fat distribution, although no quantification of fat was provided, and all subjects were under 10 years of age (33). The authors suggest that lipin-2 expression in adipose tissue may compensate for lack of lipin-1, as lipin-2 expression has been detected in human adipose tissue (10). At present, it is unclear what the effect of lipin-1 deficiency will be in human adults and whether they will develop peripheral neuropathy as is also observed in adult lipin-1-deficient mice.

In addition to the mutations in human lipin-1 described above, *LPIN1* polymorphisms have been associated with numerous metabolic traits. Among these are insulin and/or glucose levels (17, 34, 35), resting metabolic rate (34), and systolic blood pressure (36, 37). *LPIN1* polymorphisms that are associated with response of type 2 diabetic patients to rosiglitazone have also been reported (36). One particularly notable *LPIN1* polymorphism causes an amino acid substitution within the C-LIP domain and is associated with statin-induced myopathy (33), an unfortunate side effect experienced by some of individuals who take statin drugs to treat hypercholesterolemia [reviewed in (38)]. This *LPIN1* variant merits further study in larger numbers of individuals.

LIPIN-2 GENE MUTATIONS AND DISEASE

LPIN2 mutations cause Majeed syndrome, an inflammatory disorder characterized by recurrent sterile osteomyelitis, cutaneous inflammation, and dyserythropoietic anemia (39, 40). Three independent *LPIN2* mutations have been described, two of which result in truncated protein or decayed mRNA, and a third point change altering a highly conserved amino acid residue downstream of the PAP active site in the C-LIP domain (see Fig. 1). It is unclear what the normal physiological role of lipin-2 is and whether the inflammatory symptoms observed in Majeed syndrome are direct effects of lipin-2 deficiency in tissues such as bone, skin, and erythrocytes, or perhaps secondary effects resulting from altered lipid homeostasis in other tissues. Finally, a polymorphism in the 3′ untranslated region of *LPIN2* has been linked to diabetes risk (41).

SUMMARY AND FUTURE DIRECTIONS

The lipin proteins represent relatively new identities for an "old" function, the PAP enzyme activity that is critical in glycerolipid biosynthesis. Lipin-1 (and most likely lipin-2 and lipin-3) leads a double life as a transcriptional

coactivator that promotes fatty acid oxidation, a function that, paradoxically, has the opposite effect on lipid storage as PAP enzyme activity. The dual functions of lipin proteins may allow them to adapt their activity to cellular lipid storage requirements. Many questions remain, particularly regarding the specific roles of lipin-2 and lipin-3, and the interrelationships among the family members in tissues where multiple lipins are expressed. These questions will be addressed in the coming years by identifying additional informative genetic variants in the human population and by the generation of genetically modified mouse models.

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