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Review

Lipins, lipinopathies, and the modulation of cellular lipid storage and signaling

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ABSTRACT

Members of the lipin protein family are phosphatidate phosphatase (PAP) enzymes, which catalyze the dephosphorylation of phosphatidic acid to diacylglycerol, the penultimate step in TAG synthesis. Lipins are unique among the glycerolipid biosynthetic enzymes in that they also promote fatty acid oxidation through their activity as co-regulators of gene expression by DNA-bound transcription factors. Lipin function has been evolutionarily conserved from a single ortholog in yeast to the mammalian family of three lipin proteins—lipin-1, lipin-2, and lipin-3. In mice and humans, the levels of lipin activity are a determinant of TAG storage in diverse cell types, and humans with deficiency in lipin-1 or lipin-2 have severe metabolic diseases. Recent work has highlighted the complex physiological interactions between members of the lipin protein family, which exhibit both overlapping and unique functions in specific tissues. The analysis of "lipinopathies" in mouse models and in humans has revealed an important role for lipin activity in the regulation of lipid intermediates (phosphatidate and diacylglycerol), which influence fundamental cellular processes including adipocyte and nerve cell differentiation, adipocyte lipolysis, and hepatic insulin signaling. The elucidation of lipin molecular and physiological functions could lead to novel approaches to modulate cellular lipid storage and metabolic disease.

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1. Introduction and overview

Glycerolipids serve a variety of vital cellular functions. Phospholipids are a major component of cellular plasma membranes and intracellular membranes. Triacylglycerol (TAG) is critical for long-term energy storage in adipose tissue and provides a source of fatty acids for oxidation in skeletal muscle and cardiac muscle. TAG is also essential for the production of very low-density lipoproteins in the liver and chylomicrons in the intestine, as well as for the production of milk by mammary epithelial cells [1,2]. Derangements in TAG synthesis and storage, including those occurring in the setting of obesity and lipodystrophy, are highly relevant to public health because they can increase susceptibility to cardiovascular disease, diabetes mellitus, and dyslipidemia [3–6].

In eukaryotes, TAG is synthesized by two pathways—the glycerol phosphate pathway and the monoacylglycerol pathway. The glycerol phosphate pathway is the primary pathway in most cell types [1,2]. The acylation of glycerol 3-phosphate occurs in a stepwise fashion, with each acyl group added by a distinct class of acyltransferases. Lipins catalyze the penultimate step in the glycerol phosphate pathway—converting phosphatidic acid (PA) to diacylglycerol (DAG) (Fig. 1). By contrast, TAG synthesis in the small intestine is thought to occur predominantly by the monoacylglycerol pathway, which uses monoacylglycerol produced by the hydrolysis of dietary fats [7,8].

The lipin gene family was first identified through studies of a spontaneous mutant mouse strain (i.e., the fatty liver dystrophy mouse) that exhibited dysregulated TAG storage in multiple tissues, leading to lipodystrophy and neonatal fatty liver [9,10]. The cloning and sequencing of *Lpin1* (encoding lipin-1) also made it possible to identify two related mammalian genes, *Lpin2* and *Lpin3*, as well as orthologous genes in organisms as evolutionarily distant as yeast [11]. In the ensuing decade, numerous studies of lipin protein function have been performed in a wide range of experimental organisms. In addition, human diseases caused by mutation in *LPIN1* or *LPIN2* have been identified [12,13]. Because of the critical roles that lipin proteins play in lipid homeostasis and metabolism, it is important to better define their molecular and physiological functions. Several excellent reviews on mammalian and yeast lipin protein function have appeared in the past few years [14–22]. Here, we will briefly highlight some aspects of the history of the lipin field and well-established molecular functions of the lipin proteins, and then will focus on recent studies of mouse and human lipin deficiencies that have provided insights into the physiological activities of, and relationships between, different members of the lipin family.

2. Lipin protein molecular functions

2.1. Lipin phosphatidate phosphatase (PAP) activity

The activities of the enzymes in the glycerol phosphate pathway [glycerol-3-phosphate acyltransferases (GPATs), acylglycerol-3-phosphate acyltransferases (AGPATs), acyl coenzyme-A:diacylglycerol acyltransferases (DGATs) and phosphatidate phosphatases (PAPs)] have been studied for decades [1,2]. PAP activity, which converts PA to DAG, was first demonstrated by Eugene Kennedy in seminal work that established the connection between PA synthesized from glycerol and the downstream synthesis of phosphatidylcholine and TAG [23]. Subsequent attempts to purify PAP activity from mammalian liver were unsuccessful, likely thwarted by instability of the protein and the requirement at that time for large amounts of protein for sequence determination. Nevertheless, studies of PAP activity in rat liver revealed important features of the enzyme. Particularly noteworthy was the fact that PAP activity resides in the cytosol until stimulated with fatty acids, which causes translocation to internal membranes [24]. That characteristic distinguishes PAP from all of the acyltransferase enzymes in the glycerol phosphate pathway, which are integral membrane proteins.

The molecular cloning of members of the GPAT, AGPAT, and DGAT protein families in the 1990s provided insights into the physiology and biochemistry of these protein families [1,2]. The identity of the PAP activity in the glycerol phosphate pathway was revealed only recently, and involved both classical biochemical purification studies in yeast and mouse genetics. In 2006, Carman and colleagues purified PAP activity from Saccharomyces cerevisiae and obtained protein sequence [15,25]. The sequence revealed that the yeast PAP, Pah1p, corresponded to the yeast ortholog of the mammalian lipin family [11]. Whereas yeast and invertebrates have a single lipin ortholog, plants have two lipin genes, and mammals have three, encoding lipin-1, lipin-2, and lipin-3 (Fig. 2).

Following the determination that yeast and human lipin-1 proteins exhibit PAP activity [25], it was shown that mouse lipin-1, lipin-2, and lipin-3 are all PAP enzymes, requiring Mg^{2+} for activity and exhibiting sensitivity to inhibition by *N*-ethylmaleimide [26]. Of the three family members, lipin-1 has substantially higher PAP specific activity than lipin-2 and lipin-3 [26]. It was also shown that the activity of all three lipin proteins is specific for PA as a substrate, with no activity against other lipid phosphates [26]. At present, it is unclear whether there are differences in substrate preferences among the mammalian lipin isoforms, and this is a fertile area for future research. It should be noted that a family of proteins that are structurally unrelated to lipin proteins, known as lipid phosphate phosphatases, also exhibit PAP activity. Importantly, however, lipid phosphate phosphatases are localized to the plasma membrane and do not contribute to cellular TAG or phospholipid biosynthesis [27,28]. Biochemically, the two types of PAP enzymes are distinguishable by the fact that lipid phosphate phosphatases act on a wide variety of substrates in addition to PA, do not require Mg^{2+} for activity, and are resistant to *N*-ethylmaleimide inhibition.

2.2. Lipin-1 protein nuclear activity

The acyltransferase enzymes of the glycerol phosphate pathway are integral ER membrane proteins [1,2]. By contrast, lipin proteins reside in the cytosol and transiently associate with the ER membrane during the PAP enzyme reaction. In addition, lipin proteins can localize to the nucleus [11,29–33]. Exciting clues about lipin-1 nuclear function were first provided by Finck and colleagues, who demonstrated that lipin-1 interacts with the nuclear factor PPARα and the transcriptional coactivator PGC-1α to induce fatty acid oxidation genes in response to fasting [34]. Lipin-1 also activates PPARγ and myocyte enhancer factor 2 (MEF2), and represses nuclear factor of activated *T*-cells c4 (NFATc4) [30,35,36]. Lipin-1 is present in complexes associated with the promoters of some target genes, but not others, and it appears that the mechanisms of lipin-1 co-regulatory activity may differ with individual transcription factors [34,35,37]. Most data are consistent with a model in which