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Lipase Maturation Factor 1: a lipase chaperone involved in lipid metabolism

Miklós Péterfy*

Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles and Department of Medicine, University of California, Los Angeles

Abstract

Mutations in lipase maturation factor 1 (*LMF1*) are associated with severe hypertriglyceridemia in mice and human subjects. The underlying cause is impaired lipid clearance due to lipase deficiency. *LMF1* is a chaperone of the endoplasmic reticulum (ER) and it is critically required for the post-translational activation of three vascular lipases: lipoprotein lipase (LPL), hepatic lipase (HL) and endothelial lipase (EL). As *LMF1* is only required for the maturation of homodimeric, but not monomeric, lipases, it is likely involved in the assembly of inactive lipase subunits into active enzymes and/or the stabilization of active dimers. Herein, we provide an overview of current understanding of *LMF1* function and propose that it may play a regulatory role in lipase activation and lipid metabolism. Further studies will be required to test this hypothesis and elucidate the full spectrum of phenotypes in combined lipase deficiency.

Keywords

Lipase maturation factor; Lipoprotein lipase; Hepatic lipase; Endothelial lipase; Hypertriglyceridemia

1. Introduction

Plasma lipids are important risk factors for cardiovascular disease (CVD) and the strong genetic determination of their plasma levels has long been appreciated (1, 2). During the last several decades, biochemical studies identified principal genes and pathways involved in lipid metabolism, some of which led to major advances in the treatment of dyslipidemia and CVD (3). More recently, hypothesis-free genetic approaches have been successfully applied to discover novel genes and mechanisms in lipid metabolism. In particular, genome-wide association studies (GWAS) provided dozens of genetic loci implicated in the determination of plasma lipid levels in the general population and in dyslipidemic individuals (4, 5). However, it is increasingly clear that only a small portion of the genetic component affecting lipid traits has been identified in even the largest of such studies (4). Emerging evidence suggests that this may be due to the collective contribution of many individually rare genetic variants, which are not accessible by GWAS (6). Although whole genome and exome sequencing has recently become feasible, identification of disease genes harboring rare

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*Correspondence to: Miklos Peterfy, Cedars-Sinai Medical Center, 8700 Beverly Blvd., D-4091, Los Angeles, CA 90048. Tel.: (310)-423-0314; fax: (310)-423-0299; mpeterfy@ucla.edu.

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variants in human populations remains a challenge. Thus, “classical” approaches of disease-gene discovery, such as family-based linkage studies and positional cloning in mouse models, continue to provide important insights into disease mechanisms. For example, identification of *Sorcs1* and *Zfp69*, *Tbc1d1*, and *Gpihbp1* in mouse models of type 2 diabetes, obesity and hyperlipidemia, respectively, revealed novel genes relevant to human disease (7–10). Herein, we review recent progress on the characterization of lipase maturation factor 1 (*Lmf1*), a gene initially identified in a mouse model of hypertriglyceridemia (HTG) (11). We discuss the role of *Lmf1* in lipase expression and raise the hypothesis that *Lmf1* is a novel determinant of plasma lipid metabolism through the post-translational regulation of lipase activity.

2. Identification of LMF1 in a mouse model of hypertriglyceridemia

Almost 30 years ago, a recessive mouse mutation called *combined lipase deficiency* (*cld*) was described (12). Homozygous *cld* mice died within the first few days of life apparently due to a massive accumulation of chylomicron particles resulting in circulatory problems and cyanosis. The development of HTG was dependent on suckling, which suggested impaired lipid clearance as the underlying cause of the phenotype. Indeed, lipoprotein lipase (LPL) activity was greatly diminished in plasma and tissues of *cld* mice. Similar to the *cld* mutation, a defect in the LPL structural gene is also associated with HTG and neonatal lethality suggesting that the *cld* phenotype is likely due to LPL deficiency (13). Interestingly, however, the activity of hepatic lipase (HL) was also virtually absent in *cld* mice, and we have recently found that endothelial lipase (EL) activity is also impaired (14). Thus, the *cld* mutation affected a *trans*-acting factor required for the expression of active lipases. Using a positional cloning approach, this factor was identified as *Tmem112*, a previously uncharacterized membrane protein (11). *Tmem112* is disrupted by a retroviral integration event in *cld* mice resulting in premature transcriptional termination and C-terminal truncation of the encoded protein (Fig. 1). To better reflect its function, *Tmem112* has subsequently been renamed as lipase maturation factor 1 (*Lmf1*).

3. Lmf1 in the post-translational maturation of lipases

Even before the identification of *Lmf1*, biochemical studies in *cld* cells and tissues provided important clues about the role of this protein in lipase expression. Despite the virtual absence of LPL activity in plasma and tissues, lipase mRNA and protein expression appeared normal in *cld* mice indicating a defect in the posttranslational attainment of lipase activity (15). It was also demonstrated that inactive LPL formed high-molecular weight aggregates and was retained within the endoplasmic reticulum (ER) of *cld* cells consistent with misfolding and ER quality control preventing the release of inactive lipase (16). In contrast, serum levels of adipsin were unaffected by *cld*, arguing against a global defect in protein folding or secretion (15). Collectively, these studies suggested that the gene affected by the *cld* mutation (i.e. *Lmf1*) was a lipase-specific chaperone required for the post-translational maturation of lipases into active enzymes.

Lmf1 is a multi-pass transmembrane protein of the ER with three soluble domains protruding into the ER lumen (Fig. 1). This subcellular localization is consistent with the post-translational effect of *Lmf1* on lipases, as these enzymes attain catalytic activity within the ER (17, 18). Co-immunoprecipitation studies revealed that *Lmf1* physically interacts with LPL, HL and EL, but not with pancreatic lipase (PL), a related enzyme whose activity is unaffected by the *cld* mutation (14, 19, 20). Although a lipase interaction site has been mapped to one of the ER-facing loops of *Lmf1* (Fig. 1), it is clear that other domains also play a critical role in lipase maturation (19). For example, *cld* and the human Y439X mutation (see below), both of which cause C-terminal truncations of *Lmf1*, completely

abolish the maturation of LPL, even though lipase binding remains unaffected. These results suggest complex interactions between Lmf1 and lipases involving multiple protein domains. The location of Lmf1-interaction site(s) within lipases remains to be identified.

What are the molecular mechanisms underlying the lipase-chaperone function of Lmf1? An important clue in this regard is that Lmf1 deficiency only affects lipases that are active as homodimers (LPL, HL and EL), whereas a monomeric member of the lipase superfamily (PL) is unaffected (20). This observation suggests that Lmf1 is involved in the assembly of inactive lipase monomers into active dimers and/or the stabilization and maintenance of the homodimer structure. Indeed, the LPL dimer is prone to rapid dissociation and inactivation unless stabilized by factors such as heparin *in vitro*, or anchoring proteins (heparan sulfate proteoglycans and Gpihbp1) at the endothelial surface *in vivo* (21, 22). In contrast, active LPL is highly stable within the ER (23). Thus, it is likely that the dimeric lipase structure is maintained by a stabilizing chaperone in this compartment. We propose that Lmf1 is the ER chaperone that plays this role.

4. LMF1 in human lipid metabolism

Identification of *Lmf1* in the *cld* mouse model implicated the human ortholog (*LMF1*) as a candidate gene in human HTG. Indeed, re-sequencing in HTG cohorts identified two individuals with homozygous nonsense *LMF1* mutations (Y439X and W464X) (11, 24). In both cases, severe HTG (>2,500 mg/dl) is associated with repeated episodes of pancreatitis and combined lipase deficiency, consistent with the *cld* phenotype. However, some aspects of the phenotype are unique to Y439X, such as the development of tuberous xanthomas and partial lipodystrophy affecting the limbs and buttocks (11). Interestingly, lipodystrophy was not associated with W464X; the patient was in fact overweight with a BMI of 29 (24). The explanation for divergent phenotypes may lie in the slightly shorter C-terminal truncation resulting from W464X (Fig. 1). Whereas LMF1-Y439X is completely deficient in supporting LPL maturation in an *in vitro* assay (25), LMF1-W464X retains ~40% of wild-type LMF1 function (11, 24). Importantly, lipodystrophy has not been reported in patients with defects of individual lipases (26, 27) raising the possibility that this phenotype may be a consequence of combined lipase deficiency. Viable *Lmf1*-deficient mouse models will be required to test this hypothesis.

5. Lmf1 as a regulator of lipase activity: a hypothesis

Vascular triglyceride lipases (i.e. LPL, HL and EL) emerged during early vertebrate evolution (28). One of the defining structural features of these enzymes is their homodimeric quaternary structure. However, catalytic activity is unlikely to be the driving force behind this evolutionary innovation, because triglyceride hydrolysis can be achieved through a monomeric structure, as exemplified by PL. Instead, we propose that the emergence of dimeric lipase structure created a platform for the evolution of novel regulatory mechanisms. Specifically, the assembly and dissociation of homodimers may allow rapid activation and inactivation of lipases. Indeed, factors involved in lipase subunit remodeling have already been identified (Fig. 2). Angiopoietin-like 4 (Angptl4) is a plasma protein, which inhibits LPL activity by promoting the conversion of active dimers into inactive monomers (29). Angptl4 also exerts inhibitory effects on HL and EL, presumably through a similar mechanism (30, 31). Angptl4 expression in adipose tissue is induced by fasting, which results in decreased LPL activity and a shift from fat storage in adipose to fat utilization in other tissues (29). Another protein that may regulate LPL activity through lipase dimerization is Gpihbp1, a membrane-bound factor involved in the trans-endothelial transport and anchoring of LPL on capillary endothelial cells (10, 32). Recent data indicate that Gpihbp1 not only binds, but also stabilizes the LPL homodimer and counteracts the

effect of Angptl 4 (22). Although Gpihbp1 expression is induced by fasting in several tissues (33), the physiological contexts in which modulation of LPL activity by this protein is relevant remain to be identified.

The above studies demonstrate that inactivation through dimer dissociation at the endothelial surface is an important post-translational mechanism in the regulation of vascular lipases. We propose that assembly of dimers within the ER represents an additional potential regulatory point in the expression of active lipases. Supporting this possibility, dimer assembly appears to be a bottleneck in the generation of lipase activity. For example, only a fraction of LPL polypeptides synthesized by adipocytes are successfully assembled into active homodimers within the ER, whereas the rest forms inactive, high-molecular weight aggregates destined for degradation (17, 34). Consistently, only 25–50% of total LPL protein mass is present in catalytically active dimeric form in human adipose tissue (35, 36). Thus, modulation of the rate of dimer assembly is a plausible mechanism of active lipase expression. As a chaperone involved in the maturation of homodimeric lipases, Lmf1 is ideally positioned to perform such a post-translational regulatory role. Its polytopic ER membrane organization enables Lmf1 to receive signaling cues from the cytoplasm to rapidly modulate its chaperone function through post-translational modification. Furthermore, altered Lmf1 expression may result in longer-term regulation of lipase assembly. Indeed, recent experimental evidence is consistent with this possibility. In transgenic mouse models, Lmf1 overexpression increased tissue LPL activity, whereas heterozygous *Lmf1*-deficiency (*Lmf1*^{+/-}) decreased post-heparin lipase activity in neonatal mice (our unpublished data). Although common variants of human *LMF1* were not associated with plasma lipid traits in GWAS (4), accumulation of rare *LMF1* variants was observed in subjects with HTG (R. Hegele, unpublished data). Collectively, these results suggest that variation in LMF1 protein level and/or function may modulate lipase activities and lipoprotein metabolism. Further studies will be required to explore mechanisms regulating LMF1 expression and function.

6. Future perspectives

The analysis of loss-of-function mutations in mice and humans demonstrated that LMF1 plays a critical role in the expression of active lipases and lipid homeostasis. It is also clear that LMF1 is involved in the post-translational maturation of lipase polypeptide chains within the ER. However, several important aspects of LMF1 biology remain to be explored further. At the molecular level, the function of LMF1 in the process of lipase maturation remains unclear. Is it responsible for the assembly of lipase monomers into active homodimers, or is it involved in the stabilization of dimers already formed, or perhaps both? A related question is whether and how LMF1 function is integrated with other chaperones known to be involved in the folding of lipases, such as the calnexin/calreticulin and BiP/Grp94 systems (19, 21). An intriguing observation in this context is that calnexin expression is reduced in *cld* cells and tissues (16).

Stemming from the dramatic lipid phenotype observed in its absence, LMF1 has so far been characterized in the context of lipases. However, it is conceivable that LMF1 may affect the metabolism of a broader range of proteins within the ER by either direct interactions with novel client proteins or indirect effects through other chaperones, such as calnexin. Consistent with this possibility, the tissue expression pattern of *Lmf1* is ubiquitous and does not seem to correlate with that of lipases (11). Furthermore, global analysis of gene expression patterns in C57BL/6 and BTBR mice revealed that *Lmf1* expression is highly correlated with that of genes involved in protein biosynthesis in pancreatic islets (37). The extension of Lmf1 function beyond lipases awaits the identification of additional Lmf1 clients or other interacting proteins within the ER.

The key role of LMF1 in the activation of all three vascular lipases suggests that LMF1 deficiency may have complex effects on plasma and tissue lipid metabolism. LPL, HL and EL exhibit overlapping enzymatic activities, substrate specificities and tissue expression patterns. Such functional redundancy lends itself to compensation for the deficiency of one lipase with the activity of another. In support of this idea, upregulation of EL in LPL-deficiency, and LPL and HL in EL-deficiency have been reported (38, 39). Furthermore, HL/EL double knock-out mice show phenotypes (e.g. accumulation of small LDL particles) that neither single knock-outs exhibit (40). Thus, functional deficiency of all three lipases may lead to unique phenotypes in *Lmf1*-deficient mice that may not be apparent in single lipase-deficient mouse models or humans, and may unmask previously unanticipated physiological pathways affected by lipase activity. Unfortunately, neonatal lethality of *cld* mutant mice limits the depth of metabolic characterization possible in this model. Conditional and tissue-specific knock-out mouse models will be required to uncover the full spectrum of *Lmf1*-deficiency phenotypes.

Highlights

- Mutations in LMF1 cause lipase deficiency and hypertriglyceridemia
- LMF1 is an ER chaperone
- LMF1 is required for the post-translational activation of LPL, HL and EL

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Fig. 1. LMF1 structure and function. LMF1 is an ER membrane protein and it interacts with lipases through an ER-facing loop. The C-terminal fragment is also required for lipase maturation, but lipase interaction with this region is hypothetical. LMF1 is likely involved in the assembly of inactive lipase subunits (shown in yellow) or stabilization of active dimers (shown in blue). Mouse (*cld*) and human (Y439X and W464X) mutations resulting in C-terminal truncations of LMF1 are indicated by red circles.

Fig. 2. Post-translational regulation of lipase activity through the modulation of lipase quaternary structure. ANGPTL4 and GPIHBP1 play positive and negative regulatory roles, respectively, in the dissociation (i.e. inactivation) of lipase homodimers at the endothelial surface. The involvement of LMF1 in the regulation of lipase subunit assembly (i.e. activation) within the ER is hypothetical.