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Comparative gene identification-58/α/β hydrolase domain 5: more than just an adipose triglyceride lipase activator?

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Abstract

Purpose of review—Comparative gene identification-58 (CGI-58) is a lipid droplet-associated protein that controls intracellular triglyceride levels by its ability to activate adipose triglyceride lipase (ATGL). Additionally, CGI-58 was described to exhibit lysophosphatidic acid acyl transferase (LPAAT) activity. This review focuses on the significance of CGI-58 in energy metabolism in adipose and nonadipose tissue.

Recent findings—Recent studies with transgenic and CGI-58-deficient mouse strains underscored the importance of CGI-58 as a regulator of intracellular energy homeostasis by modulating ATGL-driven triglyceride hydrolysis. In accordance with this function, mice and humans that lack CGI-58 accumulate triglyceride in multiple tissues. Additionally, CGI-58-deficient mice develop an ATGL-independent severe skin barrier defect and die soon after birth. Although the premature death prevented a phenotypical characterization of adult global CGI-58 knockout mice, the characterization of mice with tissue-specific CGI-58 deficiency revealed new insights into its role in neutral lipid and energy metabolism. Concerning the ATGL-independent function of CGI-58, a recently identified LPAAT activity for CGI-58 was shown to be involved in the generation of signaling molecules regulating inflammatory processes and insulin action.

Summary—Although the function of CGI-58 in the catabolism of cellular triglyceride depots via ATGL is well established, further studies are required to consolidate the function of CGI-58 as LPAAT and to clarify the involvement of CGI-58 in the metabolism of skin lipids.

Keywords

cardiomyopathy; hepatosteatosis; ichthyosis; lipid signaling; lipolysis

INTRODUCTION

Neutral lipid storage disease with ichthyosis (NLSDI), also designated Chanarin–Dorfman Syndrome, is a rare but severe disorder, characterized by systemic triglyceride accumulation leading to hepatomegaly and hepatosteatosis, ichthyosis and muscle weakness (reviewed by Schweiger *et al*. [1]). In 2001, Lefevre *et al*. [2] identified mutations in the gene encoding

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for comparative gene identification-58 (CGI-58) to be causative for the development of NLSDI. CGI-58 belongs to the α/β hydrolase domain-containing protein family and, according to these structural properties, was also designated α/β hydrolase domain 5 (ABHD5) [3,4,5▪]. Importantly, the protein lacks intrinsic hydrolase/esterase activity due to the absence of a nucleophilic serine at amino acid position 155 within a putative catalytic triad [2]. Nevertheless, CGI-58 has been demonstrated to be a critical regulator of intracellular triglyceride homeostasis by coactivating the major cytoplasmic triglyceride hydrolase adipose triglyceride lipase [6,7]. Similar to individuals with CGI-58 deficiency, patients with mutated ATGL alleles also develop neutral lipid storage disease, but some clinical manifestations differ from those observed in NLSDI patients. These differences include the absence of a skin defect in ATGL deficiency, milder hepatosteatosis, and a more pronounced triglyceride accumulation in skeletal muscle and cardiac muscle. The defect in cardiac muscle is particularly severe and leads to the development of an, often lethal, cardiomyopathy, a condition never observed in patients who lack CGI-58 [1]. Similar phenotypical differences as in humans have also been observed in CGI-58 and ATGL-deficient mouse models (Table 1) [8,9,10▪▪, 11▪▪,12–15,16▪▪,17,18▪,19▪▪,20]. Although mice lacking CGI-58 develop a severe epidermal skin defect and die shortly after birth due to skin barrier dysfunction, ATGL-deficient animals show normal skin development, but are affected by massive cardiosteatosis and cardiomyopathy that leads to their premature death approximately 12 weeks after birth [8,12]. The divergent phenotypes in both, humans and mice in response to CGI-58 or ATGL deficiency provide compelling evidence for an ATGL-independent function of CGI-58 in the skin and possibly other tissues. One such alternative function was recently presented in two independent studies showing that CGI-58 is an enzyme with lysophosphatidic acid acyl transferase (LPAAT) activity [21,22]. However, the biochemical basis of this activity remains elusive, and the *in vivo* relevance of this assigned activity, especially in intracellular lipid signaling, requires further experimental clarification.

CGI-58, A CRITICAL COACTIVATOR OF ADIPOSE TRIGLYCERIDE LIPASE

The discovery of ATGL as the major triglyceride hydrolase for the initial and rate-limiting step in triglyceride catabolism has changed the concept of intracellular lipolysis. It revealed that every step in the sequential triglyceride hydrolysis is catalyzed by a predominant lipase, namely ATGL, hormone-sensitive lipase (HSL) and monoglyceride lipase [23–27,28▪▪, 29▪▪]. Subsequent to the discovery of ATGL, Lass *et al*. [6] demonstrated that the enzymatic activity of ATGL critically depends on the presence of CGI-58. Addition of recombinant CGI-58 to ATGL-enriched cell lysates increased ATGL-mediated triglyceride hydrolysis up to 20-fold. Strong activation of ATGL by CGI-58 with purified protein preparations indicated that enzyme activity depends on their physical interaction [30–33]. Experimental proof for protein–protein interaction between CGI-58 and ATGL was provided by ELISA experiments and pull-down assays [30,31,34]. The lipophilic N-terminal region of CGI-58 turned out to be critical for both lipid droplet binding and coactivation of ATGL [30]. A detailed description of the structural requirements of CGI-58 in the activation process of ATGL was recently published by Oberer *et al*. [35]. Interestingly, the presence of CGI-58 not only increases the lipase activity of ATGL but also broadens its substrate specificity. Whereas ATGL without CGI-58 mostly hydrolyzes the acyl-residue at the *sn*-2 position

within triglycerides it cleaves acyl residues at the *sn*-1 or *sn*-2 position in the presence of CGI-58 [36▪]. The importance of CGI-58 in regulating ATGL function implied important tissue-specific roles of this protein in lipid and energy metabolism.

ADIPOSE LIPOLYSIS AND CGI-58

The role of CGI-58 in adipose lipolysis has been extensively studied within the last years and resulted in a concept called the ‘sequestration and release’ model. In nonstimulated (basal) conditions, CGI-58 binds to Perilipin-1 (Plin1) on the surface of lipid droplets, whereas ATGL is found on lipid droplets and in the cytosol. Hormonal stimulation of lipolysis by ß-adrenergic agonists leads to the phosphorylation of Plin1 by protein kinase A (PKA) and the release of CGI-58 from Plin1 allowing it to interact with ATGL and to stimulate triglyceride hydrolysis. Simultaneously, PKA phosphorylates HSL, which is subsequently recruited from the cytosol to the lipid droplet by Plin1, thereby further enhancing lipolysis [27,28▪▪,35,37,38]. The limiting role of CGI-58 for adipocyte lipolysis has been demonstrated in cell culture experiments wherein a knockdown of CGI-58 led to impaired lipid droplet degradation without affecting adipocyte differentiation [7,39]. Consistent with these *in vitro* data, newborn CGI-58-deficient mice also exhibited defective lipolysis [8]. Reduced triglyceride catabolism is often associated with accumulation of fat mass and obesity. However, such a phenotype has never been observed in humans [1,40–44] or mice lacking CGI-58 in adipose tissue. In fact, when mice were treated with CGI-58 antisense oligonucleotides (ASO) to silence CGI-58 expression and inhibit lipolysis in adipose tissue and liver, they had smaller epididymal fat pads and were protected against diet-induced obesity [9]. This suggests that currently unknown compensatory mechanisms prevent fat accumulation in adipose tissue when CGI-58 is absent. For example, it is conceivable that CGI-58 deficiency not only interferes with lipolysis but also leads to a concomitant reduction in fat synthesis.

Mice overexpressing CGI-58 in adipocytes displayed no distinct phenotype [14]. Neither basal nor stimulated lipolysis was altered in adipocytes, and fat mass was identical in transgenic mice and control mice on chow or high-fat diet. This suggested that CGI-58 abundance is not rate limiting in adipose tissue of mice, but differed from previous *in vitro* results demonstrating that the addition of recombinant CGI-58 to wildtype adipose tissue efficiently enhanced lipolytic activity. [45]. Unlike CGI-58, transgenic overexpression of ATGL in adipose tissue in mice led to higher lipolytic activities in adipose tissue and protected mice from high-fat diet-induced obesity arguing for a rate-limiting role of the enzyme rather than for its coactivator [15].

CGI-58 IN CARDIAC AND SKELETAL MUSCLE

In contrast to adipose tissue, lipolysis in oxidative tissues such as cardiac muscle and skeletal muscle as well as the liver is less well studied. In these tissues, Plin1 is absent and replaced by Plin2 and Plin5. Both proteins have been demonstrated to interact with CGI-58 [46–48]. Plin2 is highly upregulated in Plin1-deficient adipose tissue [49] or in the liver during the development of fatty liver disease [50,51]. Mice with global Plin2 deficiency or hepatic Plin2 overexpression display decreased or increased triglyceride levels in the liver,

respectively. This indicates that, similarly as Plin1 in adipose tissue, Plin2 is a critical regulator of hepatic lipid droplet turnover and protects lipid droplet-associated triglyceride from degradation [52–56].

Plin5 is a critical regulator of triglyceride homeostasis in cardiac muscle. Plin5 directly interacts with both, CGI-58 and ATGL [47,57,58], thereby recruiting both proteins to the lipid droplet surface. Increased cellular concentrations of Plin5 as observed during anabolic conditions or transgenic overexpression inhibit lipolysis by the formation of a 'barrier' that hinders the access of lipases to lipid droplets [59,60]. The critical role of lipolysis in cardiac energy metabolism is evident from the development of severe cardiomyopathy and premature death in mice and humans with mutated ATGL alleles. Mice lacking CGI-58 specifically in cardiac muscle and skeletal muscle accumulate excessive amounts of fat in the heart and develop cardiomyopathy due to impaired triglyceride catabolism. However, the phenotype is milder than in ATGL deficiency leading to a longer life span in CGI-58-deficient mice than in ATGL-deficient mice. Similarly, as observed in ATGL knockout mice, CGI-58 deficiency in cardiac muscle results in decreased expression of peroxisome proliferator-activated receptor alpha (PPARα) target genes, mitochondrial dysfunction, and inefficient fatty acid (FA) oxidation (FAO) [16▪▪]. For ATGL, it has been shown that its activity in the heart not only provides FA as energy substrates but also generates a lipolytic product that, directly or indirectly, regulates PPARα-mediated expression of the oxidative machinery [13]. The results with muscle-specific CGI-58 knockout mice indicate that both, ATGL and CGI-58 are required for normal heart function [16▪▪]. Interestingly, the consequences of CGI-58 deficiency on cardiac metabolism and performance may be different in humans than in mice. In NLSDI, cases with severe or lethal cardiomyopathy as observed in patients with mutated ATGL alleles have not been reported [1].

In skeletal muscle, ATGL and CGI-58 are preferentially expressed in slow twitch, aerobic, type I muscle fibers. This is consistent with the relatively higher lipolytic rates observed in these fibers compared with fast twitch, anaerobic type II fibers [16▪▪,61,62▪▪]. Interestingly, muscle-specific CGI-58 deficiency provoked an increase in intramuscular triglyceride levels preferentially in type I fibers although triglyceride hydrolysis and FAO rates were essentially unchanged [16▪▪]. Furthermore, running capacity of mice lacking CGI-58 in muscle was comparable to that of control mice, suggesting that CGI-58 is not a major requirement for adenosine triphosphate production in skeletal muscle. It can be speculated that either ATGL/CGI-58-mediated lipolysis is not crucial for the provision of energy substrate in skeletal muscle or that the lipolytic defect is compensated by an adaptive increase in the uptake and direct mitochondrial oxidation of FA without preceding esterification. This assumption is supported by a recent study showing that ATGL-deficient skeletal muscle displays no changes in mitochondrial FAO [18▪]. Conversely, however, an *in vitro* study by Badin *et al*. [62▪▪] showed that overexpression of CGI-58 in myotubes increases triglyceride hydrolysis and FAO, whereas knockdown of CGI-58 has an opposite effect. Apparently, the physiological role of ATGL/CGI-58-mediated lipolysis differs in cardiac muscle and skeletal muscle, and these differences require further characterization.

CGI-58 IS REQUIRED FOR A FUNCTIONAL EPIDERMAL SKIN BARRIER

The most apparent clinical phenotype in humans and mice affected by CGI-58 mutations is nonbullous congenital ichthyosiform erythroderma, which leads to a severe skin barrier defect. In patients with NLSDI and newborn mice globally lacking CGI-58, triglyceride accumulate within the epidermis, indicating for defective epidermal triglyceride catabolism [8]. In addition, the condition is characterized by the complete absence of covalently bound ω-(O)-acylceramides [63], which are crucial intermediates for the development of a functional cornified lipid envelope and the formation of an intact skin barrier (reviewed by Radner and Fischer [64▪▪]). The absence of a skin defect in humans or mice lacking functional ATGL clearly argues for an ATGL-independent role of CGI-58 in epidermal lipid metabolism and barrier formation. Radner *et al*. [8] demonstrated a pronounced reduction in epidermal triglyceride hydrolytic activity in CGI-58-deficient epidermis compared with wildtype or the ATGL-deficient epidermis, suggesting that CGI-58 stimulates a currently unknown epidermal triglyceride lipase. However, extensive efforts to identify this lipase in our laboratory have failed so far. Considering the intrinsic LPAAT activity of CGI-58 (see below), the defect in ω-(O)-acylceramide production may also involve changes in an epidermal acyltransferase activity. Interestingly, earlier studies showed that the lipid accumulation in NLSDI fibroblasts is a consequence of impaired triglyceride recycling for glycerol-phospholipid synthesis suggesting a defect in lipid synthesis rather than reduced triglyceride hydrolysis [65,66]. However, mutations associated with NLSDI do not interfere with the *in vitro* LPAAT activity of CGI-58 [21]. Thus, the unique role of CGI-58 in skin lipid metabolism and the formation of the epidermal barrier remain mysterious and await elucidation.

CGI-58 IN LIVER LIPID AND ENERGY METABOLISM

The liver has a central role in whole body lipid and energy metabolism via its unique function in the redistribution of lipid and energy metabolites among peripheral tissues. It is the main organ for glycogen and ketone body metabolism as well as very low-density lipoprotein (VLDL) formation and secretion. The involvement of cytosolic and particularly endoplasmatic reticulum (ER)-residing lipases in hepatic VLDL synthesis, assembly, and release has been extensively discussed recently [67▪▪,68,69]. Several reports also focused on the role of ATGL/CGI-58-mediated lipolysis in hepatic metabolism and energy homeostasis [70–74]. In hepatoma cells, CGI-58 overexpression and silencing interfered with VLDL packaging and secretion, implicating a role for CGI-58 in VLDL biogenesis [73,74]. Consistent with this, ASO-mediated CGI-58 deficiency caused a reduction in circulating triglyceride levels and a reduction in hepatic VLDL release in mice [9]. However, ASO treatment is not specifically silencing CGI-58 in the liver but also inhibits CGI-58 expression in nonhepatic tissues such as adipose tissue. Accordingly, decreased plasma triglyceride and VLDL levels may result from decreased FA delivery from adipose tissue to the liver. Evidence against a role of ATGL or CGI-58 in hepatic VLDL production was provided by the studies of mice lacking CGI-58 or ATGL in the liver. In these animals, VLDL production and plasma triglyceride concentrations were comparable to wildtype. They did, however, show reduced hepatic triglyceride hydrolase activity and FAO rates resulting in hepatosteatosis. Notably, the degree of hepatosteatosis is much more

pronounced in hepatocyte-specific CGI-58-deficient than in ATGL-deficient mice [19▪▪,20]. This is in accordance with the more severe liver steatosis observed in patients with NLSDI than in patients with mutated ATGL alleles [1,41,42,44]. Further, phenotypical differences include a more pronounced fibrosis, development of steatohepatitis, and cholesteryl ester accumulation in the liver of CGI-58-deficient mice, which are not observed in ATGL-deficient mice [12,19▪▪,20,75]. Taken together, these differences provide additional evidence for an ATGL-independent role of CGI-58 also in the liver.

CGI-58 IN OTHER TISSUES

CGI-58 is expressed in many other cells and tissues including brain, pancreas, macrophages, testis, lung, kidney, and stomach [6,76]; however, its function in these tissues has not been studied. In NLSDI, mental retardation and deafness are described [1], which indicate a role for CGI-58 (and ATGL) in the brain. In ATGL-deficient mice, triglyceride hydrolase activity in the brain is reduced, resulting in increased brain triglyceride levels in cerebrovascular cells, the ependymal cell layer, and the choroid plexus. Interestingly, triglyceride hydrolysis in brain lysates from control mice can be stimulated by the addition of recombinant CGI-58, further supporting the idea that CGI-58 might be important in the brain [77]. ATGL deficiency has further been described to interfere with lipid catabolism and cell function in intestine [78▪], macrophages [79,80], and pancreatic β-cells [81▪]. Comparison studies between tissue-specific ATGL-deficient and CGI-58-deficient animals in these ‘nonclassical’ lipolytic tissues will be important to differentiate between ATGL-dependent and ATGL-independent functions of CGI-58.

CGI-58: AN LYSOPHOSPHATIDIC ACID ACYL TRANSFERASE INVOLVED IN LIPID SIGNALING?

The phenotypical differences in humans and mice lacking ATGL or CGI-58 argue for an ATGL-independent function of CGI-58 that affects aspects of lipid and energy metabolism at least in liver and epidermis. Recently, and consistent with that concept, two groups reported that CGI-58 is an enzyme exhibiting LPAAT activity, converting lysophosphatidic acid (LPA) into phosphatidic acid [21,22], which represents an important step in neutral lipid and glycerol-phospholipid biosynthesis. The results raised some skepticism because the measured acyltransferase activities of CGI-58 were rather low compared to those of classical LPAAT enzymes, CGI-58 lacks canonical acyltransferase domains in its protein structure, and mutation of a predicted catalytic histidine residue within a HX_4D consensus sequence did not abolish the LPAAT activity (unpublished own data, personal communication).

The fact that CGI-58 knockout mice accumulate rather than lack triglyceride was interpreted in a way that CGI-58 represents a specialized LPAAT responsible for the temporal and spatial generation of phosphatidic acid or degradation of LPA [9,10▪▪]. As both molecules are well known signaling molecules [5▪,78▪,79,80,81▪], it was speculated that they regulate triglyceride catabolism and insulin sensitivity rather than contribute to lipid synthesis. In accordance with this assumption, Lord *et al*. [10▪▪] showed that ASO-mediated CGI-58-knockdown leads to moderate changes in hepatic and adipose tissue LPA/phosphatidic acid ratios possibly affecting intracellular insulin and inflammatory signaling in liver and adipose

tissue [9]. Additionally, CGI-58-deficient mice suffer from severe hepatosteatosis combined with increased diglyceride and ceramide levels in hepatocytes [11▪▪]. Although these lipid species are well established mediators for insulin resistance [82–85], CGI-58 knockout mice remain insulin sensitive even on a high-fat diet [9,10▪▪,11▪▪]. To explain this apparent contradiction, Cantley *et al*. [11▪▪] proposed that the storage compartment for these lipids (lipid droplet versus membranes) is crucial for the activation profile of intracellular protein kinases and the development of insulin resistance. The concept of lipid droplets serving as a neutralization pool for putative signaling molecules has been described before [12,20, 86,87].

CONCLUSION

Recent studies highlight the crucial role of CGI-58 for the activation of ATGL-mediated lipolysis and its effects on energy metabolism in adipose and nonadipose tissue *in vivo*. In cardiac muscle, CGI-58 together with ATGL is critical for mitochondrial function and FAO. Additionally, CGI-58 exerts important ATGL-independent functions in the epidermis of the skin, the liver, and possibly other tissues. These ATGL-independent roles of CGI-58 including its activity as LPAAT require more detailed characterization both, *in vitro* and *in vivo*, to delineate their role in lipid and energy metabolism. Direct comparison of ATGL and CGI-58-deficient animal models will provide useful tools to solve these questions.

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KEY POINTS

- CGI-58 is a crucial regulator of triglyceride homeostasis and coactivates ATGL.
- CGI-58 deficiency leads to the development of ichthyosis and hepatic steatosis in humans and mice implicating a critical role for the protein in epidermal and hepatic energy metabolism.
- Recent findings suggest an ATGL-independent role for CGI-58 in energy metabolism in the skin and liver.
- Inherent LPAAT activity of CGI-58 might be involved in the generation of signaling molecules affecting organ energy homeostasis.

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Table 1

Comparison of selected comparative gene identification-58 and adipose triglyceride lipase transgene or knockout models

Mouse model	Targeted tissue	Phenotype	References
CGI-58 knockout	Total knockout	Postnatal death due to impaired skin barrier function, ichthyosis, and severe hepatosteatosis	[8]
ASO-mediated CGI-58 knockdown	Mainly liver and adipose tissue	Hepatosteatosis, reduced fat mass, protection against DIO, reduced VLDL secretion, and improved glucose and insulin tolerance	[9,10▪▪,11▪▪]
ATGL knockout	Total knockout	Premature death due to severe cardiomyopathy, mild hepatosteatosis, mild obesity, and improved glucose and insulin tolerance	[12,13]
Adipose-specific CGI-58 overexpression	Adipocytes and macrophages	No obvious phenotype	[14]
Adipose-specific ATGL overexpression	Adipocytes	Reduced body weight and fat mass, protection against DIO, increased adipocyte lipolysis, and improved insulin sensitivity	[15]
Cardiac and skeletal muscle-specific CGI-58 knockout	Cardiac muscle and skeletal muscle	Cardiomyopathy, cardiac steatosis, IMTG, normal exercise performance, improved glucose tolerance, and normal insulin sensitivity	[16▪▪]
Inducible cardiac ATGL knockout	Cardiac muscle	Cardiomyopathy, cardiac steatosis, and reduced FAO	[17]
Skeletal muscle-specific ATGL knockout	Skeletal muscle	IMTG, no effect on systemic energy homeostasis, and normal glucose and insulin sensitivity	[18▪]
Liver-specific CGI-58 knockout	Liver	Severe hepatosteatosis, progressive fibrosis, CE accumulation, normal VLDL secretion, reduced ketone bodies, and normal glucose and insulin sensitivity	[19▪▪]
Liver-specific ATGL knockout	Liver	Hepatosteatosis, normal VLDL secretion, normal ketone bodies, and normal glucose and insulin sensitivity	[20]

Phenotypes of CGI-58 or ATGL mutant mice, respectively. ATGL, adipose triglyceride lipase; CEs, cholesteryl esters; CGI-58, comparative gene identification-58; DIO, diet-induced obesity; FAO, fatty acid oxidation; IMTG, intramuscular triglycerides; VLDL, very low density lipoprotein.