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Critical Roles for α/β Hydrolase Domain 5 (ABHD5)/Comparative Gene Identification-58 (CGI-58) at the Lipid Droplet Interface and Beyond

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Abstract

Mutations in the gene encoding comparative gene identification 58 (CGI-58), also known as α β hydrolase domain-containing 5 (ABHD5), cause neutral lipid storage disorder with ichthyosis (NLSDI). This inborn error in metabolism is characterized by ectopic accumulation of triacylglycerols (TAG) within cytoplasmic lipid droplets in multiple cell types. Studies over the past decade have clearly demonstrated that CGI-58 is a potent regulator of TAG hydrolysis in the disease-relevant cell types. However, despite the reproducible genetic link between CGI-58 mutations and TAG storage, the molecular mechanisms by which CGI-58 regulates TAG hydrolysis are still incompletely understood. It is clear that CGI-58 can regulate TAG hydrolysis by activating the major TAG hydrolase adipose triglyceride lipase (ATGL), yet CGI-58 can also regulate lipid metabolism via mechanisms that do not involve ATGL. This review highlights recent progress made in defining the physiologic and biochemical function of CGI-58, and its broader role in energy homeostasis.

Keywords

ABHD5; CGI-58; ATGL; adipocyte; triacylglycerol; lipase

1. The Human Genetic Link Between CGI-58 and Abnormal TAG Storage

Over forty years ago, several patients presented to the clinic with a severe form of dry and scaly skin, which was diagnosed as a new syndrome called Chanarin-Dorfman syndrome; also known as neutral lipid storage disease with ichthyosis (NLSDI) [1–3]. These patients, and many thereafter, have been characterized with accumulation of TAG-rich cytosolic lipid

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Conflict of Interest

The authors have nothing to disclose.

droplets in keratinocytes, circulating leukocytes (known as Jordan's anomaly), hepatocytes, skeletal myocytes, and several cell types within the central nervous and auditory systems [1–3]. In an initial attempt to delineate the metabolic disturbances in NLSDI patients, several groups isolated skin fibroblasts from affected individuals and found clear defects in TAG hydrolysis and improper recycling of TAG lipolysis products into membrane phospholipids [4–6]. In 2001, a landmark study by Judith Fischer's group identified the first genetic mutations associated with NLSDI [7]. NLSDI is caused by mutations in the gene encoding comparative gene identification 58 (CGI-58), also known as α β hydrolase domain-containing 5 (ABHD5). Since this original discovery, several additional loss-of-function mutations in CGI-58 have been identified in independent NLSDI subjects [8–11]. This reproducible genetic link between CGI-58 mutations and NLSDI has provided a strong rationale to understand the mechanisms by which CGI-58 regulates TAG metabolism. Given this, many laboratories have attempted to identify molecular mechanisms by which CGI-58 regulates lipid metabolism in diverse cellular contexts. This review discusses the successes and challenges realized in this pursuit, and highlights the fundamentally important role that CGI-58 plays in cellular lipid homeostasis and systemic energy metabolism.

2. The Role of CGI-58 in Adipose Tissue Lipolysis

Given that TAG storage is most active in adipose tissue, and that the molecular underpinning of TAG lipolysis is best understood in adipocytes, the vast majority of mechanistic studies with CGI-58 have been conducted in adipocyte cell models. In mature adipocytes, CGI-58 resides primarily on cytosolic lipid droplets due to its direct interaction with the lipid droplet associated protein perilipin 1 (PLIN1) [12–15]. However, during catecholamine-stimulated lipolysis, cAMP-activated protein kinase A (PKA) phosphorylates both PLIN1 [16,17] and CGI-58 itself [18], facilitating the release of CGI-58 from the lipid droplet surface where it can subsequently interact with the major TAG hydrolase adipose triglyceride lipase (ATGL), also known as patatin-like phospholipase domain containing 2 (PNPLA2) [12–15] (Fig. 1). A seminal study by Lass and colleagues demonstrated that direct interaction between CGI-58 and ATGL potently activates ATGL-mediated TAG hydrolysis in adipocytes [19], providing the first clues into how CGI-58 impacts TAG metabolism. This study also showed that wild type recombinant CGI-58 can activate ATGL in an *in vitro* TAG hydrolysis assay, yet introduction of point mutations that are found in NLSDI patients lack the ability to activate ATGL [19]. Several independent groups have likewise found that CGI-58 co-activates ATGL during catecholamine-stimulated lipolysis in adipocytes [20–25]. Recently, the structural determinants of CGI-58-mediated ATGL co-activation in adipocytes have also been clarified [26,27]. Removal of *N*-terminal amino acids 10–31 of CGI-58 disrupts both CGI-58's ability to localize to lipid droplets and its ability to co-activate ATGL [26]. Within the *N*-terminus, three tryptophan residues (Trp21, Trp25, and Trp29) help form a tether for CGI-58 to stably interact with cytosolic lipid droplets [26]. Using a domain swapping approach from ABHD5 to a structurally similar variant of the α/β hydrolase domain-containing family ABHD4, Sanders and colleagues determined that two conserved amino acids (R299 and G328) were sufficient to confer ATGL co-activation onto ABHD4 [27]. In parallel, mutations of R299 and G328 residues in ABHD5 reduced adipocyte lipolysis without altering CGI-58's interaction with perilipin [27]. These studies provide important

clues into the structural determinants by which CGI-58 regulates lipase activity [26,27]. Another recent study also demonstrated that cytosolic fatty acid binding proteins (FABP) directly interact with CGI-58 within its helix-loop-helix cap region, and FABP-CGI-58 interactions facilitate ATGL-mediated lipolysis [28]. This FABP-CGI-58 interaction during active lipolysis may be important in shuttling fatty acid and acylglycerol lipolysis products away from the lipid droplet [28], which is clearly defective in CGI-58 deficient cells [4–6]. In fact, there is evidence that the fatty acids released from the lipid droplet under FABP-CGI-58 facilitation, are then translocated by FABP to the nucleus to act as peroxisome proliferator-activated receptor (PPAR) ligands [28]. Collectively, these studies provide a molecular mechanism by which CGI-58 directly binds to and co-activates ATGL to promote catecholamine-stimulated lipolysis in adipocytes (Fig. 1). However, it appears that CGI-58's ability to alter TAG hydrolysis is strictly dependent on ATGL specifically in adipocytes, and its interaction with ATGL does not account for CGI-58's ability to dictate lipid homeostasis in several other cell types including keratinocytes, hepatocytes, and several cancer cells as discussed in detail below.

3. CGI-58 Regulates Skin Lipid Homeostasis in an ATGL-Independent Manner

One of the defining features of NLSDI is the presence of ichthyosis, a dermatological condition where the skin appears dry and scaly [1–3]. Interestingly, genetic deficiency of CGI-58 in mice also results in dramatic alterations in lipid homeostasis and defective epidermal barrier function [29]. These two findings in human and mouse models of CGI-58 loss-of-function strongly suggest that CGI-58 plays a major role in skin lipid homeostasis. In contrast, neither loss of function human ATGL mutations [30,31] or genetic deletion of ATGL in mice [32] results in ichthyosis or other skin abnormalities. In fact, unlike CGI-58, ATGL is not abundantly expressed in the skin, creating a condition where CGI-58 most likely regulates skin lipid metabolism via a mechanism that does not rely on ATGL-coactivation. CGI-58 global knockout mice die postnatally due to a severe skin barrier defect, which is characterized by defective TAG hydrolysis and the absence of key barrier structure lipids called Ω-(O)-acylceramides [29]. These lipid abnormalities are rescued by the addition of recombinant CGI-58, but not by addition of ATGL [29], further suggesting an ATGL-independent mechanism. Recent studies in epidermal-specific CGI-58 knockout mice reveal that CGI-58 is essential for Ω-(O)-acylceramide synthesis and the formation of the cornified lipid envelope [33]. In agreement, transgenic overexpression of CGI-58 in differentiated, but not basal, keratinocytes can rescue global CGI-58$^{-/-}$ mice from lethal postnatal barrier dysfunction [33]. In human skin CGI-58 is highly enriched in the *stratum granulosum* within lamellar bodies, which is a skin microenvironment that is thought to originate from differentiated keratinocytes [34]. Several studies have shown that CGI-58 expression is elevated during keratinocyte differentiation, and knockdown of CGI-58 results in diminished expression of keratinocyte differentiation markers [29,35]. Collectively, data collected in both human and mouse models of CGI-58 deficiency support the concept that CGI-58 is necessary for the hydrolysis of TAGs and synthesis of Ω-(O)-acylceramides in the skin. Given its key roles in keratinocyte lipid metabolism, it is clear that CGI-58 is a gatekeeper of the cornified lipid envelope, which is necessary for skin barrier function.

Unfortunately, at this point the molecular mechanisms linking CGI-58 to TAG hydrolysis, Ω-(O)-acylceramide synthesis, and keratinocyte differentiation in the skin are not known. However, there is now unequivocal evidence that CGI-58 regulates skin lipid homeostasis via an ATGL-independent mechanism. The continued search for this mechanism could have broad implications in dermatological diseases such as NLSDI and other related forms of inherited ichthyosis.

4. The Role of CGI-58 in Liver Disease Progression

Much like its role in the skin, CGI-58 is a potent regulator of liver lipid metabolism via mechanisms that do not rely on ATGL co-activation. In addition to ichthyosis, another common finding in people with CGI-58 loss-of-function mutations is severe liver disease including hepatic steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis [36–40]. In contrast to CGI-58 mutations, human ATGL mutations are not associated with hepatic fat accumulation or liver disease, but instead are associated with skeletal and cardiac muscle lipid accumulation [30,31]. Mice with diminished CGI-58 function in hepatocytes, accomplished by either antisense oligonucleotide (ASO)-mediated knockdown or by hepatocyte-specific CGI-58 genetic deletion, have striking hepatic steatosis which progresses with age into NASH and fibrosis [41–43]. Although $ATGL^{-/-}$ mice also develop mild hepatic steatosis, they never progress into NASH or fibrosis [32,44]. However, it is important to note that global ATGL−/− mice die prematurely due to cardiomyopathy, which makes it difficult to know whether long-term ATGL deficiency would indeed advance towards frank fibrosis. A recent study directly tested whether CGI-58 regulates TAG metabolism via an ATGL-dependent mechanism by knocking down CGI-58 in the liver of wild type or $ATGL^{-/-}$ mice [45]. This work demonstrated that CGI-58 can regulate hepatic steatosis and inflammation in the complete genetic absence of ATGL, indicating that CGI-58 regulates hepatic TAG metabolism and inflammation via ATGL-independent mechanisms [46].

In addition to its role in regulating fatty liver and NASH, CGI-58 has also been linked to mechanisms driving viral hepatitis [46,47]. The hepatitis C virus (HCV) encodes a structural protein known as core, which directly interacts with cytosolic lipid droplets in hepatocytes via a unique lipid-binding domain [48,49]. In HCV infected individuals, core's avid interaction with cytosolic lipid droplets interferes with normal lipase activity and as a result, TAG hydrolysis is blunted [50]. A recent study demonstrated that HCV-core induced hepatic steatosis requires ATGL activity, yet unexpectedly is associated with increased interaction of ATGL and CGI-58 at the lipid droplet surface [46]. This results strongly suggests that CGI-58 and ATGL can interact at the hepatocyte lipid droplet surface, similar to what is know in adipocytes [19–25], yet unlike in adipocytes, this interaction is not coupled to ATGL activation and TAG hydrolysis [45,46]. Therefore, additional work is required to determine the functional consequence of ATGL-CGI-58 interaction in hepatocytes. In the context of HCV infection, it has recently been shown that CGI-58 is necessary for the assembly of the HCV viral particle by facilitating the hydrolysis of lipid droplet TAG stores for the re-packaging into the nascent lipo-viroparticle [47]. Previous studies in hepatocyte cell lines and ASO-treated mice have demonstrated that CGI-58 is necessary for the packaging of TAG into nascent very low density lipoproteins (VLDL) [41,51,52]. However,

hepatocyte-specific genetic deletion of CGI-58 was not associated with altered VLDL-TAG secretion [43]. Therefore, addition work is needed to determine whether CGI-58 is indeed rate-limiting for the delivery of cytosolic lipid cargo into the endoplasmic reticulum and Golgi for VLDL or HCV lipo-viroparticle assembly and secretion. In addition to its role in hepatocytes, it is important to note that CGI-58 is also expressed in non-parenchymal cells in the liver including stellate cells [53] and macrophages [54–57], and regulates TAG hydrolysis in these cells as well [53–57]. However, the cell autonomous roles of CGI-58 in stellate cells and macrophages within the liver microenvironment have not been well characterized. Additional studies are needed to determine whether CGI-58 function in these non-parenchymal cells plays a role in liver disease progression. Collectively, CGI-58 plays a major role in hepatic TAG hydrolysis and the progression of liver disease from simple steatosis to NASH and cirrhosis via mechanisms that do not appear to rely on ATGL co-activation.

5. The Collaborative Role of CGI-58 in Skeletal and Cardiac Muscle Lipid Metabolism and Signaling

Fatty acids are key energy substrates in both skeletal and cardiac myocytes, where both CGI-58 and ATGL act in concert to promote metabolic flux of fatty acids from the lipid droplet to the mitochondria in these cells. Much like its role in adipocytes, CGI-58 appears to primarily regulate muscle lipolysis and downstream oxidative metabolism via direct co-activation of ATGL (Fig. 2). In support of this concept, human mutations in either CGI-58 [2] or ATGL [30,31] result in the accumulation of TAG-rich cytosolic lipid droplets in skeletal muscle, with ATGL mutations causing a much more severe lipid accumulation phenotype. Furthermore, people with loss-of-function mutations in ATGL exhibit symptomatic muscle weakness and cardiomyopathy [30,31,58–60], whereas symptomatic myopathy is less common in people with primary CGI-58 mutations [1–3]. Given the striking cardiac and skeletal muscle lipid accumulation seen in humans with ATGL mutations, affected patients are diagnosed with a variant of NLSDI called neutral lipid storage disease with myopathy (NLSDM) [30,31,58–60]. In agreement with findings in humans, several independent groups have generated genetically modified mouse and cell models that support a clear link between CGI-58 and ATGL in myocyte lipolysis and fatty acid metabolism [30,31,58–60]. A seminal study by Haemmerle and colleagues first showed that global genetic deficiency of ATGL in mice is associated with massive skeletal and cardiac muscle TAG accumulation, which results in premature lethality due to cardiac dysfunction [32]. Young global ATGL$^{-/-}$ mice, lacking ATGL-mediated lipolysis in both cardiac and skeletal muscle, also have impaired exercise performance [61]. This issue is due in part to limited free fatty acid supply to the working muscle as well as lower basal glycogen stores in liver and skeletal muscle [61]. Highlighting the key role ATGL plays in the cardiac TAG metabolism, global ATGL$^{-/-}$ mice have profound cardiac TAG accumulation [32], and cardiomyocyte-specific reintroduction of ATGL in global ATGL$^{-/-}$ mice rescues these mice from premature lethality [62]. In addition to regulating fatty acid fuel availability in myocytes, ATGL-driven lipolysis also liberates lipid agonists for the nuclear hormone receptor peroxisome proliferator-activated receptor α (PPARα) [63,64]. Given that ATGL$^{-/-}$ mice lack ATGL-driven provision of endogenous PPARα agonists,

several groups have demonstrated that treatment with exogenous PPARα agonists can effectively rescue the lethal cardiomyopathy in global ATGL$^{-/-}$ mice [63,64].

Similar to ATGL$^{-/-}$ mice, ice lacking CGI-58 in skeletal or cardiac myocytes also exhibit TAG accumulation and diminished PPARα signaling [65,66]. Selective deletion of CGI-58 in cardiac and skeletal myocytes results in muscle TAG accumulation, decreased PPARα-target gene expression, and defective mitochondrial fatty acid oxidation [65,66]. Interestingly, myocyte-specific deletion of CGI-58 preferentially increases TAG storage in type I slow twitch muscle fibers, which are known to rely predominantly on oxidative degradation of fatty acids during endurance type of exercise. In fact, CGI-58 likely plays a key role in oxidative metabolism in human muscle as well. Overexpression of CGI-58 in human myotubes promotes TAG hydrolysis and increases fatty acid oxidation, whereas CGI-58 knockdown reciprocally diminishes mitochondrial fatty acid oxidation [67]. Interestingly, in human myotubes CGI-58 function is closely linked to the expression of peroxisome proliferator-activated receptor δ target genes (PPARδ) [67]. Furthermore, the expression levels of both CGI-58 and ATGL correlate with markers of fatty acid oxidation in human skeletal muscle [68]. During a exercise, CGI-58 and ATGL interactions are more apparent at the lipid droplet surface in both human and rodent skeletal muscle [69,70]. In the context of skeletal muscle, the ability of CGI-58 and ATGL to interact at the lipid droplet surface is likely facilitated via direct interactions of either protein with the muscle-enriched lipid droplet coat protein perilipin 5 (PLIN5) [71–73]. Collectively, a large body of evidence in humans and rodents supports a role for CGI-58 as a key regulator of muscle mitochondrial oxidative metabolism via its ability to co-activate ATGL-driven TAG lipolysis [58–73] (Fig. 2).

6. The Role of CGI-58 in Macrophage Function and Atherosclerosis

It is well known that in the context of cardiovascular disease (CVD), that lipid metabolism and lipid signaling in macrophages plays a central role in orchestrating atherosclerotic plaque formation [74]. Given CGI-58's ability to regulate TAG hydrolysis to generate endogenous ligands for peroxisome proliferator-activated receptors (PPARs) in other contexts, there has been considerable interest in the role CGI-58 plays in macrophage function in the context of CVD and other cardiometabolic diseases. To study the role of macrophage CGI-58 in the context of atherosclerosis, Goeritzer and colleagues crossed myeloid-specific CGI-58 knockout mice to the hyperlipidemic apolipoprotein E (apoE) null background [57]. Deletion of CGI-58 in macrophages did not significantly affect atherosclerosis progression, but this work did show that macrophages lacking CGI-58 are skewed towards the classical M1 activation state when maintained in culture [57]. An independent study also demonstrated that macrophage-specific deletion of CGI-58 causes macrophages to acquire an M1-like phenotype, which is associated with activation of the NLRP3 inflammasome [54]. In stark contrast to the role that CGI-58 plays in M1 skewing and inflammasome activation, macrophage-selective deficiency of ATGL has a much more dramatic effect [75–78]. ATGL deficient macrophages are polarized towards the alternative M2-like phenotype without showing signs of inflammasome activation [75–78]. Macrophage deletion of ATGL also results in significantly reduced atherosclerosis in low density lipoprotein receptor deficient mice [76]. Given the role that macrophages play in sensing

bacterial pathogens, several groups have also evaluated the role of CGI-58 and ATGL in the *in vivo* response to bacterial endotoxin (lipopolysaccharide; LPS) [79,80]. Interestingly, both global ATGL$^{-/-}$ mice and CGI-58 ASO-treated models have increased levels of circulating pro-inflammatory cytokines when challenged with LPS, yet the tissue source of these cytokines seems quite different [79,80]. CGI-58 ASO-treated mice have reduced LPS-induced cytokine gene expression in the liver [79], whereas ATGL deficient mice have elevated LPS-induced cytokine gene expression in the liver [80]. In CGI-58 ASO-treated mice, it seems that the major source of elevated circulating pro-inflammatory cytokines is white adipose tissue [79]. Collectively, multiple studies clearly indicate cell autonomous roles for both CGI-58 and ATGL in macrophage function *in vivo*. However, based on the phenotypes of macrophage-specific knockout mouse models, it is most likely that CGI-58 and ATGL impact macrophage function independent from one another.

7. The Role of CGI-58 in the Intestinal Lipid Absorption

Both CGI-58 and ATGL are abundantly expressed in the small and large intestine in rodents and non-human primates, where they help determine enterocyte TAG hydrolysis and fatty acid flux [51,81,82]. It is well known that intestinal enterocytes can transiently store dietary fatty acids after esterification into TAG in cytosolic lipid droplets [83,84]. In fact, a significant portion of absorbed fatty acids are first esterified into cytosolic lipid droplets as TAG, and then subsequently liberated by lipase action to be delivered into the endoplasmic reticulum where they are re-esterified and packaged onto nascent chylomicrons [85]. However, our understanding of the molecular mechanisms regulating intestinal TAG lipolysis and fatty acid re-esterification for packaging into nascent chylomicrons is still in its infancy. Recent studies implicate both CGI-58 and ATGL in regulation of the cytosolic TAG hydrolysis and chylomicron assembly in intestinal enterocytes [81,82]. To study the role of CGI-58 in intestinal lipid absorption, Xie and colleagues selectively deleted CGI-58 in intestinal enterocytes using Cre-LoxP technology [81]. Enterocyte-specific deletion of CGI-58 results in a 4-fold increase in intestinal TAG levels resulting from diminished TAG hydrolysis activity [81]. Moreover, enterocyte-specific CGI-58 knockout mice show significantly reduced postprandial plasma TAG levels, but total intestinal fat absorption is only reduced by <0.5% [81]. These results suggest that CGI-58 is a key determinant of the hydrolysis of cytosolic TAG in enterocytes, yet does not dramatically alter the efficient packaging of TAG into nascent chylomicrons. Using a tissue-specific genetic approach, Obrowsky and colleagues found some similar and some divergent results when deleting ATGL from enterocytes [82]. Enterocyte-specific deletion of ATGL reduced total TAG hydrolase activity and increased intestinal TAG levels [82]. Although this was not associated with alterations in postprandial TAG levels, paradoxically, intestinal cholesterol absorption decreased [82]. These studies clearly demonstrate a role for CGI-58 and ATGL in TAG and cholesterol metabolism in the intestine. However, additional work is needed to determine if CGI-58 and ATGL work through independent pathways in intestinal enterocytes.

8. The Unexpected Role of CGI-58 in Insulin Sensitivity

Given the critical roles that CGI-58 and ATGL play in intracellular fatty acid metabolism and signaling lipid generation, these two proteins are uniquely positioned to impact cellular

insulin action. It has been repeatedly reported that accumulation of lipid intermediates in the TAG biosynthetic pathway, including long chain acyl-CoAs and diacylglycerol (DAG) species, are associated with insulin resistance in rodents and humans [86]. Originally proposed by Dr. Roger Unger, the “lipotoxicity” theory of insulin resistance posits that abnormal accumulation of lipid intermediates can antagonize normal insulin action in the liver and skeletal muscle [87]. Based on the lipotoxicity theory, one would predict that CGI-58 or ATGL loss of function would result in lipotoxicity-induced insulin resistance, but this is not the case in rodents or humans. First, neither CGI-58 nor ATGL mutations are associated with insulin resistance or type 2 diabetes in humans [1–3,30,31]. Furthermore, mice lacking either ATGL [32,88,89] or CGI-58 [41,42,79,66] in the liver or skeletal muscle have improvements in systemic insulin sensitivity. Although both ATGL and CGI-58 deficient mice exhibit similar improvements in insulin sensitivity, the mechanisms driving this phenotype are quite different in the two models. In the case of CGI-58, the primary organ driving improvements in insulin sensitivity is the liver [42,79]. ASO-mediated knockdown of CGI-58 promotes a large accumulation of DAG species in the liver [41,42], and such a large accumulation of DAGs would be predicted to drive hepatic insulin resistance [86]. Despite this accumulation of DAG lipids, CGI-58 ASO-treated mice are protected from DAG-induced insulin resistance due to sequestration of DAGs in the lipid droplet and endoplasmic reticulum [42]. This lipid droplet sequestration of DAGs results in prevention of high fat diet-induced accumulation of DAGs at the plasma membrane where they normally act to negatively regulate insulin receptor-driven signaling events [86]. Collectively, the improvements in glucose tolerance seen in CGI-58 ASO treated mice stem almost exclusively from improvements in hepatic insulin action via a mechanism involving DAG sequestration [41,42,79]. In contrast, the improvements in glucose tolerance in global ATGL knockout mice have been primarily linked to improvements in skeletal muscle insulin signaling and stimulation of insulin-stimulated glucose uptake [88,89]. Therefore, the striking improvements in glucose tolerance seen with either ATGL or CGI-58 deficiency in mice derive from skeletal muscle-specific or liver-specific improvements in insulin action, respectively [41,42,79,88,89].

9. CGI-58’s Role in Colorectal Malignancy

It is well known that many types of cancers are characterized by dysregulated cellular metabolism [90]. The vast majority of cancer metabolism studies have focused on specific alterations in glycolytic pathways, but emerging evidence suggests that reorganization of CGI-58-related lipid metabolic networks also plays a role in cancer pathogenesis. Several recent reports have linked epigenetic or genetic regulation of CGI-58 function to malignant transformation in the context of skin, cervical, and colorectal cancer [56,91–94]. A study by Ou and colleagues showed that silencing of CGI-58 in normal fibroblasts is sufficient to induce malignant transformation [93]. Furthermore, enterocyte-specific deletion of CGI-58 promotes *in vivo* malignant transformation of adenomatous polyps in the colorectal cancer-prone $Apc^{Min/+}$ mouse model [93]. In this model CGI-58 deletion in enterocytes was associated with increased aerobic glycolysis and induction of epithelial-mesenchymal transition (EMT) [93]. Another report from the same group showed that transgenic overexpression of CGI-58 in macrophages promotes colorectal cancer via a mechanism that

involved suppression of spermidine synthase (SRM)-driven spermidine production in the colonic microenvironment [56]. Importantly, the ability of CGI-58 to regulate colorectal tumorigenesis does not appear to depend on co-activation of ATGL, but instead involves regulation of autophagic flux in cancer cell lines [94]. These studies support a role for CGI-58 as a tumor suppressor in the context of colorectal cancer in $Apc^{Min/+}$ mice, but whether this holds true in human malignancies is still not known. Currently, there are no reported cases of cancer (colorectal or other types) in patients with primary mutations in CGI-58 (i.e. NLSDI mutants), so additional work is needed to clarify the role of CGI-58 in malignant transformation and cancer cell metabolism in humans.

10. Conserved Roles of CGI-58 Homologues in Cellular Lipid Metabolism and Signaling

The storage of energy in the form of TAG is not unique to higher vertebrates [95]. In fact, almost all known organisms have evolved intricate systems to regulate both TAG synthesis and lipolysis to provide fatty acid fuel as well as critical signaling lipids. Much like its role in mammals, CGI-58 homologues also regulate TAG metabolism and signal transduction in several other organisms including *Arabidopsis thaliana*, *Caenorhabditis elegans*, and *Saccharomyces cerevisiae*. [96–107]. In the model plant organism *Arabidopsis thaliana*, loss of the CGI-58 homologue results in abnormal accumulation of TAG-rich lipid droplets in leaves, which do not typically store TAG [96,97]. Interestingly, plant CGI-58 does not appear to interact with an ATGL-like lipase, but instead directly interacts with an ATP-binding cassette protein known as PXA1 [98]. In plants PXA1 is critical for the uptake of fatty acids into peroxisomes for subsequent β-oxidation [98]. In addition to facilitating PXA1-driven peroxisomal β-oxidation, plant CGI-58 also facilitates PXA1's ability to generate the critical plant hormones jasmonic acid and indole acetic acid [98], both of which are critical regulators of plant growth and homeostasis [99]. Another recent report demonstrated that plant CGI-58 can also interact with spermidine synthase 1 (SPDS1), and this direct interaction facilitates the conversion of the polyamine putrescine into spermidine [100]. This report is in agreement with similar findings in human colorectal cancer cells [56]. Also, CGI-58-facilitated TAG hydrolysis in plants has recently been shown to be necessary for the physiological process of light-induced stomatal opening [101]. Therefore, in a manner similar to vertebrate CGI-58 isoforms, plant CGI-58 regulates TAG hydrolysis to provide critical fuel for ATP synthesis, but also participates in the generation of hormone-like second messengers that further shape cellular energy metabolism and physiological processes such as stomatal opening (Fig. 3). In the free-living nematode *Caenorhabditis elegans* CGI-58 likewise regulates TAG hydrolysis during periods of nutrient deprivation [102]. During times of prolonged nutrient deprivation *Caenorhabditis elgans* can enter the "dauer" stage, which represents a static developmental period that is thought to occur to facilitate survival during time of stress. During the dauer stage, worm CGI-58 interacts with the lipase ATGL-1, but facilitates lipid droplet shrinkage and TAG hydrolysis in a largely ATGL-1-independent fashion [102]. Interestingly, worm CGI-58 promotes TAG hydrolysis and preferentially liberates 20 carbon-containing polyunsaturated fatty acids [102]. Finally, homologues of CGI-58 in the model yeast organism *Saccharomyces cerevisiae* also regulates cellular TAG and phospholipid homeostasis [103]. This study found that human CGI-58 was

closely related to a yeast encoded lysophosphatidic acid acyltransferase (LPAAT) enzyme known as Ict1p [103]. Following up on this observation Ghosh and colleagues showed that introduction of human CGI-58 into *Saccharomyces cerevisiae* resulted in reduced TAG levels, and increased LPAAT activity [103]. The implications of this paper will be discussed below in detail, as this reported LPAAT activity has since been called into question. Collectively, CGI-58 appears to have a conserved role in TAG hydrolysis as well as in the generation of key hormone-like signaling molecules that impact energy homeostasis.

11. Conclusions and Perspectives: The Continued Search for ATGL-Independent Functions of CGI-58

Even though it is apparent that CGI-58 plays a fundamentally important role in TAG lipolysis and the generation of key signaling molecules in every organism studied, we still do not fully understand how this enigmatic protein achieves this regulatory role. CGI-58 is a member of the alpha beta hydrolase domain-containing (ABHD) family of enzymes, many of which possess a classic lipase catalytic triad [104]. However CGI-58 lacks the predicted nucleophile serine within the lipase active site, and by all accounts has no intrinsic lipase activity towards TAG or many other glycerolipid and glycerophospholipid substrates [104]. There is now unequivocal evidence in adipocytes [19–25], myocytes [65–69], and hepatic stellate cells [53] that CGI-58 can stimulate TAG hydrolysis and alter PPAR signaling by co-activating ATGL (Fig. 1 & 2). However, CGI-58 can regulate TAG hydrolysis and cellular signaling in many other cell types including hepatocytes [45], keratinocytes [33], and several cancer cell lines [94] via an ATGL-independent mechanism. Given these ATGL-dependent and ATGL-independent roles for CGI-58, human mutations of either CGI-58 or ATGL are associated with some shared yet several divergent phenotypes [11]. In people with primary mutations in either CGI-58 or ATGL, the main shared phenotype is ectopic TAG storage in circulating leukocytes known as Jordans' anomaly [11], In contrast to this shared phenotype, primary ATGL mutations are always associated with cardiomyopathy, yet much less frequently associated with ichthyosis, hepatomegaly, hepatic steatosis when compared to primary CGI-58 mutations [11]. Also, primary CGI-58 mutations are always associated with ichthysosis, but much less frequently associated with skeletal or cardiac myopathy [11]. Collectively, the findings in animal models and humans strongly suggest both ATGL-dependent and independent roles for CGI-58.

In the search for the elusive ATGL-independent function of CGI-58, many avenues have been explored with limited success. As mentioned above, mammalian CGI-58 has previously been reported to possess lysophosphatidic acid acyltransferase (LPAAT) activity [97,105], suggesting a potential role in the generation of the critical signaling lipid phosphatidic acid. However, subsequent investigation has revealed that the LPAAT activity originally associated with recombinant CGI-58 [97,105] was due to a bacterial contaminant LPAAT acquired during the affinity purification process [106]. This was demonstrated by the fact that mutations of the predicted acyltransferase active site of CGI-58 does not reduce LPAAT activity [106]. Moreover, affinity purification of recombinant CGI-58 from a bacterial strain that lacks the sole LPAAT found in the Escherichia coli genome (plsC) yielded no detectable LPAAT activity [106]. It is important to note that other proteins have

been mistakenly identified as LPAAT enzymes due to similar problems with affinity co-purification of bacterial LPAATs [107]. Another recent report also suggested that CGI-58 instead possesses intrinsic lysophosphatidylglycerol acyltransferase (LPGAT) activity to convert lysophosphatidylglycerols (LPG) to phosphatidylglycerol (PG) [108]. However, CGI-58 knockdown in mouse liver is associated with marked accumulation of PG lipids, which is inconsistent with a LPGAT activity for CGI-58 [41]. Moreover, an independent study recently found that both plant and mouse versions of CGI-58 do not have detectable LPGAT activity [109]. Therefore, additional work is needed to clarify whether CGI-58 indeed possesses LPGAT activity, and whether this is linked to ATGL-independent phenotypes driven by CGI-58 loss of function. In the continued search for an acyltransferase activity for CGI-58, it will be important to consider the challenges of purifying recombinant CGI-58 from bacterial expression systems [106].

Given the product of TAG hydrolysis is diacylglycerol (DAG), and CGI-58 knockdown alters hepatic DAG storage [42], it is tempting to speculate that CGI-58 may be a key regulator of cellular DAG metabolism and DAG-mediated signal transduction. CGI-58 knockdown in mice leads to increased hepatic DAG levels [41,42,45], and prevents the inflammatory cytokine-driven generation of several signaling lipids that can be derived from DAG [79]. Two recent reports also support the possibility that CGI-58 could play a direct role in the regulation of DAG metabolism or subcellular localization [42,110]. First, CGI-58 knockdown causes hepatic DAG accumulation in lipid droplets/endoplasmic reticulum, while preventing accumulation of DAG at the plasma membrane [42]. Second, CGI-58 co-activation broadens the selectivity of ATGL for the *sn*-2 position of TAG to include the *sn*-1 position, resulting in the generation of both *sn*-1,3 and *sn*-2,3 DAG [110]. It is important to note that ATGL deficiency decreases hepatic DAG levels, whereas CGI-58 knockdown increases hepatic DAG both in the presence or absence of ATGL [45]. Although the mechanism by which CGI-58 knockdown causes DAG accumulation within the lipid droplet/endoplasmic reticulum compartment is unknown, the reciprocal reduction in hepatic DAG by ATGL deficiency likely directly stems from defective TAG lipolysis to DAG in hepatocytes. In support of this concept, adipocyte-specific deletion of ATGL likewise reduces total adipose DAG levels [111]. Given that ATGL and CGI-58 reciprocally regulate hepatic DAG levels, and the fact that CGI-58 knockdown increases hepatic DAG in both the presence and absence of ATGL [45], it is tempting to speculate that CGI-58 plays an ATGL-independent role in DAG shuttling or metabolism. An early study by Subramanian and colleagues [12] showed that during active adipocyte lipolysis that CGI-58 moves away from the lipid droplet surface towards the cytoplasm. Based on this trafficking pattern [12], and alterations in cellular DAG levels with CGI-58 deficiency [41,42,45,110], it remains possible that CGI-58 may be important in shuttling the lipolytic product DAG away from the droplet and towards the generation of signaling lipids [5]. In fact, some of the earliest studies in NSLDI fibroblasts showed cleared defective shuttling of acylglycerols from TAG pools [5]. However, additional studies are required to better understand if CGI-58 has the ability to bind and shuttle specific stereoisomers of DAG away from the lipid droplet.

Another potential ATGL-independent role of CGI-58 in TAG hydrolysis could be its recently reported role in regulating cellular autophagy. In fact, autophagy of lipid droplets, also called “lipophagy”, has recently been described as a key means to regulate hepatic TAG levels

during times of excessive starvation [112]. CGI-58 has been shown to directly interact with the autophagy protein beclin 1 in colon cancer cells [94]. This work showed that CGI-58 competes for a caspase binding site on beclin 1, thereby blunting caspase-mediated cleavage of beclin 1, and also showed that CGI-58 and beclin 1 expression levels were correlated in human colorectal cancer tissue [94]. Another recent study showed that CGI-58 regulates the autophagy of mitochondria, a process known as “mitophagy” [108]. This study showed CGI-58 overexpression stimulated the activity of 5’-AMP-activated protein kinase (AMPK) and diminished the signaling of the mammalian target of rapamycin complex 1 (mTORC1), both of which are major regulatory nodes in autophagy activation [108]. Although additional work is needed, these studies provide support for the idea that CGI-58 may regulate cellular TAG storage via regulation of lipophagy and mitophagy. As the search for the elusive ATGL-independent function of CGI-58 continues it will be important to consider regulatory roles in cellular autophagy programs. Moreover, recent identification of endogenous and synthetic ligands of CGI-58 that facilitate the release of CGI-58 from perilipins on the lipid droplet surface without altering PKA activation [25] provides an extremely useful tool to further understand the ATGL-independent roles of CGI-58. Collectively, CGI-58 is a conserved regulator of intracellular TAG hydrolysis and the generation of signaling lipids. In some cellular contexts (adipocytes and myocytes), CGI-58 accomplishes this regulatory role via direct co-activation of ATGL-driven TAG hydrolysis. Whereas, in many other cell types CGI-58 potently regulates TAG hydrolysis and lipid signaling via an elusive second ATGL-independent mechanism. The identification of the ATGL-independent function(s) of CGI-58 will have broad implications both in the field of energy metabolism as well as signal transduction.

Acknowledgments

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Abbreviations

ABHD5	αβ hydrolase domain 5
ATGL	adipose triglyceride lipase
CGI-58	comparative gene identification-58
DAG	diacylglycerol
FABP	fatty acid binding protein
G0S2	G0/G1 switch gene 2
HCV	hepatitis C virus
LPA	lysophosphatidic acid (LPA)

LPAAT	lysophosphatidic acid acyltransferase
LPGAT	lysophosphatidylglycerol acyltransferase
MAG	monoacylglycerol
NLSDI	neutral lipid storage disease with ichthyosis
NLSDM	neutral lipid storage disease with myopathy
PA	phosphatidic acid
PLIN1	perilipin 1
PNPLA2	patatin-like phospholipase domain containing 2
PPARα	peroxisome proliferator-activated receptor alpha
TAG	triacylglycerol
VLDL	very low density lipoprotein

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Highlights

- Mutations in α/β-hydrolase domain (ABHD5) cause neutral lipid storage disorder.
- ABHD5/CGI-58 regulates adipose lipolysis via co-activation of ATGL.
- ABHD5/CGI-58 regulates skin barrier function in an ATGL-independent manner.
- ABHD5/CGI-58 is a key regulator of insulin action and inflammatory responses.
- The role of ABDH5/CGI-58 in neutral lipid metabolism is conserved across species.

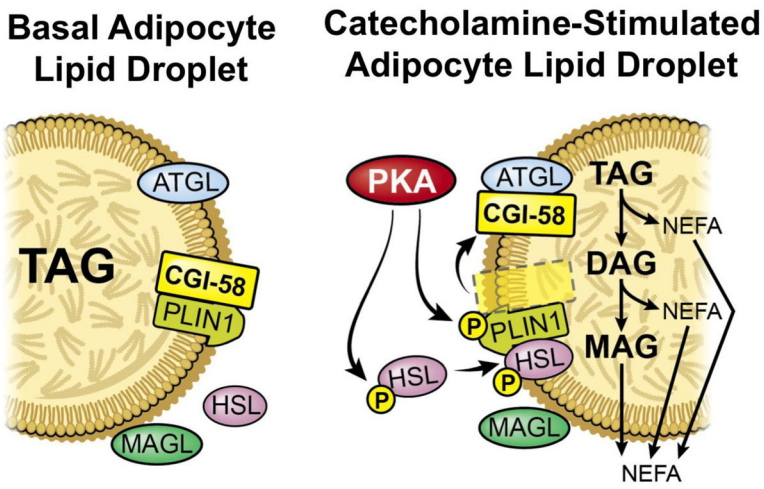

Fig. 1.

The role of CGI-58 in adipocyte lipolysis. Under basal conditions, CGI-58 interacts with perilipin 1 (PLIN1) at the lipid droplet surface, where it is tethered away from interactions with the triacylglycerol (TAG) lipase adipose triglyceride lipase (ATGL). Upon catecholamine stimulation, elevations in cellular cyclic AMP activate protein kinase A (PKA), which then phosphorylates the diacylglycerol (DAG) lipase, hormone sensitive lipase (HSL), and also PLIN1 and CGI-58. PKA-mediated phosphorylation of HSL facilitates its translocation from the cytosol to the lipid droplet surface, while phosphorylation of PLIN and CGI-58 causes dissociation of these two proteins and subsequent interaction of CGI-58 and ATGL to drive TAG hydrolysis.

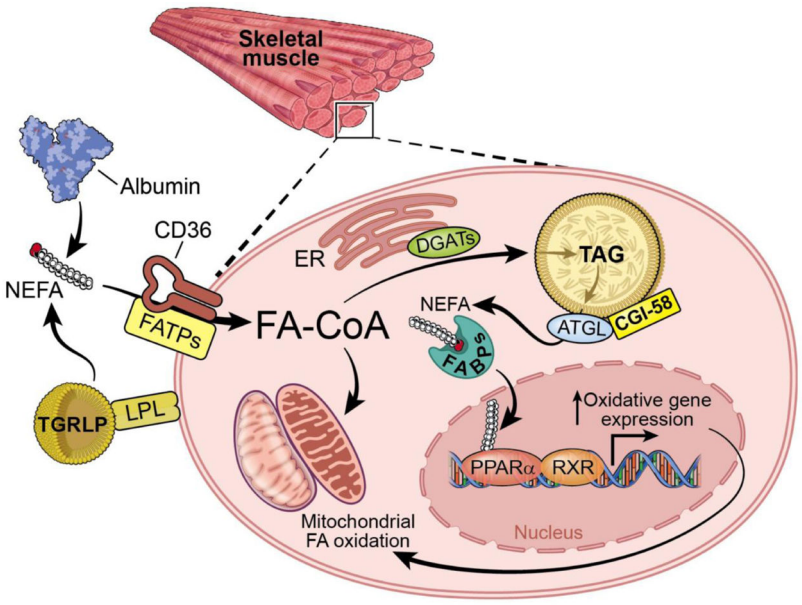

Fig. 2.

The role of CGI-58 in skeletal muscle metabolism and transcriptional regulation of mitochondrial function. Non-esterified fatty acids (NEFA) are delivered to skeletal muscle either complexed to albumin or via lipoprotein lipase-driven lipolysis of triglyceride-rich lipoproteins (TGRLP), and taken up into the cell helped by fatty acid transport proteins (FATPs) or the scavenger receptor cluster of differentiation 36 (CD36). Once inside the cell, a portion of newly delivered NEFA are activated into fatty acyl-coenzyme A (FA-CoA) molecules and either used for oxidative fuel in the mitochondria or are esterifed into triacylglycerols (TAG) via the action of diacylglycerol acyltransferase (DGAT) enzymes. At the lipid droplet surface CGI-58 co-activates adipose triglyceride lipase (ATGL) to promote hydrolysis of TAG, and the liberated NEFAs and other acylglycerol lipolysis products are delivered to either the mitochondria for oxidation or the nucleus to activate peroxisome proliferator-activated receptor α (PPARα) signaling to further drive oxidative gene expression.

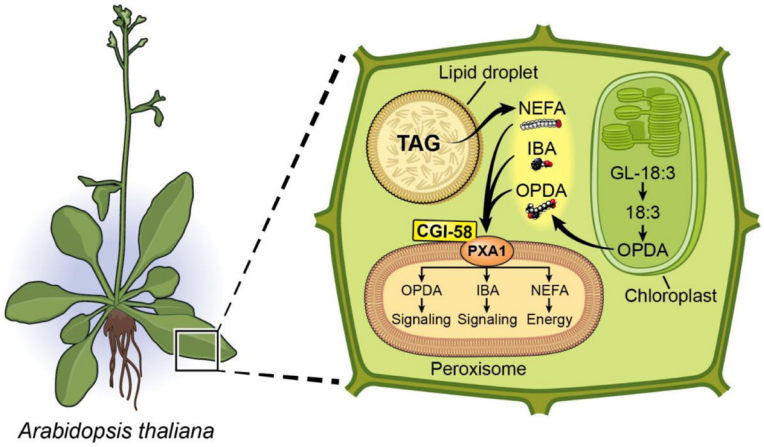

Fig. 3.

The role of CGI-58 in plant lipid metabolism and signaling. In the model plant organism *Arabidopsis thaliana* CGI-58 directly interacts with the peroxisomal ATP-binding cassette transporter PXA1. These proteins collaborate to promote transport of non-esterified fatty acids (NEFA) to provide energy and also stimulate the transport of key intermediate metabolites that are critical for plant hormone production. First, the interaction between CGI-58 and PXA1 facilitates the transport and β-oxidation of NEFA in peroxisomes. In parallel, CGI-58 facilitates PXA1-dependent transport of the plant hormone lipid intermediates 12-oxo phytodienoic acid (OPDA) and indole butyric acid (IBA) into the peroxisome where they are converted, respectively, to jasmonic acid or indole acetic acid, which are key regulatory hormones in plants promoting pathogen resistance and growth.