CGI-58: Versatile Regulator of Intracellular Lipid Droplet Homeostasis

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Liqing Yu, Yi Li, Alison Grisé, and Huan Wang

Abstract

Comparative gene identification-58 (CGI-58), also known as α/β-hydrolase domain-containing 5 (ABHD5), is a member of a large family of proteins containing an α/β-hydrolase-fold. CGI-58 is well-known as the co-activator of adipose triglyceride lipase (ATGL), which is a key enzyme initiating cytosolic lipid droplet lipolysis. Mutations in either the human CGI-58 or ATGL gene cause an autosomal recessive neutral lipid storage disease, characterized by the excessive accumulation of triglyceride (TAG)-rich lipid droplets in the cytoplasm of almost all cell types. CGI-58, however, has ATGL-independent functions. Distinct phenotypes associated with CGI-58 deficiency commonly include ichthyosis (scaly dry skin), nonalcoholic steatohepatitis, and hepatic fibrosis. Through regulated interactions with multiple protein families, CGI-58 controls many metabolic and signaling pathways, such as lipid and glucose metabolism, energy balance, insulin signaling, inflammatory responses, and thermogenesis. Recent studies have shown that CGI-58 regulates the pathogenesis of common metabolic diseases in a tissue-specific manner. Future studies are needed to molecularly define ATGL-independent functions of CGI-58, including the newly identified serine protease activity of CGI-58. Elucidation of these versatile functions of CGI-58 may uncover fundamental cellular processes governing lipid and energy homeostasis, which may help develop novel approaches that counter against obesity and its associated metabolic sequelae.

13.1 Introduction

The human *comparative gene identification-58 (CGI-58)* gene was identified through comparative gene identification studies using the *Caenorhabditis elegans* proteome and human expressed sequence tag (EST) nucleotide database [109]. Human *CGI-58* gene is located at the chromosome 3p21.33 locus, spanning about 32kb and producing several splice variants. The full-length human *CGI-58* cDNA is transcribed from seven exons and encodes a 349 amino acid

L. Yu (✉) · Y. Li · H. Wang
Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
e-mail: Lyu@som.umaryland.edu

A. Grisé
College of Computer, Math, and Natural Sciences, College of Behavioral and Social Sciences, University of Maryland, College Park, MD, USA
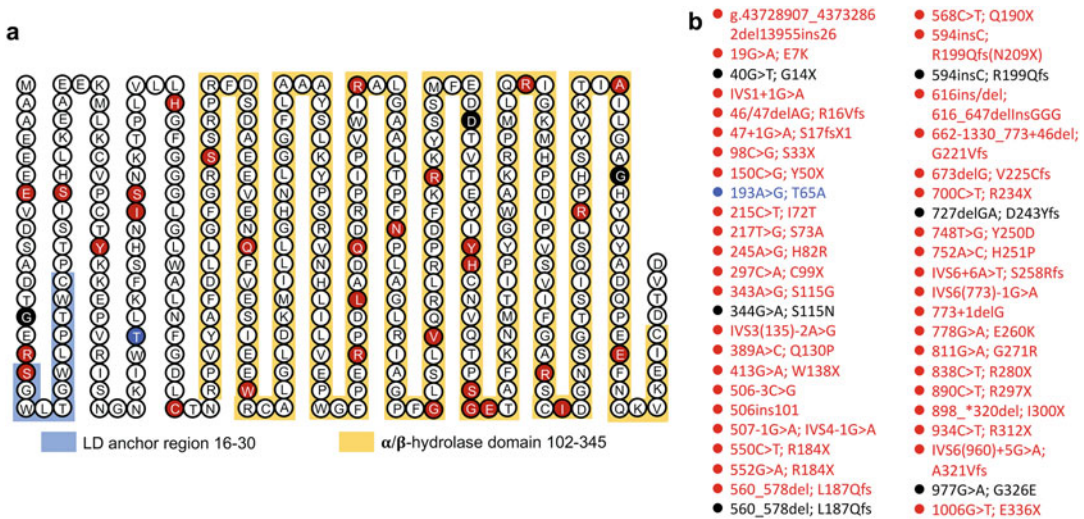
Fig. 13.1 (**a**) The amino acid sequence of human CGI-58 protein. The amino acids in red circles highlight those mutated in patients with CDS. Some altered splice donor or acceptor sites are not highlighted. According to the two studies using the mouse CGI-58 protein [16, 74], the amino acids 16–30 in the human CGI-58 protein are likely required for LD anchoring. (**b**) CGI-58 mutations reported in humans before March 2020. Biallelic mutations in red color are associated with the full phenotypes of CDS, biallelic mutations in blue color are associated with the partial phenotypes (no ichthyosis) of CDS, and those in black color denote monoallelic mutations associated with nonalcoholic fatty liver disease

protein of ~39 kDa (Fig. 13.1a). CGI-58 is also known as α/β hydrolase domain-containing 5 (ABHD5). The ABHD subfamily belongs to a large protein family defined by an α/β hydrolase fold [146, 258]. The α/β hydrolase fold has a highly conserved catalytic triad containing a nucleophile (serine, cysteine, or aspartic acid), an acidic residue, and histidine that are close in 3D structure, though apart from each other in sequence [116, 258]. The ABHD subfamily has a total of 19 members in humans and 15 members in mice [128, 202], yet the functions of most remain unknown. CGI-58 differs from other members in this subfamily in that the critical serine in the catalytic triad is substituted by asparagine [116].

Mutations in the human CGI-58 gene were identified as the cause of Chanarin-Dorfman syndrome (CDS, OMIM 275630) (Fig. 13.1), an autosomal recessive neutral lipid storage disease (NLSD) with ichthyosis (thickened dry skin) [58, 116]. CDS is characterized by the accumulation of triglyceride (TAG)-rich cytoplasmic lipid

droplets (LDs) in most cell types, including leukocytes (Jordans' anomaly) [96], hepatocytes, myocytes, and cells in the epidermis, dermis, and intestinal mucosa [33, 46, 183, 205]. Patients with CDS often manifest hepatomegaly (hepatic steatosis and steatohepatitis), myopathy, microcephaly, cataracts, hearing loss, ataxia, mild mental retardation, and short stature [33, 46, 90, 183]. Since the initial description of the disease by Dorfman and Chanarin [33, 46], about 130 cases with more than 40 different mutations spanning the entire protein sequence have been reported worldwide [7, 49]. Types of mutations include deletion, insertion, missense, nonsense, and frameshift mutations (Fig. 13.1b) [1, 3, 5, 7, 9, 12, 22–24, 49, 52, 54, 89, 92, 116, 130, 150, 151, 169, 174, 181, 187, 192, 208, 219, 224, 243, 255]. While loss-of-function mutations cause CDS (Fig. 13.1), it is currently unknown whether gain-of-function exists for CGI-58 gene.

CGI-58 is ubiquitously expressed in mammals [18, 112, 211]. It is predicted to be cytosolic [116]. Interest in the scientific community

regarding the functions of CGI-58 started in the early 2000s when three laboratories simultaneously reported that CGI-58 localizes at cytosolic LDs [121, 211, 244]. This was the time when biomedical scientists started to appreciate the cytosolic LD as an organelle that dynamically regulates energy storage and mobilization, rather than as an inert liposome-like structure that passively stores excess energy. The conceptual innovation placed cytosolic LDs at the center of cellular energy metabolism whose dysregulation is a hallmark of metabolic diseases, such as obesity, insulin resistance, type II diabetes, fatty liver, and cardiovascular disease. It was believed that excessive deposition of cytosolic lipid droplets would cause lipotoxicity, a biochemical mechanism that was widely used to explain impairments of cellular metabolism, cell signaling transduction, and redox imbalance associated with overnutrition-driven metabolic diseases [221]. Mutations in the human *CGI-58* gene were known to cause LD deposition in almost all cell types examined, which provided the biomedical research community an excellent opportunity to test how LD accumulation promotes lipotoxicity. Over the past 15 years, we have learned a great deal about the pros and cons of cytosolic LDs by studying the biochemistry, cell biology, and tissue-specific pathophysiology of CGI-58. This chapter summarizes the current knowledge about the role of CGI-58 in LD lipolysis (*i.e.*, hydrolysis of TAGs stored in cytosolic LDs) and discusses how CGI-58-dependent metabolic and signaling pathways regulate the pathogenesis of common metabolic diseases.

13.2 CGI-58 Interacts with Lipolysis-Regulatory Proteins

13.2.1 The PAT (Perilipin, Adipophilin, TIP47) Protein Family

Biochemical and cell biology studies have demonstrated that CGI-58 binds to cytosolic LDs and interacts with perilipin 1 (PLIN1), adipose differentiation-related protein (ADRP, also known as adipophilin or PLIN2), TIP47 (PLIN3), and muscle LD protein (MldP or PLIN5) [18, 63, 121, 161, 211, 244, 245]. These are members of the PAT (perilipin, adipophilin, TIP47) family that also includes S3-12 (or PLIN4) [105, 126, 133, 236]. The PAT family proteins share a highly conserved N-terminal structure. They localize at the surface of intracellular LDs of different lipid compositions and sizes, regulating energy storage and mobilization in response to nutritional fluctuations and various stimuli [126]. Using the two frame shift mutants (Leu-404fs and Val-398fs) that cause partial lipodystrophy in humans, Savage and associates have shown that the C-terminal region of human PLIN1 is essential for binding to CGI-58, and this interaction stabilizes CGI-58 localization on the LDs [63].

13.2.2 The PNPLA (Patatin-Like Phospholipase Domain Containing) Protein Family

The process that mobilizes the energy (mainly as TAGs) stored in intracellular LDs for utilization is called intracellular lipolysis (Fig. 13.2) [253]. During LD lipolysis, the three fatty acyl chains in a TAG molecule are sequentially cleaved into diacylglycerol (DAG), monoacylglycerol (MAG), and glycerol, releasing a fatty acid molecule at each step. The first enzyme that was discovered to catalyze hydrolysis of cytosolic LD-embedded TAGs is hormone-sensitive lipase (HSL) [86, 111, 177, 223]. The substrate spectrum of HSL appears to be quite broad, including DAGs, TAGs, MAGs, cholesteryl esters, and retinyl esters [40, 113, 234]. Monoacylglycerol lipase (MAGL) was reported, shortly after HSL, as a lipase that specifically hydrolyzes MAGs [98, 223]. Both HSL and MGL belong to the α/β-hydrolase fold family. For years, HSL was thought to be responsible for hydrolyzing TAGs in adipocyte LDs. However, HSL-null mice showed the accumulation of DAGs rather than TAGs in multiple tissues [77, 157, 179, 227],
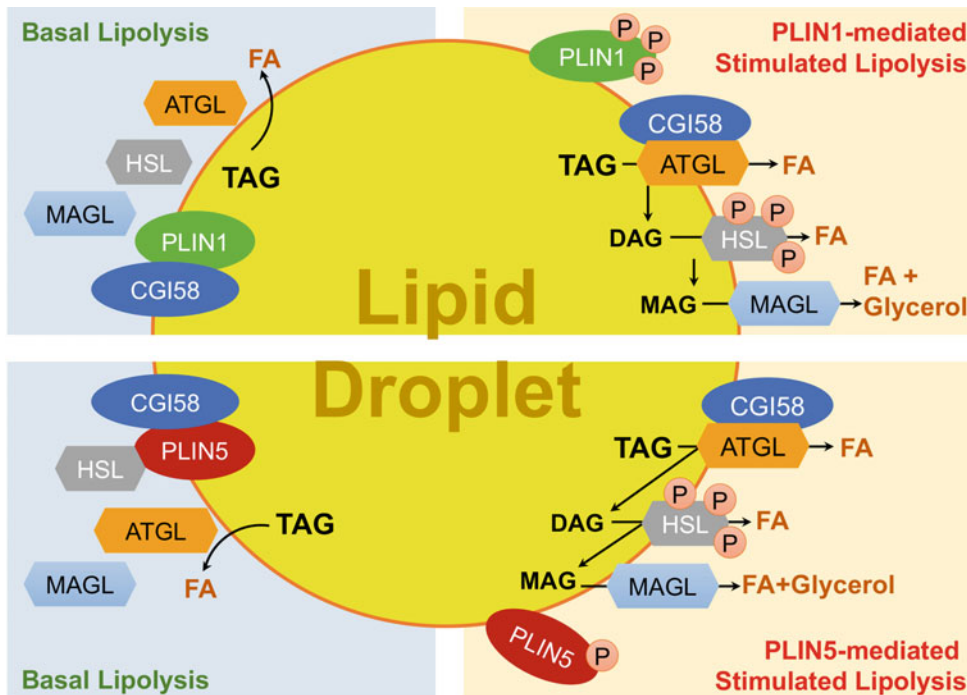
Fig. 13.2 Proposed model for CGI-58 regulation of cytosolic lipid droplet lipolysis. Lipolysis regulation differs between basal and stimulated conditions. Under the basal conditions, CGI-58 binds to PLIN1 in adipocytes or PLIN5 in oxidative nonadipocytes, preventing its interaction with ATGL. Thus, the lipolytic activity of ATGL is limited. After stimulation, perilipins are phosphorylated, resulting in the dissociation of CGI-58 from perilipins. CGI-58 then interacts with ATGL and substantially activates ATGL's TAG hydrolase activity to stimulate lipolysis, producing DAGs and fatty acids (FAs). The DAGs are then hydrolyzed to produce MAGs and FAs by HSL that was phosphorylated and recruited to the LDs during the lipolytic stimulation. Finally, the MAGs are hydrolyzed by MAGL to release the last fatty acyl chain from the glycerol backbone of a TAG molecule

indicating that other enzyme(s) are involved in the TAG hydrolysis. In 2004, three groups independently reported a new lipase possessing abundant TAG hydrolase activity, and the enzyme was named calcium-independent phospholipase $A_2\zeta$ (iPLA$_2\zeta$), desnutrin, or adipose triglyceride lipase (ATGL), respectively [95, 226, 264]. This newly discovered lipase turned out to be the rate-limiting enzyme of cytosolic LD lipolysis (Fig. 13.2), and, thus, the name ATGL became more popular than the other names. ATGL is also known as patatin-like phospholipase domain containing 2 (PNPLA2). The PNPLA protein family consists of a total of nine members, including PNPLA1 through PNPLA9, all of which seem to be implicated in lipid metabolism through their phospholipase or lipase activities, or other functions [104, 144]. Comparative studies of

ATGL and CGI-58 in the context of adipose lipolysis have resulted in a major breakthrough regarding the biochemical function of CGI-58. In 2016, Dr. Rudolf Zechner and associates reported that CGI-58 functions as a coactivator of ATGL to promote in vitro TAG hydrolysis [112]. Subsequent studies were consistent with this original finding [70, 71, 161, 228, 233, 250]. Furthermore, CGI-58 was shown to release from perilipin proteins following lipolytic stimulation, which allowed CGI-58 to interact with ATGL and activate TAG hydrolysis [70, 71, 211, 228]. In this scenario, the interaction of CGI-58 and with perilipins functions as a brake of lipolysis (Fig. 13.2), though its efficiency may be cell-type specific due to distinct perilipin compositions and the different abilities of

individual perilipins in sequestering CGI-58 in various cell types [161].

Although CGI-58 activates ATGL's TAG hydrolase activity [112], mutations in CGI-58 and ATGL cause distinct phenotypes in humans and mice [58, 65, 75, 78, 116, 135, 172, 237]. For example, human CGI-58 mutations cause NLSD with ichthyosis [33, 46, 90, 116, 183], whereas human ATGL mutations cause NSLD without skin defects but with mild myopathy [58]. Global CGI-58 knockout mice die ~16h after birth due to a skin barrier defect [172], yet global ATGL knockout mice are viable [78]. These phenotypic differences associated with mutations of the two genes indicate that CGI-58 must have ATGL-independent functions. Recently, CGI-58 was shown to interact with PNPLA1, another member of the PNPLA protein family, to stimulate PNPLA1-mediated ω-O-acylceramide production in skin [102, 154], providing a potential mechanism for skin barrier defect seen in patients with CDS. CGI-58 was also shown to functionally interact with the wild-type PNPLA3, the fatty liver-promoting PNPLA3(I148M) variant [180], and a lipase dead PNPLA3 mutant [32], suggesting that CGI-58 may coordinate with PNPLA3 and other lipases to regulate LD turnover independently of PNPLA3's lipase activity. Consistent with this scenario, two laboratories reported that PNPLA3, the fatty liver-causing PNPLA3(I148M) variant, in particular, competes with ATGL (PNPLA2) to bind with CGI-58, reducing TAG hydrolysis in the liver and brown adipocytes [233, 250]. These observations provided a mechanism for how the PNPLA3 (I148M) variant promotes fat deposition. However, such observations cannot explain why PNPLA3, including PNPLA3(I148M) but not a lipase dead mutant, retains its ability to reduce LD sizes when co-expressed with CGI-58 in the absence of ATGL [32]. It remains possible that PNPLA3 displays an in vivo lipase or transacylase activity toward specific substrates under some pathophysiological or nutritional conditions. In addition to PNPLA1-3, other members of PNPLA protein family may also interact with CGI-58 to fulfill unique functions under specific pathophysiological and nutritional conditions.

13.2.3 The Fatty Acid-Binding Protein (FABP) Family

Another group of proteins that interact with CGI-58 is the fatty acid binding protein (FABP) family members [85]. It was hypothesized that FABP interacts with CGI-58 to promote ATGL-mediated intracellular lipolysis by serving as an acceptor of free fatty acids released from TAG hydrolysis [85]. This was an important finding because it provided a mechanism for the handling of lipolytic products. Intriguingly, the lipolytic product long-chain acyl CoA was shown to bind CGI-58 and promote CGI-58 interactions with perilipins to suppress lipolysis [188]. This phenomenon seems to be an end-product feedback mechanism that fine-tunes hydrolysis of TAGs stored in intracellular LDs. The interactions of CGI-58 with LD coat proteins, lipases, and lipids suggest that CGI-58 likely play a key role in organizing major components of LD lipolysis into a functional "lipolysome" [85].

13.3 CGI-58 as a Serine Protease

The latest member of the CGI-58 interactome is histone deacetylase 4 (HDAC4). Backs and associates reported that CGI-58 functions in vitro and in vivo as a serine protease that cleaves HDAC4 in the heart in response to catecholamine stimulation, generating an N-terminal polypeptide of HDAC4 (HDAC4-NT) to protect cardiac functions [94]. This study was conceptually paradigm shifting, because it was the first to demonstrate that CGI-58 can function as a serine protease. CGI-58 was previously shown to function as a coactivator of a lipase that promotes lipolysis, and it was never thought to be a protease that promotes proteolysis. Perhaps, CGI-58 is a protein of dual function that promotes both lipolysis and proteolysis. This novel function of CGI-58 raises many new and exciting questions regarding the core function of

the protein. For example, does CGI-58 cleave other proteins interacting with it? If yes, is this proteolytic function required for CGI-58 to activate LD lipolysis? Does a lipase require proteolytic cleavage prior to digesting a lipid molecule? Answers to these questions are expected to provide fundamental insights into the molecular and biochemical bases of lipolysis and its potential crosstalk with proteolysis.

13.4   Molecular Basis for CGI-58 Activation of ATGL-Dependent Lipolysis

The cellular, structural, and biochemical bases for CGI-58 and ATGL interaction to promote TAG hydrolysis remain incompletely understood. The N-terminal amino acids 1–30 of mouse CGI-58 were shown to form a lipophilic tryptophan-rich stretch, which is essential for CGI-58 to localize at the LD and activate ATGL in cultured cells [74]. This tryptophan-rich stretch appears to anchor CGI-58 to the LD surface through its three tryptophan residues serving as the left and right anchor arms [16]. A comparative study of mouse ABHD5 (CGI-58) and ABHD4, an ABHD family member that is closely related to ABHD5 but does not activate ATGL, identified R299 and G328 as essential residues for activating ATGL's TAG hydrolase activity. However, these two amino acids of ABHD5 did not affect ATGL translocation to LDs or ABHD5 binding to PLIN1 [189]. These studies collectively suggest that the LD localization is a prerequisite for a functional CGI-58 to activate ATGL in vivo.

Studies with ATGL mutants associated with NLSD have showed that the mutations result in the expression of either enzymatically inactive proteins localizing to LDs or active TAG hydrolase lacking LD localization [196]. Whereas CGI-58 was identified as a coactivator of ATGL [112], G0/G1 switch gene 2 (G0S2) was subsequently discovered as an inhibitor of ATGL function [246, 247]. It was further demonstrated that G0S2 and CGI-58 do not appear to compete with

each other for binding to ATGL in cultured cells transfected with tag-proteins [131]. The 254 N-terminal amino acids of mouse ATGL were reported to be the minimal domain that can be activated by CGI-58 and inhibited by G0S2 [41]. Interestingly, deleting ∼220 amino acids from the C-terminus of human ATGL protein increases its interaction and activation by CGI-58 in vitro in the test tube, despite defective LD localization in vivo in cultured cells [196]. This finding indicates that the C-terminal region of ATGL is required for its targeting to LDs and plays a regulatory role in ATGL activation by CGI-58. Considering the newly identified protease function of CGI-58 [94], it would be interesting to test whether CGI-58 activates ATGL by a two-step process. In the first step, CGI-58 may cleave ATGL to release the suppressive role of ATGL's C-terminal region on its enzymatic activity, which would be consistent with the observation that ATGL protein levels are often increased in the absence of CGI-58 [75, 242, 263]. The second step may involve conformational changes of the two proteins, resulting in tight interactions and correct positioning of "lipolysome" components on the surface of LD for hydrolysis of TAG in vivo.

13.5   CGI-58 Regulation of Autophagy and Lipophagy

The role of CGI-58 as the coactivator of ATGL to promote intracellular lipolysis has been established and reproduced in a series of in vitro and in vivo studies. ATGL is a cytosolic neutral lipase that initiates cytosolic/neutral lipolysis by cleaving a fatty acyl chain from a TAG molecule stored in cytosolic LDs, thus playing a critical role in intracellular lipolysis [95, 226, 257, 264]. Recently, the lipid-specific macroautophagy (lipophagy) was shown to also digest cytosolic LDs by delivering LD-associated fat to lysosomes for degradation by lysosomal acidic lipase (lysosomal/acidic lipolysis) [203]. Autophagy refers to the "self-eating" of a

cell in response to starvation or nutrient deprivation for generating energy essential for its survival [155]. It is also a catabolic pathway for recycling of excessive or damaged organelles, such as mitochondria (mitophagy) [217]. In humans, insulin resistance suppresses CGI-58 mRNA expression in liver [99]. The nutritional and hormonal regulations of "neutral" lipolysis and lipophagy ("acidic" lipolysis) are strikingly similar. Both are induced by nutrient deprivation [45], and both are activated by glucagon or inhibited by insulin [45, 57]. It is currently unknown if CGI-58 promotes fat lipolysis by mediating lipophagy in addition to activating ATGL. It was demonstrated that ATGL, a lipase target of CGI-58, promotes autophagy and lipophagy in a sirtuin 1 (SIRT1)-dependent manner and that lipophagy is required for ATGL to promote LD catabolism and associated fatty acid oxidation in hepatocytes [190]. The crosstalk between ATGL-dependent lipolysis and autophagy was also seen in macrophages, though this crosstalk may be indirect or compensatory [66]. Some studies appear to suggest a role of CGI-58 in regulating autophagy and lipophagy. For example, in C2C12 muscle cells, CGI-58 overexpression increases, whereas CGI-58 knockdown decreases, autophagy and mitophagy through regulation of AMPK and mTORC1 signaling pathways [259]. CGI-58 was shown to bind Beclin1, a major regulator of autophagy [159, 163]. Many autophagy components can localize to LDs under some conditions [48, 51, 100, 160, 200, 203], though it is not known whether they interact with CGI-58 or other LD proteins to specifically regulate lipophagy. PLIN2, a major LD coat protein interacting with CGI-58 [244, 245], also binds the heat shock cognate protein of 70 kDa (Hsc70) for degradation via chaperone-mediated autophagy (CMA) [100]. The inhibition of CMA reduces both neutral and acidic lipolysis [100]. Hepatic CMA deficiency, like CGI-58 deletion, induces severe hepatic steatosis with liver damage and inflammation [220]. More studies are needed before the direct role of CGI-58 in the mediation of autophagy and lipophagy can be established.

13.6 Tissue-Specific Roles of CGI-58 in Energy and Lipid Metabolism

13.6.1 Adipose CGI-58 in Thermoregulation and Metabolic Health

CGI-58 is ubiquitously expressed in mammals, with the highest expression in adipose tissue. Adipose tissue is classically divided into white adipose tissue (WAT) and brown adipose tissue (BAT) that have distinct locations and opposite functions in energy balance. In general, WAT stores excess energy as TAGs in the large unilocular LD of white adipocytes, whereas BAT dissipates metabolic energy as heat for adaptive nonshivering thermogenesis in multilocular LD-containing brown adipocytes.

During prolonged fasting or increased energy demand, such as exercise and inflammation, the stored energy in WAT is mobilized via adipose LD lipolysis for utilization by cell types and pathways critical in sustaining life, meeting energetic demand, clearing infectious agents, or resolving inflammation. This process is generally defined as the stimulated adipose lipolysis, because it involves activation of a cell membrane receptor and its downstream signal transduction by neural and humoral factors in response to various stimuli [47, 108, 213, 253]. The classical signal-stimulating adipose lipolysis is the activation of β-adrenergic receptors by catecholamines released from the sympathetic nerves innervating adipose tissue. Binding of a catecholamine to the β receptor activates adenylate cyclase, which is an enzyme that uses ATP as the substrate to produce cAMP [55]. Elevation in cellular cAMP activates protein kinase A (PKA), which then phosphorylates several lipolytic components, such as PLIN1 and HSL, to stimulate lipolysis (Fig. 13.2) [213]. Thus, any stimulus that activates PKA or increases cellular cAMP levels is thus expected to stimulate adipose lipolysis. Phosphorylation of a perilipin, perhaps together with phosphorylation of CGI-58 on S239 [185], causes CGI-58 disassociation from the perilipin

for CGI-58 to interact with ATGL (Fig. 13.2) [70, 71, 211, 213, 244, 251]. It was shown that the in vitro TAG hydrolase activity of ATGL can be increased up to 20-fold with CGI-58 interaction [112]. The in vivo significance of CGI-58 as an essential mediator of the stimulated lipolysis was demonstrated in a study showing that adipose-specific inactivation of CGI-58 abolishes the isoproterenol-stimulated increase in plasma levels of free fatty acids in mice [201].

The nonshivering thermogenesis in BAT is mainly mediated by uncoupling protein 1 (UCP-1), which resides in the inner membrane of a mitochondrion, uncoupling chemical energy from ATP synthesis and dissipating the energy as heat [27]. Under some environmental and pathophysiological conditions, such as cold exposure and β-adrenergic receptor activation, a cell type with features of both white and brown adipocytes appears in the classically white fat depots. This type of adipocytes is named brite or beige adipocytes that often express UCP-1 and produce heat [165, 238]. The process that drives the appearance of brite/beige adipocytes in WAT is called WAT browning or beigeing [97]. The origin of beige adipocytes may include mature white adipocyte transdifferentiation and/or de novo adipogenesis, depending on the condition that induces WAT browning [39, 83, 114, 115, 182, 229, 230].

Cytosolic LD lipolysis was thought to be central in nonshivering thermogenesis [27]. Several animal and human studies suggested the essential role of brown fat lipolysis in thermogenesis, though the genetic or pharmacological manipulation of adipose lipolysis employed in the studies inhibited intracellular lipolysis in both BAT and WAT [4, 15, 44, 78, 107]. We created mice deficient in CGI-58 in UCP1-positive brown and beige adipocytes (BAT-KO mice) and mice lacking CGI-58 in all adipocytes (FAT-KO mice), which allowed us to directly test the role of brown adipocyte LD lipolysis in thermoregulation. To our surprise, BAT-KO mice were not cold sensitive even when food was unavailable [201]. The mice became cold sensitive only when the following two conditions were met

simultaneously: (1) deletion of CGI-58 in both WAT and BAT and (2) removal of food. Similar phenotypes were observed in mice lacking ATGL in BAT or the total adipose tissue [195]. When CGI-58 or ATGL was deleted in the total adipose tissue in mice, the in vivo lipolysis (fatty acid release from the tissue to the blood circulation) stimulated by isoproterenol, a β-adrenergic receptor agonist, was completely abolished in mice [195, 201]. The results demonstrated the indispensable role of CGI-58 or ATGL in mediating the stimulated lipolysis in the whole animal. These two animal studies also demonstrated a key role of WAT in regulating adaptive nonshivering thermogenesis, likely by providing the heat-producing cells with the metabolic fuels and/or by exposing the temperature sensors in the body to the thermogenically important adipokines or signaling molecules. It is currently unclear how food rescues the cold sensitivity of mice lacking CGI-58 or ATGL in the total adipose tissue [195, 201]. A simple explanation is that food serves as another source of metabolic fuels that may energize the heat-generating cells with glucose, fatty acids, and/or amino acids. However, we observed that only gastric gavage, but not intraperitoneal injections, of glucose can efficiently slow down hypothermia in mice lacking CGI-58 in both WAT and BAT (Wang H et al. unpublished data). This finding strongly supports a critical role of the gastrointestinal track in regulating the diet-induced thermogenesis. The gastrointestinal track is abundantly innervated and has special endocrine cells that secrete various incretins, which are important in local environment sensing and whole-body energy metabolism. Interestingly, secretin, a gut hormone that is derived from the S cells in the duodenum and jejunum of small intestine, was shown to mediate postprandial thermogenesis by activating its receptor in brown adipocytes to stimulate lipolysis and energy expenditure and to subsequently suppress satiation through the brain [119]. However, mice lacking CGI-58 or ATGL in BAT are defective in brown adipocyte lipolysis, yet they are capable of producing heat after a meal, suggesting that either other

gastrointestinal factors or non-lipolytic pathways also mediate the postprandial thermogenesis. Nonetheless, it would be interesting to test whether secretin mediates postprandial heat production in mice lacking CGI-58 or ATGL in BAT and, if not, what other gastrointestinal factors are involved.

CGI-58 deletion in UCP1-positive cells in mice increases sympathetic innervation in both BAT and WAT. The animals also exhibit enhanced WAT browning, especially after cold exposure or β3-adrenergic receptor activation [201]. This observation implies that some signals and/or BATokines (factors secreted by BAT) are generated as a result of BAT CGI-58 deficiency. These signals and batokines can somehow be sensed by the central nervous system in the brain, thereby increasing the sympathetic outflow to activate compensatory thermogenic mechanisms. It is currently unknown what these signals and batokines are and whether they work locally or remotely or must be secreted into the blood circulation, which represents an important area for future research in BAT biology. It is important to note that BAT lipolysis deficiency induced by ATGL deletion in UCP1-positive cells does not increase WAT browning as evidenced by unaltered expression levels of UCP-1 protein in the inguinal subcutaneous fat [195], suggesting that deficiency of CGI-58's ATGL-independent functions in BAT promotes browning in WAT.

Genetic deletion of BAT CGI-58 in mice improves several fat-induced metabolic disorders, such as glucose intolerance, insulin resistance, and hepatic steatosis [201]. This improvement is more profound when CGI-58 is deleted in both BAT and WAT (our unpublished data). ATGL deletion in whole body or adipose tissue also protects mice from fat-induced metabolic abnormalities [4, 87, 194, 239]. These observations indicate that inhibiting adipose lipolysis may improve whole-body glucose handling as a result of failed mobilization of fatty acids for utilization, which would be consistent with the glucose fatty acid cycle (or the Randle cycle) theory [173].

13.6.2   Epidermis CGI-58 and Skin Barrier Function

A major phenotypic distinction of human patients with CGI-58 mutations from those with ATGL mutations is ichthyosis (scaly dry skin) [58, 116]. In mice, whole body ablation of CGI-58, but not ATGL, causes skin barrier defects [78, 172]. Using whole body and cell type-specific transgenic and knockout mouse models, it was shown that CGI-58 promotes the biosynthesis of the skin barrier lipids, ω-*O*-acylceramides, locally in the keratinocytes of suprabasal epidermal layers, and such function is ATGL independent [73]. It was further shown that CGI-58 interacts directly with PNPLA1 and recruits PNPLA1 to LDs where it functions as the coactivator of PNPLA1 for the biosynthesis of ω-*O*-acylceramides [102, 154]. Like CGI-58, PNPLA1 mutations in humans also cause ichthyosis [69]. Using biochemical approaches, cell cultures, and tissue-specific PNPLA1 knockout mice, several groups have demonstrated that PNPLA1 has transacylase or acyltransferase activity, which utilizes TAGs as an acyl donor and catalyzes the esterification of ω-hydroxy ceramides with linoleic acid to synthesize ω-*O*-acylceramides [73, 84, 102, 153]. Collectively, these studies strongly suggest that the defective activation of PNPLA1 is the molecular mechanism underlying CGI-58 mutation-induced ichthyosis in humans.

13.6.3   Muscle CGI-58 in Cardiomyopathy and Insulin Sensitivity

Patients with CDS accumulate neutral lipids in their skeletal muscle [138]. Heart murmurs, muscle weakness, and mild myopathy were reported in some CDS patients [90, 138, 235]. Two laboratories have generated muscle-specific CGI-58 knockout mice using MCK-cre transgenic mice [242, 263]. MCK-cre transgenic mice express cre recombinase in both skeletal and cardiac muscles, thereby deleting a loxP-

floxed gene in both tissues [21]. Muscle CGI-58 knockout mice display intramyocellular deposition of neutral lipids in both cardiac and oxidative skeletal muscles [242, 263], implying that muscle fat deposition in human patients with CDS likely results from local CGI-58 deficiency in muscle. Neutral lipid deposition was not detected in the glycolytic skeletal muscle fibers in these animals [242]. The restriction of LD accumulation to the cardiac and oxidative (soleus) muscles highlights an essential role of CGI-58 in fatty acid oxidation in oxidative muscle types, which is consistent with other studies [10, 72].

CGI-58 deficiency in all muscles induces cardiac fibrosis, cardiac remodeling, and heart failure. The similar phenotypes were observed in muscle ATGL knockout mice [79]. In cardiac and oxidative skeletal muscles, CGI-58 interacts with PLIN3 and PLIN5, and this interaction regulates its association with ATGL [132, 167, 228]. These observations collectively suggest that CGI-58 may function through ATGL, promoting intracellular TAG hydrolysis in the muscle fibers. It was shown that cardiac ATGL-dependent TAG hydrolysis sustains mitochondrial functions by activating the PPAR-α pathway through the generation of endogenous ligands for PPAR-α [79]. CGI-58 may facilitate this pathway by activating ATGL in the cardiac muscle. Interestingly, CGI-58 was recently shown to function as a serine protease to protect heart failure by generating an N-terminal polypeptide from histone deacetylase 4 (HDAC4) through proteolysis [94]. The cardiac protective role of the HDAC4's N-terminal polypeptide generated by CGI-58 was not associated with reduction in cardiac TAG content. Although it is currently unclear whether similar mechanisms operate in other cell types, this study nonetheless uncovered a completely novel function of CGI-58 and emphasized a future direction for CGI-58 research.

Intramyocellular fat deposition in skeletal muscle is often associated with systemic insulin resistance due to accumulation of insulin signaling-suppressing lipids, such as diacylglycerols and ceramides that cause lipotoxicity [186, 222]. Despite intramyocellular accumulation of neutral lipids, mice lacking CGI-58 or ATGL in muscle are not glucose intolerant or insulin resistant [103, 204, 242]. This dissociation of cellular lipid deposition from insulin resistance suggests that how versus how much lipids are accumulated may be more important in driving tissue insulin resistance, which may be due to the differences in the molecular species of lipids deposited. Alternatively, cytosolic LD deposition, if not extremely excessive, may sequester insulin signaling-suppressing metabolites, protecting cells against lipotoxicity. Such scenario would be consistent with an observation that unsaturated fatty acids promote TAG accumulation, yet protect cells against lipotoxicity [120]. In addition, lipid deposition in different skeletal muscle fiber types may lead to different metabolic consequences [118, 123]. Mice overexpressing diacylglycerol acyltransferase 2 (DGAT2) in glycolytic (type II) muscle accumulate TAG in muscle and are insulin resistant [118]. However, mice overexpressing diacylglycerol acyltransferase 1 (DGAT1), another TG synthesis enzyme, in muscle accumulate TAG in the soleus, and these animals are not insulin resistant [122]. Endurance-trained athletes display increased fat content in their skeletal muscle, and they have enhanced insulin sensitivity ("athlete paradox") [67]. It seems that fat deposition in the glycolytic muscle is more problematic than in the oxidative muscle.

13.6.4   Liver CGI-58 in Nonalcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the United States and worldwide [254]. Patients with CDS (CGI-58 mutations) almost always display characteristics of advanced NAFLD, including severe hepatic steatosis, NASH, fibrosis, and cirrhosis [3, 24, 38, 76, 90, 139, 181, 205, 208, 215]. The CDS-causative mutations span the entire human CGI-58 protein sequence (Fig. 13.1). Interestingly, monoallelic mutations in the human *CGI-58* gene are also associated with NAFLD (Fig. 13.1b). The prevalence of CGI-58 monoallelic mutations that are associated

NAFLD was estimated to be 1 in 1,131 individuals in a normal population [255]. This study highlights an important role of CGI-58 in the pathogenesis of NAFLD in the general population. More importantly it was recently demonstrated that CGI-58 interacts with PNPLA3 [233, 250], a variant (I148M) of which is a major risk factor for fatty liver disease in all populations examined [149, 180, 207, 216]. CGI-58's association with PNPLA3 interferes with its ATGL interaction, thus inhibiting LD lipolysis [11, 233, 250]. CGI-58 is required for wildtype PNPLA3 and the PNPLA3(148M) variant to localize to hepatic LDs and for the overexpressed PNPLA3(148M) to promote hepatic steatosis [233]. It was shown that PNPLA3 accumulation on LDs, not its catalytic activity, is responsible for PNPLA3(148M)-induced hepatic steatosis [11]. While these studies provided an important mechanism for how CGI-58 coordinates with PNPLA3 and PNPLA2 (ATGL) to control cytosolic LD turnover, more research on the PNPLA3/CGI-58 interaction is needed to address why PNPLA3, including the PNPLA3(I148M) variant but not a lipase dead mutant, can substantially reduce LD size when co-expressed with CGI-58 in the absence of ATGL [32].

Antisense oligonucleotide (ASO)-mediated knockdown of CGI-58 in adult mice induced severe hepatic steatosis, though this study cannot establish a causal relationship between hepatic CGI-58 and fatty liver disease due to knockdown of CGI-58 in multiple tissues, including liver, adipose tissue, and macrophages [19, 28, 127, 129]. Selective inactivation of CGI-58 or ATGL in the liver of mice causes hepatic steatosis [75, 237], implying that fatty liver disease seen in patients with NLSD induced by CGI-58 or ATGL mutations is likely a local effect of hepatic CGI-58 or ATGL deficiency. These studies unequivocally demonstrated an important role of LD lipolysis in controlling lipid homeostasis in the liver. Besides TAGs, other species of lipids, such as DAGs, are also accumulated in mouse livers lacking CGI-58, especially when a high fat diet is used [19, 28, 75]. Although hepatic steatosis is often associated with insulin resistance and DAG accumulation is well-known to

suppress insulin signaling [186], liver CGI-58 deficiency-induced hepatic steatosis and DAG accumulation are not associated with insulin resistance in mice [19, 28, 75]. One study demonstrated that this dissociation results from the sequestration of DAGs to LDs and ER, rather than the cell membrane, which prevented PKCε translocation to the plasma membrane to inhibit insulin-receptor kinase activity [28]. The dissociation of hepatic steatosis and insulin resistance is not restricted to the CGI-58 deficiency-induced fatty liver. For instance, hepatic overexpression of DGAT2 or liver-specific deletion of histone deacetylase 3 (HDAC3) in mice induces severe hepatic accumulation of lipids including TAGs, DAGs, and ceramides without causing insulin resistance [141, 212]. In humans, a genetic variant (I148M) of PNPLA3 confers susceptibility to NAFLD in multiple populations without affecting the index of insulin resistance [149, 180, 207, 216]. African-American descendants have significantly less hepatic steatosis despite a relatively high prevalence of obesity and diabetes, while Hispanic-American descendants are the opposite [175, 193]. The variation in correlation between hepatic steatosis and insulin resistance among ethnicities suggests that other factors should also be considered. It should be emphasized that clinical studies of NAFLD only found the association between insulin resistance and hepatic steatosis whereas the relationship between insulin resistance and other liver pathologies, such as NASH and hepatic fibrosis, has yet to be established.

It is currently unknown how liver CGI-58 deficiency induces NASH and hepatic fibrosis in addition to hepatic steatosis. The albumin-cre transgenic mice (Stock #: 003574; The Jackson Laboratory) used for liver-specific inactivation of CGI-58 and ATGL can delete a gene floxed by loxP sites in hepatocytes, biliary epithelial cells (cholangiocytes), and hepatic stellate cells [50, 64, 148, 168, 171, 184, 206, 214]. Each of these cell types has distinct physiological and pathological functions. For instance, injuries of hepatocytes and other liver cells stimulate inflammatory responses, causing NASH [20, 60]. Liver damage and inflammation often trigger ductular reaction (increases in the number of small biliary

ductules lined by cholangiocytes) that may contribute to hepatic fibrogenesis to some extent [59, 176, 191]. Hepatic stellate cells increase collagen production after activation by various liver injuries, and this cell type is well accepted to be the major source of hepatic fibrosis [81, 82, 142]. Given that liver ATGL deficiency induced by the same albumin-cre transgenic mouse line does not cause these advanced pathological changes in liver [237], the mechanism underlying liver CGI-58 deficiency-induced NASH and hepatic fibrosis cannot be the inhibition of ATGL-mediated LD lipolysis in hepatocytes, cholangiocytes, or hepatic stellate cells. Consistently, patients with ATGL mutations do not develop NASH and hepatic fibrosis [6, 25, 58, 166, 197]. CGI-58, therefore, must have ATGL-independent functions in the liver. One of such functions may be its interaction with PNPLA3 [233, 250]. Like CGI-58 mutations, the PNPLA3(I148M) variant is also associated with NASH [180]. Another distinct function of CGI-58 is its interactions with almost all perilipins. This interaction may be needed for cellular processes, such as autophagy and lipophagy, besides activation of ATGL. Perilipins are coat proteins of cytosolic LDs. They are required for the biogenesis and turnover of cytosolic LDs. It has been shown that perilipins play an important role in the pathogenesis of hepatic steatosis, NASH, and hepatic fibrosis [29, 30, 34, 35, 61, 88, 91, 145, 162, 231]. Patients with NAFLD accumulate perilipins in the liver [61, 162, 209]. While perilipins may passively accumulate in the steatotic liver due to increased LDs, they may also actively increase to protect cells against lipotoxicity of free lipids. Other CGI-58 functions, such as its newly identified serine protease activity in the heart [94], may also exist in the liver and other tissues. This protease activity of CGI-58, like its lipase coactivator function, may target multiple proteins to regulate a variety of cellular processes important in lipid and energy metabolism.

Liver CGI-58 knockout mice on a regular low-energy chow diet develop a full spectrum of pathologies observed in human patients with advanced NAFLD [75]. The progression of these pathologies can be substantially facilitated by challenging the animals with a typical Western-type diet alone or in combination with fructose in drinking water (our unpublished data). Future studies are needed to discern whether CGI-58 needs to be deleted simultaneously in hepatocytes, cholangiocytes, and stellate cells or in a specific cell type to trigger NASH and fibrosis in liver. Studies are also needed to identify CGI-58's ATGL-independent mechanisms responsible for fatty liver progression, including testing the known ATGL-independent functions of CGI-58. Detailed comparative studies of liver CGI-58 and ATGL knockout mice may reveal mechanisms important in the etiology of NASH and hepatic fibrosis in general and shed light on novel drug targets against NAFLD progression.

13.6.5 Myeloid CGI-58 in Insulin Resistance, Inflammation, and Atherosclerosis

CGI-58 protein is expressed in mouse and human macrophages [13, 134]. It has been shown that myeloid cell-specific deletion of CGI-58 in mice worsens fat-induced tissue/systemic inflammation, proinflammatory activation of adipose tissue macrophages, glucose intolerance, and insulin resistance [134]. CGI-58-deficient macrophages accumulate cytosolic LDs and show reduced PPAR-γ signaling [134, 248]. Although the underlying mechanism remains unknown, sequestration of free fatty acids in cytosolic LDs may prevent these endogenous PPAR ligands from activating PPAR signaling as seen in ATGL-null cardiomyocytes [79]. As a result of PPARγ signaling suppression, CGI-58-null macrophages show mitochondrial dysfunction and accumulate reactive oxygen species, which activates NLRP3 inflammasome to promote secretion of proinflammatory cytokines [134]. Consistently, overexpression of CGI-58 in macrophages reduces inflammation in vitro and in vivo [241, 248]. The proinflammatory (M1-like) phenotype of CGI-58-null macrophages was also observed in other studies [65, 135]. In contrast, ATGL-deficient

macrophages were shown to display the anti-inflammatory M2-like phenotype [2, 65, 110]. These collective observations indicate that CGI-58 also has ATGL-independent functions in myeloid cells, including macrophages.

The anti-inflammatory role of macrophage CGI-58 is expected to protect against atherosclerosis. One study with CGI-58 overexpression in macrophages did show such an atheroprotective role through the promotion of the PPAR/LXR-dependent cholesterol efflux without altering blood cholesterol levels [241]. However, the deletion of CGI-58 in myeloid cells of apoE knockout mice, or simultaneous knockdown of CGI-58 in multiple cell types including hepatocytes, adipocytes, and macrophages in LDLR-KO mice, does not worsen atherosclerosis or alter plasma cholesterol levels [65]. It is difficult to assess atherosclerosis risk in patients with CGI-58 mutations due to the rarity of disease, existence of other abnormalities, and relatively young subjects reported. The role of macrophage CGI-58 in atherogenesis has yet to be clarified. Macrophage CGI-58 deficiency causes foam cell formation [134]. Lipopolysaccharide (LPS) and saturated fatty acids downregulate CGI-58 expression in macrophages [134]. LPS and fatty acids are atherosclerosis risk factors, and many studies have shown that they promote foam cell formation and atherosclerosis [8, 14, 53, 56, 62, 101, 117, 137, 143, 156, 170]. Oxidized (ox)-LDL, a common atherosclerosis risk factor, inhibits CGI-58 expression in THP1 human macrophages (our unpublished data). These findings suggest a potential role of CGI-58 in modulating atherosclerosis risk factor-induced atherogenesis.

13.6.6 Intestine CGI-58 in Fat Absorption and Turnover

A major function of the small intestine is the absorption of nutrients including fats. Fat absorption occurs mainly in duodenum and jejunum. After digestion by pancreatic lipases, in the intestinal lumen, fat (mainly TAGs) becomes free fatty acids and monoacylglycerols (MAGs), which then enter the absorptive enterocytes and travel to the endoplasmic reticulum (ER) for re-esterification into TAGs for packaging into chylomicrons. Intestinal fat absorption is a very efficient process. Chylomicrons are quickly secreted into the lymphatic system heading to the blood circulation. Some of absorbed fat may be temporarily stored in the cytosolic LDs, especially after ingestion of a high fat diet [31, 164, 178, 262]. The TAGs stored in the cytosolic LDs have to be hydrolyzed before they can be assembled into primordial chylomicron particles in the ER lumen. CGI-58 and ATGL are expressed in the enterocytes. Genetic deletion of CGI-58 in these cells in mice induced the accumulation of cytosolic LDs predominantly in the nutrient absorptive segment of small intestine, regardless of dietary compositions and nutritional conditions [106, 240]. These observations demonstrated an important role of intestinal CGI-58 in mobilizing intestinal LDs for local and/or systemic utilization. Consistently, hepatic steatosis is attenuated in the intestine CGI-58 single or CGI-58/ATGL double knockout mice [106, 240]. Using intestine-specific CGI-58 knockout mice fed a synthetic diet containing 40% energy from lard and 0.2% (w/w) cholesterol, our laboratory has shown that intestinal absorption of total fat and long-chain fatty acids is significantly reduced, which is associated with reduced postprandial TAG section into the blood circulation and increased plasma concentrations of free and esterified cholesterol [240]. For reasons currently unknown, another group did not find similar changes in their intestine CGI-58 and ATGL single or double knockout mice fed a diet containing 60% energy from fat [34% (w/w) crude fat] and 1% (w/w) cholesterol. They instead showed a role of intestinal CGI-58 and ATGL in the turnover of lipids derived from the basolateral side of the absorptive enterocytes [106, 152]. More studies are clearly needed to address these controversial findings.

13.7 CGI-58 and Cancer

Cancer cells often accumulate LDs in the cytoplasm [17, 210]. The underlying mechanisms remain elusive. Sequestration of lipids in cytosolic LDs may protect cancer cells from lipotoxic stress [93]. Mutations in CGI-58 cause LD deposition in cells, which led to the first study exploring the role of CGI-58 in colorectal cancer development [158]. It was shown that CGI-58 deficiency promotes the epithelial-mesenchymal transition (EMT) and invasiveness of colorectal cancer cells by increasing aerobic glycolysis (the Warburg Effect) [158]. The increase in aerobic glycolysis in CGI-58-deficient cells may result from limited availability of fatty acids due to defective LD lipolysis. In addition, CGI-58 was shown to promote colorectal tumorigenesis by impairing Beclin1-mediated autophagy [163]. A subsequent study with prostate cancer cells was consistent with the tumor suppressor role of CGI-58 [37]. However, another group using the same prostate cancer cell line found that CGI-58 sustains cancer cell growth by inhibiting cell apoptosis and death [140]. CGI-58 was recently shown to be oncogenic in endometrial cancer [261]. It was reported that CGI-58 in tumor-associated macrophages indirectly promotes colorectal cancer growth by suppressing spermidine synthesis [136]. The same group also reported that CGI-58 suppresses NFκB-dependent metalloproteinase production in macrophages to indirectly inhibit colorectal cancer cell metastasis [199]. Besides regulating tumorigenesis directly and indirectly, CGI-58 was reported to inhibit the sensitivity of colorectal cancer cells to the chemotherapy drug fluorouracil [159]. CGI-58 expression patterns and levels may serve as markers for differentiating benign and malignant tumors in some tissues [36, 158]. DNA methylation and deletion may influence CGI-58 expression in some cancer types, such as cervical cancer [198]. CGI-58 is not the only LD-associated protein that is implicated in cancer development and progression. It was shown that ATGL mediates cancer-associated cachexia [42], correlates with the risk of pancreatic ductal adenocarcinoma [68],

and promotes malignancies of breast cancer and hepatocellular carcinoma [43, 124, 125, 232, 249]. It was reported that ATGL deletion is linked to the aggressiveness of A549 lung carcinoma cells [218]. Inhibition of ATGL by the lipolysis suppressor protein G0S2 or a small molecule Atglistatin was found to attenuate the growth of cancer cells [256]. G0S2 was also observed to suppress oncogenic transformation of immortalized mouse embryonic fibroblasts [252]. Interestingly, inhibition of ATGL by hypoxia-inducible gene 2 (HIG2), unlike G0S2, was demonstrated to promote survival of colorectal cancer and renal cell carcinoma cell lines in hypoxia [260]. The role of LD-associated proteins CGI-58, ATGL, G0S2, and HIG2 in tumorigenesis may be cell type-specific, depending on how each cell type handles energy metabolism and signal transduction under different pathophysiological conditions.

13.8 CGI-58 and HCV Infection

A large proportion of patients chronically infected with hepatitis C virus (HCV) manifest LD deposition in the liver in the absence of other steatotic factors [147]. It was shown that the HCV nucleocapsid core, which is the major structural component of HCV virions, localizes at the surface of LDs to inhibit LD turnover in cultured cells and mouse livers [80]. The same group further showed that the HCV core inhibits ATGL-dependent LD lipolysis, but it unexpectedly enhances ATGL interaction with CGI-58 and the recruitment of the ATGL/CGI-58 complex to LDs [26]. Interestingly, an siRNA-based screen identified CGI-58 as a host factor that assists HCV assembly and release without affecting virus entry and replication [225]. They showed that several CDS-causing mutants of CGI-58 fail to localize at the surface of LDs, and those mutants are unable to support HCV production. Moreover, they identified a tribasic motif (KRK233-235) that is required for CGI-58 to promote lipolysis and HCV production, though not essential for CGI-58 localization to LDs. While this study may suggest that it is its lipase

coactivator function that mediates HCV assembly and release, it remains unknown whether the newly identified serine protease function of CGI-58 is implicated in HCV production [94].

13.9 Concluding Remarks

Patients with CDS accumulate TAG-rich LDs in all cell types examined. Since the discovery of *CGI-58* gene mutations as the cause of CDS in 2001, enormous interest on the function of CGI-58 has been generated in the scientific community of lipid and energy metabolism. It has been well established that CGI-58 is a LD-associated protein that promotes intracellular LD lipolysis by activating ATGL's TAG hydrolase activity. In addition to ATGL, CGI-58 interacts with many other proteins and regulates LD dynamics and functions in a cell type-specific manner. Such broad protein-protein interactions of CGI-58 have provided important insights into the biochemical basis for its ATGL-independent functions. Future studies are needed to dissect the molecular itineraries of these interactions in regulation of intracellular LD biogenesis and turnover. As a versatile regulator of intracellular LD homeostasis, CGI-58 plays a central role in governing cellular and whole-body energy balance. Genetic deletion of CGI-58 in mice has uncovered distinct effects of LD deposition in different cell types on the pathogenesis of metabolic disease. CGI-58 was recently identified to possess the serine protease activity in the heart. It is unknown if CGI-58 has this protease activity in other tissue. If yes, what are the substrates and functional significance? Is the serine protease activity of CGI-58 coordinate with its lipase coactivator function to activate intracellular lipolysis? Clearly, more studies are needed to answer these exciting new questions.

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