

CERT-Dependent Ceramide Transport, A Crucial Process in Cells

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Received date: March 24, 2021, **Accepted date:** April 19, 2021

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In mammalian cells, ceramides are central lipids in sphingolipid metabolism and serve both as signaling lipids and as precursors for other bioactive sphingolipids, ranging from complex glycosphingolipids to “simpler” lipids such as ceramide-1-phosphate, sphingomyelin (SM), sphingosine and sphingosine-1-phosphate (S1P). Ceramides are largely distributed in cell membranes where they play an important structural role. In addition, ceramides play also key roles in intracellular signaling, and regulate growth, proliferation, cell migration, apoptosis, and differentiation [1].

Ceramides consist of a spingoid long chain base to which a fatty acid is attached via an amide bond. They can be generated either by hydrolysis of sphingomyelin by sphingomyelinases, degradation of complex sphingolipids localized in lysosomes, or produced *de novo* from saturated fatty acids, like palmitic acid, in the endoplasmic reticulum (ER) [2].

Synthesis of both SM and glucosylceramides (GlcCer) from ceramide occurs into the Golgi apparatus [2]. Ceramides are transported through a non-ATP dependent vesicular transport from the ER toward the cis-Golgi, where GlcCer synthase adds a glucose molecule to ceramides to give GlcCer [3]. Ceramides are also transported to the trans-Golgi to give SM after addition of a phosphocholine by the sphingomyelin synthase 1 (SMS1) [4]. This latter transport is ensured by a specific ceramide transporter called CERT (for ceramide transporter) in an ATP-dependent manner [5].

CERT, a 68 kDa protein, possess several domains to provide its precise function. The StAR-related lipid transfer (START) domain specifically extracts the ceramide

molecule from the ER membrane to the Golgi membrane [6]. CERT also have a pleckstrin homology (PH) domain at its N-terminal side, which binds phosphatidylinositol 4-phosphate (PIP₄), abundant phospholipid found in the trans-Golgi region (Figure 1) [7]. Two phenylalanine residues localized in the acidic tract (FFAT) domain allows CERT to bind the VAMP-associated protein (VAP) in the ER membrane [7]. FFAT domain can be phosphorylated on its serine 315 (S₃₁₅), which improves ceramide transport from ER to Golgi, since CERT displays a higher affinity to VAP when S₃₁₅ is phosphorylated (Figure 2) [7]. CERT possess also a serine-repeated motif that can be phosphorylated by protein kinase D (PKD) to decrease its binding with PIP₄ and thus, reduces CERT ceramide transfer activity [7]. The serine-repeat motif (SRM), localized near the PH domain, carries several phosphorylation sites [7], and it has been shown that multiple phosphorylation of this site decreases CERT function, result of a conformational hindrance [7].

Two CERT isoforms exist. CERT_L – also known as Goodpasture antigen-binding protein (GPBP) which is 26 amino acids residues longer than CERT/GPBPΔ26 [8]. The two forms can be found in most tissues, but CERT_L is mainly expressed in tissues which can targeted by autoimmune response [8].

The importance of the CERT transporter is becoming increasingly evident for the regulation of intracellular concentration of ceramides and their transformation into other sphingolipid derivatives. Several studies have indeed shown that changes in expression / activity of CERT could modulate the action of ceramides on several physiological processes.

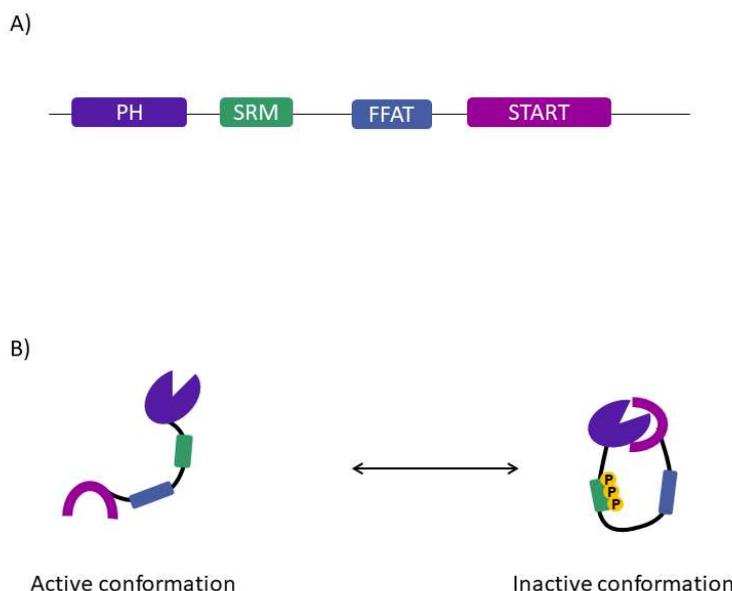


Figure 1: (A) Structure of CERT. PH: pleckstrin homology domain which ensure binding of CERT to the Golgi apparatus; SRM: serine-repeat motif which can be phosphorylated, leading to a decrease in CERT activity; FFAT: Two phenylalanine residues in acidic tract that allow CERT to bind ER membrane; START: StAR-related lipid transfer domain that extracts ceramide from the ER-membrane and carries it to the Golgi-membrane. **(B) Modification of CERT activity by phosphorylation.** Multiple phosphorylation can occur in the serine-repeat motif (SRM), leading to an inhibition of CERT activity because of conformational hindrance.

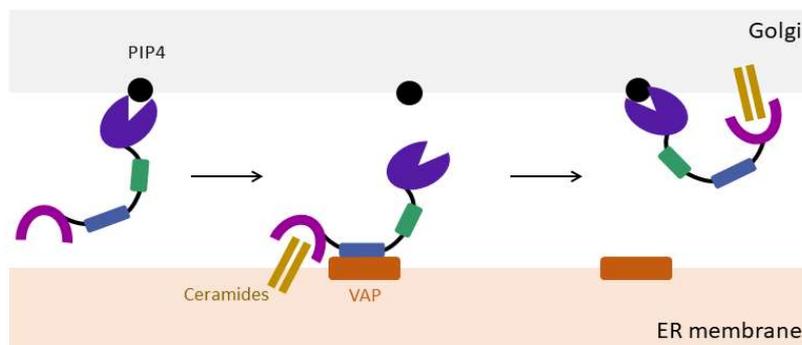


Figure 2: Model showing the mechanism by which CERT transports ceramide from the ER to the Golgi apparatus. CERT is recruited to the endoplasmic reticulum (ER) through the interaction of its FFAT domain with the vesicle-associated membrane protein-associated protein (VAP). Then, the START domain of CERT extracts ceramide from the ER and transports the lipid to the trans- Golgi regions through the interaction its PH domain with phosphatidylinositol-4-phosphate (PIP4).

CERT and Insulin Resistance

Ceramide accumulation in cells (inducing lipotoxicity) is now well known to induce insulin resistance in muscle [9], in liver [10], in adipose tissue [11], and also pancreatic beta cells death [12].

A recent study showed that the increased ceramide concentrations in response to saturated FA was associated with their defective transport from the ER to the Golgi apparatus in muscle cells [13]. The authors demonstrated that CERT expression was decreased in the muscle cell line C2C12 after palmitate treatment to induce cell insulin

resistance, muscle cells from diabetic mice and also in muscle from human diabetic patient, and that this drop in expression was the consequence of ceramide-dependent CERT cleavage by caspases 3 and 9. Interestingly, *in vitro* CERT overexpression in C2C12 myotubes treated with palmitate, or *in vivo* by electro transfer in the anterior tibial muscle of diabetic mice, decreased some ceramide species content (C16, C22, C24 and C24:1-ceramides), and improved insulin sensitivity in CERT-overexpressing muscle cells [13]. Overall, this study highlighted an important and original mechanism for regulating ceramide flow in muscle cells and to prevent their accumulation under lipotoxic conditions.

Interestingly, no decrease of CERT expression in a lipotoxic context was observed in liver [14]. Indeed, primary rat hepatocytes treated with palmitic acid for 16h showed an inhibition of the insulin signal following an increase in both ceramide content and CERT expression [14]. CERT expression returned to basal level 40 h after palmitic acid incubation while ceramide content remained elevated [14]. The authors hypothesized that ceramide transported from ER to Golgi could be converted to SM, which may be hydrolyzed latter on to form more ceramide molecules that intensified ceramide accumulation and lipotoxicity in cells. It is important to note that several studies demonstrated that another lipid species, diacylglycerol's, play also an important and deleterious role in the loss of insulin sensitivity in liver in lipotoxic conditions [15].

Differences between the two articles regarding the action of ceramides on CERT expression could also be explained by the fact that, unlike what happens in muscle cells, ceramides do not really accumulate in hepatocytes [16]. Indeed, the upper study [14] and another one carried out in HepG2 liver cells showed that palmitate rapidly induced extracellular ceramide build-up in a dose- and time-dependent manner, suggesting that liver cells rapidly secreted the newly synthesized ceramide molecules [16]. As a result, it is possible that, unlike in muscle cells, ceramide concentrations remained relatively low in hepatocytes, at a level too small to induce caspase activation and to decrease CERT expression. Therefore, CERT expression remains unaffected by ceramides in hepatocytes.

Overall, these studies highlight the importance of a good ceramide transport in muscle to maintain a physiological insulin sensitivity. Maintaining a good CERT expression in cells appears to be crucial to prevent ceramide accumulation and cellular dysfunction.

CERT and Apoptosis

Some studies were interested in the role of ceramides and their transport in a context of aging. In females, advanced age induced changes in mitochondrial function and

structure of oocytes and decreased their quality. Perez and collaborators observed that oocyte from old mice showed higher apoptosis levels after ceramide injection compared to apoptosis levels of ceramide-injected oocyte from young mice [17]. Interestingly, a decrease in CERT expression in oocytes from old mice compared to CERT expression in oocytes from young mice was observed, suggesting that a defect in ceramide metabolism/localization due to the lack of CERT expression could be responsible for the decreased developmental potential observed in old oocytes. This was confirmed when co-treatment of aged oocytes with ceramide and a cytoplasmic lipid carrier (l-carnitine) enhanced mitochondrial morphology and function, suggesting that the absence of ceramide transport surely induced the lipid accumulation and prevented its transformation into other lipid derivatives less toxic for the cells [17].

A recent study investigated the possible link between ceramide and mitochondrial apoptosis. Indeed, mitochondria play a central role in apoptotic cell death. Induction of mitochondrial apoptosis occurs upon outer membrane permeabilization, leading to the release of intermembrane proteins, such as the hemeprotein cytochrome c, and through the induction of caspase activation, ultimately causing cell apoptosis [18]. Ceramide are also known to promote cell apoptosis [1], and to study a possible involvement of this sphingolipid into mitochondrial apoptosis, the authors diverted CERT-mediated ceramide transport to mitochondria by targeting CERT to the outer mitochondrial membrane (OMM) while retaining its ability to interact with VAP proteins in the ER [19]. To do so, they armed CERT with an OMM anchor and called it mitoCERT [19]. When HeLa cells were transfected by mitoCERT, an increased in cytosolic translocation of cytochrome c and caspase 9 activity was observed, leading to cell apoptosis [19]. Pre-treatment of cells with the CERT inhibitor HPA12 prevented cell death [19]. Overall, this study clearly demonstrates that transport of ceramide to mitochondria specifically induces apoptotic cell death.

All these results suggest again that CERT expression remains crucial in order to prevent ceramides to harm the cells. A dynamic between ceramide concentration and CERT expression is crucial to induce or to inhibit apoptosis in cells.

CERT and Cancer

Given the deleterious role of ceramides in the regulation of cell growth and apoptosis, a novel strategy to induce tumor cell apoptosis by modifying ceramide metabolism was looked at [20]. A study performed in three cancer cell lines (human alveolar adenocarcinoma A549; human colorectal carcinoma HCT116; human breast adenocarcinoma MDA-MB-231), observed that the inhibition of CERT activity through the use of the chemical inhibitor (HPA-12) or a

CERT siRNA, led to a higher sensitivity of tumors to cancer drugs [21]. Indeed, in HCT116 cells, HPA-12 induced the increase of an actor of the three axes of the unfolded protein response (UPR), PERK [22], leading to a chronic activation of ER stress in cells, ultimately leading to cell apoptosis [22]. In another study performed in colorectal and breast cancer cells, the authors highlighted that CERT inhibition induced ceramide accumulation in cells, leading to enhanced lysosomal-autophagosome flux [23].

These independent studies demonstrated that CERT modulation could modify cell sensitivity to certain drugs through ceramide accumulation, certainly an interesting possibility to fight cancers and other pathologies.

CERT and Brain Related Diseases

Sphingomyelin, synthesized after transport of ceramide by CERT from the ER towards the Golgi, is the most abundant sphingolipid in cell membranes [24]. SM plays crucial roles in brain myelination, which is important for brain development [25]. This is why SM dysregulation may lead to cell dysfunctions, or even important diseases [26]. In Niemann-Pick disease, for example, SM accumulates in cell lysosomes, leading to several organs dysfunction like in the central nervous system [27].

A recent study identified a novel CERT variant from a patient with intellectual disability, where the serine at position 135 (S135) was substituted by a proline in the serine-repeat motif domain [28]. This domain is crucial to downregulate CERT activity [7]. Indeed, it can be phosphorylated several times on different serine/threonine residues, and this multiple phosphorylation leads to a decrease of CERT activity [7]. The novel CERT variant cannot be phosphorylated and is abnormally active in this patient [28]. As consequence, the patient displays a strong intellectual retardation. MRI performed revealed a general cerebral atrophy [28], more specially at the frontal lobe responsible for reasoning, speaking and voluntary movement [29]. A hypoplasia of the corpus callosum, which ensures the communication between the two cerebral hemispheres, was also observed [28].

Alzheimer's disease (AD), the most common neurodegenerative disorder, is characterized by extracellular deposits of amyloid β -peptides (A β), leading to a strong crippling disease [30]. Ceramides are associated with AD because they were shown to stabilize β -secretase, one of the key enzymes that cleaves the amyloid-precursor protein (APP) into the deleterious A β . Thus, ceramides contribute to A β accumulation in the nervous central system [30]. High ceramide content was observed into the cortex from patients with mild to moderate symptoms, suggesting that ceramide accumulation could occur in the early stage of the disease [31]. As consequence, ceramide content is more elevated in brains from AD patient

compared to control patient [32].

CERT_L expression was reported to binds the amyloid-precursor protein and to be reduced in the cortex in a mouse model of familial Alzheimer disease (5xFAD) [33]. In opposite, ceramide content was elevated in brains of Alzheimer patient [33]. Interestingly, a real interaction between CERT_L and APP was observed using a co-immunoprecipitation system into primary neurons from 5xFAD brains. Addition of amyloid- β decreased cell viability but CERT_L addition was able to restore this viability. In addition, brain cortex from 5xFAD mice revealed an increase in C16-ceramides, C18-ceramides, C20-ceramides, C22-ceramide, while CERT_L expression was decreased [33].

CERT_L overexpression in 5xFAD mice through a viral vector did not affect behavior compared to mice who received a control virus [33]. However, a decrease of C16-ceramides into the cortex of 5xFAD mice overexpressing CERT_L was observed, together with an increase of C16-SM, C18-SM, and C18:1-SM. Even if plaque numbers were not reduced in brain of mice overexpressing CERT_L, the percentage of small plaque size was decreased in total brain, concomitantly with a decrease of amyloid- β in brain homogenate. In opposite, AD transgenic mice treated with the CERT inhibitor HPA-12 during 4 weeks displayed an increase of C16-ceramide, C20-ceramide, C22-ceramide and C24:1-ceramide in the cortex compared to control mice. As expected, amyloid- β was increased in brain homogenate.

All together, these data suggest that alteration of ceramide transport from ER to the Golgi, involving CERT, alters APP processing and leads to expand a critical phenomenon in Alzheimer disease.

New CERT Inhibitors

The development of HPA-12, a competitive inhibitor of CERT, helped a lot to understand the activity, function and regulation of CERT [34]. A recent study identified two others CERT inhibitors [35]. The authors used a fluorescence-based assay to measure the capacity of CERT to transfer labelled-ceramide to a liposome containing a lipid-quencher that can be tracked. This approach was combined with the Förster resonance energy transfer, technique allowing to see whether two light-sensitive molecules are close enough to carry out an energy transfer. 2000 different compounds were screened, and HPA-12 was used as a reference molecule. Following this protocol, four promising compound candidates were isolated [35]. Among them, only 2 were able to inhibit CERT and therefore decrease SM concentration, and increase ceramide content in cells. One, called Fluralaner, was already used as a veterinary drug. It targets the arthropod parasite channel and displayed an unknown target in mammals [35]. The

other one, called Lomitapide, is a human drug that had already been shown to target the human microsomal triglyceride transfer protein. Lomitapide is used to treat familial hypercholesterolemia [36]. Both CERT inhibitors, already prescribed as medication in animals and human, could also be used as tools to study ceramide transfer.

Conclusion

Considering the growing importance of related studies around ceramides, they could even become a new biomarker for detecting cardiovascular disease [37], and studying the dynamics of flows between different sphingolipids remains crucial in several fields. All these studies show that the dysregulation of ceramide transfer from the ER to the Golgi apparatus, via the alteration of the activity / expression of CERT, presents serious consequences. These studies also highlight the importance of CERT as a major regulator of ceramide metabolism. Considering the number of cellular processes affected by a dysregulation of CERT, further studies will be necessary to get a better understanding of its implication in several pathologies and to consider the use of the different and new existing CERT inhibitors to fight the diseases.

Author Contributions Statement

Conceptualization, C.L.B. and E.H.; writing-original draft preparation, C.L.B.; writing-review and editing, C.L.B. and E.H. Both authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the “Société Francophone du diabète” and the “Fondation de France”.

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