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Review

Ceramide 1-phosphate/ceramide, a switch between life and death

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Abstract

Ceramide is a well-characterized sphingolipid metabolite and second messenger that participates in numerous biological processes. In addition to serving as a precursor to complex sphingolipids, ceramide is a potent signaling molecule capable of regulating vital cellular functions. Perhaps its major role in signal transduction is to induce cell cycle arrest, and promote apoptosis. In contrast, little is known about the metabolic or signaling pathways that are regulated by the phosphorylated form of ceramide. It was first demonstrated that ceramide-1-phosphate (C1P) had mitogenic properties, and more recently it has been described as potent inhibitor of apoptosis and inducer of cell survival. C1P and ceramide are antagonistic molecules that can be interconverted in cells by kinase and phosphatase activities. An appropriate balance between the levels of these two metabolites seems to be crucial for cell and tissue homeostasis. Switching this balance towards accumulation of one or the other may result in metabolic dysfunction, or disease. Therefore, the activity of the enzymes that are involved in C1P and ceramide metabolism must be efficiently coordinated to ensure normal cell functioning.

Keywords: Apoptosis; Cell proliferation; Ceramide-1-phosphate; Phosphatidylinositol 3-kinase; Sphingosine 1-phosphate; Sphingomyelinases

Contents

1. Introduction

Tissue homeostasis in higher organisms is determined by a network of complex processes that are tightly regulated. These include systems to balance cell proliferation and cell death to ensure proper development of the organism. Any alteration of this balance can potentially lead to illnesses, including autoimmune diseases, neural degeneration, cardiovascular disease, or cancer [1–3]. Therefore, identification of effector molecules that are involved in the regulation of cell proliferation and death is crucial for developing therapeutical strategies for prevention or treatment of disease.

Abbreviations: C_2-ceramide, N-acetylsphingosine; C_8-ceramide, N-octanoylsphingosine; CERK, ceramide kinase; C1P, ceramide-1-phosphate; DAG, diacylglycerol; ERK, extracellular regulated kinase; MAPK, mitogen-activated protein kinase; M-CSF, monocyte-colony stimulating factor; PA, phosphatidate; PI3-K, phosphatidylinositol 3-kinase; PKA, cAMP-dependent protein kinase; PKB, protein kinase B; PLA_2, phospholipase A_2; PKC, protein kinase C; PLD, phospholipase D; SM, sphingomyelin; SMase, sphingomyelinase; S1P, sphingosine-1-phosphate

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Sphingolipid metabolites have emerged as important regulators of cell activation with a wide spectrum of activity to control cell growth and death, and signal transduction processes. For example, ceramides are known to be potent inhibitors of cell growth and efficient inducers of apoptosis [4–17] in most cell types. In neurons, however, the situation is controversial as ceramides can promote both apoptosis or cell survival [18–22]. Ceramides are involved in the regulation of cell proliferation, differentiation, apoptosis, or inflammatory responses [11,14,15,23–28], radiation and chemotherapy effects on tumors, bacterial and viral infections, heat or UVA injury, and ischemia–reperfusion injury (Reviewed by Gulbins and Kolesnick [29]). In addition, ceramides have been associated with insulin resistance through activation of protein phosphatase 2A and the subsequent dephosphorylation and inactivation of protein kinase B (PKB) [30–32]. By contrast, sphingosylphosphorylcholine [33], sphingosine-1-phosphate (S1P) [8,34–37], and ceramide-1-phosphate (C1P) [27,38–40] are potent stimulators of cell proliferation. Ceramides can be generated by de novo synthesis, or can be produced by the action of different sphingomyelinase (SMase) enzymes (Fig. 1). For details on SMase activities, enzymology, and compartmentalization, see [12,41,42]. Cellular ceramides typically have long *N*-acyl chains ranging from 16 to 26 carbons in length [7,43,44], and some times longer in tissues such as skin. Many studies have used a short-chain analog (N-acetylsphingosine, or C_2-ceramide) in experiments with cells in culture because it is more water soluble than long-chain ceramides, and it has been presumed that this compound did not occur in vivo. However, it was found that C_2-ceramide exists in rat liver cells [45]. The stimulation of sphingomyelinase (SMase) activity was first demonstrated by Kolesnick [9] in experiments using exogenous 1,2-dioctanoylglycerol (a permeable analog of diacylglycerol) in GH_3 pituitary cells, and by Hannun and co-workers using 1,25-dihydroxyvitamin D3 as agonist to stimulate HL-60 cells [23,46]. These actions caused sphingomyelin (SM) hydrolysis and concomitant increases in ceramide levels. It was suggested that sphingolipid-derived metabolites might function as second messengers [11,14,15,23–26].

The mechanisms whereby ceramides exert their biological actions include modulation of diverse signal transduction pathways and key regulatory enzyme activities such as specific serine/threonine kinases [10,11,47,48], protein phosphatases [49–51], protein kinase C-ζ [52], stress-activated protein kinases (SAPK) also known as Jun nuclear kinases (JNKs) [53,54], the mitogen-activated protein kinases p42/44 [35,48], phospholipase A_2 [55,56], protein kinase B (PKB) [30–32,57,58], or phospholipase D (PLD) [59–61].

Formation of ceramide is also relevant because it is the precursor of important bioactive sphingolipids that can also regulate cellular functions. For instance, stimulation of ceramidases results in generation of sphingosine (Fig. 1), which was first described as inhibitor of protein kinase C (PKC) [13]. There are numerous reports in the scientific literature showing that PKC is inhibited by exogenous addition of sphingosine to cells in culture. Of note, Merrill and co-workers demonstrated that addition of the ceramide synthase inhibitor fumonisin to J774 macrophages to increase the levels of endogenous sphingoid bases, also inhibited protein kinase C [62]. Sphingosine can control the activity of other key enzymes involved in the regulation of metabolic or cell signaling pathways such as the Mg^{2+} dependent form of phosphatidate phosphohydrolase [63,64], phospholipase D (PLD) [65], or diacylglycerol kinase (DAGK) [66,67] in different cell types. Sphingosine, in turn, can be phosphorylated by the action of sphingosine kinases to generate S1P, which is a potent mitogenic agent and can also inhibit apoptosis in many cell types [8,34–37,68]. More recently, our group demonstrated that S1P stimulates cortisol [69] and aldosterone secretion [70] in cells of the zona fasciculata or zona glomerulosa, respectively, of bovine adrenal glands. These novel actions of S1P implicate it in the regulation of steroidogenesis.

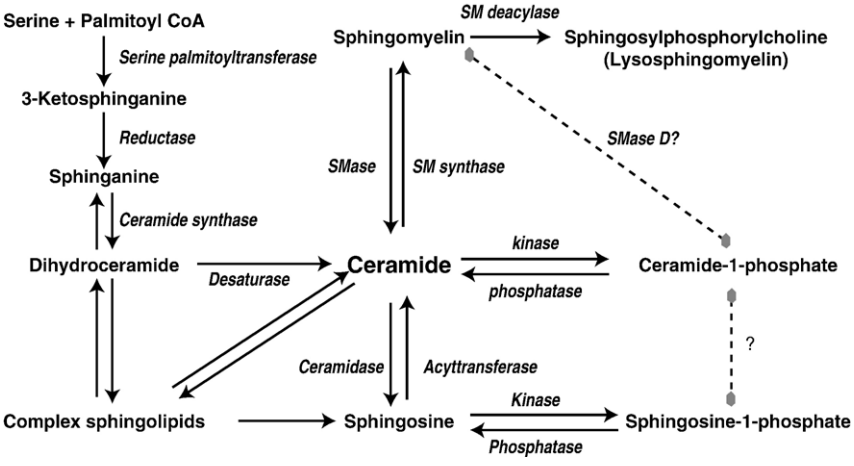

Fig. 1. Formation of bioactive sphingolipids in mammalian cells. Ceramide can be produced through degradation of sphingomyelin (SM) by sphingomyelinases (SMase), or by de novo synthesis by the concerted action of serine palmitoyltransferase and dihydroceramide synthase. It can also be generated through metabolism of complex sphingolipids. Ceramide can be metabolized to ceramide-1-phosphate by ceramide kinase. The reverse reaction is catalyzed by ceramide-1-phosphate phosphatase, or by lipid phosphate phosphatases (LPPs). Alternatively, ceramide can be degraded by ceramidases to form sphingosine, which can, in turn, be phosphorylated to sphingosine-1-phosphate by sphingosine kinases. The reverse reaction is catalyzed by sphingosine-1-phosphate phosphatases, or by lipid phosphate phosphatases. Sphingomyelin *N*-deacylase generates sphingosylphosphorylcholine.

A major metabolite of ceramide is ceramide-1-phosphate (C1P), which can be formed through direct phosphorylation of ceramide by ceramide kinase (Fig. 1). There is increasing evidence suggesting that C1P can regulate cell proliferation and apoptosis (Reviewed in [27,40]), and Chalfant's group has demonstrated that C1P is involved in inflammatory responses (reviewed in [71,72]). In addition, C1P plays a key role in phagocytosis [73,74]. The aim of the present article is to review recent developments related to the control of cell activation by C1P with special emphasis to the role of C1P as a novel regulator of cell survival.

2. Ceramide kinase and C1P generation

The existence of C1P was first reported by Dressler and Kolesnick in human leukemia (HL-60) cells [75]. These authors found that C1P was synthesized from ceramide that were derived from SM but not from glycosphingolipids, and suggested that a specific pathway extended from SM to C1P [75]. Ceramide kinase (CERK) was first identified in brain synaptic vesicles by Bajjalieh and co-workers [76], and subsequently found in HL-60 cells by Kolesnick and Hemer [10]. This activity was confined to the microsomal membrane fraction, and it phosphorylated ceramide but not 1,2-diacylglycerol, in the presence of physiologic calcium concentrations [10]. Interestingly, human CERK has been recently reported to be highly dependent on Mg^{2+} ions, and much less dependent on Ca^{2+} [77]. Human CERK was recently cloned by Sugiura and co-workers [78]. The protein sequence has 537 amino acids with two protein sequence motifs, an N-terminus that encompasses a sequence motif known as a pleckstrin homology (PH) domain (amino acids 32–121), and a C-terminal region containing a Ca^{2+}/calmodulin binding domain (amino acids 124–433). Using site-directed mutagenesis, Kim and co-workers found that leucine 10 in the PH domain is essential for its catalytic activity [79]. Also, the same group has reported recently that the interaction between the PH domain of CERK and phosphatidylinositol 4,5-bisphosphate regulates the plasma membrane targeting and C1P levels [80]. CERK also contains the five conserved sequence stretches (C1–C5) that are specific for lipid kinases (Reviewed in [81]).

With regards to substrate specificity, it was reported that phosphorylation of ceramide by CERK is stereospecific [82]. The latter report also showed that a minimum of a 12-carbon acyl chain was required for normal CERK activity, whereas the short-chain ceramide analogues C_8-ceramide, C_4-ceramide, or C_2-ceramide were poor substrates for CERK. It was concluded that CERK phosphorylates only the naturally occurring D-erythro-ceramides [82]. The importance of CERK in cell signaling was highlighted using specific RNAi to downregulate this enzyme activity in A549 lung adenocarcinoma cells. This treatment dramatically inhibited arachidonic acid release and PGE_2 production in response to ATP, the calcium ionophore A23187 and interleukin 1-β [71,83].

Recently, a human ceramide kinase-like (CERKL) enzyme was identified in retina [84], and subsequently cloned [85]. However, this enzyme was unable to phosphorylate ceramide, or other related lipids, under conditions commonly used to measure CERK activity, and therefore its role in cell biology is unclear.

In a previous report, Hinkovska-Galcheva et al. [73] observed that endogenous C1P can be generated during the phagocytosis of antibody-coated erythrocytes in human neutrophils that were primed with formylmethionylleucylphenylalanine, and more recently, the same group has established that C1P is a mediator of phagocytosis [74]. Rile et al. [86] reported that C1P can be formed in neutrophils upon addition of exogenous cell-permeable [^{3}H]*N*-hexanoylsphingosine (C_6-ceramide) to the cells. Riboni and co-workers [87] demonstrated that C1P could be generated in cerebellar granule cells both from SM-derived ceramide and through the recycling of sphingosine produced by ganglioside catabolism. C1P can be also generated by the action of interleukin 1-β on A549 lung adenocarcinoma cells [83], and plays an important role in inflammation [71,83,88–91]. We found that C1P is present in normal bone marrow-derived macrophages isolated from healthy mice [92], and that C1P levels were substantially decreased in apoptotic macrophages. This observation suggested that C1P may play an important role in cell survival [40,92]. In addition, C1P could potentially be formed by the action of SMase D, which occurs in the venom of a variety of arthropodes including spiders of the gender *Loxosceles* (the brown recluse spider *L. reclusa*, *L. amazonica, L. arizonica*, *L. intermedia*, *L. laeta)*, and also in the toxins of some bacteria such as *Corynebacterium pseudotuberculosis*, or *Vibrio damsela* [93]. Envenomation by *Loxosceles reclusa* results in dermonecrosis, erythrocyte hemolysis, platelet aggregation or renal failure, and can occasionally lead to death [94]. However, SMase D has broad substrate specificity, therefore, the toxic effects of SMaseD cannot be attributed only to the formation of C1P. Although there is no evidence for an analogous activity in mammalian cells, the possibility has not been exhaustively explored.

To date, there have been few estimates of the actual mass amounts of C1P in cells, however, the basal amounts may be surprisingly high. Recent analyses by Merrill and co-workers as part of the LipidMAPS Consortium (www.lipidmaps.org) have posted the amounts of SM, Cer and C1P in RAW 264.7 cells (see link to the 12/05/05 Kdo2-lipid A time course, http://www.lipidmaps.org/data/kdo2lipidatimecourse/index.php, and examine the time zero column) as 441, 25 and 108 pmol/μg DNA, respectively, which is equivalent to 5310, 300 and 1300 pmol/mg protein (A. Merrill, personal communication). Therefore, the C1P amounts of RAW 264.7 are about one fourth that for SM, and several fold higher than Cer. One might speculate that this high level of antiapoptotic C1P in the RAW 264.7 macrophages might be related to the relatively high resistance of these cells to enter apoptosis when they are incubated in the absence of serum, in comparison to other cell types.

3. Degradation of C1P

The identification of C1P phosphatase in rat brain [95], and hepatocytes [96], together with the existence of CERK suggested that ceramide and C1P are interconvertible in cells. C1P phosphatase was enriched in brain synaptosomes and liver plasma membrane fractions, and appeared to be distinct from the phosphatase that hydrolyzes phosphatidic acid (PA), PA

phosphohydrolase. Nonetheless, C1P can also be converted to ceramide by the action of a PA phosphohydrolase that is specifically located in the plasma membrane of cells [97]. The latter enzyme belongs to a family of at least three mammalian lipid phosphate phosphatases (LPPs) [98]. LPPs have recently been shown to regulate cell survival by controlling the levels of intracellular PA and S1P pools [99], and also to regulate leukocyte infiltration and airway inflammation [100]. Dephosphorylation of C1P might be a way of terminating its regulatory effects, although the resulting formation of ceramide could potentially be detrimental for cells. In any case, controlling the levels of ceramide, and C1P by the coordinated action of CERK and C1P phosphatases, may be of crucial importance for the metabolic or signaling pathways that are regulated by these two sphingolipids.

Another possibility for degradation of C1P might be its deacylation to S1P, which is then cleaved to a fatty aldehyde and ethanolamine phosphate [4]. However, no C1P deacylase has so far been identified in mammalian cells.

4. C1P promotes cell survival

We first reported that C1P was bioactive because it stimulated DNA synthesis and cell division in rat fibroblasts [38]. These studies were performed using synthetic short-chain C1Ps (C_2-C1P and C_8-C1P) that were enzymically synthesized using C_2- and C_8-ceramides as substrates and bacterial diacylglycerol kinase (DAGK). Also, we observed that the short-chain C1Ps could partially reverse the morphological changes that are induced in rat fibroblasts after prolonged serum deprivation, a condition that induces apoptosis in these cells, and that the short-chain C1Ps decreased the detachment of serum-starved cells from the culture dishes (reviewed in [27]). Like the short-chain C1Ps, a mixture of natural (long-chain) C1P that was obtained from bovine brain also was a potent stimulator of DNA synthesis. This action was accompanied by an increase in the levels of proliferating cell nuclear antigen [39], which is a marker of active DNA synthesis [101]. There is also evidence suggesting a possible role for C1P in stimulating cell proliferation or inhibiting apoptosis in birds, as the short-chain analog C_8-C1P increased the size of cultured chick otic vesicle explants, and inhibited DNA fragmentation in the same explants incubated in the absence of serum [102]. It should however be noted that C_8-ceramide has not been found in biological systems, and is a poor substrate for CERK [82]; so, it is unlikely that C_8-C1P occurs in vivo, and therefore, the effects of C_8-C1P should be regarded as pharmacological in nature, as previously suggested [38]. In addition, it should be borne in mind that synthetic short-chain analogs of ceramide or ceramide phosphate may not always mimic the effects of the natural (long-chain) counterparts. In fact, Ping and Barrett have shown that whereas ceramides can induce cell death in sensory neurons, short-chain ceramide analogs promote survival [18]. As well, Olivera and co-workers demonstrated that treatment of cells with exogenous sphingomyelinase, which generates natural (long-chain) ceramides in the plasma membrane, antagonized the mitogenic effect of the phorbol ester 12-O-tetradecanoylphorbol 13-acetate, while short-chain ceramide analogs had no effect [103]. Furthermore, Sot and co-workers have recently shown important differences in the biophysical behavior of short- versus long-chain ceramides suggesting that they may also behave differently in biological systems [104]. Therefore, care should be taken when interpreting results from experiments using only synthetic short-chain analogs.

The metabolic or signaling pathways that are regulated by C1P are not well characterized, but unlike other related bioactive phospholipids, including S1P, lyso-PA or PA, C1P does not affect PLD, MAPK (ERK-1/2), adenylyl cyclase, Ca^{2+} mobilization, or the expression of the early genes *c-fos* or *c-myc* in rat or mouse fibroblasts [38,39]. However, induction of ERK phosphorylation has been demonstrated in human osteoblastic cells that were stimulated with short-chain C1P [105], and C_2-C1P- or C_8-C1P-induced Ca^{2+} mobilization has been shown to occur in calf pulmonary artery endothelial (CAPE) cells [106], thyroid FRTL-5 [107], or Jurkat T-cells [108]. In the latter report, Colina and co-workers showed that Ca^{2+} mobilization by C_8-C1P was dependent upon inositol (1,4,5)-trisphosphate accumulation. By contrast, the short-chain C1Ps did not induce Ca^{2+} mobilization in fibroblasts [38,39] or neutrophils [86], and long-chain C_{16}-C1P failed to alter intracellular Ca^{2+} concentrations in lung adenocarcinoma A549 cells [88]. Whether or not natural C1P is able to affect Ca^{2+} homeostasis in any cell type still remains to be determined.

We previously demonstrated that natural C1P blocked cell death in bone marrow-derived macrophages that were incubated in the absence of macrophage-colony stimulating factor (M-CSF) [92], a condition known to induce apoptosis in these cells, [109,110]. We found that C1P blocked both DNA fragmentation and the stimulation of the caspase-9/caspase-3 pathway, thereby suggesting that the prosurvival effect of C1P was due to inhibition of apoptosis [92]. A relevant finding was that apoptotic macrophages had enhanced acid SMase activity and high levels of ceramides compared to healthy cells [110,111]. Investigation into the mechanism by which C1P exerts its antiapoptotic effects demonstrated complete inhibition of acid SMase and ceramide accumulation by C1P in intact macrophages [92]. A key observation in that study was that C1P blocked the activity of acid SMase in cell homogenates suggesting that inhibition of this enzyme occurs by direct physical interaction with C1P. It was concluded that C1P is a natural and selective inhibitor of acid SMase, and that inhibition of this enzyme activity is a major mechanism whereby C1P promotes cell survival [92]. Also, this observation suggests that inhibition of acid SMase by C1P is not mediated through receptor interaction. Acid SMase was also inhibited by S1P in intact macrophages [111], but unlike C1P the inhibitory effect of S1P did not involve direct interaction with the enzyme. Also of interest, activation of acid SMase plays an important role in pulmonary infections as it facilitates internalization of bacteria into lung epithelial cells [29]. Therefore, inhibition of acid SMase by C1P could be important to reduce or prevent infection of mammalian cells.

The physiological relevance of the prosurvival effect of C1P is underscored by the demonstration that intracellular levels of C1P are substantially decreased in apoptotic macrophages. It was hypothesized that the decrease in C1P concentration could

result in the release of acid SMase from inhibition, thereby triggering ceramide generation an apoptotic cell death [92].

A major mechanism whereby growth factors promote cell survival is the activation of phosphatidylinositol 3-kinase (PI3-K), which can lead to activation of the transcription factor NF-κB, and expression of antiapoptotic genes. Using two different experimental approaches, it was first demonstrated that PI3-K is a target of C1P in bone marrow-derived macrophages [112]. PI3-K activation was demonstrated by immunoprecipitation of the enzyme from whole cell lysates and assayed in vitro using ^{32}P-phosphatidylinositol. In addition, an in vivo approach provided evidence of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) formation in intact cells that were prelabeled with ^{32}P-orthophosphate [112]. PIP3 is a major product of PI3-K activity, and has recently been shown to directly inhibit acid SMase [113]. Therefore, PI3-K activation may potentiate the inhibitory effect of C1P on acid SMase through generation of PIP3 (Fig. 2). Whether C1P and PIP3 bind to the same or different domains of acid SMase remains to be elucidated.

C1P stimulated the phosphorylation of protein kinase B (PKB), which is a target of kinases from different signaling pathways including PI3-K [114,115], cAMP or cAMP-dependent protein kinase (PKA) [116,117], and PKC-ζ [118]. C1P-induced phosphorylation of PKB was sensitive to inhibition by wortmannin or LY294002, which are inhibitors of PI3-K activity. These two inhibitors also completely blocked the prosurvival effect of C1P in bone marrow-derived macrophages indicating that PKB is downstream of PI3-K in this system, and important for the antiapoptotic effect of C1P [112]. It was also reported that synthetic C_8-C1P induced phosphorylation of PKB in chick otic vesicle explants [119]; however, it is unclear in that study whether PKB is downstream of PKA, PKC, PI3-K or any other pathway that may be involved in PKB phosphorylation in birds. Another relevant finding was that C1P caused IkB phosphorylation and stimulation of the DNA binding activity of NF-κB in primary cultures of mouse macrophages [112]. Of note, C1P upregulated the expression of antiapoptotic Bcl-X_L, which is a downstream target of NF-κB (Fig. 2). The latter results provided the first evidence for a novel biological role of natural C1P in the regulation of cell survival by the PI3-K/PKB/NF-κB pathway in mammalian cells [112].

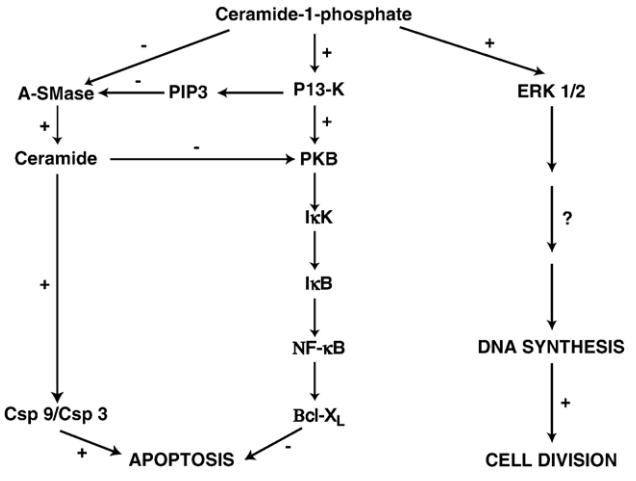

Fig. 2. Working model for the promotion of cell survival and stimulation of cell growth by Ceramide-1-phosphate. C1P prevents apoptosis by at least two primary mechanisms: (1) by inhibition of A-SMase through direct interaction with the enzyme, and the production of PIP3 (the product of PI3-K), and 2) by activating the PI3-K/PKB//NF-κB pathway leading to upregulation of antiapoptotic Bcl-X_L. C1P causes ERK1/2 activation to stimulate cell proliferation.

As mentioned above, C1P can be metabolized to ceramide by phosphatase activity, and then further converted to sphingosine and S1P by ceramidases and sphingosine kinases, respectively. Therefore, it could be speculated that the effects of C1P might be mediated through C1P-derived metabolites. However, we previously demonstrated that ceramides and C1P are antagonistic signals, and that C1P is unable to mimic many of the effects of sphingosine or S1P (i.e., PLD activation, adenylyl cyclase inhibition, or Ca^{2+} mobilization) [27,38,39,60,120]. Also, ceramides can decrease the expression of Bcl-X_L [71], whereas C1P causes its up-regulation [112]. Finally, no ceramidases capable of converting C1P to S1P have so far been identified, and S1P and C1P inhibit acid SMase by different mechanisms [92,111]. Therefore, it can be concluded that C1P acts on its own right to regulate cell functions.

It is obvious from the above observations that the activity of the enzymes involved in ceramide and C1P metabolism must be strictly regulated so that cells can keep appropriate levels of pro- versus anti-apoptotic metabolites. Any alteration in the balance between ceramides and C1P could potentially result in severe disease, or might be fatal for cells. Increasing our knowledge on the mechanisms that control ceramide and C1P levels may facilitate the ability to develop new molecular strategies for counteracting metabolic disorders.

5. Concluding remarks

The importance of C1P as regulator of cell survival is underscored by its ability to inhibit acid SMase and stimulate PI3-K. Activation of PI3-K generates PIP3, which can also inhibit acid SMase. This would reinforce the inhibitory effect of C1P on this enzyme activity to prevent ceramide production, and block apoptosis. Also, ceramides are known no inhibit PKB, downstream of PI3-K; so low levels of ceramide might facilitate signaling through the PI3-K pathway. Stimulation of PI3-K leads to activation of the transcription factor NF-κB and the subsequent upregulation of antiapoptotic Bcl-X_L. Therefore, these actions of C1P result in inhibition of cell death and promotion of cell survival. Further work will help to identify new effectors of C1P and will lead to a better understanding of the physiologic role of this intriguing phosphosphingolipid in regulating cell homeostasis.

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