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Regulation of cell growth, survival and migration by ceramide 1-phosphate - implications in lung cancer progression and inflammation

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ABSTRACT

Ceramide 1-phosphate (C1P) is a bioactive sphingolipid that is implicated in the regulation of vital cellular functions and plays key roles in a number of inflammation-associated pathologies. C1P was first described as mitogenic for fibroblasts and macrophages and was later found to promote cell survival in different cell types. The mechanisms involved in the mitogenic actions of C1P include activation of MEK/ERK1-2, PI3K/Akt/mTOR, or PKC-α, whereas promotion of cell survival required a substantial reduction of ceramide levels through inhibition of serine palmitoyl transferase or sphingomyelinase activities. C1P and ceramide kinase (CerK), the enzyme responsible for its biosynthesis in mammalian cells, play key roles in tumor promotion and dissemination. CerK-derived C1P can be secreted to the extracellular milieu by different cell types and is also present in extracellular vesicles. In this context, whilst cell proliferation is regulated by intracellularly generated C1P, stimulation of cell migration/invasion requires the intervention of exogenous C1P. Regarding inflammation, C1P was first described as pro-inflammatory in a variety of cell types. However, cigarette smoke- or lipopolysaccharide-induced lung inflammation in mouse or human cells was overcome by pretreatment with natural or synthetic C1P analogs. Both acute and chronic lung inflammation, and the development of lung emphysema were substantially reduced by exogenous C1P applications, pointing to an anti-inflammatory action of C1P in the lungs. The molecular mechanisms involved in the regulation of cell growth, survival and migration with especial emphasis in the control of lung cancer biology are discussed.

1. Introduction

Lung cancer is the most deadly cancer type throughout the world. Although it is a heterogeneous disease, cytologically it can be classified in two different subtypes, i) non-small cell lung cancer (NSCLC), which is the dominant lung cancer subtype, accounting for 80–85% of all lung cancer cases [1], and ii) small cell lung cancer (SCLC), which accounts for about 15% of all lung cancer cases. Lung cancer has a very poor prognosis, which is reflected in a 5-year survival rate of 18% [2]. In addition to morphological and histological differences, lung cancer subtypes also have distinct disease progression patterns, with SCLC showing the most rapid growth and a tendency to metastasize to distant sites of the body early in the disease. When diagnosed with distant metastases, the 5-year survival rate is less than 5% [3]. Despite decades of investigation, treatment strategies against lung cancer have proven mostly ineffective, so in order to provide better treatment options detailed understanding of the molecular mechanisms underlying initiation, progression, metastasis and resistance to chemotherapy must be a priority in clinical oncology.

It is known that sphingolipids play key roles in cancer biology, although their function in lung cancer is limited to a few key players [4]. Work from Professor Lina M. Obeid has been paramount to understand the complex world of sphingolipid metabolism and signaling in normal as well as in cancer cells. In her work entitled “Principles of bioactive lipid signaling: lessons from sphingolipids”, which was published in Nature in 2008 together with Professor Yusuf A. Hannun [5], ceramide was defined as the central hub of sphingolipid metabolism and precursor of complex sphingolipids.

As depicted in Fig. 1, there are three major pathways for synthesis of ceramides. The *de novo* synthesis pathway takes place in the endoplasmic reticulum (ER) where palmitoyl-CoA is condensed with serine to form 3-ketosphinganine, in a reaction that is catalyzed by serine palmitoyl transferase (SPT), which is the major regulatory enzyme of this

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Abbreviations

CerK	ceramide kinase
C1P	ceramide 1-phosphate
GPCR	G protein-coupled receptor
IL	interleukin
SMase	sphingomyelinase
NSCLC	non-small cell lung cancer
SCLC	small cell lung cancer
MEK	mitogen-activated protein kinase kinase
ERK	extracellularly-regulated kinase
PI3K	phosphatidylinositol 3-kinase
PKC	protein kinase C.

pathway [5,6]. Subsequently, 3-ketosphinganine is converted to sphinganine by a reductase; a fatty acid is then linked to sphinganine through an amide bond to form dihydroceramide in a reaction that is catalyzed by ceramide synthase (CerS) [7]. There are six different CerS isoforms, which substrate specificity depends of the fatty acid chain length (for details on the biology of CerS the reader is referred to elegant reviews by Futerman and co-workers [6–8]. Dihydroceramide is then converted to ceramide by the action of desaturase activity, which introduces a double bond in position 4,5 *trans*. Ceramides can then be used to synthesize complex sphingolipids including sphingomyelin, or glucosphingolipids, but can also be degraded by ceramidases to produce sphingosine. The latter can then be converted to S1P by the action of sphingosine kinases (SphK) I and II. Professor Lina M. Obeid also contributed outstanding work on the role of SphK/S1P in cell physiology and pathology, including cancer [9–11]. The second major pathway for ceramide synthesis is the sphingomyelinase (SMase) pathway, which is a catabolic pathway that takes place in the plasma membrane and lysosomes. There are at least six types of SMases in human cells, which activities depend upon the presence of different cations, including Zn^{2+} or Mg^{2+}, and optimal pH (for details on SMase biology the reader is referred to elegant reviews by L.M. Obeid and co-workers [5,12,13]). The third pathway is the salvage pathway, in which sphingosine that is derived from the metabolism of complex sphingolipids is converted back to ceramide by the action of CerS. The latter pathway takes place in the ER and mitochondria-associated membranes. There is an additional pathway for ceramide synthesis, which takes place in liver mitochondria, where sphingosine and acyl-CoA are condensed to form ceramide by the reverse activity of neutral ceramidase [14]. Perhaps the two best characterized sphingolipids controlling cancer cell growth and dissemination are ceramide and sphingosine 1-phosphate (S1P), which have opposing effects on cell fate [15]. Whilst ceramide accumulation induces cell cycle arrest and apoptosis, S1P stimulates cell growth and promotes cell survival [9–11,16].

A key metabolite of ceramide is ceramide 1-phosphate (C1P), which is synthesized by the action of ceramide kinase (CerK) acting on ceramide that is transported by CERT (ceramide transfer protein) from the ER to the Golgi apparatus where CerK resides. C1P is also present in the perinuclear region of cells [17,18]. Once generated, C1P can be transported by a ceramide phosphate transfer protein (CPTP) to the plasma

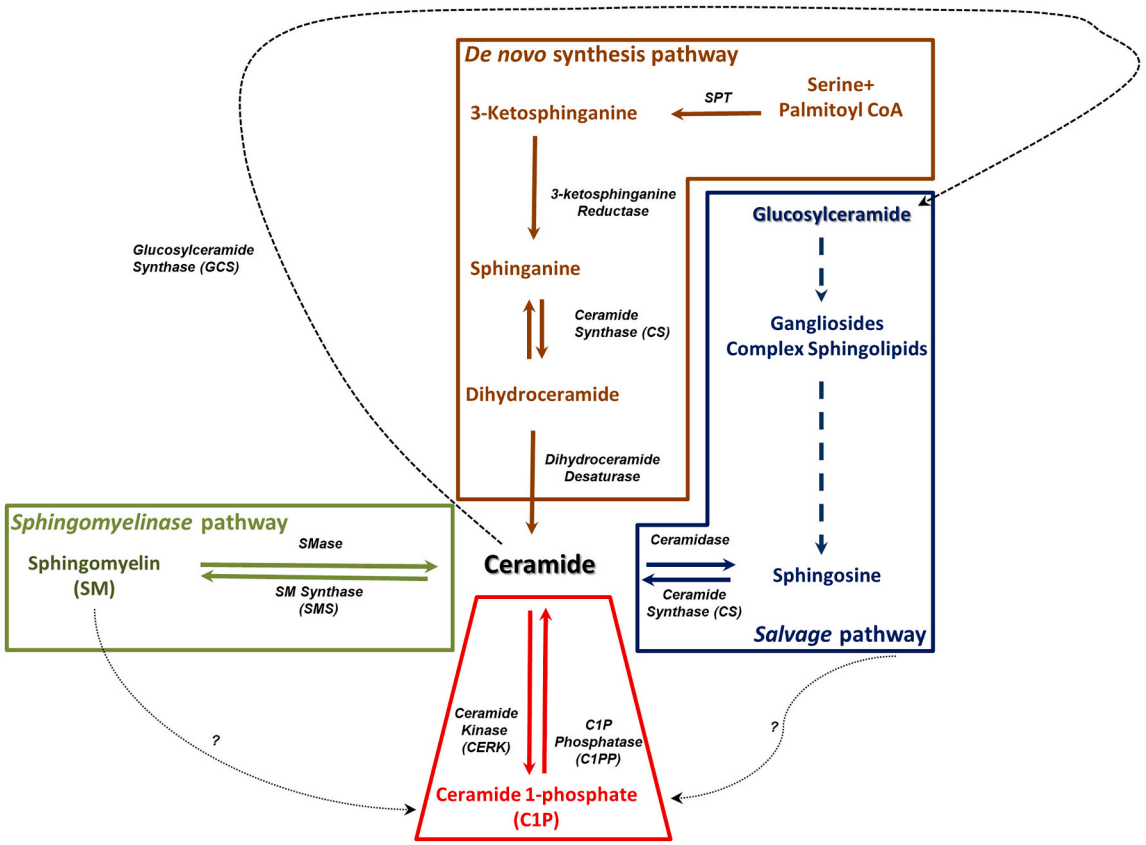

Fig. 1. Biosynthesis of sphingolipids. Ceramide is the central core of sphingolipid metabolism. Ceramide can be produced by three major pathways: (1) the *de novo* pathway (brown) involves the concerted actions of serine palmitoyl transferase (SPT) and ceramide synthase (CerS); (2) the SMase pathway (green) generates ceramide directly through degradation of SM by sphingomyelinases (SMases); (3) the salvage pathway (blue) uses sphingosine (Sph) derived from the metabolism of complex sphingolipids to form ceramide. Sph can be converted to ceramide by the action of CerS. Ceramides can be degraded by ceramidases to form Sph. Phosphorylation of Sph by SphK yields S1P. Ceramide can be phosphorylated to C1P by the action of ceramide kinase (CerK). In addition, ceramides can be generated from C1P by the action of lipid phosphate phosphatases (LPP) or C1P phosphatase (CPP).

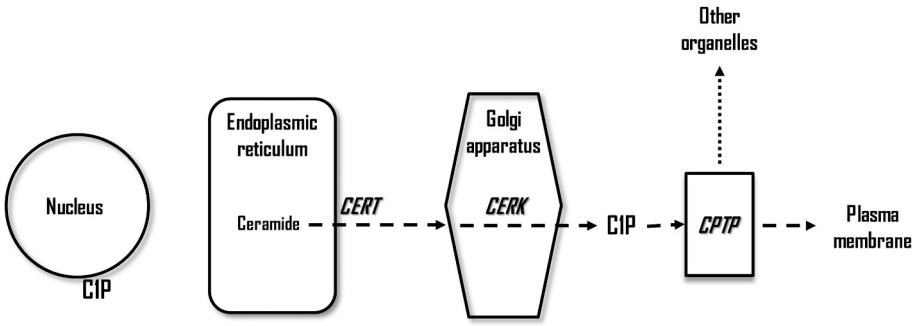

Fig. 2. Biosynthesis and intracellular transport of ceramide 1-phosphate. Ceramide 1-phosphate (C1P) is mostly synthesized in the Golgi apparatus. Ceramides are synthetized in the endoplasmic reticulum (ER) and are transported to the Golgi apparatus by ceramide transfer protein (CERT). In the Golgi, ceramide kinase (CerK) can phosphorylate ceramides to generate C1P. A C1P transfer protein (CPTP) will then transport C1P from the Golgi apparatus to the plasma membrane and probably to other organelles. C1P is also present in the perinuclear region of cells.

membrane or to other organelles, where it might regulate signal transduction processes [19] (Fig. 2), or it may traffic along the secretory pathway to reach the plasma membrane [20].

2. CerK/C1P regulates cell growth and survival. Implication in lung cancer progression

Initial studies showed that C1P stimulated DNA synthesis and proliferation in rat fibroblasts [21,22] and primary or transformed macrophages [23–25]. Subsequently, these observations were extended to other cell types including mouse myoblasts [26,27], primary rat aortic vascular smooth muscle cells [28], primary photoreceptor progenitors [29,30]; endothelial progenitors in Kaposi sarcoma [31] or mouse leukemia RAW264.7 macrophages [25]. The molecular mechanisms whereby C1P stimulates cell proliferation involve activation of different signaling pathways. Specifically, in bone marrow-derived macrophages (BMDM), C1P-stimulated cell growth was mediated by the MEK/ERK1–2 and PI3K/Akt pathways leading to upregulation of the mammalian target of rapamycin (mTORC1) and its downstream targets p70S6K and Rho-associated kinase (ROCK) [32]. In addition, C1P stimulated BMDM proliferation through production of low levels of reactive oxygen species (ROS) [33] and through activation of protein kinase C-alpha (PKC-α) [23]. However, stimulation of cell proliferation in mouse leukemia cells involved prior secretion of vascular endothelial growth factor (VEGF) and subsequent activation of its major receptor, VEGFR2 [25], and C1P-stimulated myoblast proliferation required the secretion of lysophosphatidic acid (LPA) and subsequent activation of the LPA1 and 3 receptors [27].

With regard to cell survival, C1P was first shown to inhibit cell death in BMDM incubated under apoptotic conditions. Apoptotic BMDM showed elevated levels of ceramides, which were generated by upregulation of acid SMase (ASMase) [34]; C1P blocked ASMase activity causing a sharp reduction in the levels of proapoptotic ceramide thereby promoting cell survival. C1P-induced cell survival was also enhanced by stimulation of the inducible form of nitric oxide synthase (iNOS) and the subsequent production of nitric oxide (NO) in the macrophages [35]. Interestingly, NO plays a dual role in cell biology as it induces apoptosis when generated at high concentrations whilst promoting cell survival at low concentrations. Another relevant pathway implicated in the pro-survival actions of C1P is the PI3K/Akt pathway. Activation of PI3K is a major mechanism by which many growth factors and oncogenes block cell death to promote survival in a variety of cell types [36] . The stimulation of PI3K/Akt by C1P also caused upregulation of the Nuclear transcription factor-κB (NF-κB), and the antiapoptotic Bcl-2 family member Bcl-X_L [37] leading to cell survival. Also of interest, it was recently shown that local administration of C1P drastically reduced ovarian damage induced by the anticancer drug cyclophosphamide *via* protection of the follicular reserve, restoration of hormone levels, inhibition of apoptosis and improvement of stromal vasculature, while protecting fertility, oocyte quality and uterine morphology in a mouse model of premature ovarian failure [38].

Concerning lung cells, it was first shown that C1P regulates growth and survival of A549 human lung adenocarcinoma cells. In particular, relatively low concentrations of C1P ranging 0.5–1 μM enhanced lung cell proliferation, whereas relatively high concentrations (5–25 μM) decreased cell viability [39]. Similar findings were reported on rat fibroblasts where C1P concentrations higher than 5 μM were less effective than lower C1P concentrations at stimulating fibroblast proliferation [21]. Also, downregulation of CerK using specific siRNA to silence the gene encoding this kinase increased the number of apoptotic lung cells by about 10-fold suggesting that intracellular C1P is responsible for the maintenance of cell viability. Cell apoptosis correlated with degradation of endogenous C1P to proapoptotic ceramides [39], an action that was also observed in BMDM incubated in the absence of monocyte/macrophage colony-stimulating factor (M-CSF), which is a hematopoietic growth factor essential for maintenance of macrophage viability and proliferation [34]. On the same line of investigation, Huwiler and coworkers showed that the CerK inhibitor NVP-231 reduced lung cancer cell viability and DNA synthesis by triggering cell death. The CerK inhibitor led to M phase arrest of the cell cycle and potently activated the caspase 9/caspase 3 pathway to promote apoptosis in the lung cancer cells [40]. More recently, the same group showed that CerK is upregulated in metastatic breast cancer cells. CerK contributed to cell migration also by activation of the PI3K/Akt pathway, as discussed below [41]. C1P also promoted cell survival in normal rat alveolar macrophages that were maintained in culture under apoptotic conditions. Specifically, incubation of the alveolar macrophages in the absence of serum caused upregulation of SPT, which as mentioned above is the major regulatory enzyme of the *de novo* pathway of ceramide synthesis, thereby causing accumulation of proapoptotic ceramides [42]. Noteworthy, C1P potently inhibited SPT causing a sharp depletion in the levels of ceramides, and upregulated Akt phosphorylation and its downstream effector NF-κB leading to macrophage survival. It can then be concluded that a major mechanism by which C1P promotes cell survival involves the reduction of proapoptotic ceramide levels by blockade of their synthesis through inhibition of SMase or SPT activities.

3. CerK/C1P regulates cell migration. Implication in lung cancer cell dissemination

Cell migration is a physiological process that is crucial for the maintenance and development of multicellular organisms. In particular, the directed motility of cells in response to chemoattractants is essential for embryogenesis, organogenesis, tissue regeneration, wound healing or immune responses. However, when directed migration is altered and cells move to inappropriate sites within the organism chronic inflammation may arise. This may result in the development of inflammation-associated illnesses such as, multiple sclerosis, inflammatory bowel disease (namely Crohn's disease and ulcerative colitis), asthma or cancer. Tumors that arise at sites of chronic inflammation are characterized by the presence of infiltrating leukocytes, namely macrophages [43], which actively participate in tumor progression and dissemination by

releasing a variety of cytokines or chemokines. From this perspective, the migration of cells from primary tumors would end up colonizing surrounding or distal tissues to establish secondary malignant neoplasms in the context of metastasis.

Initial studies using RAW264.7 mouse leukemia cells identified C1P as a novel chemoattractant agent for macrophages [44]. Subsequent studies demonstrated the ability of C1P to also stimulate migration of acute monocyte human leukemia THP-1 cells and mouse J774.A1 reticulum cell sarcoma [45]. In all of these cell types, C1P-induced migration was suppressed by preincubation of the cells with pertussin toxin (Ptx), a potent inhibitor of Gi/o proteins, suggesting the participation of a Gi protein-coupled receptor (GPCR) in this action. In fact, a putative GiPCR receptor for C1P has been partially characterized [44–46]. The stimulation of cell migration by C1P has been confirmed in different cell systems, including hematopoietic stem progenitor cells, smooth muscle cells, multipotent stromal cells and human umbilical vein endothelial cells [47–49]; coronary artery macrovascular endothelial cells and retinal microvascular endothelial cells [50]. The latter report also showed that C1P stimulated cell migration and invasion through interaction with anexin a2-p11, a heterotetrameric protein complex serving as a receptor platform for multiple proteins implicated in vascular invasion through the extracellular matrix. C1P levels also increase during the process of wound healing to stimulate the migration of fibroblasts to the wound sites [51]. More recently, CerK and C1P were found to regulate invasion and migration of human pancreatic cancer cells. Whilst exogenous C1P enhanced migration and invasion of the pancreatic cancer cells through interaction with a GPCR, CerK-generated intracellular C1P mediated the spontaneous migration of pancreatic cancer cells in a GPCR-independent manner [52]. Noteworthy, joined efforts by Hannun's and Obeid's groups identified a novel pathway in which ASMase-derived ceramide was converted to C1P by CerK to promote invasion of MDA-MB-231 breast carcinoma cells [12]. Also, CerK was shown to be upregulated in the MDA-MB-231 breast cancer cells and treatment with the CerK inhibitor NVP-231 potently reduced the migratory and invasive capacity of these cells [41].

A particularly sensitive cancer type to the chemotactic actions of C1P is lung cancer. Both NSCLC and SCLC responded to relatively low concentrations of extracellular C1P to accomplish migration. Specifically, C1P (0.5 μM) was more potent than its counterpart S1P (at 1 μM) to stimulate migration of the human NSCLC A549, HTB177, HTB183 and CRL5803 cells, and was as potent as the classical chemoattractants LPA or hepatocyte growth factor/scatter factor (HGF/SF, at supraphysiological concentrations). Likewise, C1P was more potent than S1P at stimulating migration of the CRL2062 and CRL5853 SCLC cells [53] . However, although in the latter report C1P, S1P and LPA were shown to enhance the phosphorylation levels of p42/44 MAPK and Akt in all NSCLC and SCLC cells that were tested, participation of these kinases in the chemotactic effects of C1P in the lung cells was not examined. Of interest, and contrary to the actions of exogenous C1P, Tomizawa and coworkers [54] have recently reported that CerK, the enzyme that produces C1P intracellularly, exerts inhibitory effects on lamellipodium formation, cell migration and metastasis of the NSCLC A549 cells. In particular, knockdown of CerK using shCerK in A549 cells increased the formation of lamellipodia, which are membrane protussions coupled to cell migration, whereas overexpression of CerK inhibited cell migration. The inhibitory effect of intracellularly generated C1P on lung cancer cell migration was reproduced in MCF-7 breast cancer cells [54]. Although these C1P actions on cell migration seem to be contradictory it should be borne in mind that intra and extracellular C1P may exert different effects on cells. In fact, contrary to extracellularly applied C1P, increasing the intracellular concentration of C1P using CerK-activating stimuli [44] or cell-permeable light-sensitive caged C1P analogs stimulated macrophage proliferation but failed to induce cell migration [55,56]. The latter findings are consistent with other work using 3T3-L1 cells to study preadipocyte differentiation into mature adipocytes. It was observed that whilst upregulation of CerK is positively implicated in adipogenesis [57], extracellularly applied C1P inhibited this process [58]. Also, the effects of C1P on cells may dependent on other factors such as cellular compartmentalization where C1P can be differentially synthesized, the ability of cells to secrete C1P to the extracellular milieu, or the different molecular species of C1P that can be generated under distinct experimental conditions.

4. Control of inflammatory responses by ceramides and C1P in the lungs

Ceramides have been implicated in inflammatory responses in different cell types, and are particularly important in lung inflammation where they play key roles in a variety of pathologies including chronic obstructive pulmonary disease (COPD), asthma, or lung fibrosis [59–62]. Ceramides are also the molecular mediators of pulmonary edema induced by platelet-activating factor (PAF) [63], and participate in the development of emphysema in humans or mice exposed to cigarette smoke [61,62,64–66]. Nonetheless, some of the proinflammatory actions of ceramides were attributed to its direct metabolite C1P. In fact, initial studies by Chalfant and coworkers showed that C1P promoted inflammation in different cell types [67–73], an action that was associated with translocation and stimulation of cytosolic phospholipase A_2 ($cPLA_2$) and the subsequent formation of proinflammatory eicosanoids [69–78] . The latter findings were supported by the reduced levels of proinflammatory cytokines observed in a genetic ablation model of CerK in mice [79]. Also, knockdown of CerK with specific siRNA led to inhibition of NADPH oxidase (NOX) and the reduction of eicosanoid levels in neuroblastoma cells, thereby implicating this enzyme in brain inflammation [80]. However, exogenously applied C1P inhibited cigarette smoke-induced airway inflammation in mice and human airway epithelial cells, pointing to an anti-inflammatory action of exogenous C1P in lung tissue. Specifically, C1P reduced both cigarette smoke-induced acute and chronic inflammation and the development of emphysema in mice, actions that were associated with a reduction of neutral SMase activity and ceramide levels, and subsequent blockade of the proinflammatory transcription factor NF-κB in the lungs. These inhibitory actions of C1P also reduced the release of the proinflammatory cytokines interleukin (IL)-1β, IL-6, keratinocyte chemoattractant (KC) protein and macrophage inflammatory protein-2 (MIP-2), as well as the infiltration of immune cells (namely macrophages and neutrophils) in the lungs of mice exposed to cigarette smoke [81]. The anti-inflammatory effects of C1P on cigarette smoke-induced lung inflammation were not limited to the modulation of structural cells, as C1P also reduced the upregulation of neutral SMase and NF-κB expression, and the production of IL-8 that were elicited by cigarette smoke in human neutrophils [81]. In a follow-up study using a mouse model of acute lung inflammation and human neutrophils it was demonstrated that C1P attenuated lipopolysaccharide (LPS)-induced acute lung injury by preventing NF-κB activation in neutrophils [82]. Specifically, the intrapulmonary application of C1P before (prophylactic) or 24 h after (therapeutic) LPS instillation decreased neutrophil trafficking to the lungs, reduced the levels of the proinflammatory cytokines IL-1β, IL-6, KC and migration inhibitory factor (MIF) in bronchoalveolar lavage fluid, blocked LPS-induced NF-κB phosphorylation and IL-8 production in human neutrophils, and attenuated alveolar capillary leakage, suggesting that C1P could be a valuable tool for treatment of acute lung injury. In addition to the latter observations, in healthy individuals as well as in asthmatic patients exposed to second hand smoke, which is a proinflammatory condition, C1P levels, particularly the $C_{28:1}$1P species, were significantly decreased further supporting the notion of an anti-inflammatory action of C1P in the lungs [83]. The potential of C1P as a novel therapeutic agent in pulmonary inflammation has been previously discussed [84].

5. Concluding remarks

Whilst the mitogenic, prosurvival and chemotactic properties of C1P are well established, published data are often contradictory. For example, exogenously applied C1P to human A549 lung cancer cells results in stimulation of cell migration, whereas knockdown of CerK, the enzyme that catalyzes the intracellular biosynthesis of C1P, also causes upregulation of lung cancer cell chemotaxis. Likewise, and contrary to exogenously applied C1P, increasing the intracellular concentration of C1P in mouse leukemia RAW264.7 macrophages resulted in cell proliferation but did not cause cell migration. All of these observations suggest that C1P has dual, and often different, effects on cells depending on whether C1P acts endogenously or extracellularly. Noteworthy, the stimulation of cell proliferation by intracellular C1P seems to be a receptor-independent effect, whereas stimulation of cell migration by exogenous C1P can be fully blocked by GPCR inhibitors, including pertussis toxin, suggesting that this is a receptor-dependent action of C1P. Concerning inflammation, there are also differential effects of C1P, or CerK, in cells although in this particular case C1P actions seem to be dependent upon cell type. In particular, although C1P promotes inflammation in many cell types, it exerts anti-inflammatory actions in lung tissue. Taken together, these observations indicate that C1P actions may vary depending on the particular experimental settings, cell type, and context of the studies that may be underway under specific circumstances.

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Credit author statement

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