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Ceramide 1-Phosphate: First, Second, or Dual Messenger?

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The concept that lipids, including Sphingolipids (SL), are essential components of cell architecture has been known for decades. Lipid biology gained extraordinary interest among scientists from diverse fields of research after the discovery that structural lipids could serve as substrates for generation of second messengers, or regulators of cell metabolism. First, it was discovered that phospholipids such as phosphatidylinositols or phosphatidylcholine, could be hydrolyzed by specific C-type phospholipases to produce Diacylglycerol (DAG), a metabolite later found to be the physiological activator of Protein Kinase C (PKC), which comprises a family of enzymes that regulate vital cellular functions including cell growth and survival [1]. Phospholipids are asymmetrically distributed between the inner and outer monolayer of cell membranes, with Sphingomyelin (SM) being preferentially located in the outer membrane leaflet. Much of the cell SM can be found in specific membrane domains named rafts, which appear to act as platforms to colocalize proteins involved in intracellular signaling pathways. SM can be acted upon by sphingomyelinases, which are esterases with phospholipase C activity that specifically degrade SM to produce ceramide, a metabolite with anti-proliferative and pro-apoptotic properties [2]. Ceramide can be further metabolized to sphingosine by the action of ceramidases, and sphingosine, in turn, can be phosphorylated to produce sphingosine phosphate by the action of sphingosine kinases. The effects of sphingosine phosphate on cells and animal models have been extensively studied; in particular, this phosphosphingolipid has been shown to regulate a number of biological functions including angiogenesis, chemotaxis, differentiation or cell growth and survival [3].

A major metabolite of ceramide is Ceramide 1-Phosphate (C1P), which is formed by the action of Ceramide Kinase (CerK) on ceramide [4]. This pathway seems to be the only one responsible for C1P generation in mammalian cells although some studies suggest that other pathways may also exist. In particular, it was reported that Bone Marrow-Derived Macrophages (BMDM) from CerK-null mice (CerK-/-) still had significant levels of C1P [5]. Two alternative pathways for generation of C1P in cells might be: i) acylation of S1P by a putative acyl transferase that would catalyze the formation of a N-linked fatty acid thereby generating C1P, and ii) cleavage of Sphingomyelin (SM) by the action of SMase D, which would generate choline and C1P. However, none of these pathways have so far been reported to exist in mammalian tissues [6].

C1P was first observed in human leukemia HL-60 cells [4] but its role in cell biology was unknown until the discovery that it stimulated DNA synthesis and cell proliferation in rat fibroblasts [7]. Subsequent studies, also by our group, using primary macrophages revealed that the mechanism by which C1P exerts this action involves activation of various signaling pathways including Mitogen-Activated Protein Kinase Kinase (MEK)/Extracellularly Regulated Kinases 1-2 (ERK1-2), Phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (PKB, also known as Akt), c-Jun N-terminal Kinase (JNK), activation of Sphingomyelin Synthase (SMS), an enzyme that produces DAG resulting in activation of PKC (reviewed in [6]), and activation of the mammalian Target of Rapamycin (mTOR) [8]. Subsequently, it was found that C1P promoted cell survival. In particular, it was demonstrated that C1P blocked apoptosis by decreasing the accumulation of pro-apoptotic ceramides through inhibition of acid sphingomyelinase [9] or serine palmitoyl transferase [10], depending on cell type.

A more recent study has established that C1P is a potent stimulator of cell migration [11]. Noteworthy, this action could only be observed when C1P was administered to the cells exogenously, whilst augmentation of the intracellular levels of C1P, using different strategies, failed to stimulate cell motility. This observation led to the discovery of a putative C1P receptor. This receptor was found to be coupled to Gi proteins and led to stimulation of the PI3K/PKB, MEK/ERK, and JNK signaling pathways upon ligation with C1P [11]. Therefore, it seems plausible that C1P can act as first messenger to stimulate cell migration. These findings raised the question as to whether the mitogenic and anti-apoptotic effects of C1P might also be mediated through activation of this receptor. To address this point, the levels of intracellular C1P were increased by overexpressing CerK, or by using a photolabile C1P analogue bearing 4-Bromo-5-Hydroxy-2-Nitrobenzhydryl (BHNB). The BHNB-C1P compound bypasses cell surface receptors and can be released in the cytosol upon photolysis using light of wavelength that does not damage cellular components [12]. By doing this, it was demonstrated that only C1P generated intracellularly was able to stimulate cell proliferation, and that cell migration could only be activated when C1P was applied exogenously to the cells. These findings clearly show that C1P can act both intracellularly to stimulate cell growth and inhibit apoptosis, or exogenously to stimulate chemotaxis. Therefore, it can be concluded that C1P has properties of both first and second messenger in cell biology. These features of C1P make it a suitable candidate for participation in pathological processes that are associated to cell proliferation and migration, as it occurs in tumorigenesis and inflammation. In fact, the involvement of C1P in inflammatory responses has been well characterized [13]. Although it is now clear that C1P has dual messenger functions, further studies are necessary to completely elucidate the mechanisms by which C1P exerts its actions and to establish the signaling pathways involved in C1P biosynthesis and compartmentalization. The results obtained from these investigations will be crucial for understanding the physiological and pathological processes in which sphingolipids are known to participate.

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