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# Euro Cancer 2018: Regulation of pancreatic cancer cell migration by the axis ceramide kinase/ceramide 1-phosphate - Antonio Gomez-Munoz - University of the Basque Country

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Pancreatic cancer is an aggressive disease characterized by invasiveness, rapid progression and profound resistance to treatment. It is the fourth leading cause of cancer mortality with a 5-year survival rate of only 6%. Accumulating evidence indicates that sphingolipids play critical roles in cancer growth and dissemination. In particular, ceramide 1- phosphate (C1P), which is formed by the action of ceramide kinase on ceramide, stimulates cell proliferation (1), and promotes cell survival (2, 3). The mechanisms by which C1P stimulates cell growth involves activation of extra cellularly regulated kinases 1 and 2 (ERK1/2), phosphatidylinositol 3-kinase (PI3K), c-Jun N-terminal kinase (JNK), or mammalian target of rapamycin (mTOR), whereas C1P-enhanced cell survival implicates inhibition of serine palmitoyl transferase (SPT) and acid sphingomylinase (ASMase) (4). More recently, we found that C1P enhances human pancreatic cancer cell migration and invasion potently and that this effect is completely abolished by pertussis toxin (PTX), suggesting the participation of a Gi protein-coupled receptor in this process. We also observed that human pancreatic cancer cells migrate spontaneously. However, contrary to the effect of C1P, spontaneous cell migration was insensitive to treatment with PTX (5). Investigation into the mechanisms responsible for spontaneous migration of the pancreatic cancer cells revealed that ceramide kinase (CerK) is a key enzyme in the regulation of this process. In fact, inhibition of CerK activity, or treatment with specific CerK siRNA to silence the gene encoding this kinase, potently reduced migration of the pancreatic cancer cells. By contrast, overexpression of CerK stimulated cell migration, an action that was concomitant with prolonged phosphorylation of ERK1-2 and Akt, in a PTX independent manner. It can be concluded that the axis CerK/C1P plays a critical role in pancreatic cancer cell migration/invasion, and that targeting CerK expression or activity may be a relevant factor for controlling pancreatic cancer cell dissemination.

Ceramide 1-phosphate (C1P) is bioactive sphingolipid metabolite first shown to regulate cell growth and death of the cell. The subsequent studies revealed to C1P was a potent stimulator of cytosolic phospholipase A2 (cPLA2) with ensuing release the arachidonic acid and prostaglandin biosynthesis. The latter findings placed C1P on the list of pro-inflammatory metabolites. As more recently C1P was found to potently stimulate cell migration an action that is associated to diverse physiological effects and as well as to inflammatory responses following with tumor dissemination. The implication of C1P in inflammation has gained further interest in last few years due to the discovery it can exert anti-inflammatory actions in some of the cell types and tissues. In particular, C1P has been demonstrated to inhibit pro-inflammatory cytokine release & blockade of pro-inflammatory transcription factor NF-κB in some cell types, as to reduce airway inflammation and lung emphysema. The present review is focused on novel aspects of the C1P regulation of cell migration and impact of C1P as novel anti-inflammatory agent. Gloss: Ceramide 1-phosphate (C1P) is phosphosphingolipid with potent biological activities. It promotes cell growth and survival and is a key regulator of cell migration. Both C1P and the enzyme that catalyzes its biosynthesis, ceramide kinase are implicated in inflammatory responses. Although C1P has pro-inflammatory properties it reduces pulmonary emphysema and exerts anti-inflammatory actions in the lung. Synthetic C1P analogs may be promising tools to treat lung inflammation.

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