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Implication of Ceramide 1-Phosphate in Pancreatic Cancer

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Abstract

One of the most aggressive types of cancer is pancreatic cancer, which is characterized by invasiveness, rapid progression and profound resistance to treatment. Although the molecular mechanisms implicated in this type of cancer are not well understood recent evidence indicates that bioactive sphingolipids play critical roles in cancer growth and dissemination. In this context, we first demonstrated that ceramide 1- phosphate (C1P), which the product of ceramide kinase (CerK), stimulates cell proliferation, and promotes cell survival. The mechanisms by which C1P stimulates cell growth involves activation of extracellularly regulated kinases 1 and 2 (ERK1/2), phosphatidylinositol 3-kinase (PI3K), c-Jun N-terminal kinase (JNK), mammalian target of rapamycin (mTOR), or protein kinase C, whereas C1P-enhanced cell survival implicates inhibition of serine palmitoyl transferase (SPT) and acid sphingomylinase (ASMase). 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, spontaneous cell migration was insensitive to treatment with PTX. Investigation into the mechanisms responsible for spontaneous migration of the pancreatic cancer cells revealed that CerK is a key enzyme in the regulation of this process. In fact, inhibition of this enzyme, potently reduced migration of the pancreatic cancer cells, whereas overexpression of CerK stimulated cell migration. The latter action was concomitant with prolonged phosphorylation of ERK1-2 and Akt, in a PTX independent manner. Hence, 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 metastasis of pancreatic cancer cells

Keywords: Pancreatic cancer, sphingolipids, ceramide kinase, ceramide-1-phosphate

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