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Regulation of pancreatic cancer cell migration by the axis ceramide kinase/ceramide 1-phosphate

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 extracellularly 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 sphingomyelinase (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.

Recent Publications

1. Rivera I G, Ordoñez M, Gangoiti P, Presa N, Gomez-Larrauri A, et al. (2016) Ceramide 1-phosphate regulates cell migration and invasion of human pancreatic cancer cells, *Biochem. Pharmacol* 102:107–119.
2. Granado M H, Gangoiti P, Ouro A, Arana L and Gomez-Munoz A (2009) Ceramide 1-phosphate inhibits serine palmitoyltransferase and blocks apoptosis in alveolar macrophages. *Biochim Biophys Acta* 1791(4):263–272.
3. Gomez-Munoz A, Kong J Y, Parhar K, Wang S W, Gangoiti P, et al. (2005) Ceramide-1-phosphate promotes cell survival through activation of the phosphatidylinositol 3-kinase/protein kinase B pathway. *FEBS Lett.* 579(17):3744–3750.
4. Gomez-Munoz A, Kong J Y, Salh B and Steinbrecher U P (2004) Ceramide-1-phosphate blocks apoptosis through inhibition of acid sphingomyelinase in macrophages. *J. Lipid Res.* 45(1):99–105.
5. Gomez-Munoz A, Duffy P A, Martin A, O'Brien L, Byun H S, et al. (1995) Short-chain ceramide-1-phosphates are novel stimulators of DNA synthesis and cell division antagonism by cell-permeable ceramides. *Mol Pharmacol* 47(5):833–839.

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Biography

Antonio Gomez-Muñoz received his PhD in Biochemistry and Molecular Biology from the University of the Basque Country (Bilbao, Spain) in 1988. Part of his thesis was developed at the Medical School of the University of Nottingham in the UK during 1987. He achieved postdoctoral training at the University of Alberta (Edmonton, Alberta, Canada) from 1988 to 1994. He then accepted a Research position at the Spanish Research Council (CSIC) from 1995 to 1996. From 1997 to 1998 he worked as Researcher in the Faculty of Medicine, University of British Columbia (Vancouver, British Columbia, Canada). He then returned to the University of the Basque Country where he is currently Professor of Biochemistry and Molecular Biology. His major research interest is on the targeting of sphingolipid metabolism with the aim of developing new strategies for prevention of inflammatory diseases, obesity, and cancer. He has produced over 100 publications in the field.

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