

Investigation on physiological roles of sphingosine-1-phosphate signaling system using genetically engineered mice

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2003 Fiscal Year Final Research Report Summary

Investigation on physiological roles of sphingosine-1-phosphate signaling system using genetically engineered mice.

Research Project

Project/Area Number

14570102

Research Category

Grant-in-Aid for Scientific Research (C)

Allocation Type

Single-year Grants

Section

一般

Research Field

General medical chemistry

Research Institution

KANAZAWA UNIVERSITY

Principal Investigator

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Project Period (FY)

2002 – 2003

Keywords

Sphingosine-1-phosphate / G protein-coupled receptor / cell movement / lung metastasis model / low molecular weight G protein / PDGF / 血管平滑筋

Research Abstract

We have identified sphingosine-1-phosphate(S1P) receptor isoform S1P₂ as the first G protein-coupled receptor that negatively regulates cell mobility. In the present study we demonstrated that endogenously expressed S1P₂ in mouse melanoma B16-F10 cells indeed mediated inhibition of cell migration and invasion in in vitro system. In addition, we found that pretreatment of B16 cells with S1P potently inhibited pulmonary metastasis in vivo in tail vein injection model, via endogenously expressed S1P₂. These results raises an intriguing possibility that S1P₂-selective agonist could serve as an inhibitor of tumor cell invasion and metastasis in a subset of human malignancies. In sharp contrast to S1P₂, we and others have demonstrated that S1P₁ and

S1P₃ mediates S1P stimulation of cell migration, thereby acting as chemotactic receptors. Indeed, overexpression of either of the latter receptor isoforms in B16 melanoma cells resulted in stimulation of migration and invasion in vitro, and aggravation of lung metastasis in vivo in response to S1P treatment. In addition, we have recently found that S1P₁ mediated S1P stimulation of platelet-derived growth factor upregulation in cultured vascular smooth muscle cells, through the action of a transcription factor KLF5. The results may implicate pathophysiological role for S1P₁ in development of atherosclerosis. In an attempt to elucidate physiological role of S1P signaling system in vivo, we have created S1P₂ knockout mice and sphingosine kinase transgenic mice. Investigation on these genetically engineered mice is now underway.

Research Products (20 results)

All Other

All Publications (20 results)

- [Publications] Y.Ryu et al.: "Sphingosine-1-phosphate, a platelet-derived lysophospholipid mediator, negatively regulates cellular Rac activity and cell migration in vascular smooth muscle cells." *Circ Res.* 90. 325-332 (2002) ▼
- [Publications] K.Takami et al.: "Interferon-gamma inhibits hepatocyte growth factor-stimulated cell proliferation of human bronchial epithelial cells : upregulation of p27(kip1) cyclin-dependent kinase inhibitor." *Am J Respir Cell Mol Biol.* 26. 231-238 (2002) ▼
- [Publications] Y.Takuwa et al.: "The edg family G protein-coupled receptors for lysophospholipids : their signaling properties and biological activities." *J.Biochem(Tokyo).* 131. 767-771 (2002) ▼
- [Publications] Y.Banno et al.: "Involvement of phospholipase D in insulin-like growth factor-I-induced activation of extracellular signal-regulated kinase, but not phosphatidylinositol 3-kinase or Akt, in Chinese hamster ovary cells." *Biochem.J.* 369. 363-368 (2003) ▼
- [Publications] N.Sugimoto et al.: "Inhibitory and stimulatory regulation of Rap and cell motility by the G_{<12/13>}-Rho and the G_i-pathways integrated downstream of a single G protein coupled sphingosine-1-phosphate receptor isoform." *Mol.Cell.Biol.* 23. 1534-1545 (2003) ▼
- [Publications] K.Arikawa et al.: "Ligand-dependent inhibition of 16 melanoma cell migration and invasion via endogenous S1P₂ G protein-coupled receptor requirement of inhibition of cellular Rac activity" *J.Biol.Chem.* 278. 32841-32851 (2003) ▼
- [Publications] H.Yamaguchi et al.: "Sphingosine-1-phosphate receptor subtype-specific positive and negative regulation of Rac and hematogenous metastasis of melanoma cells." *Biochem.J.* 374. 715-722 (2003) ▼
- [Publications] N.Sugimoto et al.: "Molecular mechanisms of sphingosine-1-phosphate receptor S1P₂/Edg5-mediated inhibition of Rac and cell migration." *Seikagaku.* 75(7). 597-600 (2003) ▼
- [Publications] S.Sakurada et al.: "Ca²⁺-dependent activation of Rho and Rho kinase in membrane depolarization-induced and receptor stimulation-induced vascular smooth muscle contraction." *Circ Res.* 93(6). 548-556 (2003) ▼
- [Publications] S.Usui et al.: "Boold lipid mediator sphingosine-1-phosphate potently stimulates platelet derived growth factor-A and -B chain expression through S1P₁-Gi-Ras-MAPK-dependent induction of kruppel-like factor 5." *J.Biol.Chem.* 279. 12300-12311 (2004) ▼
- [Publications] Y.Ryu, N.Takuwa, N.Sugimoto, S.Sakurada, S.Usui, H.Okamoto, O.Matsui, Y.Takuwa: "Sphingosine-1-phosphate, a platelet-derived lysophospholipid mediator, negatively regulates cellular Rac activity and cell migration in vascular smooth muscle cells." *Am J Respir Cell Mol Biol.* 26(2). 231-238 (2002) ▼
- [Publications] K.Takami, N.Takuwa, H.Okazaki, M.Kobayashi, T.Ohtoshi, S.Kawasaki, M.Dohi, K.Yamamoto, T.Nakamura, M.Tanaka, K.Nakahara, Y.Takuwa, H.Takizawa: "Interferon-gamma inhibits hepatocyte growth factor-stimulated cell proliferation of human bronchial epithelial cells' upregulation of p27(kip1) cyclin-dependent kinase inhibitor." *Circ Res.* 90(3). 325-332 (2002) ▼
- [Publications] Y.Takuwa, N.Takuwa, N.Sugimoto: "The Edg family G protein-coupled receptors for lysophospholipids : their signaling properties and biological activities." *J Biochem(Tokyo).* 131(6). 767-771 (2002) ▼
- [Publications] Y.Banno, Y.Takuwa, M.Yamada, N.Takuwa, K.Ohguchi, A.Hara, Y.Nozaawa: "Involvement of phospholipase D in insulin-like growth factor-I-induced activation of extracellular signal-regulated kinase, but not phosphoinositide 3-kinase or Akt, in Chinese hamster ovary cells." *Biochem J.* 369(Pt 2). 363-368 (2003) ▼
- [Publications] N.Sugimoto, N.Takuwa, H.Okamoto, S.Sakurada, Y.Takuwa: "Inhibitory and stimulatory regulation of Rac and cell motility by the G_{<12/13>}-Rho and Gi pathways integrated downstream of a single G protein-coupled sphingosine-1-phosphate receptor isoform." *Mol Cell Biol.* 23(5). 1534-1545 (2003) ▼

- [Publications] K.Arikawa, N.Takuwa, H.Yamaguchi, N.Sugimoto, J.Kitayama, H.Nagawa, K.Takehara, Y.Takuwa: "Ligand-dependent inhibition of B16 melanoma cell migration and invasion via endogenous S1P2 G protein-coupled receptor. Requirement of inhibition of cellular RAC activity." J Biol Chem.. 278(35). 32841-32851 (2003) ▼
- [Publications] H.Yamaguchi, J.Kitayama, N.Takuwa, K.Arikawa, I.Inoki, K.Takehara, H.Nagawa, Y.Takuwa: "Sphingosine-1-phosphate receptor subtype-specific positive and negative regulation of Rac and haematogenous metastasis of melanoma cells." Biochem J.. 374(Pt 3). 715-722 (2003) ▼
- [Publications] N.Sugimoto, N.Takuwa, Y.Takuwa: "Molecular mechanisms of sphingosine-1-phosphate receptor S1P2/Edg5-mediated inhibition of Rac and cell migration." Seikagaku. 75(7). 597-600 (2003) ▼
- [Publications] S.Sakurada, N.Takuwa, N.Sugimoto, Y.Wang, M.Seto, Y.Sasaki, Y.Takuwa: "Ca²⁺-dependent activation of Rho and Rho kinase in membrane depolarization-induced and receptor stimulation-induced vascular smooth muscle contraction." Circ Res.. 93(6). 548-556 (2003) ▼
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