スフィンゴシン-1-リン酸情報伝達系の生理学・病態生理学:個体レベルにおける解析

2005 Fiscal Year Final Research Report Summary

Physiological and pathophysiological roles of the S1P signaling system : an in vivo study

Research Project

Project/Area Number

16590221

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 Graduate School of Medicine

Principal Investigator

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Project Period (FY)

2004 – 2005

Keywords

sphingosine-1-phosphate / sphingosine kinase / cardiac fibrosis / oxidative stress / low molecular weightG proteins / 血小板 / モデル動物 / 遺伝子改変マウス

Research Abstract

The sphingosine-1-phosphate (S1P) signaling system plays crucial roles in diverse biological phenomena, which include embryonic vascular maturation and lymphocyte trafficking. It is also implicated in development of certain diseases such as cancer. In an attempt to elucidate pathophysiological role, if any, of the S1P signaling system, we have generated transgenic (TG) mice that overexpress SPHK1 in diverse tissues, with up to several ten fold increases in the enzymatic activity. Although TG x TG matings yielded a slightly reduced litter size, the TG mice grew normally without any obvious abnormality. Notably, TG mice with a high but not a low level of SPHK1 expression in the heart showed age-dependent, progressive cardiac fibrosis. Transgenic heart tissues showed embryonic gene upregulation, elevated Rac1 and RhoA activities and increased oxidative stress. Treatment of TG mice with an HMG-CoA reductase inhibitor or an antioxidant N-2-mercaptopropyonylglycine, but not an angiotensin II type 1 receptor blocker, resulted in alleviation of cardiac fibrosis. TG mice also developed modest renal glomerular dysfunction with age. Unexpectedly, the TG mice did not show a propensity for spontaneous malignancy or reduced lifespan as compared to the wild type littermates. These results provide evidence for a pathophysiological role of SPHK1 in cardiac remodeling and glomerular injury.

Research Products (8 results)

All | 2006 | 2005 | 2004

All | Journal Article

[Journal Article] Rho-dependent, Rho kinase-independent inhibitory regulation of Rac and cell migration by LPA(1) receptor in G(i)-inactivated CHO cells. 2006

[Journal Article] Class II phosphoinositide 3-kinase alpha-isoform regulates Rho, myosin phosphatase and contraction in vascular smooth muscle. 2006

[Journal Article] Class II phosphoinositide 3-kinase alpha-isoform regulates Rho, myosin phosphatase and contraction in vascular smooth muscle. 2006

[Journal Article] Inhibition of Rac activation as a mechanism for negative regulation of actin cytoskeletal reorganization and cell motility by cAMP. 2005

[Journal Article] スフィンゴシン1リン酸受容体による癌浸潤・転移の制御とその分子機構 2005

[Journal Article] Inhibition of Rac activation as a mechanism for negative regulation of actin cytoskeletal reorganization and cell motility by cAMP. 2005

[Journal Article] Blood 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 2004

[Journal Article] スフィンゴシン-1-リン酸受容体による癌浸潤・転移の制御 受容体サブタイプ特異的な促進・抑制二方向性制御とその分子機構 2004

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