

# モルフォージェン活性を有する新規生理活性脂質S1P の生理機能の分子生物学的解析

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# 2002 Fiscal Year Final Research Report Summary

## Molecular biological analysis of the lipid morphogen sphingosine-1-phosphate

Research Project

### Project/Area Number

13470008

### Research Category

Grant-in-Aid for Scientific Research (B)

### Allocation Type

Single-year Grants

### Section

一般

### Research Field

General physiology

### Research Institution

Kanazawa University

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### Project Period (FY)

2001 – 2002

### Keywords

Sphingosme-1-phosphate / EDG / AGR-16 / Receptor / Rac / Rho / Cell migration / gene targeting

### Research Abstract

We tried to determine physiological and pathological roles of the sphingosine-1-phosphate (S1P)/Edg receptor axis, by using gene targeting and transgenic techniques and cell biological analysis.

We generated Edg5 knockout mice, by the standard method. We found that mice homozygous for null mutation of Edg5 receptor gene are born, accordingly to the Mendelian law. Gross abnormality in the appearance and behavior of Edg5<sup>-/-</sup> mice is not observed. After birth, approximately 40 % of Edg5<sup>-/-</sup> mice die within 1 month.

The reason of this increased mortality in the early stage is not known at present. Adult Edg5<sup>-/-</sup> mice display slightly lower blood pressure. Sphingosine kinase is a rate-limiting enzyme for the production of S1P. In sphingosine kinase-transgenic mice, the wound-healing process is promoted compared to wild type mice. Edg5 has unique activities to suppress cell migration and cellular Rac, different from Edg1 or Edg3, which both inhibit Rac activity cell migration. We found for the first time that Edg5 couples to inhibition of Rac via G12/13 and the small GTPase Rho. We observed that Edg5 exerts inhibition of cell motility and invasion of tumor cells, resulting in suppression of metastasis in vivo.

## Research Products (33 results)

All Other  
All Publications

- [Publications] N.Takuwa et al.: "Regulation of cell cycle molecules by the Ras effector system" *Mol.Cell.Endocrinol.* 177. 25-23 (2001) ▼
- [Publications] Y.Takuwa et al.: "Subtype-Specific, Differential Activities of the EDG Family Receptors for Sphingosine-1-Phosphate, a Novel Lysophospholipid Mediator" *Mol.Cell.Endocrinol.* 177 : 3-11, 2001. 177. 3-11 (2001) ▼
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- [Publications] S.Sakurada et al.: "Rho activation in excitatory agonist-stimulated vascular smooth muscle" *Am.J.Physiol.(Cell Physiol).* 281. C571-C578 (2001) ▼
- [Publications] Y.Banno et al.: "Involvement of phospholipase D in sphingosine 1-phosphate-induced activation of phosphatidylinositol 3-kinase and Akt in chinese hamster ovary cells overexpressing EDG3<sup>Δ\*</sup>" *J.Biol.Chem.* 276. 35622-35628 (2001) ▼
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- [Publications] Y.Takuwa et al.: "The Edg G protein-coupled receptors for lysophospholipids : Their signaling properties and biological activities" *J.Biochem.* 131. 767-771 (2002) ▼
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- [Publications] H.Ikeda et al.: "Antiproliferative action of sphingosine 1-phosphate in rat hepatocytes involves activation of Rho via Edg-5" *Gastroenterology.* (In press). (2003) ▼
- [Publications] K.Ito et al.: "Mechanisms responsible for Ca<sup>2+</sup> sensitization of prostaglandin F2 $\alpha$ -induced contraction of vascular smooth muscle" *J.Physiol.* (In press). (2003) ▼
- [Publications] N.Sugimoto et al.: "Inhibitory and stimulatory regulation of Rac and cell motility by the G<sub>12/13</sub>-Rho-and the G<sub>i</sub>-pathways integrated downstream of a single G protein coupled sphingosine-1-phosphate receptor isoform" *Mol.Cell.Biol.* 23. 1534-1545 (2003) ▼
- [Publications] D.Shida et al.: "Lysophosphatidic acid enhances metastatic potential of human colon carcinoma DLD1 cells through LPA1" *Cancer Res.* (In press). (2003) ▼
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