Curriculum Vitae

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EDUCATION AND PROFESSIONAL EXPERIENCE

1979	Graduated from University of Tokyo School of Medicine
1979	Resident and Clinical Fellow, Department of Internal Medicine, Faculty of Medicine, University of Tokyo.
1984	Instructor, Department of Internal Medicine, Faculty of Medicine, University of Tokyo.
1985	Visiting Research Scientist, Division of Endocrinology (Laboratory of Dr. Howard Rasmussen), Department of Medicine, Yale University School of Medicine.
1987	Assistant Professor, Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba.
1991	Associate Professor, Department of Cardiovascular Biology, Faculty of Medicine, University of Tokyo.
1999	Professor and Chief, Department of Physiology (Molecular Vascular Physiology), Kanazawa University School of Medicine.

Bimodal regulation by the S1P-Edg signaling system of Rho family GTPase and invasion/metastasis in cancer cells

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Blood lipid mediator sphingosine 1-phosphate (S1P), which acts via endothelial differentiation gene (Edg) family of G protein-coupled receptors including Edgs-1, -3, and -5, exerts unique bimodal regulatory activities on cell motility; Edgs-1 and –3 are positive regulators of cell migration, whereas Edg5 is a negative regulator. S1P inhibits cell migration of mouse B16 melanoma cells in both transwell migration assay and wound healing assay. S1P also inhibits invasion of B16 cells through the Matrigel in vitro. Concomitantly, S1P induces stimulation and inhibition, respectively, of RhoA and Rac. We observed that these S1P actions are mediated via endogenous Edg5. The expression of N17Rac inhibits migration and invasion, suggesting that the negative regulation of Rac underlies S1P inhibition of the motility responses. Inhibition of Rho by C3 toxin rather reverses the S1P inhibition, indicating that Rho mediates the inhibition. In contrast, either Edg1 or Edg3 that is forcedly expressed counteracts endogenous Eg5-mediated inhibition of migration and invasion, or confers slight stimulatory responses to S1P. Edg1 and Edg3 also counteract inhibition of cellular Rac activity. B16 cells that are injected into the tail vein of mice form multiple colonies in the lung 3 weeks later. Treatment of B16 cells with S1P before injection or daily administration of S1P inhibits colony formation in the lung. The N17Rac expression in B16 cells suppresses colony formation. Forced expression of either Edg1 or Edg3 antagonizes Edg5-mediated inhibition or confers slight S1P stimulation of colony formation. These observations provide evidence that G protein-coupled receptors could participate in the regulation of invasion and metastasis of cancer cells in a ligand-dependent, subtype-specific manner through the mechanisms involving the regulation of Rac activity.