論文内容の要旨

(論文題目)

Role of LPA_4 in blood and lymphatic vessel formation

during mouse embryogenesis

和訳： マウス発生期の血管・リンパ管形成における

リゾホスファチジン酸第 **4** 受容体の役割

指導教員　　佐藤　伸一　教授

委託先指導教員　　清水　孝雄　教授

東京大学大学院医学系研究科

平成 **19** 年 **4** 月入学　　医学博士課程 外科学専攻

住田　隼一

Lysophosphatidic acid (LPA) is a potent lipid mediator with a wide variety of biological actions including neurogenesis, myelination, angiogenesis, wound healing, and cancer progression. It has been demonstrated that cell-surface G protein-coupled receptors (GPCRs) mediate the effects of LPA, and at least six subtypes of LPA receptors ($LPA_{1–6}$) have been identified. In 2003, Noguchi *et al*. identified the fourth LPA receptor, LPA_4, and subsequent

studies have shown that LPA_4 couples to $G\alpha_{13}$. However, its physiological or pathological roles have not been revealed. In this thesis, I show that LPA_4 has important roles in the development of blood and lymphatic vessels.

During the breeding of LPA_4-deficient mice, I noticed that the number of LPA_4-deficient mice was about 30% less than the value expected from Mendelian ratios at weaning on postnatal day 21. At multiple embryonic stages, a subset of LPA_4-deficient embryos displayed various abnormalities in many organs, including pericardial effusion, subcutaneous hemorrhages and/or edema, and bleeding in the pericardial cavities. Furthermore, immunohistochemical analysis of α-smooth muscle actin (α-SMA) revealed that some of the dilated blood vessels in LPA_4-deficient embryos were poorly covered with $\alpha\text{-SMA}^+$ cells, namely smooth muscle cells and pericytes. Consistently, Matrigel plug assays showed decreased mural cell coverage of endothelial cells in the neovessels of LPA_4-deficient adult mice. *In situ* hybridization detected *Lpa4* mRNA in the endothelium of some blood vessels of embryos. These data suggest that the LPA_4 signaling pathway in the vascular endothelium is important for blood vessel development, especially for mural cell recruitment to endothelial cells.

The lymphatic vessel abnormalities were also observed in LPA_4-deficient embryos. In both edematous and apparently normal LPA_4-deficient embryos at embryonic day (E) 14.5, significant dilation of the jugular lymph sacs was observed. Moreover, LPA_4-deficient

embryos at E18.5 showed lymphatic vessel dilation in the small intestine, lung, and skin. These results indicated that LPA_4 is also important for the regulation of lymphatic development and patterning in mice.

In conclusion, I demonstrated a novel role of LPA_4 in the formation and function of blood/lymphatic vessels during mouse embryogenesis. Considering the critical role of autotoxin, an enzyme involved in LPA production, and $G\alpha_{13}$ in vascular development, I suggest that LPA_4 provides a link between these two molecules. Combined with the fact that maturation of blood/lymphatic vessels affects the inherited vascular diseases or tumor progression, LPA_4 might be a therapeutic target for such human diseases.