論　文　概　要 (Thesis Abstract)

○ 論 文 題 目

Physiological functions of the phospholipid-metabolizing enzyme Phospholipase D2 in anti-tumor immunity: regulation of $CD8^+$ T lymphocyte proliferation

（腫瘍免疫におけるリン脂質代謝酵素 PLD2 の生理機能：$CD8^+$ T リンパ球の細胞増殖制御）

○ 指 導 教 員

人間総合科学研究科　　生命システム医学専攻　　**金保安則　教授**

Graduate School of Comprehensive Human Sciences

Doctoral Program in Biomedical Sciences

Professor Yasunori Kanaho

（所　属）　**筑波大学大学院人間総合科学研究科**　　生命システム医学**専攻**

（氏　名）　NGO THAI BICH VAN

目　　的:

To clarify the roles of PLD2 in tumor microenvironment for further understanding of its physiological functions in tumorigenesis.

対象と方法:

Subcutaneously transplant cancer cells into wild-type and *Pld2*-knockout mice to form tumors and analyze tumor-infiltrating T cells.

Examine the *in vitro* proliferation of primary $CD8^+$ T cells under co-stimulation of CD3/CD28.

Examine the CD3/CD28-dependent activation of Erk and Ras in primary $CD8^+$ T cells.

結　　果:

Growth of the tumor formed by subcutaneously transplanted cancer cells is enhanced in *Pld2*$^{-/-}$ mice. Interestingly, the number of $CD8^+$ T cells, which are known to induce cancer cell death, is significantly decreased in *Pld2*$^{-/-}$ tumor sections. In addition, CD3/CD28-stimulated proliferation of primary cultured $CD8^+$ T cells isolated from the *Pld2*$^{-/-}$ spleen is significantly suppressed compared to that of WT $CD8^+$ T cells. Furthermore, CD3/CD28-dependent activation of Erk1/2 and Ras and IL-2 production are inhibited in *Pld2*$^{-/-}$ $CD8^+$ T cells.

考　　察:

Previous reports provide evidences for the central role of $CD8^+$ T cells in anti-tumor immunity and are consistent with the notion that impaired $CD8^+$ T cell infiltration into tumor microenvironment in *Pld2*$^{-/-}$ mice promoted tumor growth. In the present study, we focused on the function of PLD2 in $CD4^+$ and $CD8^+$ T cells. However, PLD2 in other cell types may have effect on tumorigenesis.

In dissecting the signaling pathway involved in PLD2-mediated T cell proliferation, we found that PLD2 is required for CD3/CD28-stimulated Ras activation and Erk phosphorylation in primary $CD8^+$ T cells. Other reports showed that PLD2 can active Ras through the action of RasGEF. Taken together, it is reasonable to speculate that, upon TCR engagement of $CD8^+$ T cells, PLD2 recruits a Ras GEF to the specific compartment such as the plasma membrane, inducing compartmentalized and temporal activation of Ras-Erk signaling to promote cell proliferation and survival. The detailed mechanism remains to be elucidated for the future analysis.

結　　論:

The result obtained suggest that PLD2 promotes $CD8^+$ T cell proliferation upon TCR engagement in the spleen through the activation of Ras-Erk pathway and IL-2 production, thereby potentiating the anti-tumor immune response. The findings revealed a novel function of PLD2 in the immune system, which may contribute to eliminate cancer cells.