

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

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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<sup>+</sup> 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<sup>+</sup> T リンパ球の細胞増殖制御)

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## 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<sup>+</sup> T cells under co-stimulation of CD3/CD28.

Examine the CD3/CD28-dependent activation of Erk and Ras in primary CD8<sup>+</sup> T cells.

## 結 果:

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

## 考 察:

Previous reports provide evidences for the central role of CD8<sup>+</sup> T cells in anti-tumor immunity and are consistent with the notion that impaired CD8<sup>+</sup> T cell infiltration into tumor microenvironment in *Pld2*<sup>-/-</sup> mice promoted tumor growth. In the present study, we focused on the function of PLD2 in CD4<sup>+</sup> and CD8<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> 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<sup>+</sup> 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.