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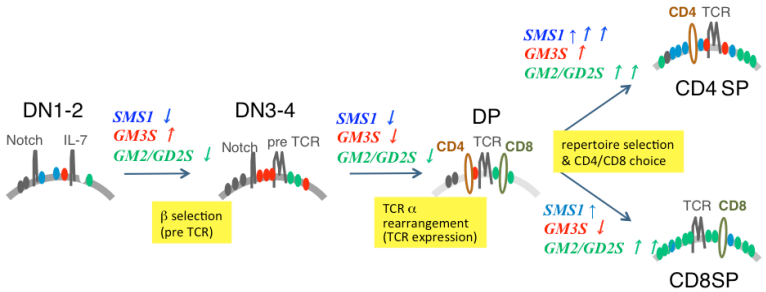
Grant Title: Roles of gangliosides and sphingomyelin on T cell development and function

Abstract

Aim and scope: $CD4^+$ Th cells and $CD8^+$ Tc cells are closely similar in the mechanisms of TCR-mediated signaling despite playing distinct immune functions. Interestingly, the two T cell subsets express different levels of gangliosides as well as different kinds of ganglioside species, which provide the appropriate distinct intracellular signaling events for immune function of each T cell subset. Here, we extended our research to elucidate the roles of sphingolipids including sphingomyelin on T cell development and function.

Results and Discussion: We have determined the structures of gangliosides in immature thymocytes, and $CD4^+$ T and $CD8^+$ T cells isolated from mouse lymphoid organs by LC-MS/MS analysis [**1,2**]. All T cell subsets commonly express the six distinct species (GM1a, GM1b, GD1b, GD1c, GalNAcGM1b and extended-GM1b), but their expression levels are remarkably different in each subset. The expression of o-series gangliosides (GalNAcGM1b and extended-GM1b) is greatly enhanced by the differentiation from thymocytes to $CD4^+$ T cells and $CD8^+$ T cells. It is noteworthy that almost all gangliosides expressed in $CD8^+$ T cells are o-series species. The expression of GM1b is maintained among T cell subsets, but GM1a is expressed in both thymocytes and $CD4^+$ T cells but only trace amounts in $CD8^+$ T cells. Then we interested in expression of an another class of sphingolipid, sphingomyelin, on T cell development. For this purpose, we examined the each step of T cell subsets during T cell development in thymus by FITC-cholera-toxin B subunit and lysenin staining for the detection of gangliosides and sphingomielin, respectively. As shown in the figure,
We observed the contrasting expression profiles of gangliosides and sphingomyelin during T cell development and maturation processes. The selection of specific T cells from the thymocyte stage (repertoire selection) seems to be accompanied by selective sphingolipid expression in individual T-cell subsets. This sphingolipid selection process may be indispensable for the formation of distinct and functional lipid rafts in mature T cells.



Sphingolipid selection process may be indispensable for the formation of distinct and functional lipid rafts for T cell development and maturation.

References:

[1] Nagafuku M, Okuyama K., Onimaru Y., Suzuki A., Odagiri Y., Yamashita T., Iwasaki K., Fujiwara M., Takayanagi M., Ohno I. and *Inokuhi J. (2012) CD4 and CD8 T cells require different membrane gangliosides for activation. ***Proc. Natl. Acad. Sci.USA*** 109. E336-E342

[2] *Inokuchi J, Nagafuku M, Ohno I. and Suzuki A. (2013) Heterogeneity of gangliosides among T cell subsets. ***Cell. Mol. Life Sci.*** 70, 3067-75.