News release

$CD8^+CD122^+CD49d^{low}$ regulatory T cells maintain T-cell homeostasis by killing activated T cells via Fas/FasL-mediated cytotoxicity.

Key Points:

- Among memory-like $CD8^+$ cells, $CD8^+CD122^+CD49d^{low}$ cells have apparently higher activity of regulatory cells than $CD8^+CD122^+CD49d^{high}$ cells.
- $CD8^+$ regulatory T cells recognize activated T cells by using their TCR (T-Cell Receptor).
- $CD8^+$ regulatory T cells perform their immuno-regulatory activity by inducing cell death via Fas/FasL in activated T cells.

Summary

Fas/FasL system is a well-known apoptosis-inducing system that is tightly related with immune regulation. However, its role in the whole living body is not precisely understood. Associate Professor Haruhiko Suzuki (Department of Immunology) and Guest Researcher Kazuyuki Akane (Department of Immunology) in Nagoya University Graduate School of Medicine (Dean; Masahide Takahashi, M.D., Ph. D.) performed both *in vitro* and *in vivo* assays and elucidated that the cell population of $CD8^+CD122^+CD49d^{low}$ is that of regulatory T cells and that Fas/FasL is an important system which works when $CD8^+CD122^+CD49d^{low}$ regulatory T cells reduce the number of activated T cells by inducing apoptosis in the phase of diminishing immune reaction.

Research Background

Proper immunity requires proper suppression, and there are many different mechanisms to suppress immune reaction. It is popularly known that a special subset of T cells called regulatory T cells exists and suppress the immune reaction. The majority of such regulatory T cells are $CD4^+$ cells that respond to exogenous antigen, while other regulatory T cells originated from $CD8^+$ cells that make another major T cell population and respond to endogenous antigens would be necessary for the balance of total immune reaction. Associate Professor Haruhiko Suzuki (Department of Immunology) in Nagoya University Gradate School of Medicine, (Dean; Masahide Takahashi, M.D., Ph. D.) has been working to generate and analyze the CD122 (IL-2 receptor β chain)-knockout mice (Science, 268:1472-6, 1995) and found that the increase of abnormally activated T cells in the CD122-knockout mice is caused by the defect of some regulatory T cells (J Exp Med, 190:1561-72, 1999). He further published such regulatory cells exist in the population of $CD8^+CD122^+$ (J Exp Med, 200:1123-34, 2004)

One of the molecular system that is related to the immune regulation described above is Fas and FasL. Fas was first discovered by Dr. Shin Yonehara, the Metropolitan Institute of Medical Science (at that time), in 1989 and the gene for Fas was cloned by the group of Dr. Shigekazu Nagata, Osaka Unversty (at that time), in 1991. The gene for FasL, the binding molecule of Fas, was also cloned by the group of Dr. Nagata in 1993. However, the precise mechanism of Fas/FasL, such as

in which cells of the whole living body and in which situation of immune regulation they work, has not been clarified long time.

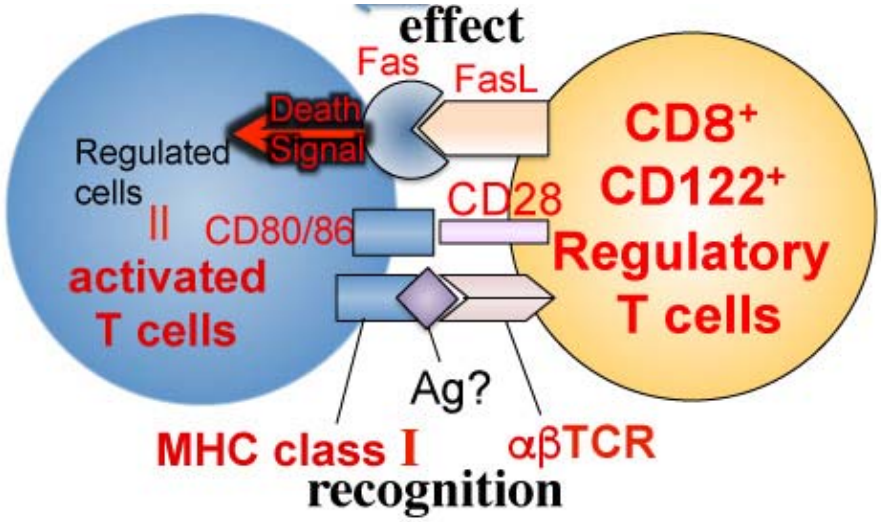
In the present article, the authors insist that the formerly described $CD8^+CD122^+$ regulatory T cells can be further narrowed by the expression of CD49d and the mechanism of the regulation is cytotoxicity mediated by Fas/FasL.

Research Results

We found that the $CD8^+$ regulatory T cells ($CD8^+CD122^+$ cells) can be further divided into some populations by the expression level of CD49d, a cell surface marker molecule. Among those populations defined by CD49d, $CD49d^{low}$ cells showed the strongest cytotoxic activity against activated T cells. After the co-culture of $CD8^+CD122^+CD49d^{low}$ cells and $CD8^+CD122^-$ cells that were formerly activated by the stimulation to TCR, $CD8^+CD122^-$ cells selectively reduce their number but such reduction is not observed in the co-culture of $CD8^+CD122^+CD49d^{high}$ cells and $CD8^+CD122^-$ cells.

In the *in vivo* experiment, lymphocyte-deficient ($RAG\text{-}2^{-/-}$) mice that have received only $CD8^+CD122^-$ cells rapidly die within 120 days after the T cell transfer but addition of $CD8^+CD122^+CD49d^{low}$ cells effectively elongate the survival of mice.

In addition to these experiments, we performed experiments using cells derived from β2-microglobulin knockout mice, experiments using cells obtained from *lpr* mice or *gld* mice, and those just using such Fas/FasL-mutated mice themselves. We are convinced that $CD8^+CD122^+CD49d^{low}$ cells are the regulatory cells that work for the maintenance of immune homeostasis, and such regulatory T cells recognize activated T cells as their targets by the interaction between TCR and MHC class I and finally perform their cytotoxic effect to the target cells by Fas/FasL interaction.



Research Summary and Future Perspective

The memory T-cell-like $CD8^+$ regulatory T cells we identified ($CD8^+CD122^+CD49d^{low}$ cells) are very

similar to memory T cells that are thought to be at the center of immune memory in terms of both their surface markers and functional molecules. It is necessary to expand the research with keeping the difference and equality between them in mind. Fas/FasL system is an apoptosis-inducing system well-known for long time and strictly related with immune regulation. However, at which timing exactly or which cell-population precisely the Fas/FasL system works has been largely unknown. The present study revealed that it works as the effector molecules for $CD8^{+}CD122^{+}CD49d^{low}$ regulatory T cells, however it is required to elucidate the role of the system in the relation with other immune regulatory molecules such as PD-1.

Furthermore, by the analysis of some gene-targeted mice that were developed in our laboratory, it is now clarified that $CD8^{+}CD122^{+}CD49d^{low}$ T cells are tightly related with many kinds of immune disorders including colitis, anemia, myeloid hyperplasia, etc. The expansion of the analysis of these mice promises the success in search for the target of therapy for ulcerative colitis and Crohn's disease, and should be connected to the development of new animal model for intestinal inflammation and new methods of therapy for them.

Article

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Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2015/CD8_20160211jp.pdf