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論文 / 著書情報
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題目(和文)	末梢における免疫細胞の生存制御機構の解明に向けたB細胞の非線形的刺激応答の解析
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種別(和文)	論文要旨
Type(English)	Summary

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（博士課程）
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論 文 要 旨

THESIS SUMMARY

専攻： Department of	知能システム科学　専攻	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of　（　理学　）
学生氏名： Student's Name	安田翔也	指導教員（主）： Academic Supervisor(main)	山村雅幸
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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

B cells express an enormously diversified antigen receptors (BCR) capable of recognizing various foreign antigens (Ag). Such diversified BCR may also react with self Ag. Immunological tolerance functions to prevent the appearance or activation of potentially self-reactive B cells. Breakdown of immune tolerance can lead to severe immune disorders such as rheumatoid arthritis and type I diabetes. It is now clear that the B cell central tolerance is achieved by self Ag-mediated apoptosis of self-reactive immature B cells in the bone marrow. However, it remains elusive how self-reactive mature B cells in the spleen or lymph node are inactivated.

As a clue to elucidate peripheral immune tolerance, we focused on the following two unexplained phenomena. One is that B cells exhibit a nonlinear survival response against antigenic stimulation. In general, B cells are more activated depending on Ag doses. However, it is also known that B cells will not respond until Ag stimulation reaches certain strength. Besides, the current study has revealed that B cells tend to die at very low doses of Ag stimulation. Therefore, even with the same Ag stimulation, as the Ag dose increases, B cells change their responses from death to non-responsiveness and then to increased survival. Such distinct responses to different doses of Ag stimulation are likely related to B cell peripheral tolerance but the mechanism remains unknown.

The other phenomenon is that BCR change from $IgM^{high}IgD^{-}$ to $IgM^{low}IgD^{high}$ during B cell maturation. Some functional differences between IgM and IgD have been noted. However, the function of one of them can be compensated for by the other so it is unclear why both are needed for B cells. Studies thus far indicate that IgD responds poorly to Ag stimulation suggesting that B cells become less sensitive as they mature and express higher levels of IgD. The increased IgD expression is also likely related to peripheral B cell tolerance but again the mechanism is unclear.

There are several reasons that prevent detailed investigation of these phenomena. The tonic signal, which has been shown by genetic studies to support B cell survival in the periphery, is very weak and difficult to be detected by conventional experiments. B cell lines, which are derived from B lymphomas and can survive indefinitely, are obviously not suitable for the current study and therefore purified primary B cells are used. To overcome these difficulties and to obtain key suggestions for future experiments, we decided to take a mathematical/computational approach.

In this study, we first constructed a mathematical model taking into consideration of B cell signaling pathway and binding reaction between BCR and the Ag (in this case $F(ab')_2$-anti-IgM antibodies as pseudo Ag). Next, we analyzed the above two phenomena through computer simulations. As a result, we confirmed the existence of a threshold for B cell survival upon Ag stimulation. Interestingly, this threshold was found to depend not on the amount, but the density, of Ag-bound BCR. In addition, by shifting to the $IgM^{low}IgD^{high}$ type B cells decrease their responsiveness to Ag stimulation as a safety guard to prevent unwanted activation while maintaining the tonic signal required for their survival. These findings provide a new and reasonable principle for understanding the mechanism of immune tolerance that is critical for preventing autoimmune diseases.

Based on these results, we proposed several practical experiments that might lead to additional discovery in peripheral tolerance. One is to examine the relationship between B cell survival and the amount and density of antigen-bound BCR. In this experiment, the density of antigen-bound BCR may have a greater influence on survival than the amount of antigen-bound BCR. The second is an experiment to investigate the relationship between BCR expression level and differentiation. In our insight, the ability to differentiate into memory B cells or antibody-secreting plasma cells may be determined by the BCR expression level. Finally, we proposed to investigate the relationship between the ratio of IgM/IgD and B cell activation in individual cells. Cells with higher IgD level may be more difficult to be activated. These new ideas have been raised based on the results of our mathematical modeling, and have been overlooked from the perspective of experimental immunology.

We hope that our suggested experiments will lead to further understanding of the mechanism of immune tolerance and provide additional clue for treating autoimmune diseases. Moreover, we expect that our approach on B cells will also be applicable to other immune cells such as T cells.

備考 ： 論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。
Note : Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1copy of 800 Words (English).

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