学 位 論 文 の 要 旨

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学 位 論 文 名　Regulatory Role of Lymphoid Chemokine CCL19 and CCL21 in the Control of Allergic Rhinitis

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論 文 内 容 の 要 旨

INTRODUCTION

The CCR7 ligands CCL19 and CCL21 are lymphoid chemokines involved in the chemotaxis of lymphoid cells such as leukocytes and dendritic cells (DCs). Indeed, these chemokines play important roles in the formation of appropriate cellular micro-compartmentalization and homeostasis in lymphoid tissues such as nasopharynx-associated lymphoid tissue (NALT). However, their role in allergic responses remains unclear, and so our current study aims to shed light on the role of CCL19/CCL21 in the development of allergic rhinitis (AR) by using an experimental murine AR model.

MATERIALS AND METHODS

For the induction of allergic rhinitis in mice, mice were pre-sensitized by means of an intraperitoneal injection of ovalbumin (OVA) with aluminum hydroxide hydrate gel on days 0, 7, and 14. Thereafter, mice were challenged by nasal administration of OVA for 14 consecutive

days from day 21 to 34. On days 20 (after three times of intraperitoneal sensitization), 27 and 34 (after 7 and 14 times of nasal challenge, respectively), the instances of sneezing and nasal rubbing were counted for five minutes after the last nasal challenge.

For the nasal CCL19/CCL21 DNA treatment, mice were nasally administered with plasmid encoding DNA of CCL19 or CCL21 on days -1, 6, and 13 (24 hours before systemic sensitization) and from day 20 to 33 (before nasal challenge). Nasal symptoms were observed, and sera and mononuclear cells in several tissues were harvested for further examination.

RESULTS AND DISCUSSION

After nasal challenge with OVA, OVA-sensitized *plt* (paucity of lymph node T cells) mice which are deficient in CCL19/CCL21, showed more severe allergic symptoms than did identically treated wild-type (WT) mice. . The serum of *plt* mice showed significantly higher levels of OVA-specific IgE and of total IgE antibodies than did that of identically treated WT mice. Th2 cytokine production and messenger RNA expression of GATA-3, a Th2-associated transcription factor, were enhanced in *plt* mice. When serum histamine levels were measured by enzyme-linked immunosorbent assay (ELISA), *plt* mice were found to produce significantly higher levels of histamine than WT mice. Histological analysis showed higher numbers of eosinophils infiltrated in nasal tissue of *plt* mice than in WT mice. Moreover, in *plt* mice, the number of $CCR7^+$ regulatory T cells (Tregs) declined in the secondary lymphoid tissues, while the number of Th2-inducer-type $CD8\alpha^-CD11b^+$ myeloid dendritic cells (m-DCs) increased in cervical lymph nodes (CLN) and NALT. These findings suggest that, under CCL19- and CCL21-deficient conditions, severe AR is associated with a reduction in $CD4^+CD25^+$ naturally occurring Tregs and an increase in the frequency and the number of m-DCs in the nasal mucosa-associated lymphoid tissues. When the nasal chemokine plasmid treatment was tested, nasal administration of the plasmid encoding DNA of CCL19 resulted in the reduction of m-DCs in the secondary lymphoid tissues and the suppression of allergic responses in *plt* mice.

CONCLUSION

In summary, we demonstrated enhanced allergic responses in *plt* mice lacking the lymphoid chemokines CCL19 and CCL21. We also showed that these lymphoid chemokines are involved in the recruitment of CCR7-expressing naturally occurring Tregs in the secondary lymphoid tissues and the suppression of pathological Th2 environment induced by m-DCs during the development of AR. Taken together, these findings underline the importance of the lymphoid chemokines CCL19/CCL21 as regulatory molecules for the control of allergic disease.