学 位 論 文 の 要 旨

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学 位 論 文 名　IL-15 Prevents Allergic Rhinitis Through Reactivation of Antigen-Specific $CD8^+$ Cells

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論 文 内 容 の 要 旨

Introduction

Allergic rhinitis is one of the most common allergic inflammatory diseases characterized by a predominant T_H2 response with antigen-specific IgE synthesis. Interleukin-15 (IL-15) plays important roles in activation and maintenance of memory $CD8^+$ T cells capable of producing IFN-γ, which regulates T_H2 responses. To investigate the roles of endogenous IL-15 in allergic inflammation, we examined allergic rhinitis in IL-15 knockout (KO) mice sensitized with ovalbumin (OVA) followed by intranasal challenge with OVA.

Materials and Methods

IL-15KO mice were sensitized intraperitoneally with OVA and complete Freund's adjuvant on day 0, and with OVA and incomplete Freund's adjuvant on day 7. Then those were intranasally

challenged with OVA on days 21, 22, 23, 24, and 25. Nasal symptoms and histological changes of nasal mucosa were examined. Serum IgE and cytokine production of $CD4^+$ T cells from cervical LNs were measured by ELISA. Purified $CD8^+$ T cells were transferred into OVA-sensitized IL-15KO and WT mice. Finally, recombinant IL-15 (rIL-15) were intranasally challenged with OVA to investigate the role of IL-15.

Results and discussion

The levels of IgE production and T_H2 responses in IL-15KO mice were comparable to those in control mice after OVA sensitization. However, sneezing, infiltration of eosinophils into the nasal mucosa, and T_H2 cytokine production of $CD4^+$ T cells from cervical LNs were aggravated in OVA-sensitized IL-15KO mice after intranasal challenge with OVA. Adoptive transfer of $CD8^+$ T cells from OVA-sensitized mice suppressed the T_H2 responses in WT mice but not in IL-15KO mice. Administration of rIL-15 with OVA significantly prevented the development of allergic rhinitis in OVA-sensitized mice.

There are several lines of evidence that IL-15 affects $CD4^+$ T_H1 or T_H2 responses at the induction phase after primary immunization. IL-15 has been reported to induce IL-12 receptor β1 directly on murine T cells at the transcriptional level via activation of signal transducer and activator of transcription. We have reported that overexpression of IL-15 induced $CD4^+$ T_H1 response after *Listeria monocytogenes* infection via bystander activation of memory $CD8^+$ T cells producing IFN-γ. We have also reported that the $CD4^+$ T_H2 response was significantly reduced in IL-15 transgenic mice sensitized with OVA. On the other hand, IL-15 has been shown to induce IL-5 production of human T_H2 clones and to induce proliferation of activated B cells *in vitro*, corresponding to the enhancement of IgE and IgG. We found that OVA-specific $CD8^+$ T cells are responsible for suppression of the T_H2 response in regional LNs at the effector phase of allergic rhinitis. Notably, transfer of $CD8^+$ T cells from OVA-sensitized WT mice could not control infiltration of eosinophils into the nasal mucosa and the T_H2 response in regional LNs at the effecter phase in IL-15KO mice, suggesting that the regulatory function in

the $CD8^+$ T cells is totally dependent on IL-15 at the effecter phase. IL-15-dependent $CD8^+$ T cells may be mainly responsible for suppression of allergic rhinitis at the effector phase. It is notable that administration of exogenous IL-15 together with allergen prevented allergic rhinitis in mice. Our results obtained by using IL-15KO mice revealed that antigen-specific $CD8^+$ T cells downregulated T_H2 response at the effector phase of allergic rhinitis in the presence of endogenous IL-15. These results provide an insight into a therapeutic approach to control allergic rhinitis by IL-15.

Conclusion

We demonstrate with IL-15KO mice that endogenous IL-15 plays an important role in suppression of allergic rhinitis at effector phase. Intranasal administration of IL-15 is useful as a therapeutic approach to control allergic rhinitis.