論 文 要 旨

（ Long-acting muscarinic antagonist regulates group 2 innate lymphoid cell-dependent airway eosinophilic inflammation ）

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Background: Tiotropium bromide, a long-acting muscarinic antagonist, reduces the frequency of exacerbation in patients with moderate to severe asthma, but its underlying mechanism is not clear. Asthma exacerbations are associated with exposure to external stimuli, and group 2 innate lymphoid cells (ILC2s) are considered to be involved in the pathophysiology of asthma exacerbation. We investigated whether tiotropium modulates airway inflammation through ILC2 functions.

Methods: Mice were administered papain intranasally to induce innate-type airway inflammation with or without tiotropium pretreatment, and bronchoalveolar lavage fluids (BALF) and lung tissues were collected. Lung-derived ILC2s and bone-marrow-derived basophils were stimulated *in vitro* with IL-33 in the presence or absence of tiotropium. Muscarinic 3 receptor (M3R) expression on immune cells was assessed by RNA sequence.

Results: Papain induced airway eosinophilic inflammation, and tiotropium reduced the numbers of eosinophils in BALF. The concentrations of IL-4, IL-5 and IL-13, and the numbers of ILC2s in BALF were also reduced by tiotropium treatment. However, tiotropium did not affect IL-33-induced IL-5 and IL-13 production from ILC2s, suggesting that tiotropium regulates ILC2s indirectly. Gene-expression analysis showed that basophils predominantly expressed M3R mRNA among murine immune cells. Tiotropium reduced IL-4 production from basophils derived from mouse bone marrow and human basophils after stimulation with IL-33.

Conclusions: These findings suggest that tiotropium attenuates ILC2-dependent airway inflammation by suppressing IL-4 production from basophils and, subsequently, regulating ILC2 activation. The inhibitory effects of long-acting muscarinic antagonists on the innate response may contribute to reducing asthma exacerbation.