論　文　の　要　約

報告番号	甲　創　　第　33　号	氏　名	Aurpita Shaha
学位論文題目	Exploration of new therapeutics for allergy from Honey bee products having suppressive effect on H1R gene and IL-9 gene transcriptions （アレルギー疾患新規治療のためのミツバチ生産物由来 H1R 遺伝子、IL-9 遺伝子転写抑制化合物の探索）		

Alleviation of acute allergic symptoms using antihistamines is suggested by the suppression of histamine H_1 receptor gene expression in nasal mucosa. The significant correlation between nasal symptom scores and level of histamine H_1 receptor (H1R) mRNA in nasal mucosa was also observed in patients with pollinosis, suggesting that H1R gene is an allergic disease sensitive gene. We demonstrated that H1R and interleukin (IL)-9 gene are the allergic rhinitis (AR)-sensitive genes and protein kinase Cδ (PKCδ) signaling and nuclear factor of activated T-cells (NFAT) signaling are involved in their expressions, respectively. In-addition, the pathological mechanism of chronic symptoms remains to be elucidated, and therapeutics for chronic symptoms have not developed yet. Eosinophils play an important role in chronic symptoms of allergy. Correlation between IL-33 mRNA level and eosinophil was examined using nasal mucosal samples from pollinosis patient. The positive correlation between number of eosinophils and IL-33 mRNA levels in nasal mucosa of pollinosis patients was observed. IL-33 mRNA level was up-regulated in phorbol-12-myristate-13-acetate (PMA)-induced Swiss 3T3 cells, and was suppressed by rottlerin. Honey bee products have been used to treat allergic diseases. However, their pathological mechanism remains to be elucidated. In the present study, we investigated the mechanism of the anti-allergic effect of royal jelly (RJ) and Brazilian green propolis (BGPP).

Treatment with RJ and BGPP decreased in the number of sneezing on toluene 2,4-diissocyanate-stimulated rats. The remarkable suppression of H1R mRNA in nasal mucosa was observed. RJ and BGPP also suppressed the expression of IL-4, IL-5 genes that are related to histamine signaling as well as IL-9 gene expression. RJ and BGPP suppressed PMA-induced Tyr^{311} phosphorylation of PKCδ in HeLa cells. In RBL-2H3 cells, RJ and BGPP also suppressed NFAT-mediated IL-9 gene expression. BGPP suppressed IL-33 mRNA up-regulation. After partitioning with different solvent systems and subsequent purification by Silica gel column chromatography followed by LH-20 Sephradex afforded a compound (Compound-A) which suppress IL-33 gene expression on Swiss 3T3 cells.

These results suggest that RJ and BGPP improve allergic symptoms by suppressing PKCδ and NFAT signaling pathways, two important signal pathways for the AR pathogenesis, and suggest that RJ and BGPP could be good therapeutics against AR. In addition, our data suggest that Compound-A, an active compound of BGPP that suppresses IL-33 gene expression could be good medicines for chronic allergic diseases and eosinophilic inflammation.