論文内容の要旨

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Investigation of the role of Prostaglandin D_2 in asthma

（喘息におけるプロスタグランジン D_2 の役割解明）

Introduction

Allergic lung inflammation is a hallmark of asthma. Prostaglandin D_2 (PGD_2) is a lipid mediator that exerts its biological function through two distinct receptors: D prostanoid receptor (DP) and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). PGD_2 metabolite, 15-deoxy-delta-12,14-PGJ_2 (15d-PGJ_2) functions via peroxisome proliferator-activated receptor-γ (PPAR-γ)-dependent signaling. Although the concentration of prostaglandin D_2 (PGD_2) is elevated in the allergic lung tissue, its contribution in disease progression remains unclear. We attempted to clarify the role of PGD_2 in ovalbumin (OVA)-induced OVA model using hematopoietic PGD synthase (H-PGDS) deficient mice.

Methods: OVA was intranasally administrated to OVA-sensitized wild-type (WT) and H-PGDS deficient mice to induce chronic allergic lung inflammation. Isolated bronchi were organ-cultured with lipopolysaccharide (LPS).

Results: Repeated administration of OVA induced respiratory failure which was accompanied by increased eosinophil infiltration and mucin production in WT mice lung. Gene deficiency of H-PGDS enhanced OVA-induced these manifestations and mRNA expression of tumor necrosis factor-α (TNF-α) and eosinophil chemoattractants including Rantes and eotaxin-1. Immunostaining showed that bronchial epithelial cells strongly expressed H-PGDS and TNF-α in the inflamed WT lung. In cultured bronchus tissue of WT, LPS stimulation increased the mRNA expression of Rantes and eotaxin-1. H-PGDS inhibition promoted LPS-induced mRNA expressions of these chemokines further, which were inhibited by PGD_2 receptor agonist or PGD_2 metabolite, 15-Deoxy-Delta-12,14-PGJ_2 (15d-PGJ_2) pretreatment. Pretreatment with TNF receptor antibody inhibited eosinophil chemoattractant expression. *In vivo,* continuous administration of PGD_2 receptor agonist or 15d-PGJ_2 also attenuated the OVA-induced allergic lung inflammation in WT mice.

Conclusion: Bronchial epithelium-derived PGD_2 acts as a negative regulator by inhibiting the expression of TNF-α and chemoattractants in asthma.
The present findings indicate that enhancement of PGD_2/DP signaling and/or 15d-PGJ_2 treatment may exert therapeutic effects in asthma.