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Editorial

Sphingosine-1-Phosphate: Biomarker, Contributor, or Target for Asthma?

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▸ See the article "Altered Sphingolipid Metabolism Is Associated With Asthma Phenotype in House Dust Mite-Allergic Patients" in volume 11 on page 330.

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Asthma is a complex and heterogeneous airway disease, since environmental and genetic factors have an effect on both susceptibility and severity of the disease.[1] Due to the inherent complexity of the disease, defining asthma phenotypes, as well as endotypes that combine clinical phenotypes with a distinct pathological mechanism, is necessary to elucidate the pathogenic mechanism of asthma and to develop targeted therapeutic strategies based on their mechanisms.[2] Systematic analysis of metabolites (metabolomics) has been used to classify the heterogeneous phenotypes and endotypes of asthma because metabolic alterations may reflect pathophysiologic changes encompassing gene-to-environment interactions.[3] Metabolic changes in asthmatic patients may be examined to detect bioactive metabolites as pathogenic mediators as well as biomarkers of asthma.[4] Sphingolipid metabolic changes represent target molecules as pathogenic and genetic susceptibility factors.

Genome-wide association studies have newly identified the orosomucoid-like 3 (ORMDL3) gene as a genetic-predisposing factor linking genetic susceptibility and the underlying pathogenesis of childhood asthma.[5] This raised clinical interest in sphingolipid metabolism due to its inhibitory action on serine palmitoyltransferase (SPT),[6] which is the rate-limiting enzyme in sphingolipid biosynthesis. Decreased activity of SPT leading to impaired sphingolipid synthesis was shown to be associated with methacholine-induced airway hyperreactivity.[7] Interestingly, several metabolomic studies on asthma addressed altered sphingolipid metabolic changes according to the phenotype of asthma.[3,8,10] Altered sphingolipid metabolism showed a relation to asthma in close association with genetic variants.[3] Increased sphingosine-1-phosphate (S1P) release in asthmatic patients was shown to be correlated with severity of asthma through metabolomics analysis.[8] Trinh *et al.*[9] demonstrated the distinct metabolic disturbance of sphingolipids in aspirin-exacerbated respiratory disease (AERD), a severe form of adult-onset eosinophilic asthma comorbid with chronic rhinosinusitis and nasal polyps.[11] They suggested the potential utility of serum S1P and urinary sphingosine as biomarkers for identifying AERD and pathogenic mediators for participating in the systemic inflammatory response of AERD.[9]

In the current issue of *Allergy, Asthma and Immunology Research*, Kowal *et al.*[10] described an association between altered intravascular sphingolipid metabolism and airway

hyperresponsiveness in house dust mite–allergic patients during allergen challenge. Especially, phosphorylated sphingolipids, S1P and sphinganine-1-phosphate, were significantly correlated with severity of airway hyperreactivity. The increase in S1P at an early stage of allergen challenge may participate in further enhancing airway hyperreactivity and subsequently contribute to the development of late-phase allergic inflammation. Although the number of asthmatic patients included in the study was small, the authors performed experimental allergen challenge carefully and obtained consistent results, making this a valuable study. The authors also suggested that sphingolipid metabolic pathways and their receptors are potential targets for preventing development of the asthma phenotype in house dust mite–allergic patients. These metabolomics studies suggest a sphingolipid metabotype according to the phenotype of asthma and altered sphingolipid metabolism as a contributing factor in the pathogenesis of asthma.

Most studies of sphingolipids and asthma have focused on allergic inflammation related to the sphingolipid mediator, S1P, by considering the cellular action of S1P on airway hyperreactivity, bronchoconstriction, and airway remodeling.[12] S1P was identified as a pathogenic contributor to asthma[7,9,12] as well as a potent bioactive lipid molecule that regulates various cellular processes including cell growth, apoptosis, and immune regulation.[13] Increased S1P level in broncho alveolar lavage fluid was reported in ragweed-allergic asthmatic patients after allergen challenge, but not in non-allergic control subjects, and was also correlated with increased airway inflammation.[12] The potential of S1P signaling as a therapeutic target for controlling asthmatic symptoms was also suggested. There is close regulation of S1P signaling through activation of sphingosine kinase to synthesize S1P and targeting by binding to G protein-coupled S1P receptors; therefore, they have been considered as potential therapeutic targets. Sphingosine kinase inhibitor decreased airway hyperresponsiveness and inflammation in a mouse model of allergic asthma.[14] FTY720, a synthetic analog of S1P, inhibited the ovalbumin-induced bronchial hyperreactivity to methacholine in mice in association with a decrease in Th1/Th2-mediated inflammation into airways.[15,16] Interestingly, FTY720 also reduced ORMDL3 expression, airway hyperresponsiveness and inflammation, and mucus production in a house dust mite–induced asthma mouse model.[17] These findings make sphingosine kinase and S1P receptors pharmacological targets of high interest for the development of antiasthmatic drugs.

In summary, there are distinct sphingolipid metabotypes according to the phenotype of asthma. Alteration of sphingolipids could represent a pathophysiological change during allergic inflammation and airway hyperreactivity to environmental factors. Thus, therapeutic strategies altering sphingolipid metabolism offer the potential for targeted approaches based on the phenotype of asthma in future.

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