An unexpected approach to treating bronchial asthma: Modify dietary fats

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Bronchial asthma, a chronic inflammatory disease of the airways that is reversible in certain cases, usually presents with cough, difficulty of breathing, and wheezing. Although most people can successfully control asthma using inhaled corticosteroids, approximately 10% of patients are resistant to treatment. Recent evidence has suggested a link between the

excessive intake of fatty acids and exacerbation of asthma, but the details of the relationship had remained elusive.

In a study recently published in the *Journal of Allergy and Clinical Immunology*, a research group from the University of Tsukuba shed light on this knowledge gap. The group focused on the function of an enzyme called ELOVL6, which is responsible for the biosynthesis of long-chain fatty acids in humans. Dysfunction of ELOVL6 has been linked to various immune-related conditions, and thus, the group hypothesized a link between ELOVL6 and asthma.

"Improper function of ELOVL6 has been linked to diseases, such as atopic dermatitis, which is similar to asthma; both are related to immune response-mediated inflammation" explains senior author Yuko Morishima. "To investigate the role of ELOVL6 in asthma, we created an asthma mouse model that was lacking the ELOVL6 enzyme and investigated its fatty acid profile and allergen-response of the mouse airways." The group also assessed the levels of ELOVL6 in the airways of severely asthmatic patients.

The data confirmed that the expression of ELOVL6 is reduced in patients with severe asthma i.e., patients whose asthma was not controlled despite intense treatment. Interestingly, there was no significant difference in the patients' BMI when compared to non-asthmatic controls, which concurs with the groups data in the mouse model that showed that a deletion of ELOVL6 affected the fatty acid composition in mouse lungs but did not contribute to weight gain. Furthermore, the mice lacking ELOVL6 had enhanced airway inflammation, as well as enhanced goblet cell hyperplasia and airway responsiveness in response to allergens.

The study revealed that deletion of ELOVL6 increased the amounts of a class of lipids called ceramides in mice airways and also resulted in

increased levels of a ceramide metabolite called S1P. "S1P is known to be potentially related to allergic inflammation, thus we wondered what effect inhibiting its synthesis would have on our ELOVL6-deficient mouse model," says Morishima. "Fascinatingly, we found that drug-induced inhibition of ceramide and S1P synthesis reduced not only airway inflammation in our model but also reduced the migration of immune cells out of lymph nodes and their cytokine production."

These results partially uncovered the mechanism of treatment-resistant asthma, showing that the composition of lipids is pivotal in the inflammatory response. Importantly, the study provided a proof-of-concept of a novel treatment method for recalcitrant asthma by modulating the lipid composition, setting the groundwork for future studies.

More information: Kazufumi Yoshida et al, ELOVL6 deficiency aggravates allergic airway inflammation through the ceramide-S1P pathway in mice, *Journal of Allergy and Clinical Immunology* (2022). DOI: 10.1016/j.jaci.2022.12.808

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