Asthma in children: Researchers envision novel drug to reduce the risk of the disease

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Scientists have reached a milestone in the research of childhood asthma. For the first time, they have clarified how a certain genetic defect in children initially leads to frequent infections and later to asthma. The study, published in the *American Journal of Respiratory and Critical Care Medicine*, offers a novel approach to therapeutic interventions. It is the result of a close collaboration between Helmholtz Munich, the Technical University of Munich (TUM), the Center of Allergy and Environment (ZAUM), and the German Center for Lung Research (DZL).

In their first years of life, one in three children develops an early form of asthma. Among those, 80% have a genetic defect on chromosome 17. These children have frequent viral-induced wheezing attacks and progress later to asthma. The mechanisms underlying the genetic defect were previously unknown, which is why pediatricians could only treat the symptoms but not the cause.

"We have now discovered why the genetic defect makes children more prone to viral infections, which is a strong risk of progression into asthma," says Dr. Constanze Jakwerth, first author of the study.

Screening among children reveals increased protein expression

Previous epidemiological studies have already suggested that the genetic defect was associated with viral infections. Therefore, the researchers investigated the nasal mucosa tissue of 261 children with wheezing using brushes to extract some cells from the nasal cavity. This method is relatively non-invasive but allows the assessment of the entire set of gene transcripts in these nasal cells (transcriptome).

Thereby, it was possible to identify changes and patterns ("nasotypes") in the gene expression that are very different in children with and without the genetic defect.

Upon close inspection, the researchers found that the genetic defect causes an increased expression of the protein GSDMB. This protein forms pores and is crucial for immune responses. The team revealed that the genetically enhanced expression of GSDMB in turn causes a disturbed interferon response.

Interferons are known to be critical for the cellular response to viral infections. There are three classes of interferons. The researchers observed that nasal cells of children with the genetic defect express more type 2 interferons but fewer type 1 and 3 interferons. The latter are, however, important for the viral defense. This is why the genetic defect ultimately makes children more prone to viral infections and consequently increases the risk of asthma.

Fewer infections might reduce the risk of asthma

"We now know that the genetic defect on chromosome 17 leads to a specific gene expression pattern that we can influence or even correct. We aim to repair the defense defect of the children's airways. We are working on novel drugs, inhalation sprays, that support the defense against the virus by stimulating the epithelial barrier for a more appropriate response," says Prof. Carsten Schmidt-Weber, who led the study at Helmholtz Munich and TUM.

"Early viral infections are likely to change the children's immune system and break the tolerance to normally harmless allergens that in turn will promote asthma development. Thus, if the infections can be controlled more efficiently with novel drugs targeting the genetic defect, we hope that fewer children will develop asthma," says Prof. Erika von Mutius,

co-lead author of the study.

More information: Constanze A. Jakwerth et al, 17q21 Variants Disturb Mucosal Host Defense in Childhood Asthma, *American Journal of Respiratory and Critical Care Medicine* (2023). DOI: 10.1164/rccm.202305-0934OC