Integrated gut metabolome and microbiome fingerprinting reveals that dysbiosis precedes allergic inflammation in IgE-mediated pediatric cow’s milk allergy

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Abstract

Background: IgE-mediated cow’s milk allergy (IgE-CMA) is one of the first allergies to arise in early childhood and may result from exposure to various milk allergens, of which β-lactoglobulin (BLG) and casein are the most important. Understanding the underlying mechanisms behind IgE-CMA is imperative for the discovery of novel biomarkers and the design of innovative treatment and prevention strategies. Methods: We report a longitudinal in vivo murine model, in which 2 mice strains (BALB/c and C57Bl/6) were sensitized to BLG using either cholera toxin or an oil emulsion (n=6 per group). After sensitization, mice were challenged orally, their clinical signs monitored, antibody (IgE and IgG1) and cytokine levels (IL-4 and IFN-γ) measured, and fecal samples subjected to metabolomics. The results of the murine models were further supported by fecal microbiome-metabolome data from our population of IgE-CMA (n=24) and healthy (n=23) children (Trial: NCT04249973), on which polar metabolomics, lipidomics and 16S rRNA metasequencing were performed. In vitro gastrointestinal digestions and multi-omics corroborated the microbial origin of proposed metabolic changes. Results: During sensitization, we observed multiple microbially derived metabolic alterations, most importantly bile acid, energy and tryptophan metabolites, that preceded allergic inflammation. The latter was reflected in a disturbed sphingolipid metabolism. We confirmed microbial dysbiosis, and its causal effect on metabolic alterations in our patient cohort, which was accompanied by metabolic signatures of low-grade inflammation. Conclusion: Our results indicate that gut dysbiosis precedes allergic inflammation and nurtures a chronic low-grade inflammation in children on elimination diets, opening important new opportunities for future prevention and treatment strategies.

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