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

Lynn Vanhaecke[1], Ellen De Paepe[1], Vera Plekhova[1], Pablo Vangeenderhuysen[1], Nele Baeck[2], Dominique Bullens MA[3], Tania Claeys[4], Marilyn De Graeve[1], Kristien Kamoen[5], Anneleen Notebaert[6], Tom Van de Wiele[7], Wim Van Den Broeck[1], Koen Vanlede[8], Myriam Van Winckel[9], Lars Vereecke[9], Chris Elliott[10], and Eric Cox[1]

[1]Universiteit Gent Faculteit Diergeneeskunde
[2]AZ Jan Palfijn Gent AV
[3]Katholieke Universiteit Leuven Departement Microbiologie Immunologie en Transplantatie
[4]AZ Sint-Jan Brugge-Oostende AV
[5]AZ Maria Middelares vzw
[6]Sint-Vincentius Ziekenhuis vzw
[7]Universiteit Gent Faculteit Bio-Ingenieurswetenschappen
[8]Vitaz
[9]Universiteit Gent Faculteit Geneeskunde en Gezondheidswetenschappen
[10]Queen's University Belfast The Institute for Global Food Security

July 10, 2023

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.

Hosted file

`Manuscript.docx` available at https://authorea.com/users/165649/articles/653732-integrated-

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