Ruminococcus gnavus heralds the onset of infantile allergic diseases: a twin cohort study

The World Health Organization has predicted that the prevalence of bronchial asthma will increase globally in forthcoming years. Early life gut microbial dysbiosis is currently recognized as a key determinant of immune dysregulation, which is associated with a broad spectrum of allergic disorders. However, we still do not know what or how gut microbes are responsible for allergy establishment. It is arguable that early and rapid colonization by Clostridium/Bacteroides/Escherichia coli and insufficient colonization by Lactobacilli/Bifidobacterium contribute to allergy development in infants. The controversy of this topic is most likely due to the use of different assay systems as well as the fact that traditional bacterial cultivation methods normally produce lower than expected numbers of detectable species. Additionally, many relevant studies have been cross-sectional and have not included serial sampling. Some studies have enrolled cases with current atopic diseases and lacked sufficient data on the microbiota configurations that existed before disease onset. The control groups in these studies deserve the most critical appraisal as the studies have usually enrolled control participants from different families unrelated to the allergic patients, as a result, the genetic and environmental factors that modulate microbial colonization could not be precisely controlled.

All of these drawbacks restrict the efficient and accurate identification of the bacteria that predisposed individuals to the development of allergies, and this represents a missed chance to achieve successful treatment.

We assumed that dysbiosis of the gut microbiota in infancy may predispose patients to later allergy development, and our intention in this study was to identify the causative bacteria. The aforementioned design drawbacks were avoided in this study because we enrolled a twin cohort to diminish the biases caused by familial and environmental determinants. We collected the twins’ stool samples serially beginning on the first day of life to allow an ample time window for the early identification of related microbial patterns before disease development. Once a pair of twins exhibited discordant clinical phenotypes, their fecal collections were compared, and we began to attempt to tease out whether this is a culprit in the disease. We employed culture-free PCR-temporal temperature gradient gel electrophoresis (TTGE) and 16S rRNA-based next-generation sequencing (NGS) to profile the entire microbiome down to the species level. By using this comprehensive and rigorous strategy, we provide the first evidence indicating that Ruminococcus gnavus is the relevant bacteria that causes allergic diseases. This bacterial species was rarely found in non-allergic subjects but was present at a significantly higher frequency prior to or concurrent with the onset of allergic manifestations.

To confirm this bedside finding in a bench study, we established an in vivo asthmatic mouse model as well as an in vitro coculture system of bacteria and murine colon tissues to corroborate the role of R. gnavus in allergic manifestations. The immunoregulatory mechanisms underlying the competence of R. gnavus to control allergy development were studied not only in lung tissues but also in the colon, where the bacteria colonized. R. gnavus has been demonstrated to be a mucolytic bacterium capable of degrading colonic mucin and consuming mucin-derived glycans. The data presented in this study further demonstrate that after it penetrated the mucus layer, R. gnavus was recognized by dendritic cells (DCs), and the colonic epithelia were stimulated to secrete epithelium-derived cytokines like IL-33. These cytokines elicited an expansion in type 2 innate lymphoid cells (ILC2s) and DCs to prime the differentiation of Th2 cells from naive T cells, thus ensuring the production of Th2 cytokines and causing tissue eosinophilic infiltration. As a result, Th2 lymphocytes and effector cells rapidly circulated to the lung via the circulatory and lymphatic systems to initiate an asthmatic inflammatory cascade.

In conclusion, we have exposed a potential microbiota-driv-
en gut-lung axis that represents a mechanism by which dysbiosis could cause allergic diseases in infants. Our data indicate that R. gravis-associated dysbiosis induced Th2-biased immunity in the colon and also exploited the gut-pulmonary axis to evoke allergic asthma, thus constituting a potential therapeutic target for the treatment and prevention of the disease.


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