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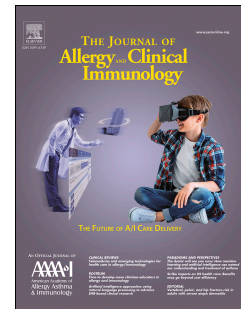
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Editorial for Airway administration of OM-85, a bacterial lysate, blocks experimental asthma by targeting dendritic cells and the epithelium/IL-33/ILC2 axis

Bacterial lysates to inhibit allergic airway disease: are they up to the challenge?

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Key Words: asthma, airway inflammation, bacterial lysates, regulatory T cells

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It has become clear that the development of allergies, and especially asthma, is very much dependent on microbial exposures. Indeed, exposure to bacteria in farm dust, parasites or other bacteria such as *Helicobacter pylori* has been shown to decrease susceptibility to the development of asthma in epidemiological studies and experimental studies.¹ In addition, there has been increasing insights into the mechanisms by which exposure to bacteria or bacterial compounds influences the immune system and reduces susceptibility for the development of allergic disease.

In this issue, Pivniouk and coworkers investigate the use of an alkaline lysate of 21 bacterial strains from five genera (*Moraxella*, *Hemophilus*, *Klebsiella*, *Staphylococcus* and *Streptococcus*), named OM-85 (Broncho-Vaxom®).² OM-85 is commercially available as capsules for ingestion and is marketed to reduce the susceptibility for airway infections. Indeed, previous experimental studies have shown that OM-85 reduced allergic airway inflammation in a murine model of allergic airway disease.³ After oral treatment with OM-85, airway inflammation was reduced, based on interleukin-10 (IL-10)-dependent and MyD88 (myeloid differentiation primary response gene (88))-dependent mechanisms. The activation of these pathways led to the conversion of T cells into FoxP3(+) regulatory T cells.

In the current investigation, the authors used a different approach by applying OM-85 not via the gastrointestinal route but directly into the airways. This should not be interpreted as an alternative route for a potential therapeutic application. Instead, the current publication is a mechanistic investigation about how bacterial components shape local immune system homeostasis and might therefore affect the development of allergic airway disease. In this study, application of OM-85 directly into the airways reduced several different hallmarks of allergic airway disease. Allergen sensitized and challenged mice that received OM-85 showed less airway inflammation, fewer T2 cytokines in bronchoalveolar lavage (BAL) fluid, and fewer goblet cells in the airways. However, local application did not affect systemic sensitization because serum levels of allergen-specific IgE were not affected by OM-85 treatment. Additional elegant experiments suggest that application of OM-85 modified dendritic cell (DC) phenotypes and induced regulatory T cells, which supposedly suppress the development of allergic airway disease. Further experiments show that *Myd88/Trif* expression in DCs was necessary for OM-85-dependent DC reprogramming. These pathways are comparable to those affected after oral administration of OM-85. However, there seems to be differences in the systemic effects of exposure in the gut or lung. Specifically, exposure in the gut resulted in reduced inflammation in the lung whereas administration into the lung had no effect on systemic sensitization.

The current results are also somewhat similar to the effects of exposure to farm-derived microbial products, showing that exposure to certain bacterial compounds via the airways reduces susceptibility to allergic airway disease.⁴ The current study gives further insight into

the underlying immunological mechanisms by showing that local administration of OM-85 induces a tolerance-promoting landscape in the lung by affecting local dendritic cells and inducing a tolerance-prone local environment. In addition to induction of regulatory dendritic cells and T cells, direct application of OM-85 on human airway epithelial cell lines maintained trans epithelial electrical resistance (TEER) following allergen exposure, suggesting the protection of epithelial integrity and preservation of epithelial barrier function, as well as a reduction in accumulation of innate lymphoid cells type 2 following exposure to Alternaria into mouse lungs. Therefore the application of OM-85 did also reduce early epithelial cells activation following allergen exposure as an effect additional to affecting dendritic cells modulation.

Despite these interesting results, the current study cannot be interpreted as supporting the use of OM-85 as a therapeutic for patients with allergic asthma. Firstly, the route of administration is completely different to what is currently possible with available OM-85 preparations. OM-85 is available in an oral formulation whereas it was administered directly into the lungs in the current study. In addition, the authors used strictly prophylactic intervention strategies, meaning that OM-85 was administered before the first dose of allergen. To test potential as a therapeutic strategy, the intervention should be investigated in secondary models or in chronic models of allergic airway disease. In these models, therapeutic interventions are administered before a secondary airway challenge or during a chronic challenge period, and therefore mimic therapeutic interventions.⁵ As a result, the current findings do not provide any information about the potential therapeutic benefits of pulmonary administration of OM-85. Interestingly, a recently published randomized, placebo-controlled trial investigated patients with severe asthma who were received oral OM-85.⁶ This smaller study showed a non-statistically significant decrease in exacerbations, especially in patients with signs of T2 inflammation. Immunological analysis revealed an increase in IL-10 and interferons following systemic administration of OM-85. Therefore, more studies in patients with T2 inflammation are needed to assess the effectiveness of this approach as an add-on treatment for asthma.

The current investigation provides additional evidence that exposure to bacteria and bacterial compounds is important for shaping the local immune system in the lung. This includes the presence of certain commensal bacteria,⁷ as well as exposure to environmental bacteria (e.g. in dust from farming houses⁴ or colonization of the gastrointestinal tract^{8, 9}). Indeed, different bacterial lysates or bacterial compounds have been used in different models of allergic disease. Similar to published studies, the suppressive effects mainly act via modulation of DCs and induction of regulatory T cells, which are the main factors in suppressing allergic airway disease.¹⁰ These are intriguing findings, which could suggest potential usefulness a therapeutic approach. However, the standardization of microbial content from house dust or lysates of different bacteria strains is complicated and not yet fully developed. The big

advantage of OM-85 is that the amount of bacterial content is standardized. It would be a great advance to have new therapeutic approaches for allergies and asthma because currently available medications, including the monoclonal antibodies, are all symptomatic therapies. Therefore, novel immune modulators that induce suppression of allergic inflammation would be very desirable. Whether or not bacterial compounds can overcome existing challenges remains to be seen. The current study further supports this approach and confirms that continuing this path of research remains promising.

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Figure 1 Legend

Effects of systemic application of OM-85 via the stomach and local application via the lung

