

EDITORIAL

Usefulness of mycobacteria in redirecting the immune response in atopic disease

H. Renz

In this issue, Shirtcliffe and co-workers from New Zealand and the UK present a negative study on the effect of repeated intradermal injections of heat-inactivated mycobacterium bacillus Calmette–Guerin (BCG) in adult asthma [1]. This study is of importance in several regards: (i) although there are several studies in the Chinese literature addressing this issue, this is the first study performed under Western medical standards employing a placebo-controlled protocol with standardized outcome variables; (ii) the study results are negative; (iii) this study underlines the continuing interest in the relationship between bacterial products and atopic disease.

In terms of the relationship between exposure to microbial products and respiratory allergies, we are still faced with the paradox situation that there is evidence for both, protection on the one hand and exacerbation on the other (Fig. 1). There is no doubt that common colds are the most frequent cause of asthma exacerbation in both children and adults [2–6]. One mode of action might be an additive effect of airway inflammation resulting from the inflammatory response to viral infections in an already inflamed mucosal tissue. Several groups have found an increased incidence of asthma in children with a history of childhood bronchiolitis [7–18]. Virus-infected patients with asthma have enhanced cytokine responses, apparently leading to prolonged lymphocytic and eosinophilic accumulation in the tissue. One of the major causes of early childhood bronchiolitis is respiratory syncytial virus infection. In addition, it is a long-known phenomenon that in atopic dermatitis, the prominent skin manifestation of the atopic syndrome, disease exacerbation is triggered by chronic colonization of the skin with *Staphylococcus aureus*. Superinfection of the skin is triggered by a variety of microbial products including bacterial, fungal and viral pathogens [19].

In contrast, there is epidemiological evidence about an inverse relationship between asthma and the overall burden of respiratory infection [7–11, 20–24]. The data from these and experimental studies in mice suggest that the timing between infection and allergen exposure may be of great importance in terms of the immunological outcome. It is now widely accepted that particularly the initial steps of allergic sensitization and acute allergic inflammation are clearly associated with the development of a Th2 phenotype. Particularly in childhood atopy the onset of these processes occur relatively early in life, sometimes maybe even already before birth. These early developments of initial allergic Th2-dominated immune responses occur at a very vulnerable period where the immune system learns and acquires immunologic tolerance and memory against a variety of environmental antigens. This complex situation leads to the concept that normal education of the immune system occurs

particularly well if there is a certain burden of microbial antigen exposure which stimulates education and memory. If this occurs early on in life the immune system is then able to handle allergens in the appropriate way, e.g. recognizing them as harmless environmental antigen and making tolerance (Fig. 2).

In this context, the relationship between mycobacterial infection and BCG vaccination represents an important model situation. Many bacterial infections are associated with increased production of IFN- γ , reflecting a requirement of Th1 immunity for defence and protection [25–28]. Cytokines produced by the innate immune system including macrophages and natural killer cells in response to mycobacterium tuberculosis and/or its components are able to shift, at least *in vitro*, the development of allergen specific T cells from a Th2/Th0 to a Th1 profile. These cytokines include IL-12 and IFN- α which play an important role in the development of Th1 effector cells.

One of the first studies which addressed this issue was published by Shirakawa et al. [3]. The authors performed a cross-sectional study and found that among BCG-immunized Japanese schoolchildren asthmatic symptoms and several other index factors of atopy were significantly less likely in positive tuberculin responders compared to negative responders. A likely interpretation of this result is the failure to respond appropriately after BCG vaccination, e.g. with the development of a specific delayed-type hypersensitivity response that is associated with the development of atopic symptoms rather than the BCG vaccination *per se*. Such an interpretation is further supported by the findings of Swedish investigators, again indicating that single immunization does not affect the prevalence of atopic diseases at school age [29, 30]. In contrast, an inverse relationship between BCG vaccination and atopy has been reported in Guinea Bissau [31]. Along this line, BCG was associated with a lower prevalence of atopic disease among Swedish immigrant children, many born in Asia and South America [32].

It is important to distinguish between BCG vaccination and mycobacterial infection. An inverse relation between the prevalence of asthma and reported rates of tuberculosis has been reported [33]. To further explore underlying mechanisms of this epidemiological phenomenon, animal models have been employed by several investigators including our own [34–36]. It is important to note that the BCG vaccine contains attenuated mycobacteria which results in severe generalized mycobacterial infection in these animals. Therefore, these studies are not meant to reflect BCG vaccination, but rather mycobacterial infection.

Mycobacteria are ubiquitous in the environment and include more than 80 species in soil and untreated water. Based on the concept that environmental mycobacteria are

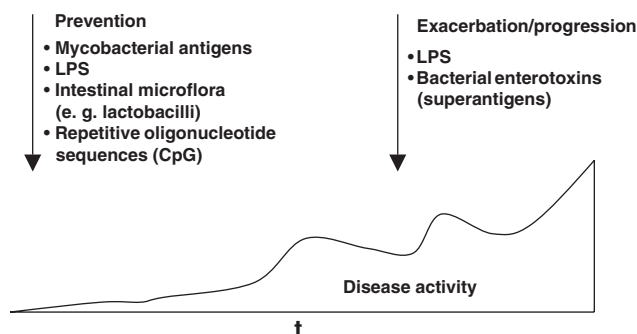


Fig. 1. Concept: Opposite effects of bacterial components on allergy development and exacerbation.

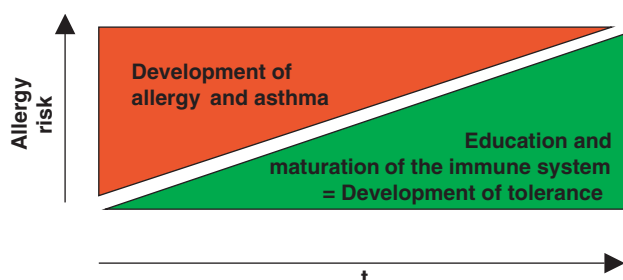


Fig. 2. The inverse relationship between development of immunological tolerance and the risk for allergy and asthma.

being able to promote Th1 cytokine responses, they have been suggested to possibly prevent allergy [2]. For this purpose, the non-pathogenic mycobacterium *Mycobacterium vaccae* has been used in two studies [37, 38]. In the first study, 42 patients with stable moderate-to-severe asthma who were skin prick test-positive to house dust mite were randomized to receive two intradermal injections of either placebo or heat-killed *M. vaccae* or delipidated decylcolipidated *M. vacca*. There were no significant differences between either treatment group and the placebo group for any of the outcome variables. In the second study, significant reduction in the extent of eczematous lesions was observed in children with atopic dermatitis 3 months after a single intradermal dose of the preparation of killed *M. vaccae*, but not in those receiving placebo. In a recent position paper by the European Academy of Allergy and Clinical Immunology, it was concluded that the results of these studies have not fulfilled the enthusiastic expectations raised on theoretical grounds [39].

The study published in this issue of the journal shows the result of repeated intradermal injections of heat-inactivated BCG in adult asthma [1]. Despite the absence of any positive effect on existing asthma a high incidence of severe local reactions has been demonstrated that further limits application of this approach. Although the study has some limitations, as extensively discussed by the authors, the results do not support the concept of modifying existing asthma by even repeated BCG applications. However, it must be noted that it still remains unclear, whether BCG positive, previously vaccinated individuals would benefit from a boosting protocol.

All of the studies published so far were performed in already pre-existing disease. However, it is quite clear that modifying the course of already ongoing inflammation is

quite difficult and requires continues inflammation-modifying therapies. Therefore, it still remains unlikely that a single or a few repeated applications of microbial immunostimulants may be able to alter the course of the disease substantially. However, the truly preventive approach has not been tested so far in a controlled clinical setting. In conclusion, the concept to prevent or modify already existing atopic disease via administration of bacterial compounds remains to be tested in more randomized and controlled clinical studies before any conclusion can be drawn on this important matter.

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H. Renz

Department of Clinical Chemistry and Molecular Diagnostics
Philipps-University Marburg
Baldinger Strasse 35033
Marburg, Germany
E-mail: renzh@med.uni-marburg.de