

EDITORIAL

Mycobacterium-based vaccines for the prevention of allergic disease: a progress report

The concept of a Mycobacterium-based vaccine to reduce the risk of developing allergic disorders, or modify their severity is not new, with the Chinese having used such an approach for many decades [1, 2]. However, recent attempts to develop Mycobacterium-based vaccines that are effective in the primary or secondary prevention of atopic diseases such as asthma, rhinitis and eczema have gained considerable momentum, with a major research effort currently being undertaken world-wide. This potential therapeutic approach is based on an increasing knowledge of the immunological basis of the pathogenesis of atopic disease and the experimental and epidemiological evidence that Mycobacterium infection may modify these processes.

The paradigm of antagonism between T helper (Th) lymphocyte subsets and their cytokines, first described in murine models in the early 1990s [3], has resulted in the current widely accepted hypothesis that atopy and asthma are 'Th2 diseases'. In its simplest terms this hypothesis argues that a relative increase in Th2 responses in combination with a decrease in Th1 responses drives the allergic phenotype [4]. Amongst the numerous factors which are known to influence the balance of Th1/Th2 immune responses is infection. The working hypothesis is that a lack of microbial stimulation of sufficient intensity in early life may affect maturation of the immune system resulting in a Th2 predominance in genetically susceptible individuals and sensitization to otherwise harmless allergens in the environment [5]. Infection with various species of Mycobacterium including Mycobacterium tuberculosis (MTb), Mycobacterium vaccae (M. vaccae), and Mycobacterium bovis-bacillus Calmette Guérin (BCG) has been shown to provoke an intense Th1 response and suppression of the Th2 response [6–8]. The therapeutic potential of this property has been demonstrated in animal models of asthma with the administration of BCG and M. vaccae resulting in a reduction in the magnitude of allergen-induced airways eosinophilia [9–11].

The initial epidemiology evidence for a protective effect of natural M. Tb exposure comes from Shirakawa et al.'s landmark survey in Japanese schoolchildren [12] which found a strong inverse association between positive tuberculin responses at both 6 and 12 years and a range of atopic characteristics, including symptoms at any age and IgE levels and Th2 cytokine profiles assayed at 12 years of age. Their conclusion that a decline in tuberculous infection may be a factor in the rising severity and prevalence of atopic disorders in developed countries has been challenged by the alternative interpretation of the data that atopic disease alters delayed hypersensitivity [13]. Subsequently, there has been an inability to confirm the findings in similar studies undertaken in Norwegian [14], Chinese [15], and Turkish [16] communities, although ecological support for the hypothesis has come from the negative

association between M. Tb notification rates and asthma prevalence, both in western countries [17] and world-wide [18]. Disappointingly, BCG vaccination in infancy has not had a consistent effect in preventing the development of subsequent asthma [19–21]. Likewise, studies to date of the efficacy of Mycobacterium-based vaccines such as BCG, M. vaccae and related products in established asthma have been varied, showing modest [22] or no effect [23], or being limited by significant side-effects [24].

In the latest study in this field published in the June issue of *Clinical and Experimental Allergy*, Hattori and coworkers [25] reported that the local application of a purified protein derivative from Mycobacterium tuberculosis (PPD) inhibits the initiation but not the exacerbation of allergic rhinitis in mice. In addition to this study extending the immunotherapeutic potential of Th1-type therapy to the upper airways it re-emphasizes the importance of the therapeutic route of delivery and the failure to modify already established allergic inflammatory responses. Another important observation from this paper is that using a relatively selective preparation of proteins from Mycobacteria in the form of PPD, it was possible to inhibit an extensive range of allergic inflammatory responses. It is well recognized that in addition to priming CD4⁺ Th1 cells PPD can also trigger the adaptive immune response via classical MHC presentation of peptide epitopes for T cell recognition [26]. However, the potential exists for other mycobacterial components to have additional effects through other inflammatory pathways, for example, bacterial DNA (CpG) are known to trigger an innate immune response [27] that has in turn been shown to suppress airway inflammation [28]. Mycobacterial cell wall components such as lipoarabinomannan (LAM) also trigger an innate immune response through the Toll-like receptor (TLR) pathway [29]. Both CpG and Mycobacterium cell wall components have also been shown to alter the activity of both macrophages [30, 31] and dendritic cells [32, 33]. The multifaceted response to these molecules highlights their potential for inhibition or treatment of a broad range of allergic responses. Elucidation of the relative importance of the different active component(s) is necessary not only in terms of ensuring that the clinical trial programmes proceed with the most efficacious agent, but also in terms of our understanding of the mechanism(s) by which efficacy may be achieved.

The findings by Hattori et al. [25] are consistent with other animal work in which Mycobacterium-based vaccines have been shown to reduce the development of airway eosinophilia when given prior to or during, but not after atopic sensitization [10, 11]. Similarly, in clinical studies repeated administration of BCG, M. vaccae and its derived product delipidated deglycolipidated M. vaccae have had no effect in reducing asthma severity in adults with chronic asthma of many years duration

[23,24]. This may be due to the relatively greater role of Th1/Th2 imbalance in terms of the development rather than the maintenance of disease, and the crucial role of airways remodelling independent of Th1/Th2 imbalance in disease progression and maintenance [34, 35].

A further observation from the study by Hattori et al. is that the route of delivery of the vaccine appears important in that intranasal but not intradermal administration of PPD was effective. This was originally observed in mouse studies by Erb et al. in which the intranasal administration of BCG vaccine was considerably more effective than its intraperitoneal or intradermal administration in a mouse model of airways eosinophilia [10]. This suggests that the route of administration is crucial and that delivery of the vaccine into the lower and upper airways may be required for asthma and rhinitis, respectively. Interestingly, it has been shown that BCG administered by aerosol induces a much greater degree of protection against aerosol challenge with virulent *M. Tb* than intracutaneous BCG vaccination [36]. Furthermore, the aerosol route of vaccination was not associated with any adverse side-effects and produced a comparatively small degree of tuberculin hypersensitivity, suggesting a predominant local rather than systemic immunological response [36]. These findings suggest that the disappointing results of intradermal BCG vaccination in infancy [19–21] may be due to limitations associated with its route of administration rather than a lack of potential efficacy of BCG if it is delivered directly to the airways. The study of Hattori et al. [25] is in fact the first to concentrate on allergic rhinitis which in some respects may be considered to have the greatest potential therapeutic advantage due to the ability to deliver the vaccine directly to the end organ.

Another consideration is whether differences exist in the end organ response to this therapeutic approach with asthma, rhinitis and eczema. Although interest to date has primarily focused on asthma, it is in the treatment of eczema that the preliminary results have been particularly encouraging, with the recent placebo-controlled trial of a killed *M. vaccae* suspension [37]. In children of 5–18 years, intradermal injection of *M. vaccae* resulted in a mean 48% reduction in the surface area affected, and a mean 68% reduction in the severity score as opposed to a 4% and 18% reduction in the placebo group after 3 months of treatment. Local reactions to the injections were experienced by most children but these settled spontaneously.

The issue of safety relates to the potential to cause both acute local and long-term systemic adverse effects. With the intranasal administration of live attenuated BCG in the mouse model of airway eosinophilia the animals developed septicaemia with disseminated infection as shown by the presence of liver and lung granuloma in the treated animals [10, 11]. Furthermore, in a recent clinical study of repeated intradermal injection of heat inactivated BCG in adult asthmatics, severe local reactions led to cessation of the trial [24]. In terms of long-term effects, it will be necessary to demonstrate that influencing the Th1/Th2 balance in infancy does not adversely affect the propensity to develop Th1 dominant diseases such as diabetes. For a vaccine to be used widely in infancy an excellent safety profile will need to be established.

In conclusion, the potential of Mycobacterium-based vaccines in the prevention of atopic disease is considerable, but by no means guaranteed. Amongst the issues that require clarification include whether the Th1/Th2 paradigm described in mice

can be directly extrapolated to humans, elucidation of the most effective components of Mycobacterium, determination of the optimal administrative regime including route of delivery, dose and duration of treatment, and whether primary or secondary prevention should be the focus of therapy. There are also major ethical issues in terms of giving an immune modifying treatment to young children and the long-term effects this may have in terms of enhanced Th1 stimulation.

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