

Editorials

Atopy, asthma, and the mycobacteria

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In this issue of *Thorax* there are two articles which add to the observations on an inverse link between mycobacterial exposure and atopic disorder, and to the larger story that certain microbial exposures in early childhood may play a key part in limiting immune dysregulation. Von Mutius and colleagues report increasing tuberculosis notification rates associated with a stepwise decrease in symptoms of asthma and rhinoconjunctivitis in an international ecological study,¹ while Omenaas *et al* found no relationship between IgE levels and tuberculin responses in Norwegian adults vaccinated with BCG at 14 years of age.²

One potential explanation for the promotion of clinical tolerance to allergens by certain microbial exposures may be framed within two related immunological concepts. Firstly, adaptive immune responses may be broadly categorised into two antagonistic subtypes (Th1 and Th2), each with its own set of molecular mediators or cytokines.³⁻⁵ Secondly, the type of T helper (Th) adaptive response to one antigen may influence the type of Th response to a quite independent antigen through modification of the cytokine profile of the immune milieu.⁶⁻⁸

In atopy there is over-reactivity of Th2 immune mechanisms involving the cytokines interleukin (IL)-4, IL-5 and IL-3, which leads to IgE production and eosinophilic mucosal inflammation in response to many antigens. Atopic or allergic responses to inhaled antigen or allergen such as those from house dust particles are a potent factor in the causation of asthma.^{6,9,10} Such vigorous Th2 immune responses are naturally seen in certain helminthic infections when they provide an important element of protective immunity.¹¹⁻¹³ What then is their origin, in dysregulated form, in atopy?

Heterogeneous genetic factors are important because genetic variants at a number of chromosomal locations are linked to high IgE levels or asthma.¹⁴ Variants in the Th2 cytokine signalling pathway are important.¹⁵⁻¹⁷ In one instance a genetic variant of the IL-4 receptor (IL-4R α) strongly predicted high IgE levels and asthma in certain populations; experimental transfer of DNA has shown that the variant significantly upregulates the IL-4R α response to IL-4 stimulation resulting in increased Th2 cell growth and IgE synthesis.¹⁵ The existence of such Th2 promoting variants in human populations may relate to their potential to enhance protective Th2 immune mechanisms against helminthic infestation, a regular threat to mankind in certain environments now and almost ubiquitously so in the past. The epidemiological relationship between helminth infestation and atopy in currently underdeveloped countries is complex and unresolved, with suggestions that atopic individuals may suffer less parasitisation and that helminthic infection may moderate atopic disorder, perhaps by saturating mast cell IgE receptors with non-allergen directed IgE.¹⁸ Further investigations of these

relationships are required which need to take account of genetic variants of Th2 signalling.

The acknowledged rapid rise in the atopic disorders in developed communities points to important environmental determinants of overactive Th2 immunity and to the likelihood that these are related to socioeconomic development.¹⁹ Dietary change and greater pollution by indoor allergens or noxious agents more generally have been considered candidate mechanisms, but change in the patterns of microbial exposure is a potential mechanism which crucially relates to immune development.^{6,20} One temporal association with the increase in atopy in developed communities has been a significant fall in exposure to many microbes including the helminths already referred to and *Mycobacterium tuberculosis*. Moreover, there is a link between increased atopy and small sibships in which there may be less sharing of various microbial exposures than in larger sibships.²¹ Some data indicate that fetal and neonatal allergen specific responses are naturally Th2 in the first instance, and that these need conversion towards a Th1 type to produce the non-atopic state of clinical tolerance to allergens; Th1 promoting microbial exposures are the natural candidates for delivering such tolerance.²² Experimental animal data suggest that commensal organisms in the gut are essential for the tolerance to allergen that usually results from oral exposure.²³⁻²⁵ It is therefore interesting that two epidemiological studies have linked early life treatment with antibiotics, potent reducers of gut commensals, with subsequent atopic disorder.^{26,27} Other epidemiological studies have related less atopy with early life exposure to measles, mycobacteria, and a range of orofecal pathogens.²⁸⁻³⁰

A putative link between exposure to mycobacteria and less atopy was illustrated in a study of Japanese children³⁰ in whom strongly positive tuberculin responses in early life were associated significantly with less asthma, rhinoconjunctivitis, and eczema in later childhood. The positive tuberculin responses in early life were also associated with lower IgE levels and dominance of Th1 over Th2 in the peripheral blood cytokine profiles at 12 years of age. One part of this inverse relationship might be attributable to genetic determinants of Th1/Th2 skewing in these children who were born into a population with a notification rate for tuberculosis of about 100/100 000 and who were immunised with BCG as neonates. However, other observations within the study pointed to environmental influences, including the likelihood of varying exposures to mycobacteria. The scale of the strong tuberculin responses suggested natural early life exposure to *M tuberculosis* in addition to BCG in many of the children. The prevalence of strong tuberculin responses in the children was only about 60% of that in their parental generation, a rapid decline beyond genetic explanation which was temporally

related to the sharp fall in notified infectious tuberculosis in the Wakayama population.³⁰

In fact, mycobacteria elicit particularly strong protective Th1 immune responses. Mycobacterial lipoproteins bind to macrophage bound Toll-like receptors (TLRs) and this interaction leads to prominent synthesis of IL-12, and hence prominent Th1 switching and secretion of interferon (IFN)- γ and tumour necrosis factor (TNF)- α ,³¹ the cytokines shown to repress Th2 immune mechanisms in both *in vivo* and *in vitro* experiments.^{5 32-35} Repression of Th2 immune mechanisms and hence atopy by mycobacterial exposure therefore appears possible; in the case of *M tuberculosis* this may be as part of the development of protective Th1 mediated immunity in healthy subjects but not in patients with tuberculous disease in whom protective Th1 responses are often impaired.³⁶ Adams *et al*³⁷ reported that, in South Africans heavily exposed to both mycobacterial and helminthic infections, tuberculous disease was associated with high total and parasite specific IgE levels which fell significantly only after successful antituberculous chemotherapy.

The results reported by Von Mutius *et al* in this issue of *Thorax* are fascinating in this respect.¹ In their international ecological study they matched WHO derived tuberculosis notification rates to the prevalence of atopic symptoms in nearly a quarter of a million children within ISAAC and found that an increase in notifications of 25/100 000 was associated with an absolute decrease in wheeze ever of 4.7%. Whilst a number of interpretations are possible, the tuberculosis notification rates might be regarded as surrogates of mycobacterial exposure within each community, as the authors discuss with due caution; these results may therefore support the concept that natural exposure to *M tuberculosis* may have a role in inhibiting atopy on a world-wide scale. As yet there is no information on whether exposure to the non-tuberculous mycobacteria, ubiquitous in soil and water, may also relate to less atopy, but this is an important issue.

Formal experimental data on the inverse link between mycobacteria and atopy come from recent experiments in mice which uniformly showed that exposure to mycobacteria had impressive Th2 limiting effects.³⁸⁻⁴¹ Thus, exposure of mice susceptible to the experimental induction of allergy with ovalbumin to different mycobacterial preparations results in a major limitation of systemic or pulmonary Th2 responses, pulmonary eosinophil infiltration, and anaphylactic pulmonary reactions in response to allergens. Subcutaneous injection of heat killed *M vaccae*, an environmental mycobacterium with strong Th1 promoting properties, inhibited production of IgE and IL-5 by splenic cells.³⁸ Intranasal BCG inhibited pulmonary eosinophilia and IL-5 synthesis in response to ovalbumin and to the nematode worm *N brasiliensis*, an effect dependent on synthesis of IFN- γ .³⁹ Intravenous BCG promoted IFN- γ synthesis and inhibited a range of Th2 phenomena including secretion of IL-4/IL-5 and IgE/IgG₁₃, airway eosinophilia, and responsiveness to ovalbumin.⁴⁰ The inhibition of ovalbumin allergy in these experiments was related to the timing of mycobacterial exposure in relation to the ovalbumin sensitisation procedure (the BCG was given prior to or concurrently with ovalbumin sensitisation), the dosage of organism, and the route of administration (for BCG the intranasal route was more effective in inhibiting ovalbumin sensitisation than the intraperitoneal and subcutaneous routes).

If mycobacterial preparations can limit experimental allergy in mice, then the possibility that immunisation with mycobacterial preparations could be developed to prevent atopy and asthma in humans deserves serious consideration. From the outset it seems likely that any mycobacterial

inhibition of atopy in humans should have its maximum impact early in life—that is, before the establishment of substantial Th2 allergen responsive clones. The objective would be normalisation of the Th1/Th2 balance in allergen specific responses with the production of clinical tolerance, rather than the production of Th1 immune skewing with the theoretical risk of promoting autoimmune disorder. It is quite unlikely, given the impact of genetic factors on atopy and the response to infections in humans, that any benefit of mycobacterial immunisation in limiting atopy would be uniformly effective across a population. The route of mycobacterial administration might be of decisive importance; the murine data illustrate this point with respiratory delivery of BCG being most effective in repressing allergy, consistent with the human epidemiology in which pulmonary exposure to *M tuberculosis* is strongly linked to less asthma.^{1 29} Finally, co-exposures might be very relevant to the inhibitory impact of any mycobacterial preparation on atopy, including exposure to allergens, to antibiotics as mentioned above, and to other immunisation agents, some of which may have sensitising properties.²⁶

There are now reported retrospective analyses of BCG immunisation programmes in relation to atopy, but their findings are conflicting.⁴²⁻⁴⁴ The report by Omenaas *et al* in this issue of *Thorax* is relevant here.² Alm *et al*⁴² have previously reported that the rates of atopic disorder were similar in Norwegian children given BCG immunisation before six months of age to those in a selected group of children who had not received BCG, and in which the analysis focused on children with a family history of atopy.⁴³ Aaby *et al* reported less atopy (by allergen skin prick testing) in infants receiving BCG in Guinea-Bissau, particularly if the BCG was administered in the first week of life.⁴⁴ Omenaas *et al* now report that tuberculin responses in young adult Norwegians receiving BCG at 14 years of age were not related to atopy as determined by skin prick tests or IgE serological testing; the authors conclude that any such relationship might only hold when mycobacterial exposure occurs early in life.²

It is very difficult to compare these studies and to draw firm conclusions from them, particularly deciding whether or not BCG given by intradermal injection inhibits atopy in humans or whether it might if given very early in life. I suspect that retrospective analyses cannot enable us to judge the matter, given the vagaries of methods used and the interaction of uncontrolled but important genetic and co-exposure variables; the actions of BCG in preventing tuberculosis under different circumstances have been difficult enough to judge. Prospective controlled studies, which carefully take account of genetic and other variables, are therefore urgently needed to test the potential of mycobacterial preparations or products given in early life to limit atopic disorder in humans. BCG immunisation by intradermal inoculation represents one safe and tested method for investigation, but the advance of molecular methodologies⁴⁵ opens up other exciting possibilities.

The story linking the epidemic of atopy and asthma to changing patterns of microbial exposure looks increasingly interesting. The possibility that microbial products, as educators of immunity, might be thoughtfully developed to limit atopic disorder in many people is intriguing. What a sweet irony it would be if the products of *M tuberculosis*, or its cousins, could be used to control asthma.

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