

CORRESPONDENCE

A proposed explanation for increased risk of active tuberculosis in children with allergic disease

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To the Editor,

A recent cross-sectional multinational study established a significant association between active tuberculosis and allergic disease (1). The authors mentioned in their discussion the polarization of T-helper cells in asthma but did not provide an explanation of this association. The key to understanding the link between allergic airway inflammation and susceptibility to active tuberculosis appears to be the action of IL-4. IL-4 is expressed in abundance in airways of patients with allergic airway inflammation (2, 3). IL-4 enhances macrophage endocytosis via the mannose receptor, which binds mycobacterial lipoarabinomannan, thus representing a major route of entry of mycobacterium tuberculosis into macrophages. IL-4 reduces nitric oxide synthase expression and hereby the action of IFN-gamma-induced nitric oxide, which represents the key mechanism for intracellular killing of mycobacterium tuberculosis (4). This was confirmed in a tuberculosis mouse model: 3 weeks after infection with mycobacterium tuberculosis, bacterial load quantified by numbers of colony-forming units (CFU) in the lungs of IL-4 knock-out mice was significantly

reduced when compared with concurrently tested wild-type (WT) BALB/c mice (4). Decreased expression of the mannose receptor following IL-4 depletion could explain the observed reduced infection in IL-4-depleted mice. Reconstitution of IL-4 levels by intravenous inoculation with mouse recombinant IL-4 restored the CFU counts to the infection level of WT mice.

Several inhibitors of IL-4 production or action, including anti-IL-4 antibodies and soluble IL-4 receptor, are currently being developed for the treatment for asthma. Such inhibitors should be investigated as a way of immunoprophylaxis of tuberculosis for people at high risk of being infected and of developing active tuberculosis after infection. Development of future vaccines against tuberculosis should aim at induction of an immune response reducing IL-4 production.

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References

1. Flohr C, Nagel G, Weinmayr G, et al. Tuberculosis, bacillus Calmette-Guerin vaccination, and allergic disease: findings from the International Study of asthma and allergies in childhood phase two. *Pediatr Allergy Immunol* 2012; **23**: 324–31.
2. Saggini A, Maccauro G, Tripodi D, et al. Allergic inflammation: role of cytokines with special emphasis on IL-4. *Int J Immunopathol Pharmacol* 2011; **24**: 305–11.
3. Matsunaga K, Yanagisawa S, Ichikawa T, et al. Airway cytokine expression measured by means of protein array in exhaled breath condensate: correlation with physiologic properties in asthmatic patients. *J Allergy Clin Immunol* 2006; **118**: 84–90.
4. Buccheri S, Reljic R, Caccamo N, et al. IL-4 depletion enhances host resistance and passive IgA protection against tuberculosis infection in BALB/c mice. *Eur J Immunol* 2007; **37**: 729–37.