Akbari *et al.* reply:

Das *et al.* state that NKT cells are not required for the development of airway inflammation (defined by airway mucous production and airway eosinophilia). Whereas airway inflammation is often used as a marker of asthma, it does not always correlate with asthma. A better measure of asthma is airway hyperresponsiveness (AHR), the *sine qua non* of asthma[1], which is measured as the responsiveness to methacholine or histamine and is generally considered to be one of the best clinical diagnostic tests for asthma. Studies of asthma, particularly in mice, that fail to measure AHR often arrive at false conclusions.

At least two studies have demonstrated that invariant (*i*NKT) cells are required for the induction of allergen-induced AHR (refs. 2,3). These studies indicate that airway inflammation is diminished, though not absent, in *i*NKT cell–deficient mice but, more importantly, that AHR is grossly deficient in these mice. T-helper type 2 (T_H2) cells, which develop normally in the absence of *i*NKT cells, can induce a degree of airway inflammation in the absence of *i*NKT cells. However, the studies with *i*NKT cell–deficient mice indicate that T_H2 cells have a less important role in, and are not sufficient for, the induction of AHR. The inability of T_H2 cells to induce AHR in these mice may reflect a common clinical scenario: many individuals develop allergic rhinitis (hay fever, caused by the presence of allergen-specific T_H2 cells) but not asthma (characterized by the presence of AHR). We therefore believe that *i*NKT cells must regulate additional elements in the lower respiratory tract that are required for the development of AHR.

We agree with Das *et al.* that protein allergen–induced AHR requires the presence of T_H2 cells, because *i*NKT cells cannot recognize protein antigens. Although not sufficient for the development of AHR, T_H2 cells are clearly activated by allergen administration, and this activation of T_H2 cells may lead to tissue expression of endogenous glycolipids that then activate *i*NKT cells to induce AHR. This is likely, as the direct activation of *i*NKT cells with glycolipid agents in the complete absence of MHC class II–restricted T cells results in severe AHR and airway inflammation[4]. Moreover, the induction of *i*NKT cell anergy with glycolipid agents before challenge with allergen prevents the development of AHR (refs. 5–7). These results together demonstrate the important role of *i*NKT cells in the development of AHR.

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