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EDITORIAL

Is there a place for intrinsic asthma as a distinct immunopathological entity?

C. Kroegel, L. Jäger*, C. Walker+

Allergic asthma is usually diagnosed on the basis of the medical history, recurrent airway obstruction, bronchial hyperresponsiveness and the presence of an underlying allergic diathesis as assessed by skin provocation, variably increased eosinophil numbers in the blood and sputum, and the detection of allergen-specific immunoglobulin E (IgE). Based on the above criteria many cases of asthma can be diagnosed. In addition, increased total IgE, specific IgE and increased blood or sputum eosinophils may also help to differentiate between asthma and chronic obstructive pulmonary disease (COPD). There are, however, individuals who fulfil most diagnostic criteria for asthma, but have neither a detectable skin test reactivity to common allergens nor an increased total or specific IgE, despite a raised eosinophil count in the blood and/or sputum.

In 1940 RACKEMANN [1] introduced the term "intrinsic" asthma in order to emphasize that this type is distinct from allergic extrinsic asthma with respect to the absence of an obvious precipitating exogenous cause. Since then, intrinsic asthma has been the subject of numerous reports and additional features related to the nonatopic variant were established. For instance, intrinsic asthmatics characteristically have a later onset of symptoms with a more severe clinical course of the disease than those with allergic asthma. Further, there is usually no family history of asthma or allergy and the female sex appears to be affected more often. In addition, a respiratory flu-like disease or cold often precedes the development of symptoms in intrinsic asthma. Finally, nasal polyps and aspirin sensitivity seems to occur more frequently in the nonatopic form of the disease. Due to its operational definition and continuous incidence, the terms intrinsic and nonallergic asthma have established themselves in clinical practice, referring to those asthmatic patients without an apparent underlying allergic disorder.

Although widely accepted by many clinicians, the existence of intrinsic asthma has been questioned by others with respect to epidemiological data and the role of allergens in the pathogenesis of asthma. For instance, based on the relationship between total serum IgE levels and airway hyperreactivity, it has been suggested that virtually all patients suffering from asthma have an atopic component [2, 3]. Indeed, apart from the subtle clinical and laboratory differences mentioned above, there are no data available to date which allow a clear distinction between intrinsic and extrinsic asthma. Even more important to the ongoing discussion, neither the putative aetiologic agent nor the underlying immunopathogenesis of intrinsic asthma have yet been established. Therefore, much hope rests on recent advances in modern immunological and molecular techniques that may help to solve this controversy.

In recent years, a number of studies have demonstrated that an immunological distinction between extrinsic and intrinsic asthma may indeed exist. For instance, both CD4+ and CD8+ T-lymphocytes in the blood of nonatopic asthmatics persistently express the cellular activation markers including interleukin (IL)-2R human leucocyte antigen (HLA)-DR, and very late activation antigen (VLA)-1 surface antigens throughout the year even during symptom-free periods [4, 5, 6], whereas T-cells obtained from subjects with atopic asthma show increased absolute numbers of CD4+IL-2R+ T-cells. Moreover, CD45RO+ "memory" T-cells are prominent in nonatopic subjects with asthma [5, 6]. Further analysis of both blood and bronchoalveolar lavage cells as well as bronchial biopsies from patients with allergic asthma revealed a predominant activation of T-helper (Th)2-like T-lymphocytes, producing IL-4 and IL-5 but no IL-2 or interferon (IFN)-γ [6, 7, 8]. In contrast, nonallergic asthmatics appear to have a more pronounced T-cell activation pattern, and the analysis of the cytokine profile demonstrates significantly raised levels of IL-5 and IL-2 but not IL-4, a cytokine pattern incompatible with a pure Th2-like cell response [6]. Since IL-4 is required for Th2-like cell differentiation and is intimately involved in the regulation of IgE production, the low levels of this cytokine in intrinsic asthma would be a reasonable explanation for the lack of elevated IgE concentrations in this group of asthmatic patients.

The hypothesis that intrinsic asthma is, in fact, a distinct immunopathological entity was, at least in part, supported by the demonstration that stimulated peripheral blood T-cells from atopic children secrete significantly more IL-4 and less IFN-γ than those obtained from nonatopic asthmatics and normal controls [9]. Moreover, the production of IL-4 closely correlated with the total serum IgE concentration, suggesting that increased synthesis of IL-4 by T-cells may be required for the development of allergic asthma but not for asthma *per se*. Taken together, the results provided by the above studies suggest that intrinsic asthma differs from the atopy-associated form of the disease with regard to both

Correspondence: C. Kroegel, Pneumology, Department IV, Medical University Clinics, Friedrich-Schiller-University, Erlanger Allee 101, D-07747 Jena, Germany. *Department of Clinical Immunology, Friedrich-Schiller-University, Am Johannisfriedhof 3, D-07740 Jena, Germany. +Norvatis Pharma Inc., Department of Respiratory Diseases, CH-4002 Basel, Switzerland.

the phenotype of T-lymphocytes and the production of IL-4.

Recently, two additional papers comparing immunological and molecular features of allergic and nonallergic asthma have been published and these will undoubtedly refuel the discussion over the existence of intrinsic asthma as a distinct immunopathological entity. In the first, HUMBERT *et al*. [10] employed semiquantitative reverse transcriptase-polymerase chain reaction (RT-PCR), *in situ* hybridisation and immunohistochemistry to compare the expression of IL-4 and IL-5 messenger ribonucleic acid (mRNA) and their respective protein products in bronchial biopsies obtained from symptomatic atopic and nonatopic asthmatics. The results show that airway epithelium of both asthma variants expressed higher numbers of IL-4 and IL-5 mRNA copies when compared to healthy and nonatopic controls. In addition, both intrinsic and extrinsic asthmatics showed an increased number of cells expressing IL-4 and IL-5. Further, the numbers of CD4+ T-lymphocytes were elevated in both asthma variants to a similar extent. These data together with the predominant eosinophil airway infiltration indicate that atopic and nonatopic asthma do not differ with respect to immunological parameters, such as synthesis and expression of both cytokines as well as the occurrence of CD4+ cells within the airway mucosa.

The second paper by TANG and co-workers [11] appears in this month's issue of the Journal. In contrast to the paper by HUMBERT *et al*. [10] they examined the *ex vivo* production of the Th2-type cytokine IL-5 and Th1-type cytokine IFN-γ by peripheral blood mononuclear cells (PBMC) and bronchoalveolar cells obtained from nonatopic asthmatics and atopics sensitized against the house dust mite. The results demonstrate that nonstimulated PBMC and BAL cells from both atopic and nonatopic asthmatics cultured for 72 h produce more IL-5 than controls and nonasthmatic atopics. When cells were exposed *ex vivo* to house dust mite antigen, elevated IL-5 concentrations were observed in the atopic groups, but not in subjects suffering from intrinsic asthma. In addition, spontaneous IFN-γ production by PBMC was lower in both atopic and nonatopic asthma compared to healthy controls and nonasthmatic atopics, although significance was reached only for nonatopic asthmatics compared to healthy controls. Following exposure to house dust mite antigen, only IFN-γ production by PBMC from atopic asthmatics increased, while cytokine secretion by cells obtained from nonatopic asthmatics, nonasthmatic atopics, and healthy controls remained unchanged. In contrast, bronchoalveolar lavage fluid (BALF) cells of all groups showed no significant increase in IFN-γ production. Finally, both asthma variants had raised numbers of activated CD25+CD4+ cells in BALF when compared to the nonasthmatic groups. Following house dust mite antigen exposure, an increase in CD25+ CD4+ lymphocytes was only observed in the atopy groups, with cells from nonatopic asthmatics remaining unchanged.

Taken together, the results obtained from these investigations, essentially provide evidence for a number of similarities in the pathogenesis in both asthmatic diseases. Firstly, in accordance with previous studies [6, 8, 12, 13], asthmatic inflammation is accompanied by an increase in CD4+ and IL-2R bearing CD4+ cells, irrespective of whether an underlying atopy was identified. Secondly, expression of IL-5 mRNA and its respective proteins appears to be involved in both allergic and nonallergic asthma when compared to healthy subjects. Thirdly, in contrast to previous studies [5, 6], the data of HUMBERT *et al*. [10] provide evidence that IL-4 can also be detected in intrinsic asthmatics when molecular and immunohistochemical methods are employed. The latter finding essentially adds an immunological feature to intrinsic asthma, previously believed to be exclusively associated with the allergic asthma variant.

So what do we make of this? Is this the end of nonatopic asthma as we know it? Does this observation really provide "evidence against intrinsic asthma being a distinct immunopathological entity" [10]. May we understand intrinsic and extrinsic asthma as one disease entity stretching from detectable allergy on the one hand to nondetectable atopy on the other? Clearly, on the basis of the data summarized above, this is not the case. The results presented by HUMBERT *et al*. [10] and TANG and co-workers [11] merely suggest that the distal immune response in both extrinsic and intrinsic asthma share some similarities not only with respect to the dominance of eosinophils but also regarding the presence of activated CD4+ cells and the expression of IL-5 and possible IL-4.

There are also several aspects that need to be explained before the conclusion of a concomitant secretion of IL-5 and IL-4 in intrinsic asthma can be accepted. For instance, in contrast to IL-5, expression of IL-4 at both the mRNA or protein level, did not correlate with either bronchial reactivity or asthma severity and was not specific to asthma [10]. This observation is surprising since it essentially questions the Th2 cell dependence of the eosinophilic inflammatory response in atopic asthma as well as the functional consequences of IL-4 production in asthma. In view of the role of IL-4 in IgE switching of B-lymphocytes, it remains to be determined why nonallergic asthmatic subjects have no elevated IgE serum concentrations, although we cannot rule out the possibility of a local IgE production in the bronchial mucosa.

In addition, there are a number of explanations that may account for the apparent discrepancy relating to the presence or absence of IL-4 in nonallergic asthma, including the miscellaneous experimental approaches, the sensitivity of the methods in detecting IL-4, and the different types of tissue analysed. Alternatively, although transcribed and stored, IL-4 may not be released in intrinsic asthma. Another possible explanation for the presence of IL-4 in intrinsic asthma without a corresponding elevation of IgE serum levels may be that the cells obtained from nonallergic asthmatics preferentially produce the nonfunctional, alternative slice variant of IL-4 [14]. Providing that one or more of the above explanations holds true, the question arises whether IL-5 production by activated CD4+ T-lymphocytes is possible without a concomitant secretion of IL-4.

The answer is yes. Several studies have, indeed, demonstrated that elevated secretion of IL-5 may occur without a simultaneous secretion of IL-4. Firstly, the expression of IL-4 and IL-5 in T-cells was shown to be independently regulated [15]. Secondly, cytokine production in patients with chronic eosinophilic pneumonitis is characterized by an elevated concentration of

IL-5, whereas IL-4 was not detected at the mRNA or protein level [16, 17]. Taken together, the data regarding potential immunological differences between extrinsic and intrinsic asthma, in particular on IL-4 and IgE production, are far from clear and require clarification through further studies with larger patient populations and more controlled use of modern immunomolecular techniques.

Whether or not immunological and molecular differences exist between allergic and nonallergic asthma, the crucial question that remains to be answered is how a condition that is not triggered by allergens, produces inflammatory changes within the airways leading to asthma. Although we are far from answering this question, a number of clues are available. For instance, an autoantibody directed against a 55 kDa epithelial antigen has been detected in a significant number of intrinsic asthmatics [18]. In addition, both intrinsic and occupational asthma show an increased number of CD8+ cells in the airway wall [12, 19, 20]. Unlike CD4+ cells, most cytotoxic CD8+ T-lymphocytes recognize endogenous antigens, and are mainly involved in the response to intracellular infectious agents, tumours and autoreactive processes. Thus, it may be that the intrinsic variant of asthma is a form of autoimmune disease [21]. Consistent with this hypothesis are observations made previously in autoimmune-susceptible mice, demonstrating that auto-reactive T-cell clones may show a unique phenotype expressing features of both Th1 and Th2 cells [22, 23].

The controversy over the existence of intrinsic asthma as a separate immunopathological entity will continue. We will have to wait a little longer before we know whether there is a place on earth for intrinsic asthma or whether it was just a wheezing pink elephant in the sky we were after.

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