

EDITORIAL

T-helper polarization in atopic disease — how early does it occur?

One in seven children in the United Kingdom suffer from asthma, with 95% of cases being associated with atopy. As the incidence of asthma and allergic disease increases, so has the drive to define the underlying molecular mechanisms involved and the point at which they become established. As it is thought that the immune responses underlying the expression of allergic disease are initiated in infancy it is logical that future research should target this age group. However, as this group remains largely unresearched it continues to represent a significant and potentially fruitful area within this field. Large epidemiological birth cohort studies [1,2] have clearly demonstrated that the majority of wheezing in infancy does not develop into atopic asthma. Considering that wheezing in infancy is the single most common reason for referral to a paediatric respiratory clinic, it seems extraordinary that we remain unable to predict which infants will develop asthma, or even appropriately target those most at risk, based on the current lack of research data in this age group. Of particular interest is the role of the helper T cell. Although the importance of T cell driven inflammation has become established over the last decade, the exact mechanisms involved and the timing of events remain uncertain. However, it is logical to assume that intervention at an early stage in this activation process may prove to be the best approach if we are to manipulate this key element of the immune response, and hope to alter the course of allergic sensitization with any degree of success.

The clearly inherited nature of atopic disease has led us to search for the gene loci common to this trait. Genetic linkage, to chromosome 11q12–13, has been demonstrated in maternally derived alleles, and the atopy locus has been associated with the important candidate gene FCERIB [3]. However, this article focuses more on the influences which appear to modify the immune response in susceptible individuals, during early childhood, resulting in the development of atopic disease. Renewed interest about the role of the T-lymphocyte, and in particular the functional diversity of the CD4⁺ T cell, in allergy has elucidated many of the mechanisms underlying the pathogenesis of asthma, and the nature of host responsiveness to inhaled antigens appears to be a direct reflection of the type of T-helper cell dominating the specific immunological memory. The response leading to allergic disease is predominantly TH₂ like. Conversely, a memory pool dominated by TH₁ cells results in apparent unresponsiveness in terms of allergic

reactivity [4]. It is this TH₁ vs TH₂ model that has provided such a valuable basis for research, enabling us to elucidate many of the immune responses involved in both initiating and the sustaining of atopic disease. Although evidence has rapidly accumulated about the type of antibody responses stimulated by TH₁ and TH₂ clones, thereby providing a neat explanation for the variation of disease expression, little is still known about the exact events or the timing initiating this immune process within the atopic population.

The establishment, by whatever mechanisms, of distinct T-helper pathways would appear to occur via a 'switch' mechanism which presumably occurs in early childhood and determines allergic phenotype. Environmental factors are undoubtedly important, and in particular early exposure to inhaled allergens in combination with the presence or absence of other antigens at the mucosal surfaces, appears to trigger the developing immune system. Animal models indicate that the regulatory mechanisms involved appear to have optimal effect at an early stage in the immune response and are less likely to deviate an already established memory pool [5]. This process, termed Immune Deviation, assumes specific T-cell expansion in response to allergen exposure resulting in a mutually exclusive TH₁ or TH₂ phenotype [6]. Each T-cell subset produces specific cytokines that act in an autocrine fashion promoting further differentiation and maturation into that subset. These same cytokines also appear to have cross-regulating inhibitory effects on proliferation of other T-helper cell subsets resulting in further commitment to an established T-helper phenotype. Assuming that we accept the theory of immune deviation and commitment to one or other T-cell subset, then our next logical objective is to define the timing of these events in order to target at-risk infants at a presensitization stage and prior to commitment during immune development. However, the more recent ability to measure cytokines at the single cell level has made it increasingly apparent that classification into TH₁ or TH₂ subsets may not be as clear cut as originally thought, and that T-helper cells retain an ability for heterogeneous cytokine production that infers a functional diversity not fully appreciated [7]. In fact, the work by Kelso *et al.* using T-cell clones, in which diversity of cytokine production was clearly demonstrated, has led to the counter claim that classification into TH₁ and TH₂ subsets is an oversimplification of what is more likely to be a spectrum of possible phenotypes and functions [8]. However, we should

not lose sight of the fact that manipulation within the laboratory may alter the environment sufficiently to prevent us correlating *in vitro* and *in vivo* events, and the weight of evidence supports the existence of functionally diverse subsets, and that their role is central to disease expression. Several bodies of work support this functional division of the T cell. This is particularly true of the immune responses seen in chronic infections with microbes such as leishmania, listeria and mycobacteria where it has been possible to show a clear cut dichotomy of the T-helper cell function, and more importantly demonstrate its importance *in vivo* [9]. Yamamura *et al.* also showed specific TH₁/TH₂ cytokine patterns by analysing total tissue RNA without the potential distortion of cell culture and cloning [10]. However, it remains unestablished at what point a helper T cell becomes committed to one or other phenotype and loses its functional diversity. The chronic nature of these infections provides a model of a mature and developed immune response, but it is likely that in the earlier stages of the illness the whole range of potentially diverse functions of the CD4⁺ TH₀ cell may still be retained. If so these stages could be compared with the initiating and ongoing inflammatory processes involved in the development of asthma, where early intervention may allow manipulation of the T cell's functional role that may prove impossible in a later stage of the disease. Another group in Japan looked at the T-helper cell responses in 12-year-old children, after completion of their vaccination programme for tuberculosis, in which they showed an inverse association between the tuberculin response and development of atopic disease. Those children with positive tuberculin responses had a lower incidence of asthma, lower serum IgE and this correlated with a cytokine profile biased towards the TH₁ phenotype [11]. These findings are at the centre of the debate about whether the immune system can be manipulated to manifest a persistent and dominant TH₁ or TH₂ response, and thereby be used to develop immunoprophylactic techniques that might alter the course of immune development. Further evidence for the environmental factors involved has been provided by von von Mutius *et al.* who took advantage of the newly re-united Germany to compare the prevalence of atopy and asthma between the heavily polluted Leipzig and relatively clean Munich. By comparing socio-economic status, episodes of infection in early childhood and over-crowding they found that the prevalence of asthma and atopy were significantly lower in the East, this despite the higher pollution in Leipzig. However, the incidence of respiratory infection was much higher and, moreover, they also found that the youngest children of large families, who also experienced earlier and more frequent respiratory tract infections, were less prone to allergic sensitization and development of asthma [12,13]. What remains unclear is whether the incidence of asthma in

Western society has increased because our immune system is relatively unoccupied, with recurrent childhood infection, and is therefore, susceptible to sensitization with otherwise trivial allergens in the environment, or whether it is due to the positive actions of some toxic environmental factor. As a definite cause-effect link has not been established with industrial pollution, then it can be argued that the former hypothesis has some validity, despite remaining unproven.

Immunotherapy, a valuable research tool, appears to confer protection from symptoms by inducing a 'switch' from the TH₂ pathway by promoting an inhibitory TH₁ phenotype [14]. In clinical practice, however, it has been disappointing in the treatment of allergic disease, its use restricted by the majority of cases developing hypersensitivity to a range of allergens. Therefore, the recent work by Yabuhara *et al.* is timely in extending molecular and immunocytochemistry techniques into the infant and paediatric population in order to better elucidate the timing of allergic sensitization in the preschool child [15]. This point is important because work by Kelso [8] and others [16,17], has shown that irreversible polarization to either the TH₁ or TH₂ phenotype is more likely with chronic disease states than early after T-cell activation. Yabuhara has also added weight to the theories of T-cell anergy and immune deviation which are proposed to be involved in shaping and educating the immune response. By comparing oral and inhaled antigens their results correlate nicely with models showing that antigen dose influences not only how helper T cells differentiate, but that this is likely to happen by high zone vs low zone tolerance. Low antigen concentrations tend preferentially to induce TH₁ responses, whereas high doses tend to TH₂ development [18]. Although the mechanisms by which antigen dose effects T-cell responses remain poorly understood, it has been postulated that high levels of antigen, as in oral exposure to ova, leads to repeated T-cell stimulation with the ultimate result of 'switching' off the response, causing immunological tolerance [high zone tolerance or anergy]. In contrast, the lower levels of inhaled antigen encountered at the mucosal surfaces are consistent with low-zone tolerance, which in theory leads to immune deviation, with potential development of the TH₂ functional phenotype. However, to further test these observations Yabuhara's group have an ideal opportunity to follow these subjects prospectively and assess individually the developing pattern of the T-cell response from infancy, whilst correlating them with clinical disease expression. Further to the argument that early T-cell responses are less committed to either TH₁ or TH₂ subsets, but may yet retain the potential for either type of cytokine production [TH₀], this group have also neatly demonstrated, that commitment to a TH₂ phenotype in atopics appears to occur between the ages of 2 and 5 years. Although much work is required to test the validity of these hypotheses, the implication is that

within the first 2 years of life there exists a window of opportunity for immunoprophylaxis should it prove possible to manipulate the immune response *in vivo*.

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