

## Editorials

### Allergic respiratory disease: strategic targets for primary prevention during childhood

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It is now generally accepted that allergic respiratory disease in adulthood is associated with active T cell immunity to common inhalant allergens that is skewed towards the T helper (Th) 2 cytokine phenotype, in contrast to the expression of Th1 skewed immunity in non-responsive normal subjects.<sup>1,2</sup> The question of how these two different patterns of T cell immunity develop in individuals is therefore central to our understanding of the aetiology of diseases such as atopic asthma and rhinitis and is the subject of intensive investigation.

The studies in experimental animals which originally described T helper 1 and 2 subtypes demonstrated that they operated in a yin-yang fashion during systemic immune responses via the production of mutually antagonistic cytokines and, further, that the nature of the long term immunity that subsequently developed was dependent upon the cytokine phenotype of the Th cells that eventually achieved dominance in the specific T cell memory compartment.<sup>3</sup> This Th cell dominance is reinforced at each subsequent re-exposure to the antigen, a process which

has been described as “locking in” the immune response to a particular (polarised) cytokine pattern.<sup>4</sup>

Consistent with this general model, it has now been shown that the development of T cell immunity during chronic exposure of rats and mice to passively inhaled and ingested allergens is regulated by a comparable set of immune deviation mechanisms, and that the key cytokine-mediated events which control the selection of relevant Th memory cells occur during the early phase of allergen exposure.<sup>5-7</sup>

In relation to the aetiology of human allergic disease, these findings serve to focus attention on the life phase during which environmental allergens are first encountered – that is, the perinatal period. There is now a wide body of evidence that initial priming of the T cell system to these allergens commonly occurs during late gestation (fig 1).<sup>7-9</sup> In the case of inhalants, this is followed postnatally by a period of Th cell selection in response to repeated exposure to environmental allergen involving cross-regulation between competing Th1 and Th2 cells. In most

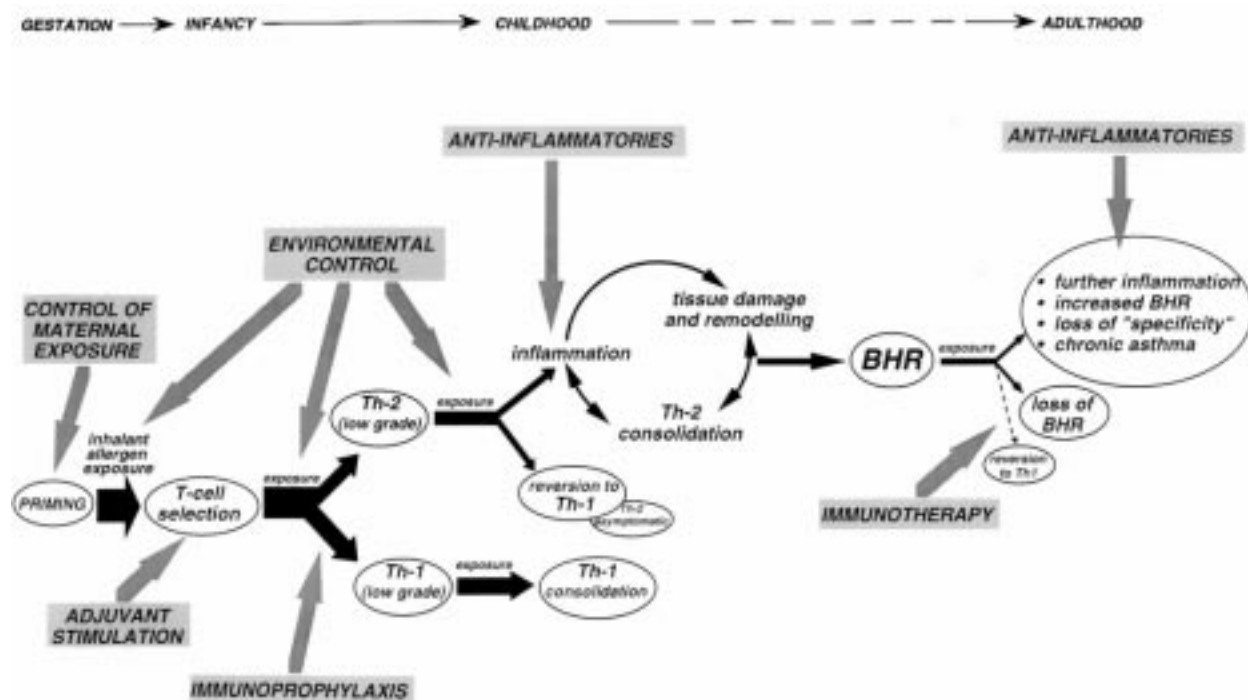


Figure 1 Key immunological processes underlying responsiveness to inhalant allergens. BHR=bronchial hyperresponsiveness.

subjects this process results in the development of Th1 skewed immunity, but in a significant subset of children the initial expression of allergen-specific immunity is polarised towards the Th2 phenotype as evidenced by the appearance of low titres of specific IgE antibodies.<sup>8,10</sup> However, this is not in itself predictive of subsequent allergic respiratory disease as a high proportion of these early IgE responses decline (permanently) with continuing exposure,<sup>8,10</sup> leaving a smaller residual population of persistent Th2 responders.

On the basis of a wide body of epidemiological evidence from cross sectional studies,<sup>11-14</sup> these persistent Th2 responders constitute the high risk group for subsequent development of severe bronchial hyperreactivity which, in a significant proportion, will progressively worsen into adulthood resulting in chronic asthma. However, it may again be inferred from cross sectional studies demonstrating age related declines in both Th2 dependent IgE production and skin prick test (SPT) reactivity<sup>15</sup> and also in bronchial hyperresponsiveness<sup>16</sup> that the capacity for “self healing” in this process is preserved beyond the stage at which severe atopic respiratory disease develops.

Treatment of established disease is currently based on blocking the effector arm of the inflammatory cascade at sites of allergen induced tissue damage, or on immunotherapeutic inhibition of upstream Th cell immunity which is believed to provide the principal drive for both the induction and maintenance of atopic disease. In principle, this involves preferential stimulation of Th1 selection mechanisms<sup>17</sup> which are presumably analogous to those which dominate Th1/Th2 switch regulation in allergen-specific immune responses in normal (non-atopic) infants.

The success of these treatments is highly variable, especially in chronic disease. Additionally, it is apparent that the prevalence of allergic respiratory disease, particularly atopic asthma, is progressively increasing and there is, accordingly, growing interest in prevention of this disease through early intervention during childhood. The discussion below focuses upon the growing list of potential intervention strategies which are illustrated in fig 1 and the theoretical basis underlying each approach.

### Potential intervention strategies

#### CONTROL OF MATERNAL EXPOSURE TO ALLERGENS

As noted above, transplacental priming of the T cell system against environmental allergens appears relatively common<sup>7-9</sup> and it has been proposed that, in neonates genetically at high risk for atopy, this process may be intrinsically skewed away from the Th1 phenotype.<sup>18</sup> This proposal is based upon a preliminary study on in vitro T cell responses to food allergens such as  $\beta$ -lactoglobulin which is present in relatively high concentrations in the maternal circulation. The more complex questions relating to the significance of potential transplacental transfer of inhalant allergens to which the mother is exposed have not been addressed.

#### ADJUVANT STIMULATION OF THE INFANT IMMUNE SYSTEM

There is now evidence from a series of independent laboratories<sup>8</sup> that maturation of the capacity to produce Th1 cytokines such as interferon gamma ( $IFN\gamma$ ) is delayed in children genetically at risk for development of atopic disease, and it has been proposed that this may be an aetiological factor in primary allergic sensitisation.<sup>19</sup> This initial skewing of the immune system towards the Th2 phenotype may be a subtle distortion of a normal process which is operative in all neonates. This surmise is based on recent evidence that the immunological milieu at the fetal/maternal interface is constitutively skewed towards

Th2<sup>20</sup> which is apparently an evolutionary adaptation for protection of the fetoplacental unit against the toxic effects of Th1 cytokines such as  $IFN\gamma$ .<sup>21,22</sup> It is clear from data on experimental animals<sup>23,24</sup> and on human infants<sup>8</sup> that this Th2 skew is maintained for variable periods postnatally.

There is also a substantial body of evidence that the normal trigger for maturation of adaptive immune function after birth is provided by stimulation with microbial antigens from both commensal organisms and pathogens.<sup>8</sup> This may underlie the epidemiological findings suggestive of a “protective” role for infections during childhood in the aetiology of allergic disease<sup>8,25-27</sup> via mechanisms such as bystander stimulation of Th1 selective cytokine pathways during host antimicrobial responses.<sup>2</sup>

It may be possible in the future to reproduce the immunostimulatory effects of normal postnatal microbial exposure via the use of appropriate Th1 selective adjuvants which are under development in a number of centres, and if successful they may prove useful in high risk subgroups in which objective evidence of sluggish T cell function can be identified. The potential pitfalls of such an approach are excessive amplification of Th1 immunity leading to allergen specific delayed type hypersensitivity and stimulation of covert Th1 mediated disease processes including autoimmunity; both possibilities could be pretested in appropriate animal models.

#### ALLERGEN-SPECIFIC IMMUNOPROPHYLAXIS

This suggested approach which has been described in detail previously<sup>7,28</sup> involves enhancing the efficiency of normal Th1 selection in early immune responses to inhalant allergens. It is based on observations which indicate that low level allergen specific IgE titres in individual children typically seesaw for several years before either disappearing permanently (development of dominant Th1 immunity) or progressing into the responder range (dominant Th2 immunity). This latter period of Th1/Th2 crossregulation preceding the development of dominance by either Th cell type theoretically provides a “window” for immunoprophylaxis – that is, for tipping the balance towards selection of protective Th1 immunity.

One possibility may be to exploit the consistent findings that repeated exposure of the upper respiratory or gastrointestinal mucosae to microgram levels of protein antigen leads to the preferential suppression of Th2 dependent IgE production via immune deviation.<sup>7</sup> Both intranasal and oral allergen exposure have previously been employed for immunotherapy in established allergic disease with mixed success, but the evidence from experimental systems argues that they are likely to be considerably more successful when applied earlier in the immune response – that is, before Th2 memory becomes consolidated.

In principle, such a procedure would employ a mixture comprising the 3–4 dominant inhalant allergens from a particular environment. The main issue to be resolved in this context is whether such a regime has the potential for overstimulation of Th1 immunity (resulting in delayed type hypersensitivity) or whether it may amplify covert Th2 responses in some subjects. It is also important to note that such procedures could not be employed in early infancy when the risk of development of Th2 skewed immunity is maximal.

#### ENVIRONMENTAL CONTROL OF ALLERGEN LEVELS IN THE NURSERY

There is convincing epidemiological evidence that exposure to high levels of inhalant allergens during the first three months of life predisposes to primary allergic sensitisation

and thus to the acquisition of long term Th2 as opposed to Th1 dependent immunity,<sup>29</sup> and this presumably derives from the intrinsic skewing of perinatal Th cell function described above. As noted earlier,<sup>7,29</sup> mucosal allergen exposure of newborn experimental animals also fails to tolerate IgE responses. Thus, in principle, measures to minimise levels of inhalant allergens in the nursery are likely to be beneficial.

This question may prove to be more complex than expected in view of the fact that, as illustrated in fig 1, the process of Th1/Th2 switch regulation which normally leads to the development and consolidation of protective Th1 immunity is itself an antigen (allergen)-driven process. In this context, recent studies have demonstrated house dust mite-specific T cell reactivity in the majority of Swedish children from an environment where levels of house dust mite were 10–100 times lower than the threshold associated with expression of house dust mite mediated allergic respiratory disease.<sup>27,30</sup> This suggests nonetheless that successful Th1 selection can occur at “safe” levels of allergen exposure.

#### ENVIRONMENTAL CONTROL OF ALLERGEN EXPOSURE BEYOND INFANCY

The inverse relationship between age and IgE titres/SPT reactivity/bronchial hyperresponsiveness<sup>15,16</sup> indicates that Th2 skewed allergen-specific immunity acquired in childhood is in many cases reversible with continuing allergen exposure. However, a significant subset of subjects instead consolidate their Th2 reactivity with age and become represented in the group with chronic airways hyperresponsiveness. The nature of the factor(s) which determine whether an individual's inhalant allergen-specific T cell reactivity reverses or progresses to ultimate expression of allergen induced bronchial hyperresponsiveness remains one of the key issues in this area.

A widely held view is that the development of bronchial hyperresponsiveness is the end result of sustained tissue damage and associated remodelling induced by increasingly intense cycles of Th2 dependent cellular inflammation (fig 1), in particular involving eosinophils.<sup>31</sup> If this is the case, the removal of relevant inflammatory stimuli should halt this vicious cycle and potentially allow re-establishment of normal homeostasis.

In support of this notion, both the intensity of SPT reactivity to house dust mite allergen and bronchial hyperresponsiveness in children is strongly correlated with environmental levels of house dust mite, and isolation of house dust mite reactive subjects into an environment free of house dust mite leads to marked improvement in airways responsiveness.<sup>32</sup> Accordingly, environmental control measures, provided they are effective against a sufficiently wide range of the allergens which trigger Th2 responses in individual children, may contribute to reversal of the disease process.

#### USE OF ANTI-INFLAMMATORY DRUGS DURING CHILDHOOD

A logical extension of the above argument is that halting the cycle of tissue damage and remodelling during childhood with appropriate anti-inflammatory drugs may achieve the same end. Such an approach has the potential advantage of providing cover against the pro-inflammatory effects of a broad spectrum of allergens without the necessity of instituting costly (and often inefficient) environmental control measures.

The most obvious candidate drug for this purpose would appear to be topical steroids which are increasingly being used in paediatric practice. However, it should be noted

that there is currently very little information available on the potential immunological side effects of these drugs in young children, particularly on Th1/Th2 switch regulation. In this context, there is now evidence that systemic and inhaled steroids exert marked effects on the turnover of the dendritic cell network in the airway epithelium.<sup>33,34</sup> These dendritic cells regulate the presentation of inhaled allergen to the T cell system, particularly during the early stages of immune responses, and consequently any steroid-mediated changes in their functions may have significant (and as yet undefined) effects on the development of allergen-specific Th cell memory. Questions have also been raised in relation to the potential effects of inhaled steroids on lung growth in this age range.

Another candidate may be the cromolyns which have been used for many years in paediatric practice with little evidence of side effects. However, recent information demonstrating inhibition of aspects of B cell function including IgE production<sup>35</sup> suggest that their safe usage in this context may require close monitoring of allergen-specific Th cell activity in order to demonstrate that any improvement in IgE titres and/or SPT reactivity during treatment is not accompanied by covert increases in Th2 memory which could be read out later by the B cell system after withdrawal of the drug.

#### Conclusion

The information now available on the aetiology and pathogenesis of atopic respiratory disease, while incomplete, has reached the stage where informed debate on potential primary prevention strategies can be carried out. It is imperative that relevant ethical issues remain paramount in these discussions, as inappropriate interference in the development of allergen-specific immunological memory during childhood may have lifelong consequences. Nevertheless, the potential that helping the immune system to “get it right” early in life may prevent a lifetime of suffering is a goal that is worthy of vigorous pursuit.

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