Prevention of adult asthma by early intervention during childhood: potential value of new generation immunomodulatory drugs

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Current treatment regimens for asthma are based principally upon active suppression of inflammatory processes within airway tissues of sufferers, and one of the major thrusts of research in this area is towards development of increasingly more selective and more potent anti-inflammatory drugs. The impetus for much of the recent activity in relation to drug development in this field stems from an increased understanding of the contribution of immunologically mediated mechanisms towards inflammation induced tissue damage in the asthmatic airway, and this has led to the identification of a new spectrum of drug targets associated specifically with T helper 2 (Th2) cell functions.

However, we argue below that this overall drug development/testing process may be conceptually flawed, not in relation to drug design per se, but at the key stage of selection of subjects for subsequent clinical studies. In brief, we suggest that the practice of testing new selective anti-inflammatory and/or immunomodulatory drugs exclusively in adult asthmatic subjects with established disease inadvertently selects for equivocal or, at worst, negative results in relation to efficacy because the disease process in these patients will frequently have progressed beyond a stage at which it is susceptible to such agents. If so, the potential value of newly developed therapeutic agents which may be efficacious at earlier stages of the disease, including those capable of blocking the progression from trivial allergy to persistent asthma, is unlikely to be recognised unless the testing process is redesigned specifically to address this important possibility.

Asthma as a multi-stage process: T cell sensitisation versus airways inflammation versus symptomatology

On the basis of studies from our group and others on the immunology and epidemiology of asthma in early life, we have developed a general working model for the relationship between respiratory allergy and persistent asthma which is summarised in fig 1.1–3

This model envisages the development of asthma occurring in multiple stages with different physiological/pathological processes dominating each stage.

There is now convincing evidence from a number of independent laboratories that the immune system develops initial cognisance of environmental allergens during fetal life, presumably via transplacental leakage of allergens to which the mother is exposed during

Figure 1 Immunoinflammatory events at different stages during asthma development. Insert: time dependent phenotypic changes in allergic hyperreactivity (AHR) over the same time scale. Respiratory symptoms at different ages are envisaged to reflect the cumulative effects of transient episodic AHR induced by viral infection or allergic responses, superimposed on those due to age associated changes in airway calibre and/or those resulting from chronic airway remodelling.
pregnancy. The immunological milieu at the fetomaternal interface is maintained in a tightly controlled state to limit the impact of potential two way fetal-maternal immune responses resulting from HLA disparity, particularly responses involving generation of toxic Th1 cytokines such as interferon (IFN) $\gamma$.

This control involves suppressive mechanisms such as expression of FasL on fetal cells which triggers apoptosis of any activated T cells encountered$^{10-13}$ and local production of T cell inhibitory tryptophan metabolites by syncytiotrophoblasts$^{14}$ and placental macrophages.$^{13}$ These operate together with other mechanisms involving secretion by the placenta of a range of molecules which effectively deviate local immune responses towards the Th1 antagonistic Th2 cytokine phenotype. Paramount amongst the latter are prostaglandin (PGE)$_2$,$^{13}$ progesterone,$^{14-15}$ IL-4, and IL-10.$^{16}$

One of the consequences of this immunoregulatory “blanket” upon fetal Th1 function is that initial allergen specific priming of fetal Th cells is effectively Th2 polarised, as shown in recent cloning studies on allergen specific CD4+ T cells in cord blood.$^{17}$ After birth these weakly primed fetal Th2 responses are subjected to a variety of immunoregulatory processes driven by direct contact with allergen from the outside environment, the outcomes of which can include effective suppression of allergen specific reactivity by T cell deletion/energy, further boosting of Th2 responses, or immune deviation towards the Th1 cytokine pattern characteristic of adult non-atopic subjects.$^{7,19}$ Consolidation of the Th2 polarised response pattern is most frequent amongst subjects with a positive atopic family history, and is associated with symptom expression by the end of infancy.$^{19-22}$

By the age of 5–6 years this response pattern defines a large subpopulation of children who exhibit skin prick test (SPT) reactivity to one or more inhalant allergens.$^{23}$ Exposure of children in this age range to inhalant allergens against which they have developed Th2 polarised memory is likely to elicit varying levels of Th2 cytokine production in the airways associated with activation of mast cells and eosinophils$^{24-25}$ and, if the resulting inflammation exceeds the requisite critical threshold, wheezing symptoms will develop. It is pertinent to note that cross sectional studies in young children have formally demonstrated an association between markers of Th2 immunity in blood and the manifestation of allergy/asthma symptoms.$^{26-28}$ The association between asthma and inhalant allergy is clearest during this life phase.$^{29}$ However, it is also evident that, while development of Th2 polarised memory against inhalant allergens is a risk factor for asthma, persistent disease develops in only one quarter to one third of sensitised children,$^{29}$ and a growing body of histopathological evidence suggests that these represent a subgroup in whom Th2 mediated airways inflammation is most intense and/or fails to resolve.$^{24,26}$ The hallmark of this subgroup is expression of persistent airways hyperreactivity (AHR) characterised by exaggerated bronchoconstrictor responses to a wide range of irritants.

Age dependent variations in AHR

The phenomenon of AHR is a complex multifactorial process, and it is evident that several distinct forms exist (insert in fig 1). Firstly, virtually all infants are hyperresponsive to a variety of stimuli and, rather than a specific “defect” being involved, the underlying cause is essentially developmental, notably small airway calibre.$^{12}$ Secondly, AHR can develop at any age (but particularly in early childhood) as an acute response to respiratory viral infection, and is believed to result from bystander damage to airway tissue during local expression of host-antiviral immunity.$^{30-32}$ The precise mechanisms underlying this “reactive” form of rapid onset AHR remain obscure, but may include inter alia unmasking of irritant receptors via damage to the overlying airway epithelium and direct effects upon NANC and/or cholinergic nerves.$^{31}$ Similar rapid onset AHR can occur in humans exposed to air pollutants such as ozone and environmental tobacco smoke$^{33}$ and can be reproduced in experimental animal models via targeted expression of either intense Th2 polarised or Th1 polarised immunity in the airways.$^{14,30}$

The latter forms of AHR are, in most situations, transient and disappear once the eliciting stimuli are removed and the inflammation resolves. However, the situation in chronic asthmatics appears quantitatively and qualitatively different. AHR in this case appears to be an adaptive response on the part of airway tissue resulting from failure to adequately resolve chronic Th2 mediated inflammation, and this failure is associated with aberrations in local repair/regeneration mechanisms leading to remodelling of the airway wall.$^{24}$

The hallmarks of this chronic remodelling process include extensive deposition of extracellular matrix proteins below the epithelial basement membrane, airway smooth muscle hyperplasia, changes in local vascularisation and innervation, and generalised submucosal thickening.$^{1,24}$ and these collectively result in major disturbance to the mechanical properties of the lung leading in turn to the manifestation of AHR. The key feature of this form of adaptive AHR is most clearly illustrated by findings relating to occupational asthma.$^{25}$ Unlike the forms discussed above, it persists for long periods (in some cases permanently) even after the removal of the initial eliciting (inflammatory) stimulus.

It is of interest to note that recent evidence suggests that the remodelling process in atopic asthma may be initiated in early childhood$^{22}$ and, if so, this may imply that many years of cumulative tissue damage are required to drive the disease process into the chronic “self-perpetuating” phase.

Asthma as a multi-stage process: implications for drug design and testing

Based on the arguments advanced above, we hypothesise that the effectiveness in asthma of therapeutic drugs based upon selective antago-
nism of Th2 associated functions will be inversely related to the stage the disease process has reached in individual patients participating in clinical trials. At one extreme, established asthma in which the mechanical properties of the lungs have been fundamentally altered by significant remodelling of airway tissues would be relatively refractory to such agents. It is possible that prolonged use of these drugs may eventually initiate reversal of this process, particularly in view of suggestions that alterations in the secretory functions of the chronically inflamed airway epithelium in asthmatics may act as an amplifying factor which promotes further Th2 mediated tissue damage. However, the fact that potent non-specific anti-inflammatory drugs such as corticosteroids have only moderate efficacy in chronic asthmatics suggests that there are limitations to this approach.

At the opposite end of the spectrum, the relationship between asthma symptoms and allergen induced airway tissue injury in school age children, in isolation or in concert with viral infection, is more direct. On this basis we hypothesise that Th2 antagonistic drugs are considerably more likely to be efficacious in short to moderate term trials in school age children with asthma. Additionally, and of potentially greater importance, it is plausible that successful interruption of the cycle of Th2 mediated inflammation and repair/regeneration in the airways of children may forestall or, ideally, permanently prevent the progression of the airway remodelling process towards the stage in which permanent functional changes (adaptive AHR) are induced. It is of interest to note that preliminary reports on the use of anti-IL-5 and anti-IgE antibodies in adult asthmatic subjects suggest a high level of effectiveness against their respective target molecules, but limited clinical efficacy.

Clinical trials in children: the ethical dilemma

Researchers in this field are faced with some increasingly urgent issues and some exciting new opportunities:

- asthma is increasing in prevalence and intensity and is manifesting as persistent disease at earlier ages than ever before;
- conventional treatment approaches using drugs which provide symptomatic relief and/or those targeted non-specifically at underlying inflammation are clearly not the long term solution to the problem;
- the explosion of knowledge concerning cellular and molecular mechanisms of tissue damage within the airway mucosa of asthmatics has had a major impact on drug development within the pharmaceutical industry, culminating in a new generation of highly selective drugs targeted at specific Th2 associated immunoinflammatory mechanisms which are at a late stage of development;
- the conventional approach towards the testing of these new drugs by trials in established adult asthmatic subjects rather than systematic testing on carefully phenotyped patient groups at different (in particular early) stages of the disease is likely to under-estimate the potential usefulness of many therapeutic agents of this type;
- the usual pattern of drug development sees large phase 3 trials carried out initially in adults, unless the drug is specifically designed for children (for example, vaccines). We would argue that new asthma drugs, particularly those aimed at controlling Th2 associated inflammatory mechanisms, should be specifically targeted to children. While the ethics of this approach need to be debated, given the recent advances in our understanding of the natural history of asthma and the spiraling impact of the disease in our community, it would be unethical to fail to engage constructively in this debate.

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