

Developmental factors associated with risk for atopic disease: implications for vaccine strategies in early childhood

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Abstract

There is growing interest in the potential interactions between infant vaccination and risk for development of atopic disease. The aspect of this issue which has dominated this debate concerns suggestions that infant vaccination may stimulate allergic sensitisation. These suggestions derive from retrospective epidemiological analyses and will remain speculative unless they can be confirmed in prospective studies, particularly as conflicting findings have been reported. However, there is a potentially more important issue surfacing in this debate, which entails the *converse* situation, i.e. that genetic risk for atopy influences capacity to respond to vaccination during infancy. Support for the latter possibility comes from recent studies on the role of developmental factors which determine immune competence during infancy, and attendant risk for inflammatory and infectious diseases. The relevant findings are reviewed briefly below.

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1. Responses to vaccines and/or microbial pathogens as potential modifiers of “risk” for allergy: the nature of the debate

The role of infant vaccines as risk factors for atopic disease is becoming increasingly controversial. On the one hand, the use of infant vaccines such as the cellular Pertussis [1] and measles [2] vaccines have been suggested to potentially promote subsequent allergic sensitisation, whilst other (in particular mycobacterial) vaccines have been discussed as possible “adjuvants” to protect against allergic sensitisation via non-specific boosting of Th1 functions [3,4]. Both sides of this debate have been challenged. Notably, large-scale studies in northern Europe suggest that measles infection may confer greater risk for atopy than measles vaccination [5], and similar studies in Scandinavia have failed to detect any protective effects of BCG vaccination on atopy prevalence [6,7].

Discussion concerning the effects of infections upon the pathogenesis of allergic disease have become comparably complex. At one end of the spectrum, a variety of epidemiological evidence argues for a protective role for infections

in this context [8], whilst paradoxically, other data points to viruses as the most frequent causes of severe exacerbations in subjects with established atopic asthma [9].

However, recent studies from a number of labs on the role of developmental factors related to immunocompetence during infancy and early childhood, are providing increasingly plausible mechanisms to reconcile many of these paradoxical findings.

2. The nature of T-cell memory against environmental allergens

Current perceptions of allergen-specific T-cell memory are based upon principles which emerged from studies of T-helper (Th) cell differentiation in the mouse, which led to the development of the Th1/Th2 model [10]. In this model, antigen-primed Th-cells differentiate into long lived Th-memory cells via two dichotomous pathways, leading to the preferential expression (at each subsequent antigen exposure) of a restricted and reciprocal pattern of Th1 (IL-2, IFN γ) or Th2 (IL-4, IL-5, IL-13) cytokines. While this pattern is somewhat more variable in humans, and in fact, the Th0 or mixed (Th1/2) cytokine pattern is the most common in atopics (e.g. [11]), the broadly dichotomous nature

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of human Th-cell differentiation pathways has been recently confirmed via studies on expression of Th-cell transcription factors during Th1 versus Th2 differentiation in vitro, the results of which mirror those described for the mouse [12].

The issue of when these reciprocal patterns of allergen-specific Th-memory are programmed in humans is central to this debate. It is becoming clear that T-cell responses to these allergens are initiated very early in life, and that adult-like patterns of allergen-specific Th-memory are usually established by the end of the preschool years [11,13]. On the order of 40% of children in developed countries like Australia manifest Th2-associated memory against ≥ 1 inhalant allergen by age 6 years [14]. Moreover, the risk for development of allergy-associated Th2-memory is markedly elevated in children with a positive atopic family history, and who are designated as being at high genetic risk of atopy [14].

3. Ontogeny of immune function and risk for atopy

A growing body of evidence suggests that resistance to atopic and other inflammatory diseases in early childhood is governed via a series of control mechanisms associated with the functional transition of the (relatively quiescent) fetal immune system to the more active/competent state which is required to survive in the extrauterine environment. During fetal life, the capacity of the fetal immune system to produce Th1 cytokines is by necessity selectively constrained, due to their toxicity towards the placenta [15,16]. This is achieved in part via “bystander” control mechanisms such as the secretion of Th1-inhibitory cytokines/mediators by the placenta [15], backed up via specific controls directed at individual cytokine genes, such as hypermethylation (and hence silencing) of the IFN γ gene in fetal CD4⁺ Th-cells [17]. After birth, recognition of microbial signals from the extrauterine environment, particularly via stimulation from intestinal microflora [18], progressively upregulates Th1 function towards the adult-equivalent range. However, the kinetics of this developmental process is highly variable within outbred human populations (e.g. [19]), and appears slowest amongst children at high genetic risk of allergy [20].

Slow maturation of Th1 function in children at high risk of atopy appears to be associated with a range of sequelae in infancy and early childhood. As well as heightened risk for development of allergic symptomatology during infancy [13], these include attenuated and Th2-polarised memory responses to DTPa vaccine [18,21], reduced humoral immune responses to pneumococcal vaccine [22], reduced capacity to generate stable Th1-memory to BCG vaccine [23], and discussion in [15]), and increased susceptibility to severe RSV infection [18,24]. Murine studies suggest that the latter may be directly attributable to the initial Th2 polarity of host adaptive immune responses in the immediate postnatal period, which would blunt capacity to generate initial “sterilising” immunity, as well as attenuating subsequent development of effective Th1 memory for protection

against reinfection [24,25]. It is noteworthy in this context that the stability of tetanus toxoid-specific Th1-memory during priming with the DTPa vaccine in human infants appears directly related to the rate at which their overall polyclonal Th1-response capacity is maturing [19]. This may be related to IL-12 gene function, as this cytokine plays a key role in stabilising the IFN γ transcriptional machinery in T-cells [26], and IL-12 production is strongly developmentally regulated in analogous fashion to IFN γ [27,28].

4. Key issues to be resolved

4.1. Which genes are responsible for regulation of the kinetics of postnatal maturation of Th1 function(s)?

Given that interactions with microbial signals are responsible for triggering postnatal upregulation of Th1 functions, it is likely that pattern recognition receptors such as CD14 and the TLR family play essential roles in this process. Recent studies from our lab and elsewhere have implicated polymorphisms in CD14 [29], TLR-4 [30] and IL-12p40 [31] as contributors to variations in allergy risk and/or severity amongst children, and other genes such as IFN γ are also likely to be involved.

It is feasible that the effects of vaccines and/or pathogens on allergy-associated processes may be directly related to variations in the frequency of these (and other) gene polymorphisms. For example, while BCG vaccination during infancy appeared not to influence subsequent allergy frequency amongst native Swedes, some potentially protective effects were observed amongst immigrant children of ethnic middle-eastern origin [6,7] and in other studies, similar effects have been observed in African children [32]. Similarly, measles infection versus vaccination appears to have markedly disparate effects on atopic risk comparing Finnish and African populations [2,5]. These observations collectively suggest that genetic differences may be important determinants of susceptibility to the immunomodulatory effects of vaccines and/or pathogens. In this context, it is relevant to note the recent report from Le Souëf et al. [33] highlighting the marked differences in frequency of the proinflammatory alleles of CD14, CC16, MCC and the $\beta 2$ -adrenergic receptor between Europeans and non-Europeans, and more detailed studies in this area are clearly warranted.

4.2. What is the time frame for immunologically-associated disease risk in early life?

Recent studies from our group suggest that children at high genetic risk of allergy express maximal Th2 bias up to 12 months of age [19]. After transiting through this developmental “window”, this subgroup appears to overcompensate for the initial deficiency in Th1 function and markedly upregulate capacity to generate Th1 immunity, to the extent that by 18 months of age they display higher levels of

vaccine-specific Th1 memory than their atopic family history negative counterparts [19]. This trend continues such that by age 6 years, atopic children manifest considerably higher vaccine-specific Th1 immunity than non-atopics [34].

There is additional evidence from a variety of labs implicating hyperexpression of Th1 immunity as a cofactor in the pathogenesis of established atopy [35–37], and it remains to be determined whether a similar phenomenon occurs (and has clinical relevance) in relation to vaccine immunity.

4.3. What triggers upregulation of systemic Th1 immunity at or beyond 12 months?

A notable finding from our recent cohort study was that at the population level, the major developmental upswing in Th1 function does not occur until approximately the first birthday [19]. This prompts the question of what trigger(s) might be operative at this specific time, or whether the delay relates to developmental changes in relevant pattern recognition receptor expression or associated intracellular signalling mechanisms. One possibility which merits further testing is the MMR vaccine, which is often given for the first time at around 1 year, and which potentially may influence overall Th1 function. Preliminary studies are in progress in our laboratories, to address this and related possibilities.

4.4. Boosting of vaccine-priming responses in early infancy: does maternal antibody have a role?

Given the intrinsic developmental deficiencies noted above within the T-cell system (e.g. [17]), and also within antigen presenting cell (APC) populations within the innate immune system (e.g. [38]), it is valid to consider the possible role of antibodies available to the infant immune system, as potential modulators of T-cell immunity.

In some situations, it appears feasible that maternal antibody transferred across the placenta or via milk, may potentially limit the efficiency of infant vaccination, via limiting the access of APC to antigen. Conversely, antibody plays an important adjuvant role in many immune responses via targeted delivery of bound antigen to Fc receptors on APC. We have recently carried out a retrospective analysis in our large vaccine cohort data set [19], of the relationship between maternal IgG-antitetanus toxoid present in the blood of infants at the time of their initial DTPa vaccination, and their subsequent development of Th-cell memory to the vaccine antigen. Our preliminary findings (to be published) suggest a consistent positive relationship between maternal IgG, and subsequent infant T-cell memory with respect to IL-4, IL-5 and IL-13 responses to tetanus toxoid, but without parallel effects on infant antibody responses. These findings require further detailed follow up, in large study cohorts. Of particular interest is the potential relevance of such a mechanism to RSV immunity in early infancy.

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