

EDITORIAL

Cutting the cord: is birth already too late for primary prevention of allergy?

Though long recognized, the fundamental basis of the familial nature of asthma and atopy remains elusive. Much effort is currently being focused on identifying genetic markers associated with them, with several different loci being suggested as candidates [1–4]. Segregation analysis suggests that it is unlikely that the genetic factors associated with these disorders are limited to a single or even a few loci, and that other, non-genetic factors influence the overall phenotypic expression of these loci [5]. Thus it would appear that there is an interplay between a number of factors, genetic and environmental, which interact to determine the propensity for an individual to develop atopic disease.

When might environment come into play? The role of postnatal exposures in the expression of atopy and asthma have been the subject of much scrutiny. Might not there be influences which exert their effect(s) prenatally, perhaps even affecting the very development of immune function before the foetus has been exposed (in the classical sense) to direct immune challenges from the extra-uterine environment?

There is an increasing body of literature suggesting that in newborns the development of specific T-cell response to environmental antigens may occur prior to any first-hand exposure to those antigens, that is, before birth. Szepfalusi and colleagues, in this issue of *Clinical and Experimental Allergy* [6], provide further evidence of prenatal priming of T-cells. They document proliferative responses of cord blood mononuclear cells to the cow milk proteins alpha-lactalbumin, beta-lactoglobulin and alpha-casein which were specific and required the presence of antigen presenting cells to occur. These responses were seen in nearly all of the 39 infants tested. The relevance of these responses to the later development of asthma and/or atopy is unclear, as this and other reports of such responses do not consistently show a relationship to either parental history of atopic disease or subsequent development of such disorders in the infant, though the work reported herein lacks adequate numbers of subjects to conclusively demonstrate the absence of such an association. It would be of interest to know if similar proliferative responses could be elicited by the same antigens in T cells from the mothers, since an association between maternal history of allergy and detectable cord blood IgE and the subsequent development of eczema and wheezing during infancy, an association not found with paternal history of allergy, has been shown [7].

How might antenatal exposure to antigen (and subsequent

priming) occur? It is unlikely that intact, whole protein of the sizes used in this study could traverse the placenta. Even so, it is not clear that the foetal immune system is capable of providing the accessory cell function needed to generate a T cell response to them, at least early in gestation [8]. Alternatively, peptides, already 'processed' by the mother, might gain access to the foetal circulation, either independently or in the form of antigen:IgG complexes.

The larger question still remains, however. If the majority of infants undergo antigen/allergen priming *in utero* what other factors might influence the character of their response to antigen exposure and bring about allergic disease later in childhood?

A crucial factor in the priming of T cells may be antigen dose. Piccinni and coworkers [9] demonstrated cord blood T cell proliferation in response to Dermatophagoides group I (Der p I) and Lolium group I (Lol p I) allergen, both inhalant allergens, in an unselected group of infants. While response to Der p I was found in virtually all of the infants, response to Lol p I was found only in those infants studied around the time of highest environmental levels of that allergen, leading the investigators to suggest that it was the near continuous exposure to Der p I which accounted for the difference. The mother's atopic status may also affect foetal allergen exposure, in that mothers with a predominately IgG response to a given antigen might clear circulating antigen more effectively than mothers with a predominately IgE response. In addition, high dose antigen exposure may shift the nature of the response in a Th2 direction [10].

Along with the dose of antigen presented, the nature of antigen presentation may influence subsequent response. The antigen presenting cell (APC), particularly the dendritic cell (referred to by some as the 'professional APC'), may play a crucial role in directing response to antigen. It has been proposed by Matzinger that if naive lymphocytes encounter antigen in the absence of a second signal from a professional APC they will die [11]. A second signal from an appropriate APC, on the other hand, allows the T cell to become a resting effector cell, ready to respond upon secondary stimulation by antigen. Exactly how the work of Szepfalusi *et al.* fits into this schema is not clear as the source of (irradiated) APCs used is not specified. However, presumably the effector cells involved were monocytes and/or macrophages, and not dendritic cells, providing further support that the reactive T cells were 'experienced'.

As mentioned previously, there is some suggestion that maternal history of atopy and/or asthma is more strongly

associated with atopic disease in offspring than is paternal history. While both mother and father contribute to the genetic transmission of susceptibility, there may be additional environmental effects exerted through the mother which modulate the expression of the genetic endowment. The placenta, the site of intimate maternal–foetal interface, represents an immunologic dilemma. It is essentially a naturally occurring allograft, which should prompt a brisk cellular immune response from the mother by virtue of its continuous, low-level expression of paternal MHC antigen. While there are some subtle systemic manifestations of altered maternal immune function during pregnancy, it appears from animal studies that the immunomodulation necessary to preserve the developing embryo and foetus occurs predominately in the local placental environment [12]. These studies further suggest that it is an alteration in the cytokine milieu at the maternal–foetal interface itself which effects these changes. Interestingly, this change in milieu is that of a shift away from those cytokines which promote cell-mediated immunity (Th1 activity) and towards those which induce humoral immunity (Th2 activity) [12].

Thus, one of the earliest factors potentially influencing the development or polarization of the foetal immune system towards an atopic phenotype is its exposure to the placental cytokine milieu. This idea is further supported by the observation that Th1 and Th2-related cytokines promote the development of T cells into cells of like type, and suppress the development of the opposite type [13]. That is, the Th1 cytokine IFN γ promotes differentiation of naive T-helper cells into Th1 cells while inhibiting the development of Th2 cells. Likewise, IL-4, a Th2 cytokine, promotes the development of Th2 cells while inhibiting the development of Th1 cells. Thus, the relative predominance of Th1 or Th2 cytokine production by the placenta could serve to bias the development of naïve foetal T cells in one direction or the other. This hypothesis is congruent with the finding of decreased IFN γ production by T cells from newborns born into families with a history of atopy [14]. Similar findings in adults with atopic dermatitis [15] may be a demonstration of the life-long nature of such an early influence. A difference in the character of placental influences in atopic as compared to non-atopic mothers may be only one of many environmental factors modulating the expression of multiple genetic determinants of susceptibility to atopy and asthma, but its timing, coming very early in development, may afford it a pivotal role in setting the direction of future immune development.

Extra-uterine environmental stimuli are also crucial. Factors such as the frequency and type of respiratory infections experienced in early childhood [16], exposure to cigarette smoke and other aerotoxins [17], and increased exposure to aeroallergens because of home construction

practices [18] have all been discussed as possible contributors to disease development. Clearly it is not one or even a few factors or events which determine the ultimate development of the atopic/asthmatic phenotype, but a complex interplay of genetic endowment and environmental exposures (nature and nurture) which govern the outcome. The genetic endowment probably exerts its influence at a number of steps, from susceptibility to priming by a particular antigen, to the ability of APCs to provide appropriate signalling, to perhaps a propensity for polarization to proceed preferentially in one direction or another. Degree or dose of antigen exposure obviously governs the opportunity to respond, but may influence polarization as well. Finally, the environments, external and cellular, in which the process takes place may colour the final response.

The stage may largely be set, however, before the first breath is ever taken.

References

- 1 Cookson WOCM, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989; **i**:1292–5.
- 2 Shirakawa T, Airon L, Dubowitz M et al. Association between atopy and variants of the beta subunit of the high-affinity immunoglobulin E receptor. *Nat Genet* 1994; **7**:125–9.
- 3 Marsh DG, Neeley JD, Breazeale DR et al. Linkage analysis of IL4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. *Science* 1994; **264**:1152–6.
- 4 Meyers DA, Postma DS, Panhuysen CI et al. Evidence for a locus regulating total serum IgE levels mapping to chromosome 5q. *Genomics* 1994; **23**:464–70.
- 5 Holberg CJ, Elston RC, Halonen M et al. Segregation analysis of physician-diagnosed asthma in hispanic and non-hispanic white families. *Am J Respir Crit Care Med* 1996; **154**:144–50.
- 6 Szépfalusi ZS, Nentwich I, Gerstmayr M et al. Prenatal allergen contact with milk proteins. *Clin Exper Allergy* 1997; **27**:28–35.
- 7 Halonen M, Stern D, Taussig L et al. The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory illnesses and eczema in infants. *Am Rev Respir Dis* 1992; **146**:866–70.
- 8 Von Hoegen P, Sarin S, Krowka JF. Deficiency in T cell responses of human foetal lymph node cells: a lack of accessory cells. *Immunol Cell Biol* 1995; **73**:353–61.
- 9 Piccinni MP, Mecacci F, Sampognaro S et al. Aeroallergen sensitization can occur during fetal life. *Int Arch Allergy Immunol* 1993; **102**:301–3.
- 10 Sarzotti M, Robbins DS, Hoffman PM. Induction of protective CTL responses in newborn mice by a murine retrovirus. *Science* 1996; **271**:1726–8.
- 11 Matzinger P. Tolerance, danger and the extended family. *Annu Rev Immunol* 1994; **12**:991–1045.
- 12 Lin H, Mosmann TR, Guilbert L, Tuntipopipat S, Wegmann TG. Synthesis of T helper 2-type cytokines at the maternal-fetal interface. *J Immunol* 1993; **151**:4562–73.

- 13 Demeure CE, Wu CY, Shu U et al. In vitro maturation of human neonatal CD4 T lymphocytes: cytokines present at priming modulate the development of lymphokine production. *J Immunol* 1994; 152:4775–82.
- 14 Warner JA, Miles EA, Jones AC et al. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exper Allergy* 1994; 24:423–30.
- 15 Jujo K, Rnez H, Abe J, Gelfand EW, Leung DYM. Decreased interferon gamma and increased interleukin-4 production in atopic dermatitis promotes IgE synthesis. *J Allergy Clin Immunol* 1993; 90:323–31.
- 16 Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M. Association of non-wheezing lower respiratory tract illnesses in early life with persistently diminished serum IgE levels. *Thorax* 1995; 50:1067–72.
- 17 Martinez FD, Cline MG, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992; 89:21–6.
- 18 Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (*Der p* I) and the development of asthma in childhood. *New Engl J Med* 1990; 323:502–7.

MARK A. BROWN, MARILYN J. HALONEN
and FERNANDO D. MARTINEZ
Respiratory Sciences Center,
University of Arizona,
P O Box 24-5030
Tucson, AZ 85724
USA