

Maternal programming in asthma and allergy

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Summary

There has been increasing interest in the possibility that the mother has an important role to play in influencing the development of fetal and infant immune responses to allergens during gestation. This finding, by several groups, of specific immune responses of infants at birth to individual trigger factors associated with an underlying immaturity of cytokine production, is intriguing in the light of the development of subsequent allergic disease. The interactions between mother, placenta and fetus are now forming a focus for ongoing research and may be a potential target for intervention aimed at preventing allergic asthma.

Introduction

The role of the mother in programming the immune response of the infant prior to birth has not been greatly studied. Until recently, in the field of allergy, the possibility of fetal immune responses to allergens encountered by the mother during pregnancy was not recognized and the *in utero* environment had been considered the place where responses governed by genetic rather than environmental influences developed. However, allergen exposure after birth has been implicated as a major determinant of whether a baby at high genetic risk of atopy actually develops disease. Several groups investigating the predictive capacity of a raised cord blood IgE for the development of allergic disease have demonstrated that IgE specific for certain allergens can be detected at birth [1,2]. This indicates that fetal exposure to allergens must be occurring, and that it is therefore likely that the mother plays a role in facilitating this exposure. Cord blood mononuclear cell (CBMC) proliferative responses to specific allergens are another indicator that *in utero* exposure to factors which, presumably, have entered the maternal circulation during pregnancy, result in the development of early infant responses [3–5], which may be predictive of later allergic disease. Therefore the *in utero* environment created by the mother influences fetal responses in a way that may have major implications in later life. These factors might also interact with the genetic influences active at this stage which indeed are themselves enhanced, if inherited from the mother, since linkage of atopic IgE responsiveness on chromosome 11q has been

shown to be primarily detectable in maternally derived alleles [6]. Epidemiological surveys have also emphasized the enhanced risk of atopy in children of affected mothers compared with fathers. The mechanism of this is not fully elucidated, but one possibility is phenotype modification of the fetus or neonate by contact with the atopic mother or a second possibility that genomic imprinting is occurring where alleles at particular autosomal loci are silenced in a parent-specific manner for one generation at either spermatogenesis or oogenesis [7].

The mother

The findings of several groups showing that babies of allergic mothers are more likely to develop allergies themselves than babies of allergic fathers [8,9] lend further weight to the concept of *in utero* priming. This suggests that the responses generated by a mother exposed to factors that trigger her disease, whilst pregnant, also affect the developing responses of the fetus to the same factors. This has been shown by two groups in response to maternal exposure to birch pollen during pregnancy. Jones *et al.* [10] showed that the babies of mothers who had been exposed to birch pollen at 22 weeks of gestation or beyond had significantly higher CBMC proliferative responses to birch pollen at the time of birth than the babies of mothers who had either not been exposed at all during their pregnancy or whose exposure had been prior to 22 weeks. This has recently been expanded by van Duran Schmidt *et al.* [11] who showed that positive CBMC responses were only obtained to birch pollen if the mother had been exposed during months 5–7 of pregnancy and not if the only exposure had occurred before or after this time period.

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This would imply that there is a period in the early development of the immune response when exposure will not trigger the development of memory and a period in late pregnancy when exposure results in a lack of response or maybe a form of tolerance. It is known that maternal avoidance of milk and egg during the third trimester of pregnancy does not alter cord blood IgE levels nor protect against the subsequent development of allergic disease in the infant [12,13]. This is maybe not surprising in the light of babies being able to respond to allergens from 22 weeks of pregnancy, however, the path from a T-cell proliferative response to the production of IgE and the development of disease is a complex one and unlikely to be influenced by allergen exposure alone. Cytokine production by the mother and the placenta at critical points in the development of the infant immune response is doubtless able to alter the final outcome in terms of whether the reaction is of the Th1 or Th2-type to a particular trigger. Pregnancy is associated with a transient depression of specific maternal cell mediated immunity [14] and increased antibody production [15]. Indeed it has been reported in humans that pregnancy can result in the remission of chronic inflammatory diseases such as rheumatoid arthritis [16], all of which points to a Th2-like profile of maternal responses. It is still speculative as to whether an allergic mother experiences an even greater shift in this direction, and whether this influences fetal responses. It has been shown that circulating peripheral blood mononuclear cells (PBMCs) undergo significant modulations in cytokine gene expression in pregnant women, particularly in the third trimester and near parturition [17]. During the first trimester there is decrease in IL-6 mRNA expression, which is likely to be due to the action of IL-6 in delaying the attachment of the trophoblast, and which continues throughout the pregnancy. Interleukin (IL)-2 is downregulated during pregnancy until month 8, when it increases just prior to a downregulation of mRNA coding for IL-4 in month 9. The balance between these cytokines is thought to be implicated in labour and parturition. Therefore, throughout pregnancy, cytokine production in peripheral blood follows a complex, constantly modulated pattern, presumably to maintain a balance between suppression of fetal rejection and promotion of fetal growth and development. The placenta is the organ that provides the interface between mother and baby and is therefore likely to be involved in the control and passage of antigens and cytokines between the two individuals. Therefore proving that allergens are able to cross the placenta and reach the fetal circulation is vital to the theory of fetal antigen priming and we are currently establishing cytotrophoblast monolayer cultures that differentiate into syncytiotrophoblasts to investigate this passage.

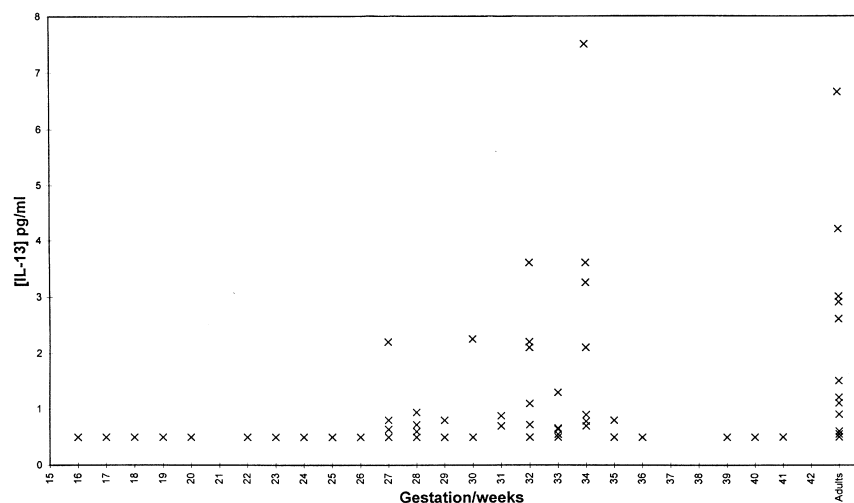
The placenta

There are indications that the altered immune response seen in the mother during pregnancy is initiated partially by factors produced by the placenta. In mice it has been observed that there are increases in IL-4 and also IL-10 and some increase in IFN- γ in PBMC cultures from maternal blood. In the placenta, increases are seen in IL-4 but not IFN- γ and IL-2 remains low [18]. In the murine model it is known that the feto-placental unit produces Interleukin-4 (IL-4), IL-5 and IL-10 during all three trimesters of pregnancy [19]. In the human placenta also, IL-10 is produced during all three trimesters of pregnancy [20] and is bioactive as determined by its ability to suppress interferon gamma (IFN- γ) production in an allogenic mixed lymphocyte reaction. It therefore can be suggested that cytotrophoblast IL-10 is an important factor that contributes to maternal tolerance of the allogeneic fetus by damping the inflammatory immune response. Maternally derived cells will only come into contact with two subpopulations of trophoblast in the placenta; the syncytiotrophoblast of the chorionic villi and the extravillous cytotrophoblast. It is therefore the immune response to these two cell types which has to be downregulated in the mother to avoid fetal rejection. IL-10 is also present in amniotic fluid and we have evidence that significantly higher concentrations of IL-10 are found in the amniotic fluid of atopic women compared to non-atopic women that may affect the developing immune responses of the fetus as amniotic fluid is swallowed. Most recently we have generated data showing that IL-13 generating cells are present in the human placenta and can be demonstrated within villi between 16 and 27 weeks of pregnancy. Beyond this time IL-13 positive cells were not present in the placenta, but interestingly this coincided with the first detectable concentrations of IL-13 being found in the supernatants of unstimulated fetal PBMCs, suggesting a feedback mechanism between fetal and placental cytokine control.

The fetus

The collection of material from preterm babies is an area fraught with difficulties, both ethically and technically. However, ethical permission has been granted by the Joint Southampton University Hospitals Trust to collect fetal umbilical cord blood samples from pregnancies being terminated (largely due to fetal abnormality, not involving the immune system) and premature babies. We have samples from 14 weeks of gestation through to term. Proliferative responses to house-dust mite, cat, birch pollen, milk and egg allergens have been demonstrated from 22 weeks' gestation [10] and these responses

Fig. 1. Graph to show IL-13 production by unstimulated fetal PBMCs during gestation compared to adult PBMC IL-13 production.



and T-cell expression of the activation marker CD25 and the memory marker CD45RO [21] have been shown to correlate with increasing gestational age, indicating augmentation of the fetal immune response to specific antigens as pregnancy progresses.

We also have data to suggest that the way fetuses downregulate the effect of exposure to increased Th2 type cytokines on the development of their own immune response is to only be able to generate very low levels of mRNA coding for IL-4 or IL-13 before 36 weeks of gestation, in comparison to much earlier expression of mRNA coding for the Th1-like cytokines IL-2 and IFN- γ . In PHA stimulated fetal PBMCs collected before 36 weeks of pregnancy either very faint signals or no signal at all could be demonstrated for these two cytokines. Analysis of the supernatants of those producing faint signals revealed that prior to 27 weeks' gestation unstimulated cells produced no detectable IL-13, but that between 27 and 34 weeks there was some constitutive production, which is again undetectable from 34 weeks up to term (Fig. 1). The start of IL-13 production by fetal PBMCs was concurrent with the end of IL-13 production by cells in the placenta, again emphasizing the interaction within the materno-placental-fetal unit. We have also shown a positive association between the expression of mRNA coding for IL-13 in ovalbumin stimulated PBMCs at birth and the development of a positive allergy skin prick test to egg by 1 year of age. This specific response seems likely to have resulted from allergen exposure *in utero* and therefore the effect of maternal and placental influences is vital to the timing and mechanism of the initiation of these reactions.

The materno-placental-fetal interface

The interactions described above provide very compelling evidence for the *in utero* development of fetal

immune responses to allergens. It is clear that, even under normal circumstances, both the mother and the placenta play important roles in the control of these responses, and an allergic mother may further direct the pathway of the fetal immune response towards the Th2 type. It is possible that control of maternal allergen exposure and maternal disease will alter the development of these responses, and research in progress is now addressing whether such interventions could prevent infant sensitization and subsequent allergic disease [22]. Our current research strategy is investigating the hypothesis that environmental modification through pregnancy as well as early infancy will prevent the development of allergy and asthma. We have a cohort of 200 families with allergic asthma enrolled in our Child Health Asthma Prevention Study (CHAPS) where an intensive inhalant allergen avoidance programme has been instituted from 18 weeks of pregnancy and continued through the child's first year of life in a controlled trial to establish whether maternal allergen

PREVENTION OF ALLERGIC DISEASE

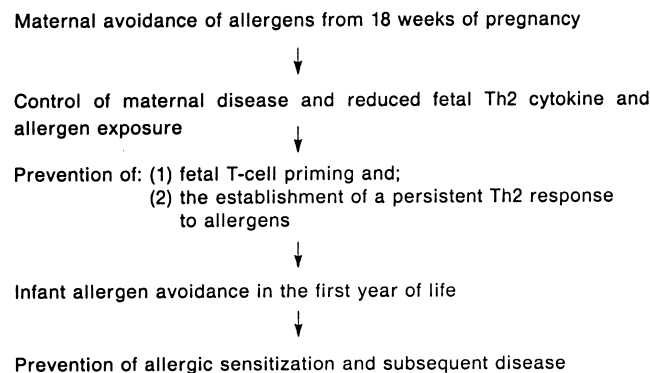


Fig. 2. Possible steps which may play a role in the prevention of allergic disease in infants.

avoidance during pregnancy and infant avoidance in the first year of life will reduce the prevalence of childhood asthma. Maternal and infant immune responses are being monitored during this period and clinical symptoms recorded. It is hoped that maternal disease will be controlled and therefore that the chance of even greater concentrations of circulating Th2 cytokines, as well as allergen, reaching the fetus will be reduced. This would then create less of a Th2-biased environment for a developing fetus, which will already, due to inherited characteristics, have a reduced capacity for the production of the Th1 cytokine IFN- γ . The immune responses of the infants at birth will provide the initial indication of whether the allergen reductions have been successful in preventing the priming of fetal cells and clinical follow-up over the next 5 years will determine whether this can be maintained with a reduction in the rates of allergic sensitization and subsequent asthma (Fig. 2).

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