

## Hypothesis paper

# Is allergic asthma associated with delayed fetal maturation or the persistence of conserved fetal genes?

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Asthma is heterogeneous, and allergic and nonallergic asthma can be distinguished, although the differences between them are not yet clearly understood (1).

Allergic asthma usually starts early in life, and most asthmatic children are allergic. Surprisingly, however, currently available epidemiologic evidence does not indicate that allergen exposure is a major risk factor in the primary causation of asthma in children (2). There are probably defects other than IgE-mediated allergic reactions that may explain allergic asthma, although it is possible that the same common mechanisms induce the increased IgE response and the bronchial abnormalities underlying asthma.

The early occurrence of allergic asthma suggests that prenatal influences are of importance (3), and it is also possible that defects in early development of the lung and the immune system are involved in the pathogenesis of asthma.

### IgE-mediated allergy

The IgE-mediated allergic diseases are associated with the functional activity of Th2 cytokines. In particular, in allergic asthma, Th2 cytokine responses are found to be increased (4, 5), albeit in patients with stable asthma a Th1 response seems to predominate in the bronchi (6).

It has been proposed that during pregnancy the

immunologic milieu of the placenta is constitutively skewed away from the Th1-dominated response and shifted toward the Th2 phenotype (7–9).

These Th2-cytokine-mediated immune responses appear to be preserved in early periods of infancy and may be perpetuated in infants who will later develop atopy (10). It has also been proposed that a generalized immaturity or suppression of both Th1- and Th2-type immune responses may occur at birth in atopy-prone babies (11). There may then be a delayed maturation of the Th1 pathways, leading to an enhanced release of the Th2 cytokines that can perpetuate the Th2-driven responses. However, this explanation may be too simplistic, since the magnitude of Th2 responses is even greater in neonates who did not develop allergic reactions during infancy (10). In infants, there is a maturational deficit in IFN- $\gamma$  production. Postnatal IFN- $\gamma$  upregulation is usually delayed until the age of 1 year and rises steadily thereafter (12). It is therefore possible that there is a persistence of the fetal state in children who are developing atopy, due to a defect in Th2-dampening mechanisms.

Several reports have suggested that allergy may start during fetal life, and that the risk of such a development may be amplified by prenatal exposure to allergens (3). The relevant observations include an increased IgE level in the cord blood of infants who will subsequently

develop atopy (13, 14), the presence of cord-blood IgE specific to foods (14), the presence of cord-blood mononuclear cell proliferation in response to various allergens, transplacental priming of the human immune system to environmental allergens (15), and the presence of activated memory T cells at birth.

The postnatal maturation of the immune system, which is characterized in allergic asthmatics by the development of an imbalanced Th2 immunity, is genetically determined and modified by the environment (16).

#### **The epithelial-mesenchymal unit and the developing lung**

During lung development, repair, and inflammation, local production of cytokines and growth by epithelial and mesenchymal cells mediate bidirectional growth control, creating an epithelial-mesenchymal trophic unit which may have features similar to those observed in asthma (17).

The complex process of lung formation is determined by the action of numerous genes that influence cell commitment, differentiation, and proliferation (18). The definitive endoderm gives rise to organs of various shapes and functions, including the respiratory system and several glands, the function of which range from maturation of the immune system to mineral and thermal homeostasis (19). Epithelial-mesenchymal interactions appear to be important in the developing mammalian lung, which, like many other organs, develops by branching morphogenesis of an epithelium (20, 21). To form a diffusible interface large enough to conduct respiratory gas exchange with the circulation, the lung endoderm undergoes extensive branching morphogenesis and alveolization, coupled with angiogenesis and vasculogenesis (22).

Signaling by the IGF, EGF, and TGF-beta/BMP pathways; extracellular matrix components (23); and integrin signaling pathways (24, 25) also direct lung morphogenesis and proximo-distal lung epithelial cell lineage differentiation (22).

In the developing lung, the induction of smooth-muscle differentiation is closely related to branching morphogenesis (26). Myofibroblast differentiation becomes manifest perinatally when expression of alpha-smooth-muscle actin escalates (27). Myofibroblasts appear only in developing small and large airways and pulmonary vessels, and they may play a critical role in branching morphogenesis during development (28). Myofibroblast-like cells containing smooth-muscle actin have been identified in lung injury and repair. The differentiation of fibroblastic cells into myofibroblasts is an early event in the development of tissue fibrosis.

Extracellular matrix components are important in the developing lung. Tenascin has been implicated in branching morphogenesis (29).

#### **Conserved genes in the developing lung and inflammation**

Molecular and genetic evidence accumulated during the past 20 years in the field of developmental biology indicates that different animal species possess many common genetic systems for embryonic patterning (30).

Many of the key factors determining the process of branching morphogenesis, particularly of the respiratory organs, are highly conserved through evolution. Genetic manipulations in *Drosophila* and mouse show that members of the sonic hedgehog (Shh)/patched/smoothed/Gli (31)/FGF/FGFR (32)/sprouty pathway are functionally conserved and extremely important in determining respiratory organogenesis through mesenchymal-epithelial inductive signaling, which induces epithelial proliferation, chemotaxis, and organ-specific gene expression (22).

Transcriptional factors, including Nkx2.1 (33, 34), HNF family fork head homologs, GATA family zinc finger factors, pou and hox (35), helix-loop-helix (HLH) factors, Id factors, and glucocorticoid and retinoic acid receptors, mediate and integrate the developmental genetic instruction of lung morphogenesis and cell-lineage determination (36).

Conserved genes also appear to be important in inflammation. These include the JAK/STAT pathway (37); Rel-containing regulatory proteins, Dif and dorsal, which are related to mammalian NF-kappa B (38); suppressor of cytokine signaling (SOCS)-family proteins containing a carboxy-terminal conserved motif termed SOCS-box (39); a fork head domain protein expressed in human T helper cells (40); and the innate immune system, which is an evolutionarily ancient form of host defense found in most multicellular organisms (41, 42). Moreover, some of the *Drosophila* conserved genes may be associated with inflammatory diseases, since components of the Wingless/Wnt signal transduction pathway (43) may be involved in the perpetuation of immune mechanisms of rheumatoid arthritis (44).

#### **Remodeling of the airways in asthma and fetal lung development**

In asthma, tissue modeling and remodeling coexist (45). "Remodeling" is defined as "model again or differently; reconstruct". This is a critical aspect of wound healing, representing a dynamic process that includes extracellular matrix (ECM) production and degradation in reaction to an inflammatory insult, leading to a normal reconstruction process (model again) or a pathologic one (model differently). The features of airways remodeling in asthma include epithelial activation, the presence of myofibroblasts beneath the basement membrane, reticular basement membrane pseudotickness, increase in smooth-muscle mass, and mucous gland enlargement (45).

Processes of wound healing have in common the fact

that the cell proliferation and differentiation involved in the restoration of the normal tissue architecture resemble to a certain degree the embryonic development of the corresponding tissue (46).

In asthma, abnormal signaling between the epithelium, which is in contact with the environment, and the underlying (myo)fibroblasts and dendritic cells may reactivate the epithelial mesenchymal trophic unit, which is involved in fetal lung development and branching (47). Not only are several features of the developing lung present in asthma, but it has also been observed that allergen exposure induces the expression of some of these features such as tenascin (48) or the development of myofibroblasts (49).

Airways inflammation and remodeling already exist in infants who will subsequently develop asthma, suggesting that the pathologic defects in asthma occur very early in life before the development of symptoms (50). It is tempting to speculate that the fetal structures have never fully matured in these children.

#### Is there delayed fetal maturation or persistence of fetal genes in allergic asthma?

It has been suggested that reactivation of the epithelial mesenchymal trophic unit may occur in asthma (47). We propose that this trophic unit still exists at birth in the neonate who will develop asthma, suggesting the persistence of immature features of the developing

lung. If this hypothesis is correct, what might be the underlying gene defect? Is it an early defect involving branching genes, and leading to a permanent abnormality of the epithelial-mesenchymal trophic unit? If so, this would suggest that gene defects in asthma do not allow the full maturation of fetal tissues, and that there is a delayed maturation of the fetal lung in asthma.

On the other hand, are there genes expressed or repressed prenatally or in early infancy under the influence of the environment? This proposal would lead to the concept of the persistence of the trophic unit and the persistence of the genes in the developing lung.

Are some of the genes involved in the developing lung and asthma conserved genes? Recent findings linking the intensity of atopy with a polymorphism in the CD14 gene may indicate the importance of these conserved genes (51). Other genes such as HOX may be involved in the branching of the respiratory tract (19), in lymphocyte differentiation (52), and in asthma (53).

Another question needs to be answered: is there a common defect or are there interrelated defects causing both the Th2-immune response of allergic asthmatics and the inflammatory and remodeling patterns seen in asthma?

Clarification of these issues may yield new information on the mechanisms of asthma and new targets for therapeutic intervention and primary prevention.

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