

A Trajectory toward Allergy: *In Utero* Uptake of Allergens Can Prime Type 2 Inflammation

Many studies now highlight that the tenor of the immune response at birth relates to both the antenatal environment, such as maternal allergy or farming exposures, and allergic disease outcomes for the child (1). The human fetus clearly can generate antigen-specific responses, as demonstrated by the presence of tetanus-specific IgM in neonates of pregnant women vaccinated to tetanus at 5 or 8 months of pregnancy (2), and other similar studies. However, the occurrence and consequences of allergen/antigen-specific priming of the immune system during fetal development remains a topic of heated debate. In this issue of the *Journal*, Chen and colleagues (pp. 934–947) have investigated the effect of allergen exposure *in utero* on allergic disease outcomes using a mouse model (3). The classical school of thought argues that in early life, the immune system of both humans and mice is immature and tolerogenic in nature. However, this concept oversimplifies the situation. More accurately, the early immune system is less primed toward type 1 inflammation (although still capable of mounting strong type 1 responses after appropriate stimuli) and more effective at eliciting type 2 immune responses (4). There might also be features of the fetal/neonatal immune system distinct from that of the adult that provide alternative defense mechanisms and effect on antigen-specific priming of T cells. An example of this includes the ability of human term and preterm neonatal, but not adult, T cells to produce IL-8, which is counter to the view of an antiinflammatory predominance in fetal life (5).

There is a growing awareness that during development, there are timeframes when environmental exposures can influence an individual's protection against or susceptibility to allergic disease in later life. Epidemiological approaches and studies in animal models highlight how maternal exposures during pregnancy shape immune function, and mucosal homeostasis in particular (6, 7). Studies of the effect of the farming environment on allergic disease outcomes have provided a framework for understanding how critical prenatal exposures are for protection against the development of atopic sensitization and respiratory tract allergic disease (7).

The challenges of gaining mechanistic insight into the consequences of intrauterine exposure to antigens and immunomodulatory factors is exemplified in the study by Chen and colleagues (3). Here the authors originally aimed to assess the tolerogenic mechanisms of *in utero* antigen exposure; however, injection of an exogenous protein (ovalbumin [OVA]) led, not to tolerance as expected, but rather to a mechanism that culminated in exaggerated postnatal inflammatory responses. In a dose-dependent manner, exposure to OVA *in utero* followed by oral gavage or subcutaneous injection of OVA in alum adjuvant postnatally resulted in anaphylaxis, whereas inhaled OVA postnatally led to allergic airway inflammation. At the core of this process were fetal phagocytes, likely to have derived from yolk sac

progenitors, that phagocytosed the antigen and retained it as a repository, delaying presentation until the immune system had matured further. These cells expressed major histocompatibility complex (MHC) class II and costimulatory molecules intracellularly, rather than at the surface, and had dendritic cell progenitor capacity. A key component of their delayed presentation was the acidification of the fetal phagocytes' lysosomes, which appeared slower than that of immature dendritic cells. This attenuated antigen proteolysis ultimately extended the time before peptide–MHC complexes could be formed. Taken together, Chen and colleagues' data suggest that *in utero* exposure to high allergen concentrations could act to prime offspring toward atopy (3). There are, of course, caveats to consider within the experimental system. First, the process of injecting fetuses *in utero*, even with no antigen, is a profound stress, leading to a substantial reduction in survival. Although this process itself did not lead to exaggerated postnatal inflammation, it could play an adjuvant role in promoting antigen uptake and subsequent presentation. Second, the OVA protein is a poor surrogate allergen, and injection of fetuses *in utero* with this is not reflective of physiological conditions. However, a similar phenomenon was described with a more relevant allergen, Derp II, and its Th2-promoting activity was notably stronger than OVA. These data clearly support the concept that if allergens reach the fetus at sufficient concentrations during this developmental period, fetal phagocytes have the capacity to sequester the allergen and to later present the allergen to T cells leading to inflammation. Building on these data, it would be intriguing to introduce further environmental stimuli, or genetic backgrounds, into the system; for example, *in utero* allergen exposure of dams exposed to farm dust, prebiotics or probiotics, or alternative scenarios that have been linked to protection against allergy. Within those contexts, could the phenotype of fetal phagocytes be skewed such that *in utero* allergen exposure actually protects against atopy?

All the necessary ingredients are present during human fetal development. Macrophage-like cells can be detected in human yolk sac at 4–6 weeks of gestation, with a minor population already expressing MHC class II (8). MHC class II–positive macrophage-like cells can also be found in the liver at 7–8 weeks, the lymph nodes at 11–13 weeks, the skin from 6 to 7 weeks, and the gastrointestinal tract from 11 weeks (8–10). Very little is known about the functionality of these or fetal dendritic cell populations, but Chen and colleagues (3) highlight where the focus of studies of these cells should lie. Exposure to allergens and other antigens undoubtedly occurs *in utero* (11), and human fetal CD4⁺ T effector memory cells that share phenotypic and functional features with conventional adult memory cells have been described (12). The challenge now is to understand the basic biology of these components and their

interactions, and to translate this to disease prevention strategies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Catherine A. Thornton, Ph.D.
Institute of Life Science
Swansea University Medical School
Swansea, United Kingdom

Benjamin J. Marsland, Ph.D.
Faculty of Biology and Medicine
University of Lausanne
Epalinges, Switzerland

References

1. Tulic MK, Hodder M, Forsberg A, McCarthy S, Richman T, D'Vaz N, van den Biggelaar AH, Thornton CA, Prescott SL. Differences in innate immune function between allergic and nonallergic children: new insights into immune ontogeny. *J Allergy Clin Immunol* 2011;127:470–478.
2. Gill TJ III, Repetti CF, Metlay LA, Rabin BS, Taylor FH, Thompson DS, Cortese AL. Transplacental immunization of the human fetus to tetanus by immunization of the mother. *J Clin Invest* 1983;72:987–996.
3. Chen J-C, Chan C-C, Wu C-J, Ou L-S, Yu H-Y, Chang H-L, Tseng L-Y, Kuo M-L. Fetal phagocytes take up allergens to initiate T-helper cell type 2 immunity and facilitate allergic airway responses. *Am J Respir Crit Care Med* 2016;194:934–947.
4. Forsthuber T, Yip HC, Lehmann PV. Induction of TH1 and TH2 immunity in neonatal mice. *Science* 1996;271:1728–1730.
5. Gibbons D, Fleming P, Virasami A, Michel ML, Sebire NJ, Costeloe K, Carr R, Klein N, Hayday A. Interleukin-8 (CXCL8) production is a signatory T cell effector function of human newborn infants. *Nat Med* 2014;20:1206–1210.
6. Conrad ML, Ferstl R, Teich R, Brand S, Blümer N, Yildirim AO, Patrascan CC, Hanuszkiewicz A, Akira S, Wagner H, et al. Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe *Acinetobacter lwoffii* F78. *J Exp Med* 2009;206:2869–2877.
7. Douwes J, Cheng S, Travier N, Cohet C, Niesink A, McKenzie J, Cunningham C, Le Gros G, von Mutius E, Pearce N. Farm exposure in utero may protect against asthma, hay fever and eczema. *Eur Respir J* 2008;32:603–611.
8. Janosy G, Bofill M, Poulter LW, Rawlings E, Burford GD, Navarrete C, Ziegler A, Kelemen E. Separate ontogeny of two macrophage-like accessory cell populations in the human fetus. *J Immunol* 1986;136:4354–4361.
9. Foster CA, Holbrook KA, Farr AG. Ontogeny of Langerhans cells in human embryonic and fetal skin: expression of HLA-DR and OKT-6 determinants. *J Invest Dermatol* 1986;86:240–243.
10. Jones CA, Vance GHS, Power LL, Pender SLF, Macdonald TT, Warner JO. Costimulatory molecules in the developing human gastrointestinal tract: a pathway for fetal allergen priming. *J Allergy Clin Immunol* 2001;108:235–241.
11. Vance GH, Lewis SA, Grimshaw KE, Wood PJ, Briggs RA, Thornton CA, Warner JO. Exposure of the fetus and infant to hens' egg ovalbumin via the placenta and breast milk in relation to maternal intake of dietary egg. *Clin Exp Allergy* 2005;35:1318–1326.
12. Zhang X, Mozeleski B, Lemoine S, Dériaud E, Lim A, Zhivaki D, Azria E, Le Ray C, Roguet G, Launay O, et al. CD4 T cells with effector memory phenotype and function develop in the sterile environment of the fetus. *Sci Transl Med* 2014;6:238ra72.

Copyright © 2016 by the American Thoracic Society

Biological Network Modeling and Systems Biology to Advance Our Understanding of Lung Disease

At about the time the human genome was mapped, Barabasi and Albert described a simple graphical model to explain how a variety of seemingly disparate data types (the neural network of the worm *Caenorhabditis elegans*, the power grid of the United States, and collaboration between actors) could all be explained by a simple type of network called the scale-free network (1).

The characteristics of scale-free networks are that they have many peripheral nodes (connecting points) and a few highly connected nodes (hubs). These networks have a few universal organizing principles. They have a “small-world” property (i.e., they are highly connected with relatively short paths between nodes). The networks are robust to failure, such that peripheral nodes can be knocked out and network function preserved, and node number can be described by a power law function. Most important, all biological data (biochemical, transcriptional, epigenomic, protein–protein interaction, and metabolomics) can be accurately modeled using scale-free networks.

As we have been rapidly expanding our omics data types over the last 15 years, from genetics to genomics, transcriptomics, epigenomics, proteomics, and metabolomics, scientists have struggled with how to organize these different data types to make meaningful

discoveries about human disease. Systems biology is a holistic approach to these data that can be applied at the level of the cell, organ, organism, or population, taking a snapshot of all these varying data types and applying network or other methods of analysis.

Goh and colleagues (2), and subsequently Barabasi and Loscalzo (3, 4), postulated that in the extension of network theory to disease, there is a human disease network in which common genes connect diseases to each other, and that clustering of diseases in the human disease network/interactome is a result of genes that are shared, or are unshared, between clustering diseases. Obviously, the human interactome of genes and diseases is currently incompletely described, but network approaches can be used to link diseases to each other and determine their similarities and differences.

With this brief background on systems biology, we are now ready to consider the article published in this issue of the *Journal* by Kusko and colleagues (pp. 948–960) (5). In this article, the authors use RNAseq on 87 chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, or normal lung samples to define connections between the two disease networks and identify that the p53/hypoxia pathway is common to both disorders and that there is over expression of several genes in this pathway. Notably, hypoxia

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.