

Prenatal Influences on the Development of Allergy and Asthma TH1/TH2 Balance

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Allergy and asthma are chronic inflammatory diseases that manifest on skin and mucosal tissues. The normal immune response against harmless environmental antigens, including pollen, foods and mites, is a state of immunological tolerance. In the case of allergies, however, an inflammatory response occurs which is characterized by a predominant TH-2 immune pattern. There is increasing evidence that, at least in the case of infancy and early childhood allergies, the maternal immune system takes part in shaping this kind of response. Cross-sectional and longitudinal studies indicate a stronger influence of maternal as compared to paternal atopy, which might be related to genetic and/or environmental factors (1, 2). Adaptive immune responses develop as early as in in-utero. Almost all newborns carry antigen-specific T-cells which recognize particularly food antigens, but also inhalant allergens (3, 4). Careful analysis of this phenomenon revealed that these T-cells result from in-utero sensitization and they are indeed of fetal origin (5). Functional analysis of these T-cells has been performed by several groups. In normal healthy neonates, the level of IFN- γ production is markedly reduced as compared to later in life (4, 6) (7). However, an even further reduced capacity to secrete TH-1 cytokines has been related to the risk and the development of allergies, particularly in the first few years of life. These and other data resulted recently in the concept that an impaired level of TH-1 immunity may favour the development of allergies. Further indirect evidence for this hypothesis comes from epidemiological studies performed in rural areas on farming infants, where prenatal contact to the farming environment conveys protection against respiratory allergies (8, 9) (10). This effect has been related to high levels of endotoxins, particularly present in stables and farm houses (2). Furthermore a recent intervention study revealed that prenatal administration of certain lactobacilli which are known as potent TH-1/TH-2 modifiers, markedly reduced the development of atopic eczema in early childhood (11).

Maternal adaptive immunity has a strong influence on immune responses of the offspring. This phenomenon has probably been best studied in diaplacental and breast milk transmission of antibodies. Not only these antibodies provide passive protection against infections, but might also actively shape childhood immunity and tolerance induction by providing the fetus and the infant with the mother's immunological experience (12). In this regards, the dia-placental transfer of IgG antibodies and the presence of high amounts of secretory IgA antibodies in breast milk might play an important role (13). However, whether the T-cell compartment might be also actively involved in regulating pre- and postnatal immunity has not been extensively studied to date.

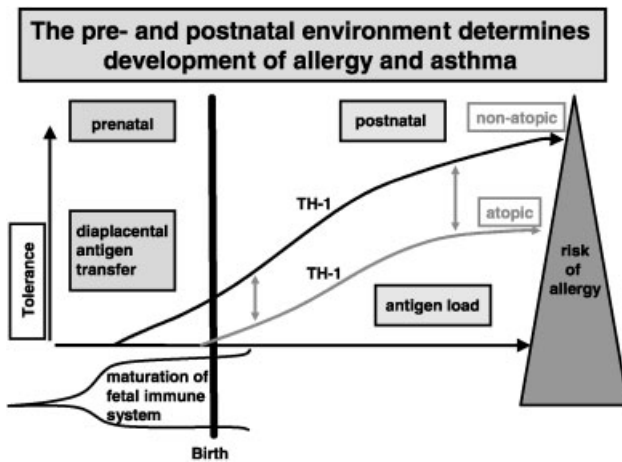
In conclusion, basic research performed particularly in a number of murine animal model systems revealed the important role of intrauterine immunity for successful pregnancy. There is ample evidence for a multidirectional interaction between maternal and fetal immunity.

During pregnancy, a profound redirection of specific T-cell effector functions occurs at the fetomaternal interface. This has direct effects on the development of specific fetal T- and B-cell responses.

These data so far provide strong evidence that the fetal immune system matures under close and strong control of maternal immunity. A key question is now what might be the impact of these regulatory events on the development of early atopy and allergy? These questions can only be

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answered through both extensive studies in suitable animal model systems in relation to allergy and asthma and by conducting clinical trials in parents/infants at risk paralleled by extensive immunological analysis. Results from such studies will provide further insights into the importance of early immune maturation for the development of allergy and asthma.

REFERENCES

1. Lewin G.R., Barde Y.A., Physiology of neurotrophins. *Annu Rev Neuroscience* 1996;19:289-317.
2. Metsis M., Genes for neurotrophic factors and their receptors: structure and regulation. *Cell Mol Life Sci* 2001;58:1014-1020.
3. Lee R., Kermani P., Teng K.K., Hempstead B.L., Regulation of cell survival by secreted proneurotrophins. *Science* 2001;294:1945-1948.
4. Chao M.V., Bothwell M., Neurotrophins: To cleave or not to cleave. *Neuron* 2002;33:9-12.
5. Lee F.S., Kim A.H., Khursigara G., Chao M.V., The uniqueness of being a neurotrophin receptor. *Curr Opin Neurobiol* 2001;11:281-286.
6. Esposito D., Patel P., Stephens R.M., et al., The cytoplasmatic and transmembrane domains of the p75 and Trk A receptors regulate high affinity binding to nerve growth factor. *J Biol Chem* 2001;276:32687-32695.
7. Lomen-Hoerth C., Shooter EM. Widespread neurotrophin receptor expression in the immune system and other nonneuronal tissues. *J Neurochem* 1995;64:1780-9.
8. Eide F.F., Vining E.R., Eide B.L., Zang K., Wang X.-Y., Reichardt L.F., Naturally occurring truncated trkB receptors have dominant inhibitory effects on brain-derived neurotrophic factor signaling. *J Neurosci* 1996;16:3123-3129.
9. Sariola H., The neurotrophic factors in non-neuronal tissues. *Cell Mol Life Sci* 2001;58:1061-1066.
10. Ernfors P., Local and target-derived actions of neurotrophins during peripheral nervous system development. *Cell Mol Life Sci* 2001;58:1036-1044.
11. van der Velden V.H., Hulsmann A.R., Autonomic innervation of human airways: structure, function and pathophysiology in asthma. *Neuroimmunomodulation* 1999;6:145-159.
12. Snider W.D., Functions of the neurotrophins during nervous system development: what the knockouts are teaching us. *Cell* 1994;77:627-638.
13. Erickson J.T., Conover J.C., Borday V., et al., Mice lacking brain-derived neurotrophic factor exhibit visceral sensory neuron losses distinct from lacking NT4 and display a severe developmental deficit in control of breathing. *J Neurosci* 1996;16:5361-537.