

What dogs may teach humans about the vertical transmission of allergy predisposition

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The paper by Barrett *et al.* in this issue¹ describes a canine model of atopic asthma where parental allergic status directly influences the disease manifestation in the offspring. Newborns of the sensitized breeder pairs were significantly more responsive to ragweed exposure through inhalation than the control offspring of non-sensitized naïve parents. Other elevated disease parameters included ragweed-specific immunoglobulin E (IgE), eosinophil counts in the bronchoalveolar lavage fluid and pulmonary resistance after ragweed inhalation. Despite the fact that, at present, these results are primarily descriptive, this dog model opens the possibility to investigate, in a controlled setting, the mechanisms of vertical transmission of allergy predisposition. Moreover, it may allow us to answer several open questions that are not possible to address in human clinical studies and are currently highly contentious.

It has been known that allergic parents are more likely to have allergic children. Whereas, nature, i.e. the genetic predisposition, clearly plays a role, it appears that perinatal nurture by allergic mothers may put children at even higher risk of becoming allergic. A clinical study demonstrated an almost five-fold higher probability of infants of atopic mothers developing atopic dermatitis in comparison with children of atopic fathers.² However, it is not clear which factors (allergens, IgE, cytokines, immune cells) play a predominant role in the transfer of the atopic bias from mother to child, or whether this transfer occurs pre- or postnatally, i.e. via the placenta or mother's milk, respectively. If the intrauterine influences are preponderant, little can be done to separate the fetus from the undesired exposure and thus prevent the allergy in the newborn. Nevertheless, at least hypothetically, allergic mothers may limit the intrauterine transfer of patho-aetiological factors by avoiding allergen contact. This theory, however, is contested by clinical observations.³

The second possible route for transmission of the pro-allergic maternal influences is by breast-feeding. Except for modern humans, mother's milk is the only dietary option for the newborn mammal. In addition to its nutritional value milk also supplements the innate and acquired host defences of the not yet fully immunocompetent newborn. This is achieved by antibodies, cytokines, chemokines and leucocytes, including T and B cells, present in milk and in especially high quantities in

colostrum. These factors, which under normal circumstances protect the newborn, may be involved in sensitization and vertical transmission of atopy predisposition from mother to child. The latter possibility makes breast-feeding by atopic individuals especially controversial.

Comprehensive review of over three decades of clinical observations concluded that extended breast-feeding protects from atopy.⁴ However, several modern reports challenge this notion. One showed that long-term exclusive breast-feeding lowers the rates of recurrent wheeze in the first years of life only, but increases the risk of asthma and recurrent wheeze in 6–13-year-old atopic children of asthmatic mothers.⁵ Another recent study demonstrated that breast-feeding failed to protect children at high risk from developing eczema.⁶ Moreover, a third cohort study of more than 1000 children provided evidence that breast-feeding for 4 weeks or longer doubled the risk of asthma in mid-childhood, irrespective of whether the mothers were atopic or not.⁷ The distinct features of the population groups studied, including socioeconomic and ethnic factors, as well as the different disease manifestations and parameters recorded, may explain the disparity of conclusions. The requirement for straightforward recommendations for atopic mothers as to whether to breast-feed or not, necessitates further experimental work to resolve the current controversy and settle the polemic debate.^{7–10}

Well-controlled mechanistic experimental models, such as the canine model established by Barrett *et al.*,¹ may provide invaluable clues as to the molecular mechanisms of vertical transfer of allergy predisposition via the mother's milk, and the relative contribution of the potential patho-aetiological factors present in it. On one hand, mother's milk is a cocktail of a wide range of immunomodulating factors, including antibodies, cytokines, chemokines and immune cells. On the other hand, it mirrors the mother's environment, exemplified by the presence in it of allergic and toxic exogenous substances. Dietary allergens are also present in mother's milk, with their peak milk concentrations expected 4–6 h after their ingestion.¹¹ This would suggest that atopic mothers that breast-feed should be encouraged to avoid food allergens, e.g. cows' milk, egg, or soy. However, this notion is contested by a clinical study³ that failed to show any beneficial effect of allergen avoidance. Actually, exposure to allergens in the mother's milk may even be beneficial because of the induction of oral tolerance in newborns. In a canine model of atopy, dogs sensitized early in life parenterally with ovalbumin (OVA) developed high OVA-specific serum IgE levels and clinical symptoms of atopy.¹²

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Oral administration of OVA in milk suppressed these allergic responses to OVA.¹³ Thus, it appears that orally administered food allergens, in conjunction with the milk milieu, may not be as harmful as initially thought, but may actually act as tolerogenic principles.

What other factors may be contributing to the potential transfer of atopy through the milk? Immunoglobulins, particularly IgA, the most abundant immunoglobulin class in milk, are responsible for the protective passive immunity transferred to the newborn and also may have immunomodulatory effects. Comparison of milk from mothers of allergic and healthy children demonstrated an association between low levels of milk IgA and a predisposition towards the development of cows' milk allergy.^{14,15} Milk IgG may also play a protective role in developing allergy in the newborn. Conversely, specific IgE present in milk, as shown for example in OVA-immunized mice, may contribute to the development of allergic predisposition in their offspring,¹⁶ possibly by fixing allergens on the surface of dendritic cells. Unfortunately, it is not possible to extrapolate these experimental findings to humans as, at the time of writing, no significant IgE has been observed in human milk.

Several cytokines—interleukin-4 (IL-4), IL-6, tumour necrosis factor- α , interferon- γ (IFN- γ), transforming growth factor- β (TGF- β) and IL-10—have been identified in the mother's milk and may skew the development of the newborn's own immunity.¹⁷ Some of them, e.g. IFN- γ and IL-4, may bias the immune responses of the newborn in T helper type 1 and type 2 (Th2) directions, respectively. Others, e.g. TGF- β and IL-10, as a result of their immunosuppressive function,¹⁸ may provide the tolerogenic background of the mother's milk. In addition, TGF- β in milk may prevent the development of atopic diseases in infants by inducing IgA, and inhibiting IgE, production in infants.^{19,20} Probiotics up-regulate TGF- β secretion in milk, and are thus thought to protect the newborn against atopic diseases.²¹

It has been known for over a decade that human milk contains several chemokines^{22–24} that may play a role in the recruitment of functional leucocyte populations into the milk. Different subsets of milk leucocytes, including T and B cells, endow the newborn with functional active immunity that mirrors the memory immune responses of the mother. There are indications, both experimental and clinical, that milk-born lymphocytes can traverse the gastrointestinal barrier of the newborn, repopulate its lymphoid organs and survive there for prolonged periods of time.²⁵ The downside of such maternal lymphocyte transplantation is that allergic mothers may transfer to their newborns the pathogenic lymphocytes which recognize allergens or produce Th2 cytokines.

It is clear that there are many mothers' milk-borne molecular players involved in modulating the immune system of the newborn. Future experimental work will show which of these and other potential mechanisms contribute to the transfer of atopic predisposition from mother to breast-fed newborn, allowing for clear recommendations, preventive interference and therapy. The canine model described by Barrett *et al.*¹ is likely to be a useful tool in achieving these aims. In the long term, to asthmatic parents and children, the dog may truly turn out to be man's best friend.

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