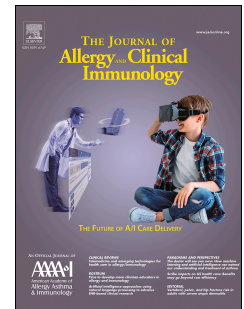


Journal Pre-proof

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PII: S0091-6749(21)00611-4

DOI: <https://doi.org/10.1016/j.jaci.2021.02.046>

Reference: YMAI 15071

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 7 January 2021

Revised Date: 7 February 2021

Accepted Date: 10 February 2021

Please cite this article as: Dwyer DF, Boyce JA, Neonatal Mast Cells and Transplacental IgE Transfer: A Mechanism of Disease Inheritance or of Passive Infant Barrier Defense?, *Journal of Allergy and Clinical Immunology* (2021), doi: <https://doi.org/10.1016/j.jaci.2021.02.046>.

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Neonatal Mast Cells and Transplacental IgE Transfer: A Mechanism of Disease Inheritance or of Passive Infant Barrier Defense?

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Key words: Mast cells, IgE, sensitization, atopy

Conflict of interest: The authors have declared that no conflict of interest exists.

This work was supported by generous contributions from the Vinik Family, the Kaye Family, by National Institutes of Health Grants AI078908, HL111113, HL117945, R37AI052353, R01AI136041, R01HL136209, R01AI130109, and U19AI095219.

Atopic diseases, including food allergy, allergic rhinitis, atopic dermatitis, and asthma, exhibit some degree of heritability. While large cohort studies suggest that this heritability emerges at least in part from the interaction of genetic, epigenetic and environmental conditions (1), studies in human and mouse have also suggested a more direct role for maternal immune status in the development of atopic disease. Murine studies have shown that sensitizing pregnant females to ovalbumin (OVA) increases the susceptibility of pups to OVA-induced bronchoconstriction; however, OVA sensitized pups were found to exhibit increased susceptibility to the unrelated protein casein, suggesting an acquired, antigen-independent transfer of atopic susceptibility (2). In humans, maternal (but not paternal) circulating total IgE concentration correlates with infant IgE levels and the development of eczema (3). While IgE plays a major role in human atopic disease, it is not thought to cross the maternal/fetal interface and is rarely detected in the circulation of either neonatal mice or humans. Thus, the mechanism(s) underlying atopic heritability are not yet fully understood.

Mast cells (MCs) are long-lived tissue-resident granulocytes that are widely recognized as central effector cells in human atopic diseases. They emerge from circulating committed progenitors that populate the tissues during embryonic life (4). In tissues such as the skin, neonatally acquired MC (at least in mice) persist into adulthood. MCs express the high affinity IgE receptor FcεR1a on their surface, through which they are able to efficiently capture circulating IgE. Following IgE cross-linking, mast cells release a broad range of pro-inflammatory mediators into the extracellular environment, including pre-formed histamine and proteases, rapidly synthesized lipid pro-inflammatory mediators, and transcriptionally regulated chemokines and cytokines. Mast cell capture of IgE also stabilizes the molecule. While circulating IgE has a half-life of only days, IgE can be maintained on the surface of MCs for

months (5). Thus, MCs have the potential to serve as a tissue resident “reservoir” of IgE even under conditions where no circulating IgE can be detected.

In a recent issue of *Science* (6), Msallam and colleagues use a series of murine model systems and ex vivo studies of human MCs to establish that fetal MCs can bind maternally derived IgE and can be subsequently activated in an antigen-specific manner both in vitro and in vivo. Pups born to ragweed-sensitized mothers and challenged intranasally with ragweed at four weeks of age developed pulmonary eosinophilia and airway hyperreactivity (AHR). The authors observed that transfer of maternal IgE is dependent on the neonatal Fc receptor (FcRN), and FcRN-knockout mice were protected from both ragweed-induced AHR and pulmonary eosinophilia. Further supporting a role for FcRN in the transfer of IgE across the maternal-fetal interface, the authors observed that IgE and IgG co-localized in placental endothelial cells of WT mice, while neither were observed on endothelial cells in FcRN-knockout mice. Finally, the authors found that MCs in 14-20-week human fetal skin and lung were histologically mature, expressed FcεR1, and were able to bind IgE. These findings suggest that maternal transfer of IgE can sensitize fetal mast cells for antigen-specific activation responses in the postnatal period.

While these results are fascinating and potentially important, additional studies will be required to determine the degree to which maternal IgE transfer influences the development of allergic disease in human children. It is possible that maternal IgE may contribute to infant sensitization to allergens via the skin, especially since maternal IgE was previously found to correlate with the development of infant eczema (3). This process could also potentially be exacerbated by genetic polymorphisms and epigenetic modifications associated with barrier integrity such as the loss-of-function allele of filaggrin that has previously been linked to both atopic dermatitis and the development of peanut allergy. Maternal IgE transfer could also help to explain why only a subset of patients with filaggrin loss-of-function polymorphisms go on to

develop atopic dermatitis, and why the risk of dermatitis in children of mothers with filaggrin mutations depends partly on the presence of maternal IgE sensitization (7,8).

While the Msallam et al convincingly demonstrates that fetal skin MCs bind maternal IgE in mice, they did not evaluate IgE binding by MCs in mouse mucosal tissues such as the lung, in which MCs exhibited greatly decreased FcεR1 expression, or in intestinal tissue, where fetal MCs undergo far more rapid turnover than in the skin (4). Experimental sensitization in mice results in high levels of specific IgE to a single antigen that may not replicate the function of endogenously generated IgE in humans. While mouse pups under experimental settings are typically weaned by three weeks of age, human development is a much slower process. Studies of MC IgE retention in hypogammaglobulinemia patients have established that IgE on adult skin MCs has a half-life of approximately 16-20 days (5). Thus, by the time a human infant is introduced to solid foods at 4-6 months of age, little maternal-derived IgE is likely to be retained on tissue MCs. Finally, while parental atopy clearly increases the risk of atopic disease development in infants, there is little evidence in the literature to support antigen-specific transmission of risk.

Given that IgE and MCs evolved to serve roles in host defense, it is possible that transfer of maternal IgE to long lived fetal MCs, especially those in the skin, may reflect evolutionary selection at some point in mammalian development (**Fig. 1**). Both MCs and IgE play a protective role in skin defense against parasitic insects such as ticks (9), suggesting that maternal IgE transfer may provide protection against ectoparasites. The same mechanism may confer passive immunity to skin invasive helminths in areas of high endemic infection rates. Additionally, a series of studies by the Galli laboratory have identified a role for MC proteases in degrading xenobiotic reptile and insect venoms(10), and a specific role for IgE was determined for honeybee venom and Russell's viper venom. Thus, maternal transmission of IgE may also

provide a degree of protection to infants against potentially otherwise lethal stings and bites, particularly in populations with high levels of exposure and sensitization.

In conclusion, Msallam et al definitively established that both IgG and IgE are capable of crossing the maternal/fetal interface via FcRN, and that IgE that passes to the fetus in this manner can be bound by MCs in both mouse and human (6). From an evolutionary perspective, maternal transmission of IgE may have evolved to help protect newborn mammals from xenobiotic venoms and ectoparasites. Although this study illustrates the potential for antigen-specific transfer of IgE sensitization, further focused studies will be required to determine whether such transfer contributes to atopic disease susceptibility and development in humans.

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Figure Legend:

Maternal IgE can access the fetal circulation via placental FcRN. The prenatally acquired IgE may be taken up by fetal mast cells (seeded in the tissues by committed progenitors from fetal liver, hematopoietic endothelium, and yolk sac). This mechanism could provide passive neonatal barrier protection against helminths, ticks, or venoms, while also potentially transmitting some risk for antigen-specific hypersensitivity.

