Published in final edited form as:

Clin Exp Allergy. 2012 December ; 42(12): 1656–1659. doi:10.1111/cea.12018.

Neonatal Fc receptor (FcRn) and maternal-to-newborn IgE absorption

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From 1949-1966, a series of experimental studies by Professor F. W. Rogers Brambell (1901-1970; memoirs (1)) revealed the transmission of immunoglobulin from the mother to the fetus and newborn (2-4). In 1966, he published a review article in *The Lancet* describing that the selective transmission of γ -globulin from the mother to the offspring could occur before birth and also after birth and that this process required the Fc portion of the γ -globulin molecule. He speculated that the transmission involved the Fc portion of the γ -globulin molecule interacted with specific receptors on the cell (2). Electron microscopy and biochemical analyses later revealed the presence of a Fc receptor on neonatal rat small intestinal cells that selectively permitted the transport of immunoglobulin of the IgG subclasses across the intestinal epithelium in a pH-dependent manner (5-10). Finally, in 1989, Simister and Mostov affinity purified FcRn from an eleven-day old rat intestine; and identified two proteins with the relative molecular masses of about 14,000 Da and 45,000-53,000 Da which were identified as β 2-microglobulin and neonatal Fc receptor (FcRn), respectively. Molecular analyses revealed the FcRn to have the predictive primary structure similar to that of class I major histocompatibility complex (MHC) antigens as it possessed three extracellular alpha domains, a single transmembrane region and a short cytoplasmic domain (11) which was later confirmed by X-ray crystallographic analyses (12, 13).

Subsequent studies revealed FcRn to be expressed in multiple tissues including gastrointestinal tract, mammary gland, placenta, lung, liver, kidney, vascular endothelium and hematopoietic compartment (11). Notably, the spatial and temporal expression of FcRn varies between species. For example, FcRn is primarily expressed in rodent (rat and mouse) intestine up to day nineteen after birth, which coincides with weaning, and the level of expression declines thereafter from distal to proximal small intestine (14-17). In contrast, FcRn has been detected in both fetal and adult human intestinal tissue (18, 19). Furthermore, FcRn is expressed in mammary gland epithelium of various animal species, whereas expression is restricted to endothelial cells in humans (11, 20). Among the hematopoietic cell lineage, FcRn expression is restricted to myeloid cells, dendritic cells and splenic B cells (11, 14, 21). Expression of FcRn on intestinal epithelial cells and myeloid cells is modulated by cytokines (TNF- α , IL-1 β and IFN- γ), hormones and corticosteroids(22-24).

Although initially described as the primary receptor responsible for IgG transplacental transport, FcRn has also been reported to be involved in IgG catabolism, albumin homeostasis, regulation of central nervous system inflammation, glomerular filtration of IgG and albumin and dendritic cell MHC class II-restricted antigen presentation (11, 14, 25).

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Disclosures: S.P.H. is a consultant for Immune Pharmaceuticals. I would like to thank Drs Kasper Hoebe and Yui-Hsi Wang for critical reading of the manuscript and S. Hottinger for editorial assistance.

Serum IgG levels in naïve FcRn^{-/-} mice are 20-30% of wild type mice, and serum albumin concentration is ~40% of normal steady-state levels (26). FcRn is thought to protect against IgG catabolism by recycling and transcytosis of IgG in the vascular beds of skeletal muscle and skin (14). The function of FcRn on hematopoietic cells, such as myeloid and dendritic cells, is thought to partially involve IgG catabolism and also priming of antigen-specific T-cell responses (14, 21). The demonstration of increased susceptibility to *Citrobacter rodentium* and *Helicobacter heimanni* infection in FcRn^{-/-} mice also suggests a role for FcRn in mucosal anti-bacterial activity which appears to be related to FcRn's role in gastric epithelium IgG luminal transport and neutralization (25, 27).

A study by Paveglio and colleagues described in this issue of *Clinical and Experimental Allergy* (28) demonstrates a previously undescribed role for FcRn in facilitating absorption of maternal antibodies other than IgG. The authors fostered FcRn^{WT}, FcRn^{+/-} and FcRn^{-/-} pups born to naïve mothers with ovalbumin (OVA)-sensitized (allergic) foster mothers. Consistent with the important role for FcRn in fetal/neonatal absorption of maternal IgG, the authors demonstrate that the levels of neonatal absorption of maternal OVA-specific IgG from breast milk was reduced in FcRn^{-/-} pups compared with FcRn^{+/-} and FcRn^{WT} pups. Interestingly, the authors also assessed levels of absorption of maternal OVA-specific IgE in fostered FcRn^{WT}, FcRn^{+/-} and FcRn^{-/-} pups. There is circumstantial evidence for maternal to newborn transfer of IgE (29), however alternative explanations such as maternal blood contamination of cord blood and fetal production of IgE have led to cautious conclusions whether or not this occurs and a lack of delineation of molecular pathways that may regulate this process. IgE has two receptors, the high-affinity IgE receptor (FcεRI) and the low-affinity receptor (FcεRII/CD23) (30, 31). Kaiserlian and colleagues have described the presence of the FcεRII on the surface of intestinal epithelial cells in infants less than 24 months of age (32), which has led to the speculation that intestinal FcεRII may be involved in maternal IgE absorption.

As expected, Paveglio and colleagues observed the presence of OVA-specific IgE in the serum of FcRn^{WT} and FcRn^{+/-} foster pups. However, much to their surprise they observed that allergen-specific IgE levels were absent in the fostered FcRn^{-/-} pups, indicating that the absorption of maternal allergen-specific IgE is also dependent on offspring FcRn expression. The authors did not assess if genetic deletion of FcRn influenced FcεRI or FcεRII/CD23 expression so one cannot rule out the involvement of altered FcεRI or FcεRII/CD23 expression. However if one assumes that FcεRI and FcεRII expression is normal in FcRn^{-/-} mice, the demonstration that IgE alone was not sufficient to enable maternal to newborn absorption of IgE indicates that the FcRn and not FcεRI and FcεRII receptors are involved in maternal transfer of IgE. Furthermore, one can exclude that the lack of OVA-specific IgE in FcRn^{-/-} offspring was likely a result of neonatal malabsorption of maternal IgE rather than defective neonatal OVA sensitization as FcRn^{-/-} mice develop OVA-specific IgE and IgG1 responses comparable to that of FcRn^{WT} mice, (33).

The authors speculated that one possible mechanism by which FcRn could modulate absorption of maternal IgE is via the presence of maternal IgG₁ antibodies directed against IgE. Indeed, they showed the presence of IgG₁ anti-IgE autoantibodies in the serum of OVA-sensitized allergic mothers. Notably, the serum concentration of IgG₁ anti-IgE-IgE immune complexes and OVA-specific IgE in OVA-sensitized foster mothers correlated with levels of IgG₁ anti-IgE-IgE immune complexes and OVA-specific IgE in the serum of FcRn-sufficient breastfed offspring. To determine whether maternal-to-new born intestinal transfer of IgG₁ anti-IgE-IgE immune complexes could explain the altered IgE levels in the FcRn^{-/-} pups, the authors generated an IgG₁ anti-IgE-IgE (TNP) immune complex, fed it to FcRn^{WT}, FcRn^{+/-} and FcRn^{-/-} mice and assessed for serum TNP-specific IgE. The authors showed that FcRn^{WT} and FcRn^{+/-} neonatal mice fed the immune complex, efficiently

absorbed the IgG1 anti-IgE-IgE immune complex, as determined by neonatal serum levels of the complex. In contrast, the IgG1 anti-IgE-IgE immune complex was undetectable in the serum of FcRn^{-/-} mice. These data suggest that FcRn can absorb IgE in the form of an IgG₁ anti-IgE-IgE immune complex and that this pathway may contribute to maternal-to-young transfer of allergen-specific IgE and thus drive allergic disease.

There is clinical evidence supporting the link between allergen sensitization and the development of autoantibodies (34). 32% of non-allergic healthy individuals and 70-95% of allergic asthmatics have been shown to possess detectable levels of IgG anti-IgE (35, 36). The biological function of these anti-IgE autoantibodies is unclear. It is possible these immune complexes could participate in the regulation of IgE production. The anti-IgE autoantibodies have been shown to be directed against the Cε2-Cε3-interdomain region of IgE, which contains part of the FcεRI binding site of IgE and therefore these antibodies can potentially block IgE binding to FcεRI (37). In addition, anti-IgE may stabilize IgE interactions with CD23 on B cells protecting CD23 from proteolytic cleavage and thus reducing soluble CD23 levels which is thought to be important in regulating IgE synthesis (38). Indeed *in vivo* studies indicate that the induction of anti-IgE autoantibodies results in a long term reduction in total and antigen-specific IgE production (39-42).

The concern of these anti-IgE autoantibodies is that they presumably can cross link surface bound IgE on mast cells and basophils and facilitate immune activation and disease. Anti-IgE autoantibodies from allergic asthmatic individuals induced a reverse type hypersensitivity reaction in healthy individuals (35). In addition, chronic idiopathic urticaria is associated with the presence of IgG autoantibodies against IgE and FcεRI (43-47) and these autoantibodies stimulate complement-dependent mast cell activation and disease pathogenesis (34). Furthermore, administration of IgG1 anti-IgE (clone EM95) to mice induces IgE-crosslinking, a mast cell-dependent anaphylactic response (48). Paveglio and colleagues do not describe any pathology from the presence of IgG autoantibodies against IgE in the OVA-sensitized mothers or the fostered pups. However they did demonstrate that the absorbed IgG₁ anti-IgE induced degranulation in a basophilic cell line *in vitro* suggesting activating properties.

There are several possible explanations for the presence of IgG anti-IgE in the absence of IgG-mediated pathology. Firstly, the level of IgG autoantibodies against IgE could be very low and thus insufficient to stimulate mast cell or, alternatively, basophil activation. Consistent with this possibility, the Paveglio and colleagues demonstrated 10⁸ ng/ml OVA-specific IgG₁ in the serum of allergic mothers and ~ 400 ng/ml IgG autoantibodies against IgE, suggesting a ratio of anti-IgE antibodies of approximately 1:2.5×10⁶. Secondly, the affinity of IgG autoantibodies for IgE could be sufficient to permit maternal-to-neonatal absorption of the IgG₁ anti-IgE-IgE immune complex via the FcRn but not sufficient to crosslink IgE on mast cells or promote basophil activation. Thirdly, that the IgG autoantibodies against IgE may bind to the Fc portion of IgE and either block IgE-FcεRI interaction or, although unlikely, possess a higher affinity for IgE and FcεRI and therefore displace IgE from the surface of mast cells and basophils and prevent cellular activation. Consistent with the former possibility, circulating IgG against IgE has been shown to be specific for the Cε2-Cε3 interdomain region of the IgE molecule, the same region that is believed to contain part of the FcεRI-binding site (49). The epitope specificity of IgG anti-IgE used in the passive transfer system was specific for the Cε4 domain of IgE, which is not involved in IgE binding to FcεRI, and thus explains the observed RBL degranulation in the presence of the absorbed IgE.

While this study raises several questions, including the biological function of anti-IgE autoantibodies, specific epitope site of IgG1 anti-IgE and why this IgG anti-IgE-IgE immune

complex does not induce disease pathology, it does place weight to the concept of maternal to newborn transfer of IgE and reveal a new intriguing mechanism by which IgE may be transferred from mother to newborn and permit allergen sensitization.

Acknowledgments

Grant support: This work was supported by NIH R01 AI073553 AND DK090119.

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