

You might owe your mother more than you think

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Main text

Mast cell (MC) activation and the subsequent release of inflammatory mediators has been historically linked to allergic responses¹. In this regard, allergen-specific immunoglobulin E (sIgE) is a potent activator of MCs through FcεRI crosslinking after allergen ligation to the IgE bound to FcεRI on the surface of MCs. This activation pathway of MCs leads to potentially life-threatening reactions such as anaphylaxis.

Nevertheless, MCs also respond to triggers other than sIgE. For example, venoms from different insects can drive MC degranulation in both antibody-dependent and -independent manners², thus providing efficient innate and adaptive protection against toxic compounds. Moreover, healthy subjects can display IgE against toxins from *Staphylococcus aureus* (SA) (SA-sIgE)³. Therefore, MCs may also have a role in the adaptive protection against venoms or toxins.

Following this idea, the so-called *toxin hypothesis*^{4,5}, Starkl *et al.*⁶ investigated the contribution of MCs and sIgE to the host's resistance against SA. Using a mouse model, the authors showed that the epicutaneous inoculation of SA induces an early serum increase of functional SA-sIgG1/sIgE and total IgE. This is followed by an expansion of T follicular helper (Tfh) cells in the inguinal lymph nodes, especially of cell subsets directly involved in high-affinity IgE production such as Tfh13^{7,8}. SA toxins also induced peripheral CD4+ and CD8+ T-cell proliferation and IgE synthesis via monoclonal and polyclonal mechanisms in the absence of live bacteria. Interestingly, a single skin inoculation of SA suffices to mount a systemic immune that yields SA-sIgE. Upon subsequent infections, MCs from different organs release high amounts of bactericidal compounds and chemoattractants through SA-sIgE-mediated mechanisms. Some of these chemotactic factors (such as TNF and CXCL1/2)⁶ are involved in neutrophil recruitment, thus reducing bacterial load and improving SA clearance. Collectively, IgE immunity confers an evolutionary advantage which translates into a higher survival rate and a quicker recovery following severe SA infections, including pneumonia. Curiously, bactericidal compounds are also released when MCs are activated by antigens other than SA toxin, which generally confers potential antibacterial activities to allergic reactions.

In addition to the adulthood, sIgE might also exert protective roles from the embryological development. Msallam *et al.* have recently investigated the interactions between fetal MCs and maternal sIgE to shed light on their relationship in fetal priming of immune and allergic responses in mice and humans⁹. Mouse fetal MCs acquire a semi-mature phenotype according to FcεRI and heparin expression, and increase in number during early development stages, which suggests that they might be functional before birth. Of note, the skin and the airways hosted significant mouse fetal MCs populations. Furthermore, the neonatal Fc receptor (FcRN) can translocate maternal IgE to the fetus, thus allowing the sensitization of mouse fetal MCs. Intriguing, the authors also showed that maternal sIgE can induce degranulation of mouse fetal MCs, but this effect was progressively lost during the 6 weeks following the offspring's birth. Moreover, the authors partially replicated these findings in humans as they identified a subset of human fetal MCs that were phenotypically mature (based on FcεRI and CD63) since the second trimester of pregnancy. Lastly, they showed that human fetal MCs can also be sensitized with IgE *in utero*.

Overall, these data suggest that the offspring of atopic mothers can become passively sensitized *in utero*, thus being able to experience allergic reactions during the perinatal period without previous contact with the allergen. This passive sensitization phenomenon event constitutes a novel and clinically-relevant concept in newborns of allergic mothers. On the other hand, fetal MCs sensitization with maternal IgE might provide

temporary protection from toxins and venoms. This defence may be of paramount importance during the first weeks of life given that the offspring is still developing immunity. Future research should expand these findings and investigate how to apply them for the development of antibacterial and antivenom approaches without the risk of suffering allergic reactions. By and large, these findings contribute to expand the growing list of homeostatic and protective roles of IgE^{4,5,6,10}.

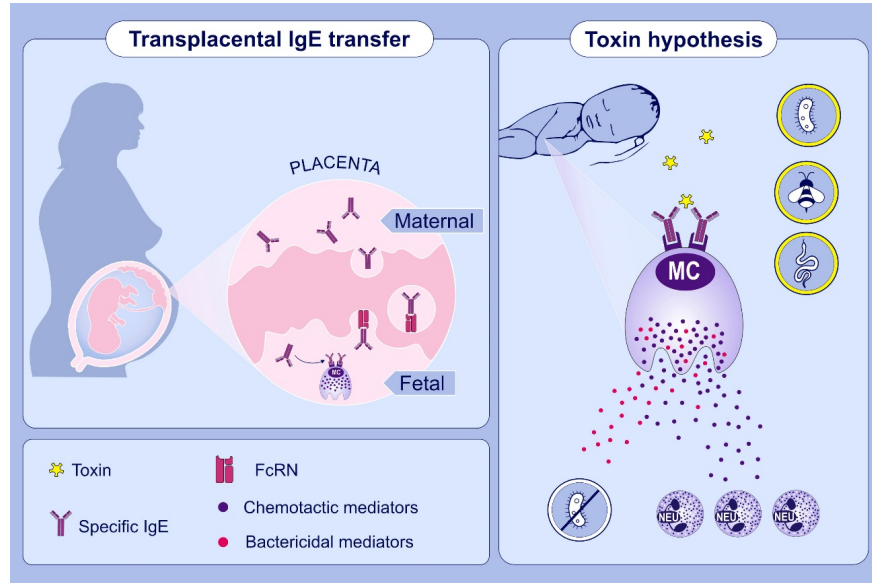


Figure 1 . Scheme of IgE's vertical transmission and the sensitization of fetal MCs for allergen-specific degranulation by IgE of maternal origin through the neonatal Fc receptor (FcRN) (left side). Prenatal sensitization may include protective functions in the offspring described by the "Toxin hypothesis", in which mast cells confer adaptive protection against venoms and bacterial toxins (left side).

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