

DR. LETICIA DE LAS VECILLAS (Orcid ID : 0000-0003-4969-5678)

DR. IBON EGUILUZ-GRACIA (Orcid ID : 0000-0002-3774-931X)

DR. MATTIA GIOVANNINI (Orcid ID : 0000-0001-9568-6882)

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Authors: Leticia de las Vecillas¹, Ibon Eguiluz-Gracia², Mattia Giovannini³

¹Allergy Department, Marqués de Valdecilla University Hospital-Instituto de Investigación Marqués de Valdecilla (IDIVAL), Santander, Spain. leticia.delasveci@gmail.com; ORCID 0000-0003-4969-5678

²Allergy Unit, ARADyAL, IBIMA-Hospital Regional Universitario de Malaga-UMA, Malaga, Spain. iboneguiluz@gmail.com; ORCID 0000-0002-3774-931X

³Allergy Unit, Department of Pediatrics, Meyer Children's University Hospital, Florence, Italy. mattia.giovannini@unifi.it; ORCID 0000-0001-9568-6882

Correspondence to:

Leticia de las Vecillas, Allergy Department, Marqués de Valdecilla University Hospital-Instituto de Investigación Marqués de Valdecilla (IDIVAL), Santander, Spain. Email: leticia.delasveci@gmail.com; ORCID 0000-0003-4969-5678.

Mattia Giovannini, Allergy Unit, Department of Pediatrics, Meyer Children's University Hospital, Florence, Italy. mattia.giovannini@unifi.it; ORCID 0000-0001-9568-6882

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transplacental transfer, toxin hypothesis.

Abbreviations: CXCL1/2, chemokine (C-X-C motif) ligand 1/2; FcεRI, high-affinity receptor for the Fc region of IgE; FcRN, neonatal Fc receptor; MC, mast cell; SA, *Staphylococcus aureus*; sIgE, specific immunoglobulin E; Tfh13, T follicular helper 13; TNF, tumor necrosis factor.

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Main text

Immunoglobulin E (IgE)-mediated activation of mast cells (MC) has been historically linked to allergic reactions [1]. Nevertheless, antibody-dependent MC degranulation can also be triggered by venoms from insects or reptiles. Of note, MC mediators provide efficient protection against the toxic compounds of venoms [2].

Interestingly, antigen-specific (s)IgE-dependent MC activation could occur in newborns who are not able yet to mount functional antibody responses. In a recent article, Msallamet al. investigated the interactions among fetal MC, maternal sIgE and fetal immune responses in mice and humans [3]. Mouse fetal MC acquire a semi-mature phenotype according to their FcεRI and heparin expression levels, and increase in number during early development stages. These observations suggest that they might be functional before birth. Of note, the skin and the airways hosted robust MC populations in mouse fetuses. Furthermore, the neonatal Fc receptor can translocate maternal IgE to the fetus, thus allowing the sensitization of MC. Intriguingly, the authors also showed that maternal sIgE can induce degranulation of fetal MC in mice, but this effect was progressively lost during the 6 weeks following the birth of the offspring. Moreover, the authors partially replicated these findings in humans as they identified a subset of fetal MC that were phenotypically mature (based on FcεRI and CD63 expression level) since the second trimester of pregnancy. Lastly, they showed that human fetal MC can also become passively sensitized with maternal IgE *in utero*.

These findings raise the question of the evolutionary advantage provided by maternal sIgE transfer during the prenatal period. In this regard, bacterial toxins, such as those derived from *Staphylococcus aureus* (SA), are potent triggers of IgE synthesis, and SA-sIgE might confer protection against the deleterious effects of bacterial toxins [4]. Following this idea, the so-called toxin hypothesis [5, 6], Starklet al. [7] investigated the contribution of MC and sIgE to the host's resistance against SA. Using a mouse model of SA infection, the authors showed that the epicutaneous inoculation of SA induces an early increase of functional SA-sIgG1 and -sIgE antibodies in serum. This phenomenon is followed by an expansion of T follicular helper (Tfh) cells in the inguinal lymph nodes, especially of Tfh13 cells [7], a subset directly involved in the production of high-affinity IgE [8, 9]. SA toxins also mediate peripheral CD4⁺ and CD8⁺ T-cell proliferation and IgE synthesis via monoclonal and polyclonal mechanisms. This effect is observed even in the absence of live bacteria. Interestingly, a single skin inoculation of SA

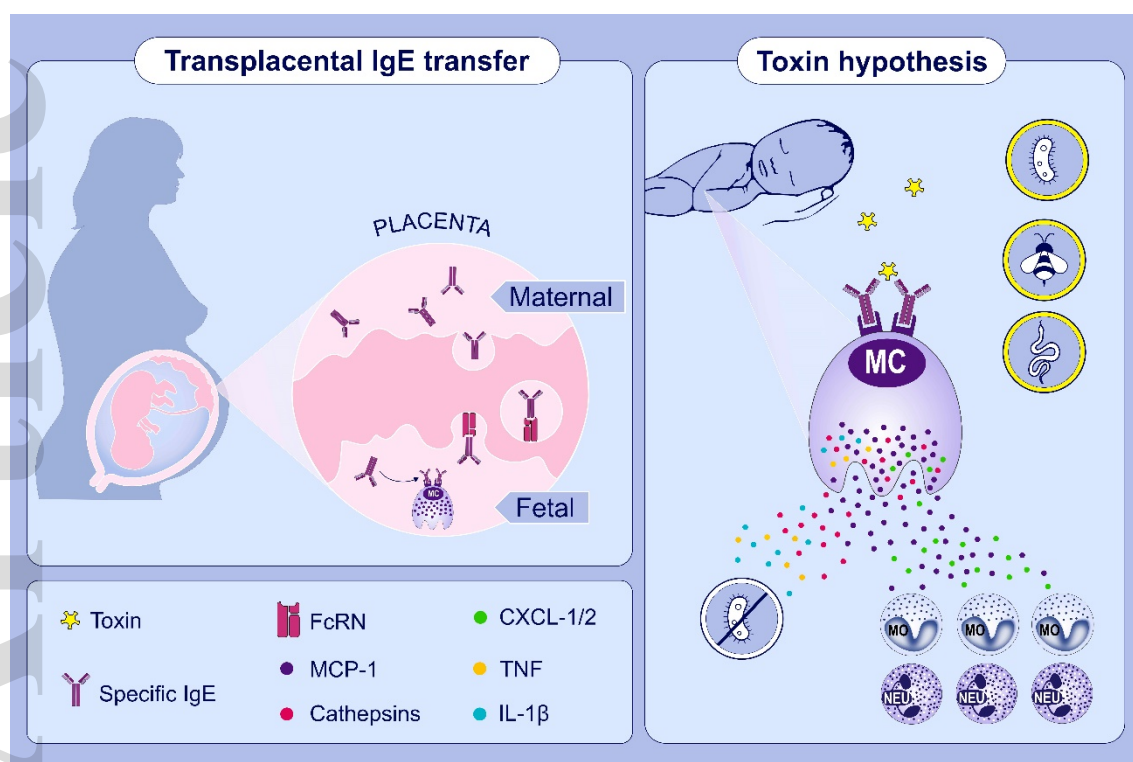
suffices to mount a systemic immune response including the production of SA-sIgE. Upon subsequent infections, MC from different organs release high amounts of bactericidal compounds, cytokines, and chemoattractant factors (e.g. TNF, MCP-1, IL1 β and CXCL1/2) through SA-sIgE-mediated mechanisms. These compounds recruit neutrophils and monocytes (Figure 1), which in turn reduce the load and accelerate the clearance of SA. Interestingly, this observation indicates a bactericidal potential for sIgE-dependent MC activation during allergic reactions. Importantly, these findings suggest that IgE immunity might confer an evolutionary advantage consisting on a higher survival rate and a quicker recovery after severe SA infections, including pneumonia.

In summary, the sensitization of fetal MC might provide temporary protection against bacterial toxins and venoms [2, 10], and this defence mechanism could be paramount during the first weeks of life, when the newborn is not able to produce functional antibodies. On the other hand, the MC of the offspring of atopic mothers might become passively sensitized so the offspring might experience allergic reactions without a previous contact with the culprit allergen. Either way, these findings contribute to expand our understanding on the homeostatic roles of IgE. The development of treatment strategies profiting from the anti-toxin potential of MC while blocking their allergen-triggered activation warrants further investigation.

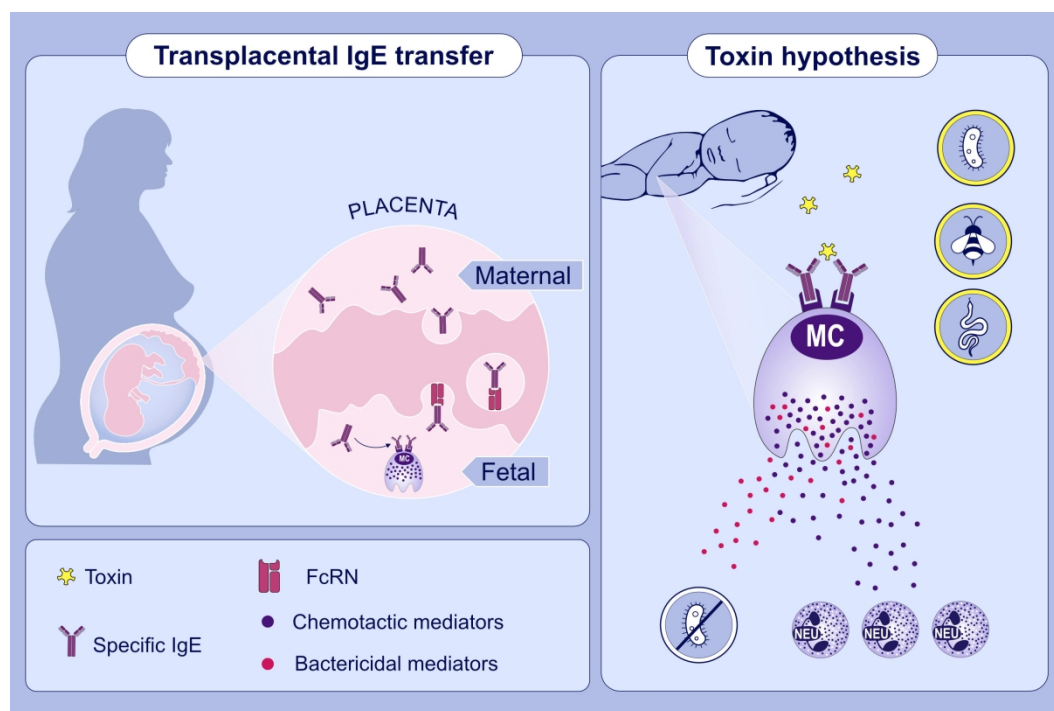
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Legend for figure 1: Scheme of the placental translocation of maternal IgE through the neonatal Fc receptor (FcRN) (right side). Prenatal sensitization of mast cells might confer adaptive protection against venoms and bacterial toxins to the offspring through the IgE-dependent degranulation of mast cells, and the subsequent release of anti-bacterial peptides, cytokines and chemokines. These mediators will ultimately recruit and activate neutrophils and monocytes (left side). CXCL-1: chemokine (C-X-C motif) ligand 1; IL1- β : interleukin 1-beta; MC: mast cells; MCP-1: monocyte chemoattractant protein-1; MO: monocytes; NEU: neutrophils; TNF: tumor necrosis factor.



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