Received: 23 June 2022 | Revised: 4 March 2023 | Accepted: 8 March 2023

DOI: 10.1111/pai.13943

REVIEW ARTICLE

WILEY

# Mast cells—fetal mast cells crosstalk with maternal interfaces during pregnancy: Friend or foe?

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**Editor:** Carmen Riggioni

## Abstract

Mast cells (MC) are hematopoietic immune cells that play a major role during allergic reactions in adults by releasing a myriad of vasoactive and inflammatory mediators. MC seed all vascularized tissues and are most prominent in organs with a barrier function such as skin, lungs, and intestines. These secreted molecules cause mild symptoms such as localized itchiness and sneezing to life-threatening symptoms (i.e., anaphylactic shock). Presently, despite the extensive research on Th2-mediated immune responses in allergic diseases in adults, we are still unable to determine the mechanisms of the role of MC in developing pediatric allergic (PA) disorders. In this review, we will summarize the most recent findings on the origin of MC and discuss the underappreciated contribution of MC in the sensitization phase to maternal antibodies during pregnancy in allergic reactions and other diseases such as infectious diseases. Then, we will lay out potential MC-dependent therapeutic strategies to be considered in future investigations to understand the remaining gaps in MC research for a better quality of life for these young patients.

**KEYWORDS**
allergic diseases, fetal, immunity, mast cells, maternal, MC, vertical transmission

## 1 | INTRODUCTION

Allergic diseases are noncommunicable diseases (NCD), which affect 8%–10% of the global population.[1] Allergic diseases are considered the immunological-caused subcategory of hypersensitivity disorders and include asthma, food allergy, and cutaneous allergies.[2] World Health Organization (WHO) estimated asthma to affect 262 million people in 2019 and caused hundreds of thousands of deaths in the past 30 years[3]; meanwhile, food allergy has been announced as an alerting burden during childhood globally.[4] The accessibility to high-resolution technologies and the clinical analysis of the cohorts of allergic patients worldwide enhanced the updated categorization of allergic diseases in children and adults. Recent clinical research data underline the complexity of the development of allergies suggesting an allergic march to occur, in which patients develop sequences of allergic diseases with increasing health impact from an early age after birth (infantile stage) and developing pediatric allergies (PA).[5–7] For instance, atopic dermatitis shows a high incidence in children under 5 years old, and food allergies are increasingly clinically detected in toddlers and infants.[8–10]

## 2 | THE PHYSIOPATHOLOGY OF ALLERGIC DISEASES

Allergic diseases occur after an exposure of the body to exogenous molecules called allergens, a phase that is called sensitization. Following a second or multiple exposures to the same allergens

(known as elicitation phase), a cascade of adaptive and innate immune reactions leads to the secretion of allergen-specific antibodies (IgE or IgG) by B cells, upregulation of type-2 cytokines such as IL-4, IL-5, IL-9, and IL-13, maturation of dendritic cells (DC) and activation of innate immune cells such as mast cells (MC), respectively.[11–13] The severity of the innate and adaptive immune responses contributes to the acceleration of the timing of disease development[2] and is accompanied by high levels of circulating IgE. The reports show controversy in identifying the environmental, developmental, or genetic factors that might help in the PA triggers; however, these disorders may either persist during life span or may also show resolution with increasing age, for reasons yet to be elucidated.[14,15] Despite the ongoing efforts to develop guidelines, sensitive clinical tests for early detection of PA, and effective immunotherapies for an early intervention,[16–18] some children show a sudden development of PA even for children who manifest negative results to the standard allergen tests. In addition, some clinical reports describe the presence of cases of tolerance to conventional medication used to reduce allergic reactions such as antihistamines.[19–23] Hence, there is an urgent need to identify new targets linked to the physiopathology of PA and to find novel treatments that would minimize the symptoms and enhance the quality of life of these young patients. The desensitization of MC in IgE-dependent allergic diseases is considered one of the promising approaches in allergic disease management[24,25] that could not only reduce the life-threatening reactions but offer a prolonged protection or even a full recovery from the aggravated consequences of MC activation during allergic reactions.

**Key findings box**

- Fetal Mast cells (fMC) are present at the early stage of fetus development and seed fetal tissues such as brain, skin, and lung.
- Neonatal Fc receptors (FcRn) are the transporters of maternal allergen-specific—IgE towards the fetal circulation.
- Continuation of allergic immunotherapy (AIT) in allergic pregnant mothers may minimize the vertical transfer of allergen-specific IgE
- fMC express FcRs such as FcεRI and FcγRs on their surface, which can be upregulated prior to capturing the influx of maternal antibodies transferred by maternal-fetal Interface (MFI). Sensitized fMC may trigger allergic reactions upon re-exposure to the same allergen after birth.
- Sensitization of fMC by antigen-specific Ig's (i.e., IgE or IgGs) is a potential mechanism to explain the role of fMC in modulating the fetal and neonatal immune responses.
- fMC contributes to acquiring protective or pathological fetal/neonatal immune responses against the pathogens infecting mothers during pregnancy.

**Key Message**

The finding that IgE can be transferred from mother to child needs further research to address important outstanding questions. How long would maternal IgE be present in babies and what antigen/allergen specificities can be found? Would maternal IgE-allergen complexes transfer to the fetus? Does vertically transferred IgE contribute to allergic reactions or promote the development of Th2 immune responses in early childhood? In what respect could transfer contribute to protection against bacterial and viral infections? The answers to these questions will determine whether interfering in IgE transfer or targeting fetal MC may be of clinical interest to reduce/prevent the development of pediatric allergies.

## 3 | MAST CELLS IN ALLERGIC DISEASES

MC are granulated innate immune cells and play a crucial role in allergic reactions. MC express a wide array of receptors including but not limited to high-affinity receptors to immunoglobulin E (IgE) known as (FcεRI) and high and low-affinity receptors to different subclasses of Immunoglobulin G (IgGs) known as FcγRs.[26–30] These receptors are involved in hypersensitivity type I, and Type II reactions triggering MC activation leading to degranulation and the release of a myriad of preformed mediators stocked in their cytoplasmic granules such as heparin, histamine, tryptases, and chymases, and cytokines. MC activation also leads to the rapid synthesis of prostaglandins and leukotrienes, followed by gene transcription and synthesis of a great diversity of cytokines and chemokines.

## 4 | MC HETEROGENEITY AND ORIGIN

MC shows heterogeneity across tissues due to their granule contents, in addition to its tissue residency, and origin.[31] The characterization, depending on the contents of their granules, could differentiate between connective tissues MC where granules have chymase and tryptase (CTMC), and are residents of connective tissues such as the skin, tongue, peritoneal cavity, and heart, and known to be radioresistant, or mucosal mast cells (MMC) found in mucosal tissues such as the lung and know to be radiosenstive.[31] In some tissues like gastrointestinal (GI) tract, resident intestinal MC (iMC) subsets are a mix of both subsets CTMC and MMC.[20,32] Interestingly, recent RNA sequencing data has shown subsets of MCs based on their gene signature[33] and (IMMGEN: https://www.immgen.org/Databrowser19/DatabrowserPage.html). MC are also found in the central nervous system (CNS) described as neural MC (NMC), but we are still missing in-depth knowledge about the physiological and/or pathological role of NMC.[34]

Originally, bone marrow was considered the main source of all MC precursors (preMC) in adulthood. However, the use of

single-cell RNA sequencing (scRNA) in murine and human MC and using fate-mapping mouse models revealed that the origin of MC is more complex and may start from the fetal stage with fetal MC (fMC) present in the different organs such as brain, skin, and lung. For instance, CTMC subsets consist of different waves of precursors (preMC). A first wave can be detected in fetal skin and lung as early as day 12.5 of pregnancy in mice and seeding skin, peritoneal cavity, and lung, arising from yolk sac or so-called primary fMC and the second wave of precursors emerges from the fetal liver and seeds the tissues around day 10.5 of pregnancy in mice. These are the so-called definitive MC.[20,35,36] In humans, reports showed a similarity of distinct origins of fMC and hematopoiesis of MC from yolk sac and then fetal liver during the fetal development.[37,38] After birth, by using fate-mapping mice models,[35] it was shown that fMC from the two waves co-exists in the tissues, Later, primary fMC subsets disappear and the definitive MC lineage becomes the dominant subset in the tissues.[35] Another study showed that, in case of localized allergic reactions in the organs, a third wave of pMC appears coming from bone marrow might seed the tissues due to the inflammation leading to leukocyte leakage from blood vessels including circulating preMC expressing a higher level of inflammatory genetic signatures.[39,40]

## 5 | ROLE OF FMC IN THE FETAL-MATERNAL IMMUNE RESPONSES DURING INFECTION IN PREGNANT WOMEN

The placenta forms what is called the maternal-fetal interface (MFI) and is the window for maternal-fetal immunity crosstalk. The anatomy of human placenta is known as hemochorial placenta, in which the contact of the maternal blood with the fetal chorion facilitates the continuous exchange by crossing the placenta via this MFI, known as vertical transmission (VT). These factors vary from vital factors such as nutrients, immunoglobulins, oxygen, and hormones to even harmful pathogens such as viruses and parasites capable of crossing the MFI and which may cause developmental and pregnancy complications with life-threatening consequences.[41,42] There is a gap in our understanding of the humoral and cellular crosstalk among the components of the MFI including fMC in allergic mothers or in pre-existing infection diseases such as worm or other kind of parasites. For instance, it was reported that Covid19-positive pregnant women show the presence of viral particles in cord blood but not in the fetuses. Therefore, it is important to deepen our focus to understand the complexity and the dynamics of the immunity of MFI.[43–45] Antibodies such as (IgG) are known to cross the placenta and have a role in providing humoral immunity in fetuses against some infectious diseases.[46] New studies also report the capacity of maternal IgE to cross the placenta, unraveling a new axis of maternal immunity to prime the fetal immune system and develop allergic diseases in the newborn. This suggests a potential relationship between the status of circulating allergen-specific antibodies including IgE in pregnant mothers and the activation of fetal immune cells such as fMC. The expression of receptors with variable affinity to the maternal antibodies could be a potential explanatory mechanism of developing PA in infants from early life after birth.[6,47–50]

Most studies about MC function are focused on the adulthood stage. This comes from the idea that the function of MC is bound to the expression of high-affinity IgE receptor, FcεRI, which is considered until recently the sole marker of mature mast cells (i.e., effector MC ready to degranulate as an immune response upon exposure to allergens).[51] Recently, different studies shed light on the possible involvement of fetal immune cells in priming or regulating the immune response during pregnancy and after birth. For instance, it was shown that fetal regulatory T cells can maintain suppressed fetal immune systems via arginase-2 among other mechanisms.[52-54] Clinically, the Basophil Activation Test (BAT) is considered a gold standard test to identify allergic diseases[16,55] Nevertheless, this test focuses on one subset of innate immune cells (i.e., basophils) and it does not take into investigate MC reactivity to the tested allergens.[56] Furthermore, some clinical cases of the food allergy were reported as IgE-mediated anaphylactic with negative basophil activation signs, suggesting other cells playing a role, such as mast cells.[57] Herein, identification of the factors leading to a potential sensitization of fMC during pregnancy by allergen-specific antibodies, coming from the maternal blood, could explain the high incidence of the PA with high relevance to maternal immunoglobulins (Igs) and especially IgE despite the negative results of BAT. In mouse and human studies, it was shown that maternal IgE can cross the placenta via neonatal Fc Receptors (FcRn).[58-62] Studies suggest that IgE could be transferred as a monomer in mouse models[50] or as an IgG-IgE complex in humans,[63] facilitating vertical transmission across the placenta. The presence of IgE in the fetal environment will lead to an upregulation of the expression of fetal FcεRI on the surface of fMC and could activate fMC.[58,59] In case of exposure to the same allergen after birth, the challenge phase will be launched by crosslinking specific IgE on the surface of the presensitized MC leading to the degranulation and the allergic reactions in newborns.[50] Interestingly, mast cells can interact with T cells[25] such as regulatory T cells (Tregs) via multiple immunological synapses such as OX40-OX40L and TCR/MHCII.[64-66] Thus, it could be interesting to investigate the potential crosstalk between fetal T cells and fMC, which could explain a transient inhibition of fMC degranulation during pregnancy despite acquiring a maturation profile (increasing CD63 (Lamp3), FcγRs, and FcεRI),[50] following an accumulated exposure to maternal IgG and IgE. As it is previously reported that the fetal immune system diverges into adult trajectory by replacing some fetal immune subsets with thymic or bone marrow-derived immune cells as in Treg and myeloid cells, respectively. This could explain why MCs regain their capacity to degranulate ex vivo or after birth in vivo due to a reduction in fetal Treg, leading to allergic reactions. Hence, it will be important to conduct future studies start focusing on the crosstalk between MC and other immune subsets during the fetal stage and after birth.[19,67-69]

Recently, it was reported that Omalizumab can transfer allergen to the fetus via a complex with IgE/allergen and transport via the

FcRn,[62,70] opening the door to evaluate the possible transmission of other promising AIT[16] through MFI and the impact the AIT transmission on the modulation and the sensitivity of the fetal and neonatal immune subsets including fMC.

## 6 | RESEARCH LIMITATIONS

The preclinical studies have limitations in translating the findings into clinical settings due to the difference in the anatomy of the placenta in mice compared with humans. Furthermore, there is a difference in cells expressing FcεRI. In murine immune system, only basophils and mast cells express this receptor, while in human, various immune cells, e.g., mast cells, basophils, neutrophils, eosinophils, dendritic cells, and some subsets of macrophages and monocytes, express FcεRI. Furthermore, some reports showed that human samples such as cord blood are dispensable and cannot be used as a predictive sample for prenatal immunity or to correlate the immune phenotype of the newborn with the parents.[19]

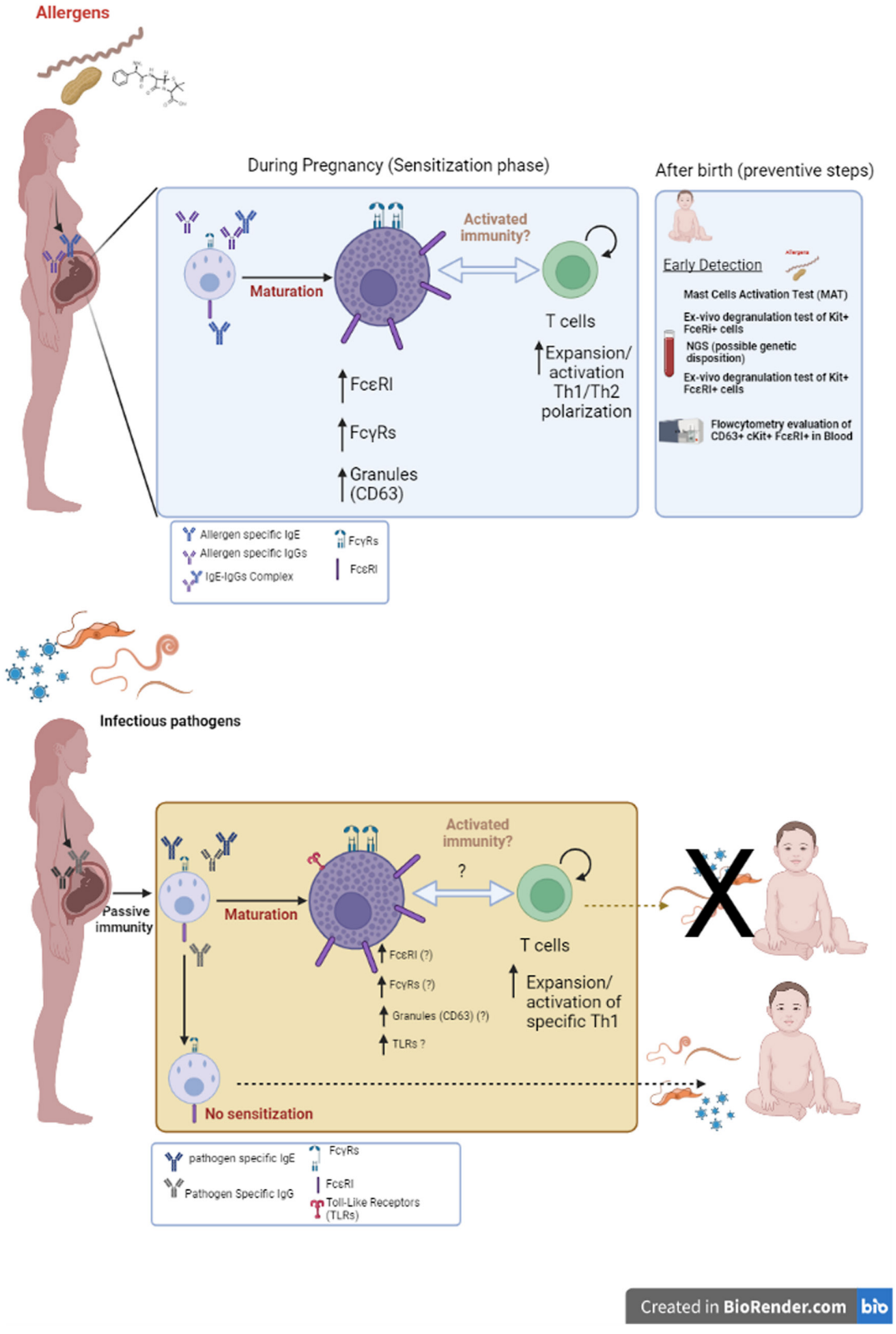
## 7 | ROLE OF FMC DURING PREGNANCY: FUTURE PERSPECTIVES

Importantly, the role of MC can be extended beyond allergic reactions. MC contribute to orchestrating an immune response against external insults such as parasites and viral infections.[71] Since fMC exhibit a similar phenotype of expressed receptors during pregnancy compared with adult MC (Table 1), then it is important to include fMC subsets in the research investigating the impact of the exposure of pregnant mothers to infections on the immunity of the offspring,

**TABLE 1** Surface markers to identify mast cells in fetal and adult MC in mouse and human by multicolor flow cytometry. *Heterogenous expression identifies the activation status or maturation of MC subsets in adults. The signs represent the level of expression of the marker as: + for positive expression; − for negative expression, and −/+ negative in precursors and positive in mature and/or activated MC; ? for unavailable data.

| | Mouse | | Human | | |
|---|---|---|---|---|---|
| Marker | Fetus | Adult | Fetus | Adult | References |
| CD117 (cKit) | + | + | + | + | 35,50,72,73 |
| CD200R | + | + | −/+ | + | |
| CD16/32 | + | + | ? | ? | |
| CD45 | + | Intermediate | Intermediate | Intermediate | |
| CD11b | − | − | − | − | |
| CD45RA | ? | ? | −/+ | + | |
| CD33 | ? | ? | −/+ | + | |
| FcεRI | Low* | + | Low*/+ | Low*/+ | |
| CD63 | Intermediate/+ | +* | −/+ | +/++ | |
| CD107 | −/+ | −/+ | ? | ? | |
| Integrinβ7 | + | + | ? | ? | |
| T1/ST2 | + | + | ? | + | |
| CD11b | − | − | − | − | |
| CD11c | − | − | − | − | |
| Celc10A | + (Peritoneal MC) | + (Peritoneal MC) | ? | ? | |
| CD90 | − | − | − | − | |

**FIGURE 1** Scheme of the crosstalk between immunoglobulin (IgG, IgE, and IgG-IgE complex) and fetal mast cells. In allergic diseases, there will be an increase in allergen-specific IgE and IgG in mother's blood; some of these antibodies can cross the placenta and leads to maturation (increase the expression of FcεR and FcγRs) on the surface of fetal mast cells, which leads to the secretion of an array of cytokines affecting adaptive immune system during pregnancy or after birth and leading to the priming of T cells. Then, the evaluation of MC activation status in the newborn can be evaluated by minimal invasive methods such as MAT, which is similar to BAT; however, it uses patients' plasma to sensitize LAD2 mast cells (a human mast cell line named after the NIH Laboratory of Allergic Diseases) before stimulation with allergen or controls and followed by flow cytometry.[55] Knowing the potential activation in pregnant mothers who have pre-existing exposure to pathogens such as parasites, the mothers will have pathogen-specific IgE and IgG. When some of these antibodies will cross the placenta as a passive immunity for the fetus. This would either does not have an impact on the activation of mast cells, or the activation could happen via FcεR and FcγRs or even TLRs in case the pathogen itself could cross the placenta, leading to the secretion of different cytokines that will prime Th1 responses, with potential prolonged protection from the pathogen after birth.




and its involvement in acquiring specific antibodies against these pathogens in the fetal environment hence reshaping the neonatal immunity after birth.[43,46,72-76]

Vertical transfer of immunoglobulins and allergens from mother to fetus adds another dimension to the development of pediatric allergies. Adding fMC as a target in controlling pediatric allergies, could implicate novel targets specific to mast cells to be tackled to diminish the risk of neonatal allergic reactions, and may give the possibility to reduce MC activation after birth (Figure 1). Future research is needed to answer the question whether the possible transfer of maternal IgE and allergens to fetus in humans is important in developing pediatric allergies. Interestingly, recent studies indicated

that IgG anti-IgE-IgE-allergen complexes can be transported via the FcRn receptor-mediated transport. The safety of continuing allergic immunotherapy (AIT) during pregnancy suggests the potential of using AIT to minimize the possibility of vertically transferred allergen-specific IgE to the fetus during pregnancy.[77]

## CONFLICT OF INTEREST STATEMENT

RM is the chief executive officer (CEO) and founder of NGIg. FAR has no conflict of interest to declare.

## PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.13943.

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**How to cite this article:** Msallam R, Redegeld FA. Mast cells—fetal mast cells crosstalk with maternal interfaces during pregnancy: Friend or foe? *Pediatr Allergy Immunol*. 2023;34:e013943. doi:10.1111/pai.13943