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Maternal IgE Influence on Fetal and Infant Health

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ABSTRACT

Immunoglobulin E (IgE) is the most recently discovered and evolved mammalian antibody type, best known for interacting with mast cells (MCs) as immune effectors. IgE-mediated antigen sensing by MC provides protection from parasites, venomous animals, bacteria, and other insults to barrier tissues exposed to the environment. IgE and MCs act as inflammation amplifiers and immune response adjuvants. Thus, IgE production and memory formation are greatly constrained and require specific licensing. Failure of regulation gives rise to allergic disease, one of the top causes of chronic illness. Increasing evidence suggests allergy development often starts early in life, including prenatally, with maternal influence being central in shaping the offspring's immune system. Although IgE often exists before birth, an endogenous source of IgE-producing B cells has not been identified. This review discusses the mechanisms of maternal IgE transfer into the offspring, its interactions with offspring MCs and antigen-presenting cells, and the consequences for allergic inflammation and allergen sensitization development. We discuss the multifaceted effects of pre-existing IgG, IgE, and their glycosylation on maternal IgE transfer and functionality in the progeny. Understanding the IgE-mediated mechanisms predisposing for early life allergy development may allow their targeting with existing therapeutics and guide the development of new ones.

1 | Introduction

IgE is an antibody isotype most well-known for its role as a central component of allergic disease pathophysiology, together with mast cells (MC) as its primary leukocyte partner. Individuals with allergy produce IgE specific for antigens derived from harmless environmental substances [1], such as pollen, house dust mites (HDM), animal dander, or food, due to a breakdown of immunological tolerance. The outcome is a MC-initiated inflammation at the site of allergen exposure, manifesting as dermatitis, rhinitis, asthma, or food allergy, which can result in chronic tissue changes or be acutely fatal (e.g., asthma attack, and anaphylaxis) [2]. In contrast, the beneficial roles of IgE are less well studied, apart from its role in protection from macroparasites [3].

It has long been observed that Th2-associated [4] allergic diseases start in early childhood [5]. Apart from heritable risk factors and postnatal allergen exposure, an increasing number of epidemiological studies support the role of maternal organism in pediatric allergy risk. Maternal influence is important in early life, between conception to about the age of 2 years. During this time, inherited genetic [6, 7] and epigenetic [8] variants interact with signals derived from the maternal internal environment and maternal exposome and exert programming influence [9]. The offspring immune system is a major target of such influence, with the maternal immune system often being the source [10]. Maladaptive programming may result in the subsequent development of chronic disease, the consequences of which can persist into adulthood [11]. Specifically, maternal atopy or allergy promotes the risk up to

fivefold over that of paternal allergy across different population cohorts [12–17].

One of the best described vertical transfer mechanisms of immune components is that of maternal antibodies [18]. These are required to protect the offspring from infections [18], due to adaptive immune system immaturity for a few months after birth [19]. This is thought to be reserved to IgG before birth [18] and joined by secretory IgA in milk after birth [20]. Interestingly, allergen-specific IgE is often detectable in human neonatal cord blood at birth. This may be surprising, as specific class-switched immunoglobulins usually require prior antigen exposure to induce. Thus, its source, whether fetal or maternal derived, has been controversial [21, 22]. Furthermore, some infants can also exhibit allergen reactivity upon the first exposure [23, 24], suggesting that this early IgE could result in effective sensitization or potentially help promote its development. Apart from its potential transfer to the offspring, IgE can contribute to ongoing inflammation in women during pregnancy. The severity of maternal allergic disease during pregnancy can be predictive of offspring allergy development [25]. Conversely, maternal disease control with drugs was found to be protective [25, 26]. Maternal Th2 cytokine environment [27] and shifts in the Th1/Th2 cytokine ratios [28] during gestation have been linked to offspring allergy risk. Thus, IgE effects on the offspring may also be indirect.

The understanding of the maternal-offspring IgE axis biology is important. Globally, between 5%–30% of populations have an allergic disease [29]. Furthermore, the rates of IgE sensitization to one or more allergens are even higher, between 10% and 60% [30–32]. Whether maternal IgE transfers to the offspring or promotes allergic disease risk indirectly may be consequential for many people, as the prevalence of allergic disease has rapidly increased in the last six decades [29, 33]. Pediatric allergy results in a reduced quality of life during childhood [34, 35] and significant healthcare economic burden [36, 37]. Currently, no allergy therapy is truly curative [2], although IgE-targeting biologics benefit some patients [1]. Therefore, understanding the mechanisms of IgE involvement is key for enabling novel therapeutic development and potentially prevention.

In this review, we will provide an overview of the current knowledge related to IgE during pregnancy and the early life period. We focus on the origin of fetal IgE and the potential mechanisms of its transfer from the mother to the fetus in utero and neonate *post-partum*. We also discuss the effects of IgE transfer on the offspring immune system, with a particular focus on mast cells and allergic disease. Additionally, therapies that inhibit IgE may ablate its beneficial effects. Therefore, we will also discuss the current knowledge on the physiological roles of IgE.

2 | IgE Antibodies and Their Receptors

IgE is the most recently evolved immunoglobulin class unique to mammals [38]. It has many distinctive structural features compared with the better understood IgG antibodies (Figure 1A,B). In part owing to its decoration at the surface of mast cells in the steady state, it provides rapid inflammatory reactivity localized to body surfaces in contact with the external environment. However, the speed and potency of immune activation by IgE require it to be under very tight control physiologically. This is achieved through strictly controlling its production and serum concentration in ways different from other isotypes, resulting in IgE usually being the least abundant immunoglobulin type in the blood (up to 10^5 times less vs. IgG) [42].

The initiation of IgE production is intimately linked to the Th2 immune response, which requires specific types of inciting immune stimulation and is controlled by specific cytokine requirements [43]. This process usually starts when an external allergen or parasite pathogen-derived antigen contacts or intrudes across an epithelial or mucosal barrier surface. Th2 inducers tend to cause epithelial perturbation or damage [44], often due to having an intrinsic adjuvant capacity, such as protease [45] or phospholipase [46] enzymatic activity, membrane pore-forming capacity [47], or carrying TLR ligands (e.g., bacterial LPS in house dust mite products) [48]. The distressed epithelial cells or activated specialized mucosal sensory cells (e.g., tuft or club cells) release TSLP, IL-33, or IL-25 alarmin signals, and potentially damage-associated signals (e.g., Il-1β and ATP) [43]. Activation of local TRPV1+ sensory nerve fibers releases neuropeptides, such as substance P (SP) [49] and neuromedin U (NMU) [50], providing further amplification [51]. Together, the activating signals and antigen presence trigger ILC2s and MCs, which release Th2-promoting cytokines (IL-5, IL-9, and IL-13) [43]. Additionally, this stimulates tissue-specific dendritic cell (DC) subsets associated with Th2 response induction. Numerous studies in animal models deficient in DC-specific transcription factors identified the IRF4+ KLF4+ type 2 classical dendritic cells (cDC2s) to be required for Th2 response initiation in the skin, lungs, and intestine of mice exposed to allergens (e.g., HDM and ovalbumin) or infected with helminth parasites (e.g., Schistosoma and *N. brasiliensis*) [52–55]. cDC2 migration to the local draining lymph node where they present antigens via MHCII to naïve T lymphocytes, which differentiate into GATA3+ CD4+ pro-Th2 effector and BCL6+ Th2 T follicular helper (Tfh2) [52]. The Tfh2 cells use IL-4 and IL-13 cytokines, together with CD40 co-stimulation, to activate STAT6 in B cells driving their IgE class switch recombination (CSR) [56, 57]. IL-4 presence is thought to be obligatory for the IgE CSR [57, 58] and IL-13 to produce very high-affinity IgE [59].

There are several unique features of IgE+ B cell regulation that inherently limit their persistence and IgE production rate. Although IgM+ B cells can undergo class-switch recombination to IgE directly [60], this results in very low-affinity antibody being made. Production of high-affinity IgE capable of inducing anaphylactogenic responses proceeds primarily via IgG1-switched intermediate B cells that have already undergone affinity maturation, as IgG1-deficient mice exhibit profound lack of IgE affinity maturation [61, 62]. The subsequent IgE switch is probably controlled by specialized IL-4 and IL-13-expressing Tfh cell subsets [59, 63]. High-affinity IgE can rarely also be produced via IgM-switched cells [64], but the relevance of this has not been tested in Th2 allergic disease models. Already switched IgE+ B cells are thought to not undergo maturation in the germinal centers, which they rapidly exit and either differentiate into temporary plasma cells or undergo apoptosis [65–67]. Additional control of IgE levels results from negative feedback

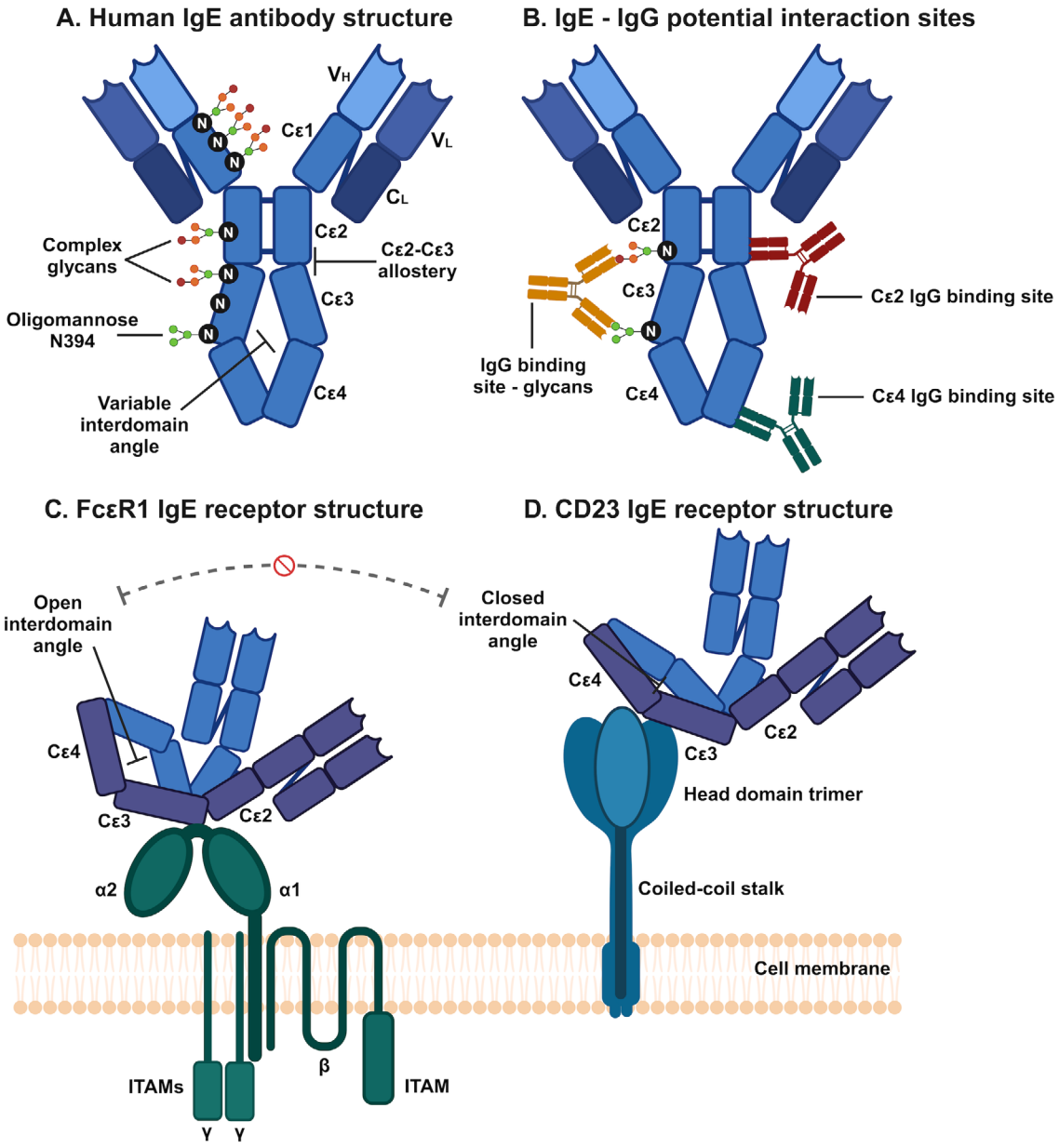

FIGURE 1 | IgE antibody structure and binding to its receptors. (A) Schematic representation of the IgE structure consisting of two light and five heavy chain domains. IgE is a very flexible protein. Cε2-Cε3 allosteric interaction introduces IgE constant region bending and Cε3 domain disordered structure promotes a variably open Cε3-Cε4 angle. Human IgE Fc has seven glycosylation sites, the N394 mannose residues are required for FcεR1 bunding and activation, the rest are occupied by complex variable glycans. (B) Representation of different anti-IgE IgG binding sites. Cε2 and Cε4 binding sites have been identified in human samples [39], and probably block or allow FcεR1 binding, respectively. Certain IgE glycans are required for IgG anti-IgE binding in animal studies [40, 41]. (C) The high-affinity receptor FcεR1 is an αβγγ hetero-tetramer, with IgE binding to the α1 and α2 domains close to the Cε3-Cε2 boundary. Binding promotes open Cε3-Cε4 inter-domain angle. (D) The low-affinity receptor CD23 is a homo-trimer. IgE binds to the head domains close to the Cε3-Cε4 linker region, leading to closing of the Cε3-Cε4 angle. Thus, CD23 and FcεR1 modulate IgE structure in a reciprocally exclusionary manner.

regulation of IgE+ plasma cells by their BCRs, as antigen detection promotes their death via caspase-3-driven apoptosis, at a rate proportional to the engagement affinity and duration [68]. However, a sub-population of IgE+ plasma cells may be shielded from such encounters, as they have been identified residing in the bone marrow [69, 70]. It is currently unclear how common they are across allergic conditions, and the extent of their contribution to overall IgE levels has not been systematically investigated.

IgE memory is also unique, as circulating IgE+ B cells are extremely rare and currently not thought to be the primary source of IgE memory [71]. Recent human studies have highlighted a specific IgG1+/IgG4+ B cell subset, poised to undergo rapid IgE switch upon antigen and Tfh2 IL-4 re-exposure, as the likely primary memory carriers [72–74]. An additional source of complexity is the potential discrepancy, wherein the systemic IgE levels may be low but locally elevated in mucosal tissues exposed to Th2 antigens. There is evidence of certain

B cells undergoing local CSR to IgE in human tissues, which has been previously described in nasal [75–77] and bronchial [78] mucosa or the gastrointestinal lamina propria [79, 80] of allergic patients.

In terms of relevance during pregnancy, these IgE regulatory features may impact maternal IgE levels under specific conditions. One question may be related to the tissue-localized CSR: whether it could take place in the placenta to potentially promote IgE secretion into the fetus. Some Th2 response-inducing conditions, for example, helminth infection, are known to affect the placenta. One example is the deposition of Schistosoma parasite eggs that are Th2-immunogenic and can deposit in the tissue and result in an increased IgE/IgG newborn blood ratio [81, 82]. Although abundant cells with detectable maternal IgE have been observed in the placenta, these were identified as myeloid-lineage Hofbauer cells [83], and other research indicates it is not produced locally [84]. However, this was found by analyzing healthy tissues without infection in non-endemic locations. Another question relates to the interaction between allergen immunotherapy (AIT) in women and the timing of pregnancy. AIT antigen exposure might drive a reduction of IgE-secreting cells by apoptosis, while at the same time promote the IgG+ memory cells to undergo CSR into IgE. Indeed, human studies of birch [72] or ragweed pollen [85] AIT have shown an initial increase in allergen-specific IgE followed by a reduction only after several months. Thus, it may not be advisable to initiate AIT too close to the start or during pregnancy if the aim is to attenuate maternal IgE levels during fetal development. These studies inform our understanding that IgE responses during pregnancy may be unique compared to nonpregnant adults, while highlighting gaps in our knowledge about its production during pregnancy and the influence of immunotherapies on IgE production specifically or the allergic state more broadly in pregnant women.

Further control of IgE levels and localization is enabled by its distinctive structure (Figure 1A) [86]. During mammalian evolution, IgE has retained five heavy chain segments (Cε1-4 constant heavy domains, V variable domain) while IgG lost its CH2 domain [38]. This makes IgE longer and more flexible, enabling its Cε3-Cε4 domain region to adopt highly variable open or closed conformations (up to 25° interdomain angle variation) [86, 87]. This is aided by the inherently less ordered state of the Cε3 domain when unbound [88, 89]. Additionally, there is also allosteric communication between Cε2 and Cε3 domains, resulting in an acutely bent heavy chain conformation [90]. All these features have major consequences for IgE binding to receptors and drugs.

The first principal IgE receptor is the FcεR1, a αβγ2 chain hetero-tetramer belonging to the same structural family as other typical FcγR antibody receptors (Figure 1C) [91]. The β and γ chains contain the immuno-tyrosine activation motif (ITAM) that mediates intracellular signaling [91]. The α chain provides the extracellular hydrophobic IgE binding site, which primarily interacts with both IgE Cε3 domains. The IgE-FcεR1 complex is stabilized by the Cε3 domain adopting a more ordered conformation upon binding [92], and allosterically by the more distant non-binding Cε2 domain bending to contact Cε3 [93]. IgE binds FcεR1 at 1:1 stoichiometry with uniquely high affinity ($K_d \approx 10^{10}\,M^{-1}$) compared to IgG-FcγR interactions ($K_d \approx 10^{6-8}\,M^{-1}$) [86]. The extremely slow dissociation results in very low free IgE, with a circulatory half-life of only 2–3 days (vs. ≈3 weeks of IgG), owing at least partially to its rapid binding to cells rather than its degradation [94, 95]. In contrast, the half-life of cell-bound IgE in tissues is 1–3 months [94, 95]. FcεR1 is primarily expressed on immune (MCs, basophils, DCs, macrophages, monocytes) cells but also certain non-immune cell types [96].

The best evidence of non-immune FcεR1 expression comes from respiratory tissue research. Mouse vagal TRPV1+ nociceptive sensory fibers that innervate the lungs express FcεR1 receptors [97]. Its expression is strongly enhanced by allergen sensitization [97], probably due to the stabilizing effects of IgE binding. HDM-induced airway inflammation was significantly attenuated in animals with TRPV1+ fiber-specific FcεR1 ablation [97], potentially due to the loss of Th2-promoting neuropeptides these fibers are known to release after activation [98]. Bronchial respiratory epithelial cells have been shown to express FcεR1 in biopsy samples of type 2-high asthmatics [99, 100], and also following HDM allergy induction in mice [100]. FcεR1 cross-linking evoked eicosanoid release from the isolated epithelial cells [99], and may be able to downregulate tight junction protein expression in HDM-allergic mice [100], potentially promoting increased epithelial permeability.

Among hematopoietic-lineage cells, the most prominent effect of FcεR1 cross-linking with a multivalent antigen is MC and basophil activation and inflammatory mediator release (Figures 2A and 6A). In the developmental context, FcεR1 expression on MCs may increase with their maturation from precursors and reflect their competency for inflammatory responses (Figure 2C) [104, 110]. FcεR1 was expressed on fetal cutaneous and lung MCs and was capable of IgE binding before birth [104]. Its appearance across other fetal tissues over time remains to be characterized in detail.

The second major IgE receptor is CD23, which, unlike other immunoglobulin receptors, is structurally a transmembrane C-type lectin homo-trimer (Figure 1D) [86]. The CD23 head domain contains a binding site for IgE Cε3 [86]. However, this is located at the opposite end from the site engaged by FcεR1 [111]. Although they bind non-overlapping sites, CD23 and FcεR1 binding to IgE is mutually exclusive. FcεR1 hstabilizes a very open IgE Cε3-Cε4 conformation (Figure 1C), while CD23 promotes a more closed interdomain angle (Figure 1D), resulting in mutual allosteric exclusion [111]. CD23 binding is of lower affinity ($K_d \approx 10^{6}\,M^{-1}$) although it may be boosted by increased avidity ($K_d \approx 10^{8}\,M^{-1}$), as one IgE can be bound by 2 independent CD23 trimers [112]. Although CD23 is a lectin, glycosylation does not seem to play a role in IgE binding [113]. A further difference between CD23 and FcεR1 is that they have higher affinity for an antigen-IgE immune complex or free IgE, respectively [114], helping attenuate unwanted FcεR1 activation. CD23 is expressed on both immune (B cells, DCs, macrophages) and non-immune cells (certain epithelial cells). IgE or IgE-antigen complex binding to B cell CD23 inhibits further IgE production in a negative feedback manner (Figure 3A) [118]. If IgE levels are low, bare CD23 is vulnerable to cleavage by an A Disintegrin And Metalloproteinase (ADAM) family metalloproteinase, resulting in a soluble form (sCD23) that retains

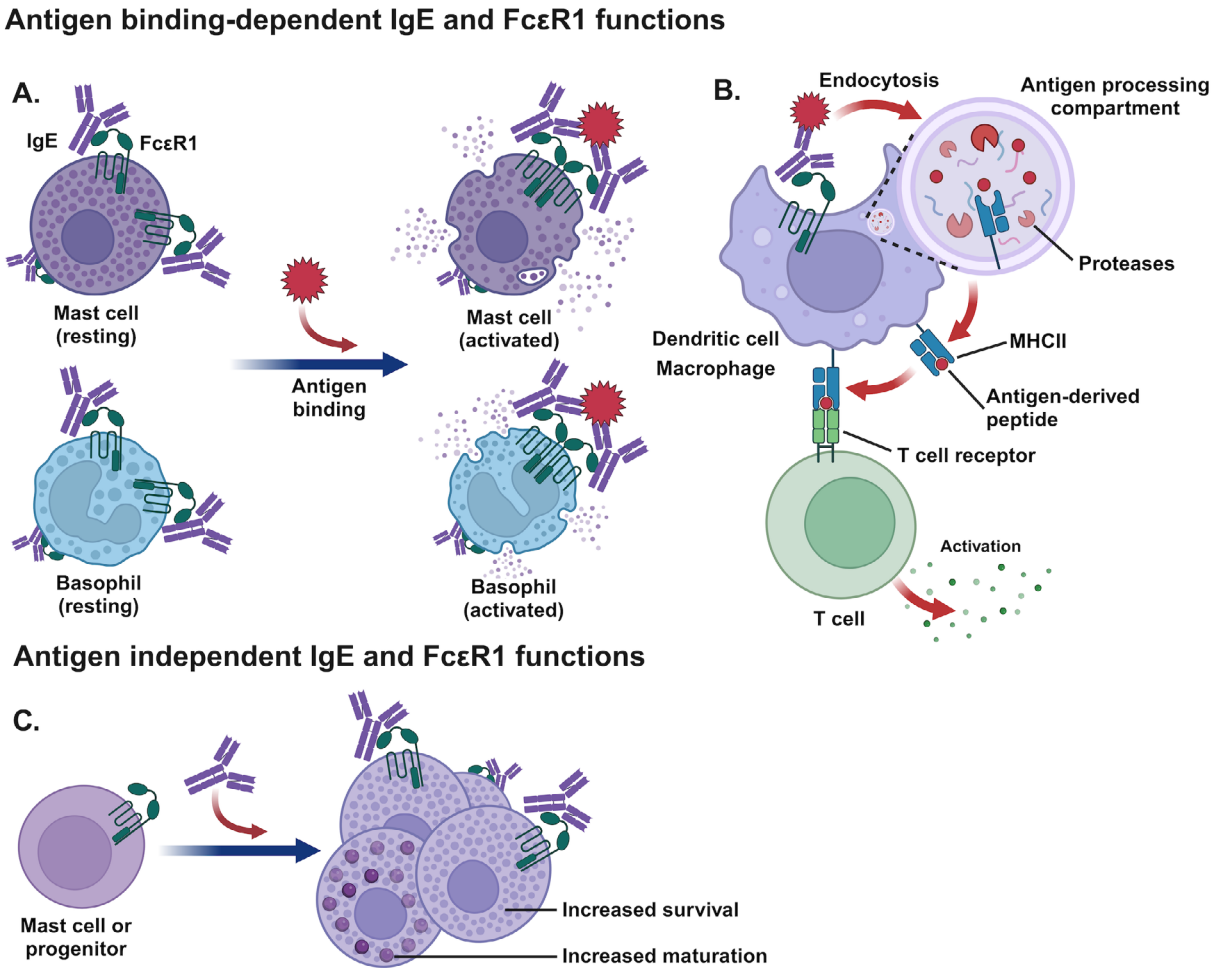

FIGURE 2 | IgE and FcεR1-mediated functions. (A) IgE binds to separate FcεR1 on mast cell (MC) and basophil surface. Antigen detection by IgE clusters the membrane IgE-receptor complexes, this FcεR1 cross-linking triggers inflammatory granule (containing proteases, monoamines, and proteoglycans) and soluble mediator (cytokines, chemokines, leukotrienes, prostaglandins) release in response. (B) FcεR1 is also expressed on human antigen-presenting cells (APCs), such as dendritic cells, which it can assist to take up IgE-bound antigens at a low concentration [101]; however, this antigen uptake pathway may not be sufficient to bias towards Th2 response development on its own [102]. (C) Homeostatic IgE binding to MC helps maintain their population size in skin and intestine in vivo [103], or increases granule maturation in MC progenitors in utero [104], without requiring antigen binding.

IgE-binding activity (Figure 3B). sCD23 binding to the transmembrane IgE on switched B cells stimulates further IgE production (Figure 3B) [118]. Thus, CD23 helps maintain IgE homeostasis via the reciprocal soluble and membrane-bound form actions.

In terms of relevance for the maternal-offspring interactions, CD23 is known to mediate IgE or IgE-immune complex transport across respiratory and intestinal epithelial cells (Figure 3C,D) [115, 119, 120]. It was shown to be expressed on fetal B cells [121]; however, it has been found only on sparse round cells on the maternal side of the human placenta [84], but not the syncytiotrophoblast. It may be relevant after birth, as functional CD23 is expressed in the human intestinal epithelium [115], potentially allowing for breastmilk IgE capture (Figure 3C,D). Its significance in early life allergy has not been investigated, but studies in adult mouse models produced seemingly discordant results [114, 116]. In one study, wild-type mice developed anaphylaxis when passively sensitized with free feline allergen-specific IgE and later challenged with the allergen, but resisted anaphylaxis when sensitized with IgE-allergen complexes [114]. In contrast, CD23-deficient mice developed anaphylaxis after immune complex treatment [114]. Reduced pathology could be due to a combination of faster IgE-antigen clearance via CD23 and reduced immune complex binding to MC FcεR1 [114]. In the other study, ovalbumin (Ova)/alum-sensitized wild-type mice developed much stronger lung inflammation than CD23-deficient mice after inhaling Ova [116]. By transplanting WT bone marrow into CD23-KO lethally irradiated recipients, the authors showed that CD23 expression on lung structural cells (esp. airway epithelium) promoted allergic inflammation, while CD23 on hematopoietic cells was irrelevant [116]. This suggested epithelial CD23 promoted airway inflammation by transporting IgE luminally, allowing it to capture Ova during challenge, and re-absorb the IgE-bound Ova (Figure 3C,D) [116]. Considering both studies, one may conclude that CD23 inhibits anaphylaxis triggered by allergen intrusion into the circulation to prevent widespread FcεR1 activation [114]. At the same time, CD23-mediated IgE-allergen capture can promote trans-epithelial immune complex passage [116]. This may facilitate antigen presentation to allergen-specific Th2 CD4+ T cells in a sensitized individual [122]. Further, caveats apply to both models. Intravenous IgE

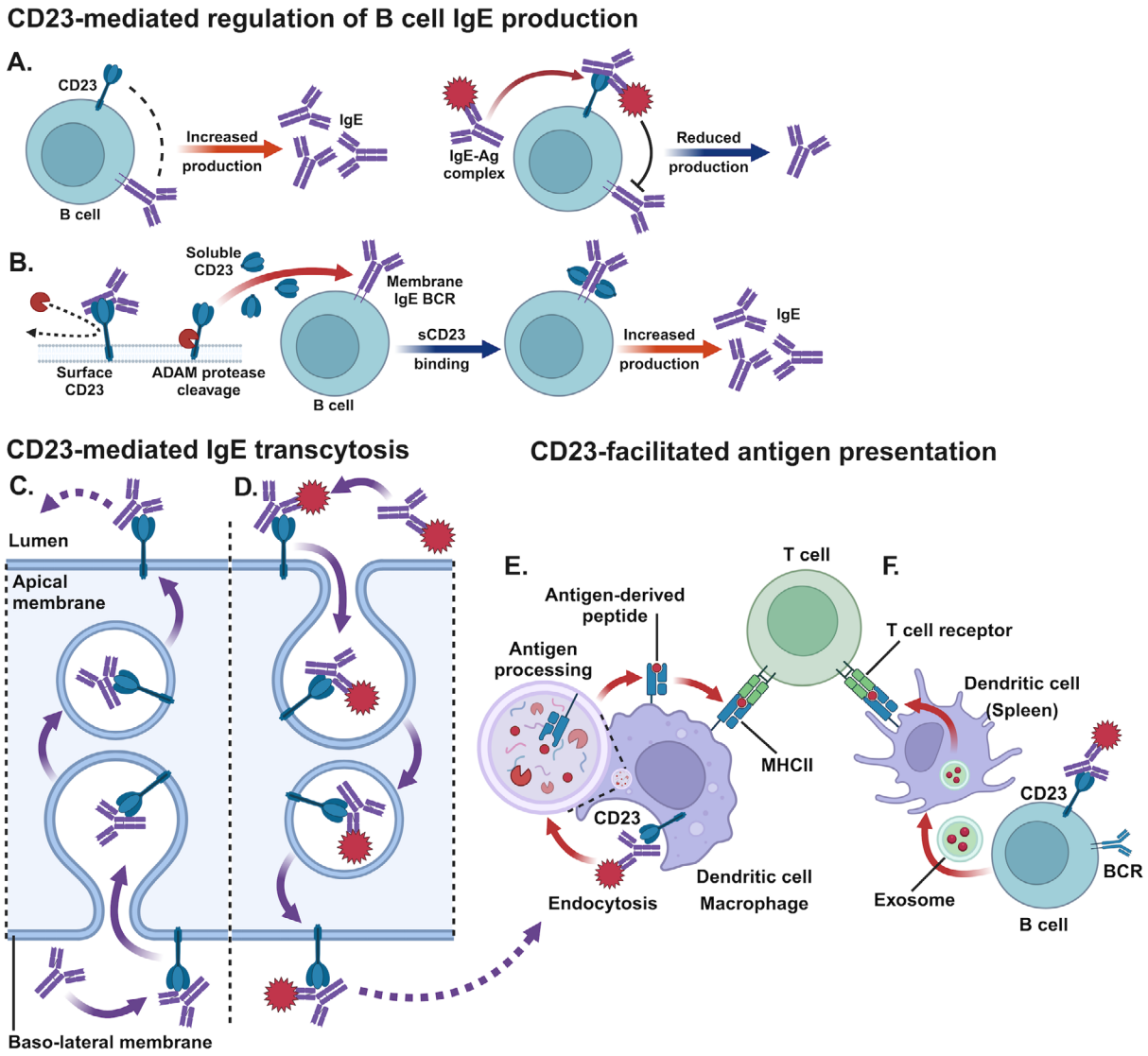

FIGURE 3 | IgE and CD23-mediated functions. (A) CD23 provides feedback regulation of IgE production by B cells. When IgE levels and antigen exposure are low, CD23 remains unoccupied, as it has reduced affinity for monomeric IgE compared with antigen-bound IgE. Under high IgE-antigen load, IgE immune complex binding to CD23 inhibits further IgE release. (B) If IgE concentration falls sufficiently, unoccupied CD23 becomes vulnerable to ADAM protease-mediated cleavage, releasing the soluble head domain trimers that can bind B cell surface IgE (i.e., the B cell receptor). This stimulates increased B cell IgE production. (C) CD23 can mediate IgE transcytosis across epithelial cells, such as IgE absorption from the intestine [115]. (D) The IgE transferred by IgE to the mucosal surface can capture cognate antigens and the resulting immune complex can be transported from the apical side to the submucosa, where it can be taken up by APCs for antigen presentation to lymphocytes [116]. (E) CD23 aids APCs in antigen-IgE complex uptake. (F) CD23 on B cells also facilitates IgE immune complex capture. B cells may transfer the antigen or its peptides to professional APCs via exosomes in the splenic follicular areas [117].

and/or allergen administration is highly artificial, as it bypasses epithelial modulation. Allergic asthma induction in the Ova/alum allergy model is known to be IgE and MC-independent due to the artificial adjuvant use, and it cannot control for allergen-specific IgG-mediated effects [123]. Thus, to properly elucidate the role of maternal IgE-offspring CD23 pathways on allergy development, different types of allergens may need to be tested in vivo. Simple allergen-monomeric IgE complexes might be more prone to CD23-mediated removal, while multivalent allergens that bind several IgE molecules could cross-link FcεR1 after epithelial passage.

All these unique aspects of IgE biology make it difficult to detect and study. This especially applies to sampling bound IgE in pregnant women and during human embryonic/fetal development. Therefore, it may often be missed, and sometimes dismissed as contamination, leading to its role in early life being underappreciated. However, the detailed understanding of IgE structure binding sites allows for it to be targeted by drugs.

3 | Mast Cells in the Maternal-Fetal Interface Setting and in Early Life

Maybe the most prominent cellular effector partners for IgE are mast cells (MCs), a type of tissue-resident myeloid-lineage innate immune and immune regulatory cell [124]. Although

basophils are also prominent carriers of the FcεR1 receptors, they tend to be restricted to circulation under physiological conditions, only entering the peripheral tissue following the onset of inflammation In contrast, MCs are found in all vascularized tissues, especially close to mucosal barriers, vasculature, nerve fibers, and tissue compartment boundaries, that is, the most likely sites of antigen exposure or tissue perturbation-derived signal propagation. There, MCs fulfill a sentinel role enabled by both their array of pathogen, endogenous stress, and danger-associated pattern recognition receptors, together with the adaptive immunity-derived antigen-specific IgE. They are poised for immediate response to antigen detection thanks to their pre-formed cytoplasmic granules comprised of mediators, including protease enzymes, serotonin, histamine, or heparin [125]. Their effects induce local inflammation, vasodilation, and changes to vascular permeability resulting in edema, changes to sensory nerve activity promoting itch and/or pain sensation, smooth muscle constriction, or enhanced mucus secretion [125]. The initial MC response is followed by a later release phase of lipid-derived prostaglandins and leukotrienes, cytokines, and chemokines they synthesize *de novo*. These signals promote the recruitment of effector cells from circulation or lymphatics, most prominently in allergic responses, eosinophils and neutrophils, but also monocytes, NK cells, and T cells [126]. Due to their ability to initiate inflammation and shape the downstream adaptive response, and their capacity to use adaptive immune system-derived IgE and IgG, MCs constitute a major innate–adaptive immune system bridging element.

The physiological roles of MCs in immune defense have been shown to include virtually all classes of pathogens [126]. In the context where MCs are involved specifically through IgE-mediated sensing, this may primarily involve defense against multicellular endoparasites [127–132] and ectoparasites [133, 134]. Apart from parasite immunity, IgE-mediated MC functions have recently been shown to be protective in a mouse model of *Staphylococcus aureus* skin and soft tissue infection [135]. In this study, IgE targeted bacterial toxins that help *S. aureus* spread, with MC degranulation products helping kill the bacteria and degrading their secretory products. The protective effect was absent in IgE or FcεR1-deficient animals [135]. Similar MC-mediated protection has been previously demonstrated for snake venoms [136–138] or insect toxins [139, 140]. In the non-infectious disease setting, MCs have been implicated in the regulation of many other systems, such as adipose tissue function [141], thermoregulation [142], cancer immunity, or behavior [143]. In the pathological context, the role of MCs is best described in allergic diseases, with their involvement consistently validated across different MC-deficient animal models [144, 145].

A further distinctive feature of MC biology relevant to the maternal-offspring setting in early life is their complex hematopoiesis. During fetal development, the formation of first blood and leukocyte precursors initially starts in the extraembryonic yolk sac (YS) (embryonic day 7 (E7-8.5) in mice; 4-6th post-conception week (PCW) in humans) [146, 147]. This primitive hematopoiesis phase outputs megakaryocytes and erythroid cells for blood formation, together with erythro-myeloid progenitors (EMPs) that give rise to the initial immune cells. This includes microglia (brain-resident macrophages) and MC progenitors, subsequently other macrophage, NK cell, and innate lymphocyte precursors [146, 147]. Thus, MC progenitor (MCp) cells are present from the earliest stages of mammalian development. Subsequently, fetal hematopoietic stem cells (HSCs), that can generate all types of immune cells, form in the intraembryonic aorta-gonad-mesonephros region (AGM) (E9; 5 PCW). Both YS EMPs and AGM HSCs seed fetal liver, which becomes the second main locus of hematopoiesis (from human post-conception week 6; mouse E10). Lastly, definitive HSCs settle in the bone marrow that becomes the final immune cell precursor source (10 weeks post-conception onwards in humans; E16.5 postnatally in mice) [124]. Thus, at least in mice, YS EMPs and AGM HSCs are thought to generate 2–3 waves of MC-lineage-committed cells before birth, with postnatal bone marrow contributing subsequently [124, 147]. MC ontogeny has not been determined in such granular detail during human intrauterine development. However, it may be reasonable to expect an analogous process, as tissue-resident myeloid cells are found by 6 PCW, that is, before the onset of liver hematopoiesis. Furthermore, MCp gene expression signatures are detectable in both human YS and fetal liver tissue in recent large single cell RNA-profiling studies [148–150].

A specific feature of myeloid hematopoiesis originally demonstrated for macrophages is that the early YS EMP-derived cells colonize tissues where they differentiate and establish long-term residence [151, 152]. Interestingly, these may be retained across the whole lifespan and self-renew independently of the bone marrow HSCs [152]. Alternatively, they may be gradually replaced with HSC-derived monocytes with tissue-specific differential replacement rates [152]. For example, mouse fate mapping models suggest that microglia originate from the YS exclusively and do not get replaced over time [153], with skin and liver also retaining cells of YS ontogeny [152]. More recent lineage tracing studies in *Cdh5*-CreERT2 (labels hemogenic endothelial cells) and *Runx1*-CreERT2 (labels pan-hematopoietic progenitors) mice showed that MCs also follow a similar pattern of gradual replacement of early YS EMP-derived cells with the subsequent fetal HSC-derived ones [154, 155]. Following birth, bone marrow-derived MCps continuously emerge into circulation in mice [110, 156] and humans [157, 158]. They home into tissues, especially the intestine [159] and the airways [160], where they differentiate into primarily mucosal-type MCs [161]. It is currently unclear what proportion of postnatal human MCs originate from each hematopoietic wave, or what the functional consequences of this heterogeneity might be.

The processes detailed above operate under physiological conditions. However, inflammation can affect hematopoietic development before and after birth, disrupting the architecture of tissue-resident immune cells. Maternal immune activation-derived inflammatory cytokines can modulate fetal HSC output in utero, resulting in changes to offspring immune cell numbers [162, 163] or their subsequent responses to activating stimuli [164]. This has been shown to translate into inflammatory disease in adult mouse offspring, including ILC2-mediated airway Th2 inflammation [165] or Th17-driven colitis [166]. Although analogous studies of MC development specifically have not been conducted for offspring, there are potential pathways through which IgE-mediated maternal allergic disease could be a source of inflammatory programming

signals. For example, maternal IL-5 elicited by HDM inhalation in allergic pregnant dams has been shown to cross the placenta to mobilize fetal eosinophil production [167, 168]. The eosinophils promoted airway sensory hyperinnervation in wild-type littermates, but these changes were absent in fetuses deficient of eosinophils due to Cre-driven diphtheria cytotoxin expression controlled by the eosinophil peroxidase (EPO) promoter [168]. Hyperinnervation translated into enhanced allergen reactivity postnatally [167, 168]. In humans, MCps found in fetal cord blood [169] and adult circulation [170] both express the IL-5 receptor. Exposure of purified MCps to IL-5 promoted their proliferation or survival in vitro [170]; thus, it is conceivable that a similar process could also promote MC expansion during development. Similarly, postnatal inflammatory responses can promote MC population expansion either via enhanced rates of blood-borne MCp entry or increased proliferation of tissue-resident MC/MCp. Such changes are inducible not only in response to an infection [171–173] but especially in different types of IgE-mediated allergy, including asthmatic lungs [174–176], chronic rhinitis [177], intestine during food allergy [178, 179], and allergic dermatitis [180, 181]. All this may result in increased susceptibility of a tissue to IgE-induced inflammation due to an increase in MCs, potentially combined with changes in their local phenotype. Although they share core features across the organism, the MCs recruited to a tissue are also targets of programming by local microenvironmental signals [182–185]. In summary, MCs are long-lived, often self-renewing cells, with a complex layered ontogeny that makes them a potential target for developmental programming by maternal and local tissue-derived signals during the perinatal period of phenotypic plasticity [11]. All these studies suggest ways that the experiences and exposures of MCs influence their abundance, phenotype, and the long-term allergic disease risk, accentuated by their role as a persistent reservoir of tissue-bound IgE after sensitization.

MCs are present at both sides of the maternal and fetal interface during gestation. As mentioned previously, they develop among the first immune cell types during mouse and human pregnancy, implying MCs may have functional relevance from very early in life. Although this has not been extensively investigated, fetal MCs may aid tissue developmental processes; however, whether IgE contributes to this process is unknown. For example, murine fetal MCs have been suggested to regulate the branching of vasculature and innervation of the cornea [186], of the mammary tissue duct branching [187], and assist with fetal skin wound healing without scar formation [188], although mouse model limitations and the fact that there is not a good model for MC deficiency during fetal development limit our understanding of how MCs contribute to these processes. Some studies also suggest that maternal IgE can affect fetal MC developmental function during pregnancy. In the rat fetal brain, MCs in the hypothalamus preoptic area are receptive to the gonadal hormone estradiol, in response to which they secrete histamine. In turn, histamine modulates the wiring of synapses responsible for controlling mating behavior in adulthood [189, 190]. Maternal IgE sensitization and allergen challenge during pregnancy were found to increase the rat offspring hypothalamic MC population at birth and affect behavior [190], although the specific mechanism is unknown. Overall, these studies indicate that MCs and their interactions with IgE likely have developmental implications.

Although fetal immune cells may adopt developmental roles during gestation, their other main function is to defend against pathogens. As the immune system is not fully developed till after birth, the early life period is associated with an increased vulnerability to infection. Several well-known congenital infections include HIV and the TORCH pathogens, including Zika virus [191]. Others, like *Staphylococcus aureus*, can also cause chorioamnionitis by infecting the placenta or amniotic fluid, and are associated with premature birth [191]. However, whether MCs mediate protection or inflammatory responses to pathogens before birth is unknown. Several studies report pro-inflammatory responses of human cord blood-derived MCs (CBMCs) to pathogens; however, these were used primarily because of their relatively accessible source and after prolonged maturation in culture from CB progenitors [192–194]. Human and rodent immune development research indicated that some fetal MCs develop inflammatory response components, such as FcεR1 or heparin granules with the associated proteases, in the first trimester [104, 150, 195, 196]. It is reasonable to expect they could be activated following pathogen detection, but it remains to be verified experimentally.

MCs also have very important functions on the maternal side of the materno-fetal interface, which forms in very early pregnancy due to the implantation of the blastocyst-stage embryo into the maternal decidua (uterine endometrial epithelium), resulting in the formation of fetally derived placenta (3 PCW human; E10 mouse) [191, 197]. The placenta anchors the fetus and mediates metabolic, endocrine, and immune exchange. During human placentation, the specialized embryonic trophoblasts invade the uterine endometrium where they remodel and dilate maternal spiral arteries [191, 197]. This enables the invading placental villi containing fetal capillaries to be bathed in maternal blood to become the primary site of materno-fetal material exchange (Figure 5B). The maternal and fetal circulations are separated by a thin continuous interfacing syncytiotrophoblast layer derived from the fetus that mediates the transport processes (Figure 5B) [191, 197].

During placentation, fetal trophoblast cells interact with maternal decidual immune cells that actively regulate the vascular remodeling and implantation [200]. This includes NK cells, macrophages, but also MCs [201–203]. Uterine MCs respond to gonadal and pregnancy-associated hormones and their population increases during decidualization [202, 204, 205]. Embryo implantation and spiral artery remodeling are partially defective in MC-deficient mice [201, 206] and rescued by reconstitution of the female mice prior to pregnancy with ex vivo grown MCs [201]. MCs may support these processes via chymase [207] and histamine [208] release, in collaboration with NK cells [206]. Additionally, there is evidence for the protective role of maternal MCs in a mouse model of uterine bacterial infection associated with pregnancy complications [209]. In mice, uterine MCs reduced *Streptococcus* dissemination and premature birth by a chymase-mediated mechanism [210].

Dysregulation of MC function during placentation may contribute to fetal growth restriction and miscarriage [211, 212],

or preeclampsia pathogenesis [208]. How the biology of MCs at the maternal-fetal interface is affected by IgE remains understudied. Uterine MCs can be sensitized by IgE, as tissue samples taken from women allergic to ragweed can respond to allergen challenge ex vivo and promote myometrial contraction [202]. Furthermore, patient cohort studies show a positive association between maternal asthma and preeclampsia or preterm birth risk [213]. Interestingly, children born to mothers with preeclampsia during pregnancy have an increased risk of allergen sensitization [214] and allergic disease development [215, 216]. It remains unclear whether the preeclampsia-allergy association stems from a shared underlying mechanism or whether one condition directly contributes to the other. It may be interesting to determine whether effective treatment or control of maternal allergic disease during pregnancy reduces the risk of preeclampsia.

4 | The Origins of Early Life IgE

Fetal and neonatal immune systems become very different later in life, initially exhibiting reduced efficacy when responding to specific antigens, manifesting in increased vulnerability to infectious diseases that are mild in later life (e.g., respiratory syncytial virus bronchiolitis) [217]. A combination of factors is thought to contribute, including adaptive immune system immaturity, increased effector response versus memory formation balance, and increased reliance on innate responses for protection [19, 218].

Distinct early life factors also apply to B lymphocytes, the cell type responsible for IgE production. Human fetal B cells are detectable from the start of the 2nd trimester, developing in a phased process, giving rise to a layered structure of their populations [219]. The initial B cells are the innate-like B-1 lymphocytes, primarily originating in the fetal liver, that tend to produce low-specificity, low-affinity polyreactive IgM antibodies with protective and regulatory functions. The more conventional B-2 cells capable of producing non-IgM isotype antibodies originate from bone marrow precursors that continue to develop in the secondary lymphoid structures (esp. spleen and lymph node follicles). Fully functioning follicles with germinal centers and some B cell subsets, like the marginal zone cells, only fully develop after birth [219, 220]. Additionally, early life B lymphocytes may be less sensitive to activation due to reduced expression of co-stimulatory molecules, such as CD40 and CD80/86, and due to lower function of Tfh cells during the same period [218]. Maturation of the immunoglobulin repertoire can also be inferred from the Ig complementarity-determining region 3 (CDR-H3) sequence lengths, which increase as VDJ junction nucleotides are added over time. In humans, immature IgM, IgG, and IgA patterns persist until about 6 months after birth, with evidence suggesting the maturation process is endogenously controlled and not significantly accelerated by antigen exposure [221–223]. Taken together, early life production of non-IgM class-switched antibodies following antigen exposure is more difficult and relatively limited until at least 6 months of age and outputs lower titre of lower affinity antibodies that wane faster [19, 224]. In the case of IgE specifically, many studies presumed low levels of endogenous fetal production. However, an analysis of human fetal tissue and infant blood samples for VDJCε transcripts presence across developmental time points revealed that IgE production does not occur prenatally [225]. The VDJCε transcripts were detected in only 2/62 liver samples and 2/133 cord blood mononuclear cell samples and remained extremely rare until about 9 months of age after birth [225].

Considering these factors, it could be reasonable to expect that the components of IgE production are missing or ineffective prenatally. Thus, the surprising findings of circulatory IgE in fetal and neonatal cord blood consistently across many human sampling studies suggest maternal origin [22, 226–234].

5 | Maternal IgE Antibody Transfer Pre- and Postnatally

The main reason why it was thought maternal IgE does not transfer into the fetus was the seeming placental barrier impermeability to IgE [235]. Also, no IgE production has been observed in the placenta, only surface binding to macrophage-like Hofbauer cells (Figure 5B) [84]. Even though maternal B cells reside at the materno-fetal interface, they are thought to help maintain protection and fetal tolerance during pregnancy [236].

Maternal IgE passage during gestation can explain many observations of human cohort studies. Chiefly, antigen-specific IgE is commonly detected in human fetal blood samples. This includes both pathogen-specific antibodies in pregnant mothers with a parasite infection [237, 238] and allergen-specific IgE [22, 226–234]. Furthermore, the ratio of allergen-specific and total IgE in maternal blood often correlates with those of offspring cord blood [239], as does the specific allergen sensitization profile [21, 228]. This is not the case for paternal IgE in allergic fathers [15, 16, 240–243]. Additionally, maternal IgE sensitization is associated with a significantly increased proportion of cord blood immune cells with FcεR1-bound IgE [244]. We confirmed maternal IgE binding to fetal tissue MC receptors in a murine model [104]. Taken together, this evidence suggests that a substantial fraction of fetal IgE can be primarily derived from the maternal organism. This could also explain how some infants experience allergic reactions upon the first exposure to an allergen [245], before 9 months of age when endogenous IgE is thought to begin properly [225]. Similarly, it may also explain how maternal and infant sensitization diverge several months after birth [21, 246], likely reflecting the decay of maternal IgE and the start of endogenous production.

In contrast to IgE, transport of maternal IgG antibodies is well understood. It is enabled by the FcRn receptor (Figure 4B). Structurally, it is a heterodimer composed of a heavy α-chain and a β_2-microglobulin light chain [248]. The MHCI-homologous α-chain has three extracellular domains. Out of these, the α1 and α2 form the IgG binding site together with β_2-microglobulin. In all the examples of FcRn-IgG binding described, whether in cellular endocytic vesicles or intestinal lumen, the process is critically dependent on acidic pH (~6.5) and IgG re-release is triggered by neutral pH [248]. IgG binding is thought to be mediated via electrostatic interactions resulting from IgG C_H2-C_H3 linker region histidine residue protonation under low pH conditions being attracted to negatively charged acidic residues in both the FcRn α2 domain and β_2 microglobulin chains [248].

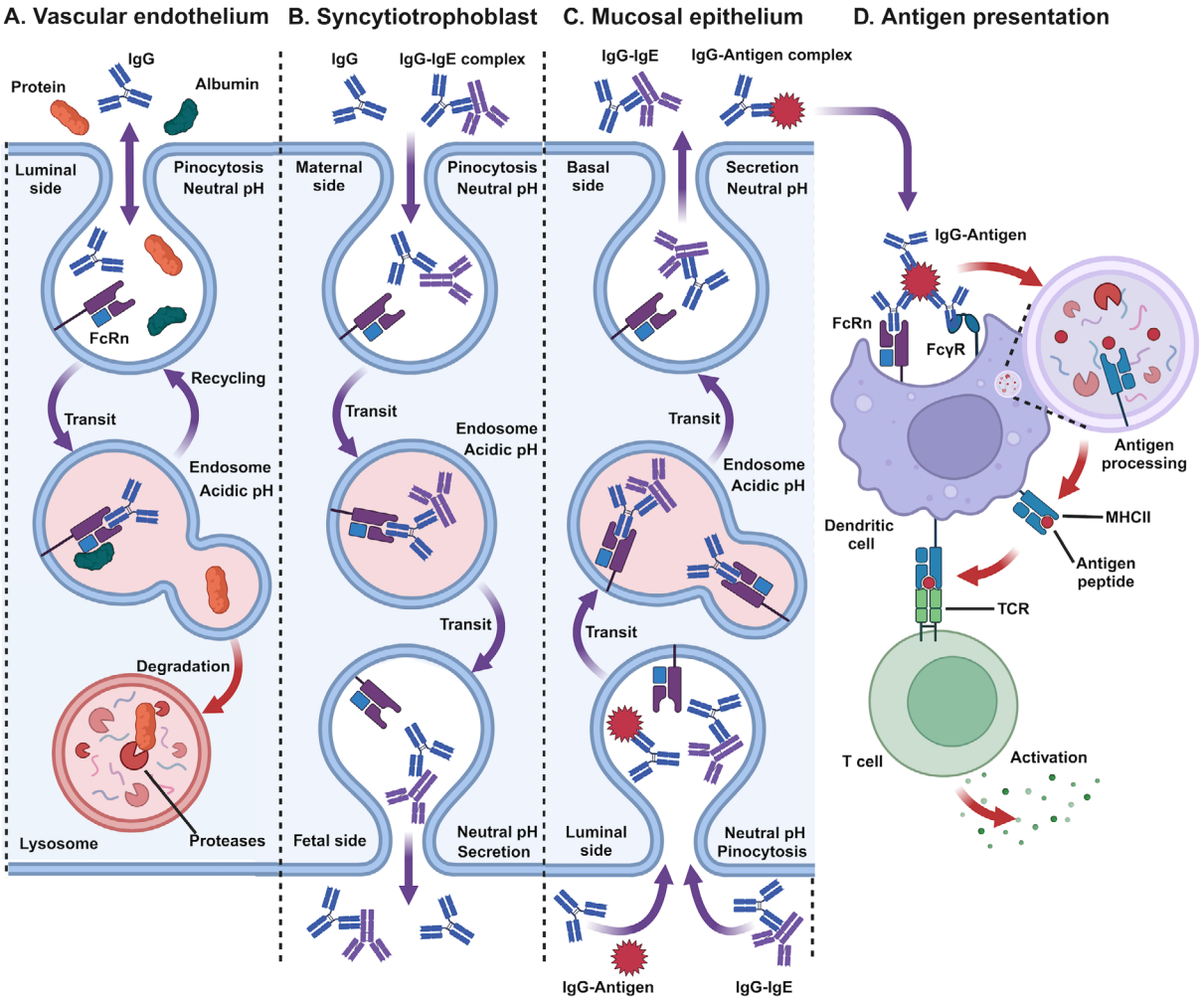

FIGURE 4 | FcRn roles in serum protein homeostasis, antibody transcytosis, and antigen presentation. (A) Vascular endothelial FcRn protects serum IgG antibodies and albumin proteins from degradation after endocytic uptake by pinocytosis. Vesicle acidification protonates IgG amino acid restudies and triggers its binding to FcRn, while albumin binds primarily via hydrophobic interactions independently of IgG at a distal site. Proteins that cannot bind FcRn may be sorted into the lysosomal degradation pathway. (B) FcRn expressed at the maternal-fetal interface syncytiotrophoblast mediates maternal IgG transcytosis across the placental barrier. FcRn also translocates immune complexes consisting of anti-IgE IgG and IgE from maternal into fetal circulation. (C) Similar mechanisms have been shown to capture IgG-antigen immune complexes from mouse intestinal lumen into the submucosa [247]. This might also allow IgG-IgE complexes to be absorbed from breast milk [198]. (D) FcRn expressed on APCs, including dendritic cells and macrophages, can help capture IgG immune complexes in collaboration with other FcγR IgG receptors for MHCII antigen-derived peptide presentation.

IgG binding does not seem to be influenced by its glycosylation, unlike other FcγRs [249]. In addition to IgG, FcRn also binds serum albumin proteins, the binding of which is thought to be primarily hydrophobic and of lower affinity [248].

In adult organisms, FcRn is critical for the maintenance of serum half-life longevity of both IgG and albumin proteins [250, 251]. This cycle consists of IgG/albumin binding, followed by retention inside vascular endothelial cell endosomes where FcRn protects them from lysosomal degradation, and recycling back into circulation (Figure 4A). IgG serum half-life in WT mice is 95 h in contrast to 22 h in FcRn-deficient animals [250]. Lastly, FcRn is also expressed by immune cells and facilitates antigen presentation by IgG-antigen complex capture (Figure 4D) [249].

In the gestational setting, FcRn is expressed on human placental syncytiotrophoblast [252] and across the analogous yolk sac endoderm in rodents (Figure 5B) [253]. These are the fetal-derived cells at the materno-fetal interface that contact maternal blood. Although other Fc receptors (FcγRII and FcγRIII) are expressed by placental cells, FcRn is the only one mediating IgG translocation [248, 254]. It is selective for IgG (prefers IgG1 and IgG4 over IgG2 and IgG3) and does not permit monomeric IgE transcytosis (Figure 5B) [248, 255].

Considering the inability of FcRn to interact with IgE, an indirect mechanism was proposed (Figures 4B and 5B). Using an in vitro model system, it has been shown that human IgG-IgE complexes, but not monomeric IgE, are actively transported across human FcRn-transfected MDCK cell layers [199]. In the same study, strongly correlated amounts of anti-IgE IgG were found in the serum of both allergic women and their neonates [199]. Additionally, cord blood IgE correlated with maternal IgG anti-IgE content in allergic mother-neonate dyads [199]. Most

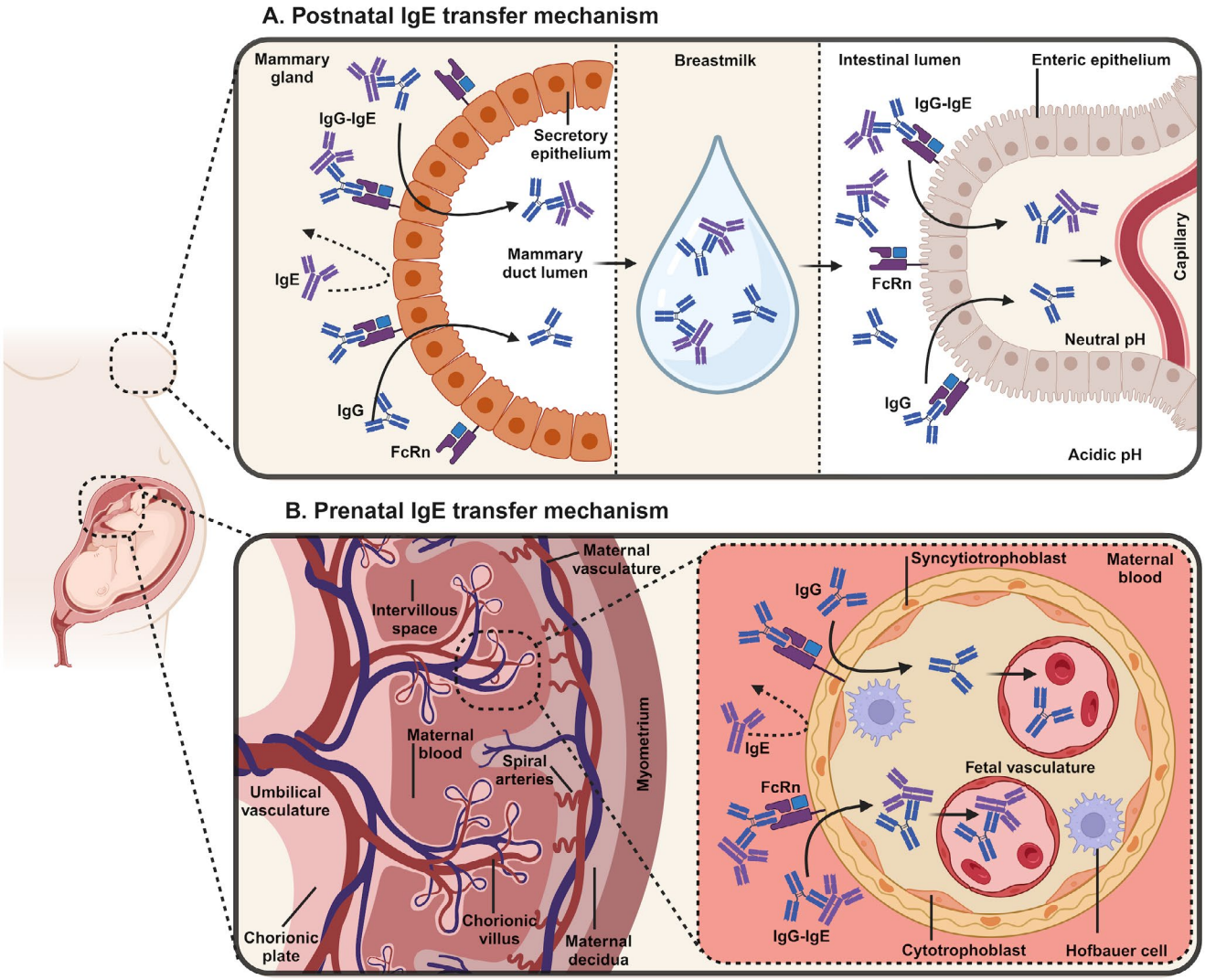

FIGURE 5 | FcRn-mediated maternal IgE transfer before and after birth. (A) FcRn-mediated transfer of IgG across the mammary gland epithelium into the ducts contributes to the abundant breastmilk immunoglobulin content. Following consumption by offspring, the milk IgG is captured by the intestinal epithelial FcRN for transfer into circulation. This pathway has been shown in mouse models to also transfer maternal allergen-IgG complexes and IgG-IgE complexes into the offspring [198]. (B) In the placenta, maternal decidual spiral arteries supply blood into the spaces around invading fetal villous tree structures to enable maternal-fetal material exchange. Fetal blood vessels are separated from the maternal blood by a layer of fused fetal cells in the form of syncytiotrophoblast, which expresses FcRn to capture maternal IgG that are critical for offspring immune defense. FcRn cannot bind monomeric IgE, but has been shown to also transfer IgG-bound maternal IgE into the fetus. This has been demonstrated in vitro [199], and recently in a murine model of maternal allergic sensitization as sufficient for offspring allergic reactivity upon the first allergen exposure [104].

cord blood IgE was present in the complexed form, as it was depleted after serum incubation with IgG-specific binding beads [199]. We confirmed this mechanism in vivo by showing that maternal IgE transferred into the offspring of both passively IgE-sensitized and wild-type but not on FcRn-deficient mouse dams allergic to ragweed [104]. Maternal IgE co-localized with IgG on the placental endothelial cells in a FcRn-dependent manner [104] and was subsequently detected on fetal skin and lung MCs in utero [104]. We also found IgE-decorated FcεR1 human fetal skin and lung tissues as early as 14 PCW [104]. Further evidence of this mechanism in humans comes from a recent study that used ex vivo artificially perfused placentas to investigate antibody transfer [256]. When the placenta was perfused with peanut-allergic plasma with added peanut allergen proteins, free IgE did not pass through. The addition of anti-IgE IgG enhanced the transfer of IgE-peanut allergen across the barrier [256]. The absence of anti-IgE IgG may explain why older studies using similar ex vivo systems failed to observe IgE transfer [235].

In addition to trans-placental transfer, there is evidence of continuing maternal IgE transmission after birth. FcRn can secrete IgG across epithelia onto the luminal surface [251]. Specifically, FcRn is also expressed in mammary tissue of both rodents and humans, where it transports IgG into breast milk (Figure 5A) [20]. Following milk ingestion, neonatal gastrointestinal epithelial FcRn captures the maternal IgG and transports it into offspring circulation (Figure 5A). This also enables offspring antigen-presenting cells and phagocytes to capture IgG-antigen immune complexes for MHC display or removal, respectively (Figure 4D) [251, 257]. This

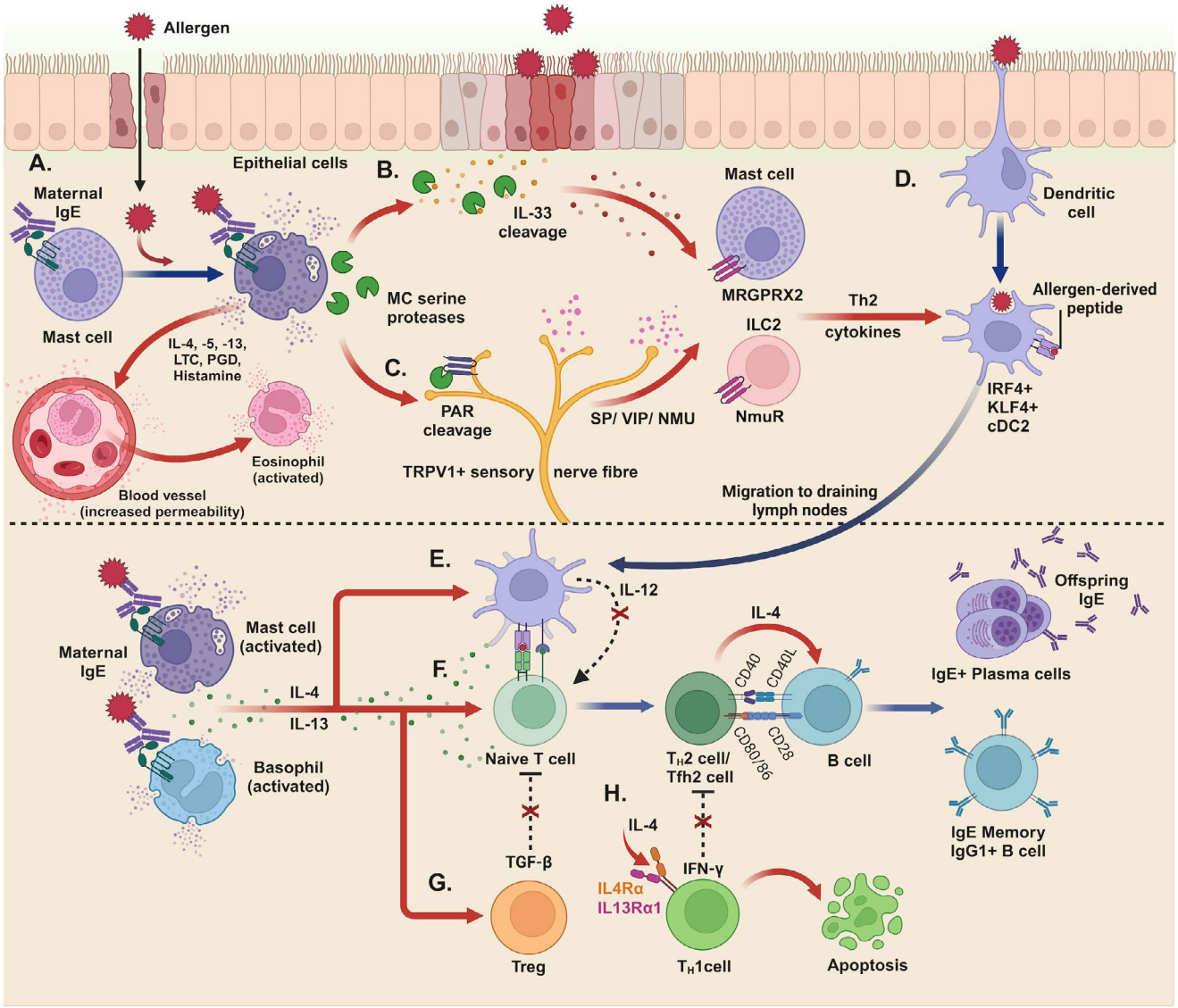

FIGURE 6 | The effects of maternal IgE transfer on offspring allergic disease development. A composite view of the multifaceted effects maternal IgE may have in offspring allergic inflammation or sensitization development based on the evidence from animal models. (A) Maternally derived IgE can sensitize offspring MCs for an allergen, resulting in their degranulation upon a future antigen encounter and eosinophilic inflammation in the airway [104]. (B) Maternal IgE-armed MCs can promote the early allergen-evoked epithelial IL-33 alarmin signals by cleaving it, due to their granule-associated serine protease release, producing fragments with increased ILC2-stimulating activity [105]. (C) MC granules and histamine can activate mucosal TRPV1+ nociceptive sensory fibers to induce neuropeptide release that further stimulates MCs and ILC2s via their MRGPRX2, NMUR, and other receptors [106]. (D) Alarmins, neuropeptides, and Th2-associated mediators (IL-4, IL-13) released by IgE-activated MCs and by ILC2s promote the activation of cDC2-type dendritic cell subset that skews the subsequent allergen-derived antigen presentation to promote Th2 CD4+ lymphocyte development. (E) MCs and basophils secrete IL-4 following IgE cross-linking. IL-4 signals inhibit dendritic cell pro-Th1 IL-12 expression [107]. (F) The presence of IL-4 signals during antigen presentation also enhances Th2 CD4+ cell differentiation. (G) T regulatory (Treg) cells express Il-4 receptors and their capacity to secrete inhibitory TGF-β is attenuated by IL-4 signals, stopping them from restraining Th2 differentiation [108]. (H) The presence of MC and basophil-derived IL-4 may also inhibit Th1 CD4+ lymphocytes that have suppressive effects on Th2 cells. The lack of IL-12 from dendritic cells lifts the repression on the Th1 cell IL13Rα1/IL4Rα heterodimeric IL-4/IL-13 receptors expression. IL-4 sensing by Th1 cells promotes their apoptosis, leading to the loss of Th1-biasing interferon-gamma (IFN-γ) signals [109]. These events, alone or in combinations, support the Th2 inflammatory environment, that culminates in the B cell IgE class switching, and the development of offspring IgE allergen memory.

mechanism may be involved in promoting neonatal tolerance to food antigens when complexed with maternal IgG in breast milk [247, 258]. However, the same FcRn-mediated pathway enables breast milk IgG-IgE absorption from the intestinal lumen (Figures 4C and 5A). When naïve mouse pups are foster nursed by Ova-allergic dams, anti-Ova IgE becomes detectable in their serum [198]. IgG1 anti-IgE was present in allergic but not naïve dam blood and was secreted into their breast milk [198]. The detection of IgE in fostered offspring was abolished in FcRn-KO, but not CD23-deficient animals [198]. This confirmed IgE was not absorbed from the intestine directly (via CD23), but in the form of a complex with IgG anti-IgE. Furthermore, the serum of mice fostered by allergic dams was able to sensitize ex vivo cultured MCs to be activated by

the antigen, showing that IgG complexation is not always sufficient to prevent its FcεR1 binding [198]. Both total IgE and allergen-specific IgE are also detectable in breast milk of lactating women [259, 260]. Unlike in rodents, human intestinal FcRn expression remains stable with age [251], enabling continuing IgE capture over the relatively prolonged human lactation period.

Lastly, another proposed mechanism of maternal IgE transfer that combines transcytosis and gastrointestinal pathways may also be explicable via FcRn actions. A pair of studies analyzed amniotic fluid samples of British women and Brazilian women for the presence of IgE [260, 261]. Amniotic IgE was first detectable at 16 PCW and was present in all full-term samples. Furthermore, amniotic and maternal serum IgE content were significantly correlated [260, 261]. Although only low IgE levels were present in fetal blood [260], this is probably due to its rapid tissue binding. It was proposed that amniotic IgE enters the fetus via continuous fluid swallowing, which is a major source of nutrition in utero [260, 262]. Amniotic fluid is primarily of maternal origin and has been shown to contain IgG, including tetanus antigen-specific IgG due to maternal vaccination [263]. Thus, it may be reasonable to expect that IgG is transported into the fluid via FcRn, which could also enable IgG-IgE complex transfer. Both free and IgG-complexed IgE could be absorbed in the fetal intestine, as it expresses both CD23 [115, 260] and FcRn receptors [251]. However, this remains to be verified experimentally.

In conclusion, in vivo model evidence and human study findings support the role of FcRn as a major transfer mechanism of maternal IgE during early life, both across the placenta in utero and via breast milk and intestinal epithelium postnatally. Thus, IgE transfer can take place for extended periods during development and result in trans-generational inheritance of maternal allergen sensitization with potentially long-lasting consequences.

6 | Endogenous IgE Production After Birth

In addition to the transferred maternal IgE, there may be another source of IgE antibodies on the offspring early after birth. This may be in the form of natural antibodies (NAbs), which are endogenous immunoglobulins formed independent of explicit antigenic stimulation. These were initially identified in animals bred under germ-free and external antigen-free conditions, that unexpectedly had relatively normal IgM antibody levels at birth [264, 265]. IgM NAbs are also found in human newborns, with specificities primarily against microbiota glycans and self-antigens [266, 267]. They are thought to have regulatory and anti-inflammatory functions, for example, assisting with damaged or apoptotic cell removal via efferocytosis [268].

Natural IgE is also found in the serum of germ-free mice [269]. It is detectable very soon after birth, with the timing being mouse strain-dependent, suggesting the influence of germline programming [269]. Interestingly, it is not ablated in athymic nude mice lacking almost all T cells or MHCII-deficient mice lacking the mechanism of antigen-specific T cell help [269, 270]. One contributing source of mouse natural IgE is thymic CD138 + Blimp1+ plasma cells, the activity of which comes online as early as 1 week of age [103]. Paradoxically, the immaturity of fetal B cells may be conducive to natural IgE production. It has been found that murine fetal liver-derived immature B cells prefer switching towards IgE production when stimulated with αCD40 and IL-4 ex vivo compared with a reduced preference in mature B cells [60]. The switch to IgE occurs from IgM directly, bypassing the need for germinal center selection and hypermutation [60]. This is in line with the observed low affinity and specificity of murine natural IgE antibodies and their lack of somatic hypermutation marks found in their transcript sequences [269]. Elevated natural IgE is also found in humans with immunodeficiency diseases that cause T cell deficiencies [271], in agreement with the murine models. However, the extent of natural IgE formation in human infants is not clear, and natural IgE-producing cells have not been directly identified at such an early age.

It is currently unclear what the effects of natural IgE are. Similarly to the natural IgM mentioned previously, natural IgE may have homeostatic roles via auto-antigen binding [269]. Based on experiments in adult mice, one proposed function might be barrier tissue maintenance following injury [272, 273], but other roles remain largely unknown. In terms of allergic pathology, a recent study provided the first evidence for the capacity of NAbs to prime airway Th2 inflammatory response in mice exposed to Ova combined with alum and uric acid crystals as adjuvant, which simulate damage-associated molecular pattern (DAMP) signals [274]. However, this study did not differentiate the contribution of specific NAb isotypes, so it remains unknown whether natural IgE contributed. Natural allergen-induced DAMPs are also sensed by several tissue-resident innate immune cell types directly, introducing redundancy in the system [43].

In contrast, natural IgE could be potentially protective from anaphylaxis. In mice, glucocorticoids have been shown to boost circulating natural IgE levels [275]. Mechanistically, dexamethasone promotes murine B cell IgE switching in vitro by substituting for or reinforcing existing CD40 stimulation [276]. The treatment also stimulated higher IgE production in already switched B cells in vivo [276]. Pre-emptive induction of natural IgE resulted in attenuated anaphylaxis in mice that have been previously tapered off the drug [276]. This was presumably due to allergen-specific IgE dilution or blocking its FcεR1 loading by natural IgE. There are indications that analogous effects could function in humans, as patients receiving long-term steroid treatment can exhibit increased total IgE induction [277]. It is unknown whether glucocorticoid stimulation could enhance allergen-specific IgE class switching if exposure coincided with the initial sensitization period.

7 | Functional Consequences of Maternal IgE Transfer

Maternal IgE transfer during pregnancy and infancy has now been demonstrated in multiple studies including diverse mammalian species, as discussed previously. Although the consequences of this process remain mostly unknown, current data support a number of potential effects maternal IgE may promote.

7.1 | Development of Offspring Allergic Inflammation

The most straightforward outcome of IgE presence in the offspring is sensitization to allergens, provided sufficient scale of antibody transfer. Allergic reactivity requires the presence of available FcεR1 receptors on cells capable of inflammatory responses. Mouse fetal tissues become colonized by MC in the E10.5–E12.5 period, where MCs begin to build up inflammatory granules and surface FcεR1 over time [104, 124]. We found that by E15.5 virtually all mouse skin MCs contain detectable heparin-bearing granules and comprise approx. 20% of all immune cells residing in E17.5 murine fetal skin [104]. Fetal lung, intestine, peritoneum, and cornea all contain MCs along a maturation gradient [104, 155, 186, 278]. Human fetal skin and lung contained FcεR1+ MC populations at the start of the 2nd trimester [104, 279]. Thus, barrier tissues contain relatively mature MC subpopulations with free FcεR1 receptors prenatally. We and others have shown that the maternally derived IgE gets captured on the FcεR1 receptors of skin and lung MCs of fetal mice and humans [104, 280], and offspring circulating basophils [199, 244, 281]. We observed maternal IgE was sufficient and necessary for MC activation in E17.5 fetal and newborn mouse skin in response to TNP-Ova detection, and in juvenile mouse lungs following ragweed allergen inhalation (Figure 6A) [104]. In summary, these findings support the potential of barrier tissue MCs being capable of inflammatory responses after the first antigen challenge during early life, when armed with transferred IgE.

Taken together, these findings could be a part of the explanation for certain clinical observations in infants, who can develop immune reactions following the first known contact with an allergen [245, 282, 283]. For example, in a US cohort of 4- to 11-month-old subjects with no history of peanut exposure, approx. 20% had a positive skin prick test or allergy at first introduction [282]. Similarly, in an Australian cohort of infants born to allergic mothers, over 30% had egg-specific IgE and allergic reactivity at the age of 4 months, before any previous egg exposure [283]. These studies point to the presence of mothers allergic IgE in infants. Even though maternally derived IgE may not remain at detectable levels in the offspring's circulation by the time of sampling in many clinical studies due to its high tissue receptor binding rate, especially in the absence of ongoing breastfeeding studies suggest that even very low IgE levels below the standard cut-off value used in specific IgE laboratory blood tests (0.35 kU/L) may be important for allergy development. For example, in adults with detectable peach allergen-specific IgE, 23% had IgE levels between 0.1 and 0.34 KU/L, and out of those, approx. one half were allergic to peach [284]. Infant sampling studies also support the importance of very low IgE levels for allergy in early life, where sub-0.35 kU/L levels at the age of 6 months are sufficient to be predictive of future broader sensitization and allergic disease in later life [285, 286].

7.2 | Development of Offspring Allergic Sensitization—Enhancing Th2-Polarizing Signals

Apart from enabling inflammation development outright, maternal IgE-decorated cells might exert a more subtle influence by promoting the development of offspring allergen sensitization (Figure 6). Even relatively low amounts of maternally derived IgE, that may not reach stably detectable levels in circulation, will concentrate on the surfaces of FcεR1 and CD23-bearing cells [287], due to their high binding affinity. Firstly, this might enable the intensification of mucosal epithelial or skin alarmin signals released by allergen exposure during the initial stages of Th2 immune response induction [43]. For example, IgE-mediated MC degranulation introduces serine proteases into the local skin or submucosal tissue microenvironment [125]. MC proteases can cleave full-length IL-33 into a fragment with 30-fold increased potency of driving IL-5 and IL-13 Th2 cytokine secretion by local ILC2s (Figure 6B) [105]. In addition, MC proteases also cleave proteinase-activated receptors (PARs) on the local mucosal and cutaneous sensory nerve endings, and together with MC histamine, stimulate them to release neuropeptides (Figure 6C) [98, 106]. These activate MCs via their MRGPRX2/Mrgprb2 (human/mouse) and other receptors (Figure 6C) [288, 289]. Thus, maternally sensitized MCs could potentially engage in local mediator crosstalk with positive feedback after allergen exposure.

The second effect of maternal IgE in offspring allergen sensitization may be enabling their leukocytes to secrete Th2 cytokines to polarize the incipient immune response against an incoming antigen. IL-4 is key during both Th2 CD4+ lymphocyte differentiation and endogenous IgE production [52]. Specifically, mouse and human MCs are much more likely to produce IL-4 when activated via FcεR1-IgE cross-linking than in response to just epithelial alarmins alone (Figure 6A,F) [290]. Direct evidence of IgE-MC importance to the emerging allergic sensitization was obtained in mice that develop spontaneous food allergy after consuming peanut butter several times [291]. IgE and MC-derived IL-4 signals during the initial series of sensitizing peanut ingestions promoted Th2 CD4+ and inhibited Treg cell induction, leading to increased IgE production (Figure 6F,G) [291]. This was abolished in both MC-deficient animals and if mice received IgE-blocking antibody treatment during peanut sensitization [291]. Tregs were unable to control peanut sensitization due to the IL-4-induced STAT6 signaling inhibiting their TGFβ secretion, which would normally restrain MCs and allergic inflammation (Figure 6G) [108]. Although the majority of fetal MCs are immature, it is conceivable their incomplete maturation in early life will not prevent their cytokine release. For example, hypogranulated MCps in the mesenteric lymph nodes of helminth-infected mice secrete IL-4 and IL-6 [292], although whether MCp activation in that model was IgE-mediated was not tested. A recent study showed that lung tissue MCps could produce the Th2 cytokine IL-13 following antigen-mediated IgE cross-linking in adult mice [293]. However, similar functionality remains to be directly demonstrated in fetal or neonatal MCs.

Apart from MCs, maternal IgE sensitization of basophils [199, 244, 281] could make them an additional Th2 cytokine source (Figure 6F). This capability is demonstrated in mice transfused with basophils loaded with TNP-specific IgE [294]. These promoted Th2 CD4+ lymphocyte differentiation in an IL-4-dependent manner after being pulsed with TNP-Ova antigen, ultimately resulting in increased IgE synthesis after antigen challenge in vivo [294]. IL-4 release can be triggered in basophils purified from horse foals born to allergic mares

by an IgE cross-linking IgG clone treatment only after, but not prior to, milk consumption [281]. This indicated the foal basophils were sensitized by maternal IgE transferred in colostrum [281].

7.3 | Development of Offspring Allergic Sensitization—Influencing DC Polarization

In addition to directly providing IL-4 and other Th2 cytokines, maternal IgE may allow offspring MCs to influence DCs during allergen sensitization (Figure 6D,E). Neonatal mouse DCs express IL-4 and IL-13 receptors (IL-4Rα/IL-13Rα1), the activation of which blocks the DC IL-12 expression (Figure 6E) [107, 295]. MC-derived IL-13 inhibits cutaneous DC IL-12 in a mouse allergic dermatitis model and in human skin ex vivo [107]. Analogous effects are mediated by neonatal basophil-derived IL-4 [295]. IL-12 functions as a pro-Th1 signal during CD4+ T cell differentiation that may be especially important to early life T cells. Specifically, DC IL-12 normally represses the Th1 T cell expression of IL-13Rα1 receptor chains (Figure 6H) [295]. Without IL-12, the presence of IL-13Rα1 sensitizes Th1 cells to the apoptotic effects of IL-4, leading to their loss and ablation of IFN-γ production (Figure 6H) [109]. Additional supportive evidence comes from a clinical study using primary human neonatal dendritic cells [296]. When exposed to histamine released from cord blood immune cells by FcεR1 cross-linking, their capacity for activation in response to pro-Th1 LPS stimulus is significantly diminished [296]. Even though basophils were the histamine source in this study, due to the ease of neonatal blood sampling, MCs are the dominant histamine reservoirs in tissue. In summary, the presence of maternal IgE may promote a Th2-biased immune response on antigen exposure during the early life developmental period.

7.4 | Development of Offspring Allergic Sensitization—Allergen Antigen Presentation Facilitation

Finally, maternal IgE may aid IgE receptor-expressing APCs in capturing allergen-derived antigens to facilitate T cell presentation, esp. for normally sub-threshold antigen quantities. DCs express the high-affinity FcεRI receptors in humans (Figure 2B), but not in mice. IgE was able to boost human patient-derived DC allergen uptake and T cell stimulation ex vivo [297, 298]. Similar results came from mice with humanized FcεRI expression in their CD11c + DCs [101]. However, research on the outcomes of IgE-mediated DC antigen presentation produced mixed results. Some animal studies showed allergic disease enhancement in an Ova-driven allergy model [101], while in another model there was attenuation [102]. This could be due to different allergens and adjuvants being used for the respective studies. However, the humanized FcεRI mice did not have reduced IgE levels, suggesting the initial sensitization was not impeded rather than downstream inflammatory processes [102].

Another major APC type expressing IgE receptors is B lymphocytes. The low-affinity CD23 receptors preferentially capture IgE-antigen complexes and facilitate their uptake without the need for antigen-specific membrane BCRs (Figure 2F), as demonstrated in human B cells in vitro [299, 300]. Similarly, wild-type mice immunized with IgE-antigen complexes develop an enhanced IgG antibody response compared with CD23-KO animals, potentially due to B cells carrying the CD23-captured antigen into the splenic B cell follicles (Figure 2F) [117, 301]. The induction of increased IgG production instead of IgE switching is probably the result of using Ova, a small protein antigen, instead of a complex natural allergen. The monomeric IgE-Ova complex capture by CD23 is not inflammatory per se, and may not elicit Th2-skewing cytokines required for an IgE response [301]. There is evidence for analogous processes in human patients allergic to birch pollen, whose B cell CD23 expression levels correlate with their IgE levels and skin prick test reactivity [302]. To summarize, although IgE-mediated antigen presentation is effective, it does not seem to promote Th2 polarization intrinsically [303]. Other sources of cytokines collaborate to provide such contextual cues, with maternal IgE-bound MCs and basophils positioned to provide these during early life.

In conclusion, maternal IgE together with MCs and other cells may be capable of serving as a multifunctional adjuvant during the offspring Th2 immune response priming and enhance their endogenous IgE sensitization in early life. However, the importance of such IgE-mediated effects remains to be specifically tested in animal models of maternal allergy at the appropriate offspring postnatal age.

7.5 | Development of Offspring Mast Cells

All the previously discussed mechanisms of maternal IgE activity involved antigen binding. However, there has long been experimental evidence suggesting IgE ligation to MC FcεR1 was sufficient to exert antigen-independent effects (Figure 2C). The initial studies primarily showed increased mouse bone marrow-derived MC survival in IgE but not IgG presence during in vitro culture, due to increased resistance to apoptosis during growth factor starvation (Figure 2C) [304, 305], and increased proliferation under normal conditions [304]. Further, different IgE clones have demonstrated different capacities for promoting MC survival [306], although the reason for this remained unclear. The proposed mechanisms included FcεR1 aggregation [306] or autocrine IL-3 cytokine secretion [307]. It was subsequently found that there is a major chance of confounding due to the nature of certain IgE clones used for in vitro experiments. In addition to supraphysiological IgE concentrations used [308], certain IgE clones exhibited self-aggregation capacity via mutual Fab region interactions [309]. However, enhanced MC survival effects were reproducible when MCs were exposed to polyclonal IgE-containing sera obtained from HDM-allergic mice and atopic dermatitis patients [310], where the aggregation effects of certain IgE monoclonals should not be present.

Effects analogous to some of the in vitro studies were also observed in vivo. For example, mice peritoneally transplanted with IgE hybridoma had an increased population of mucosal mast cells in the surrounding tissues [306]. Similarly, adoptively transferred CFSE-labeled MCs survived significantly longer in allergen-sensitized WT mice compared with IgE-KO animals due to reduced apoptosis [311]. Recently, our study provided further supportive evidence in a more physiological

setting without direct manipulation of the MCs in question [104]. We found that materno-fetal IgE transfer during development resulted in increased maturation of fetal skin MCs and increased their granule development (Figure 2C) [104]. Comparable observations came from another recent study, where the ablation of homeostatic natural IgE resulted in a reduction of mouse skin and intestinal MC populations [103]. This was sufficient to significantly attenuate the severity of systemic and local cutaneous anaphylaxis [103]. It is currently unknown whether these results apply to human MC development during the early life period. We found fetal MCs with surface IgE in the 2nd trimester fetal tissues of maternal allergy subjects [104]. Whether offspring MC population size or maturation correlate with maternal IgE levels and allergen exposure remains to be determined in the clinic.

We can consider the evidence for IgE-mediated MC maturation together with additional facts. IgE binding stabilizes the FcεR1 receptors to increase their surface expression on MCs [123]. MCs survive for long periods in their tissue of residence, esp. the connective MC type [124]. Lastly, MCs replenish their inflammatory mediator stores after degranulation, in contrast to other granulocytes [124]. Together, this implies that maternal and endogenous IgE may influence the offspring's MC numbers and activation threshold, resulting in long-term allergic inflammatory set point programming.

7.6 | Beneficial Effects of Maternal IgE Transfer

The transfer of IgE into offspring may represent a temporary conferment of maternal humoral immunity, as is the more familiar case of IgG and IgA antibodies. Maternal IgE that confers MCs reactivity may represent a temporary transfer of maternal Th2 immunological memory derived from exposures close to the time of pregnancy.

One area of protection through the maternal IgE-offspring MC axis may be in certain parasitic infections [133], suggested by the findings of human serum sampling studies of paired maternal and neonatal cord blood across the globe. Maternal hookworm (*Necator americanus*) infection was linked to the presence of pathogen-specific IgE in the neonatal cord blood [312]. Similarly, schistosome egg antigen-specific IgE was found in the cord blood of African but not European or North American neonates [313, 314]. This was also the case for other non-schistosome filarial species. The specific IgE was elevated in the cord blood of Indian mothers with *Wuchereria bancrofti* [238, 315] or *Onchocerca volvulus*-positive mothers in Togo [316], compared with samples from non-infected women. IgE transfer may be adaptive, as it could enable early detection of the pathogen-derived antigens during the initial infection and facilitate presentation to offspring lymphocytes under Th2-promoting conditions. However, the human serology data are circumstantial; whether the neonates of helminth-sensitized mothers are better at controlling postnatal infection has not been determined. Apart from helminths, analogous results for plasmodium-specific IgE have been obtained in several studies of malaria during pregnancy [317–319]. As trans-placental infection does not take place, it is reasonable to hypothesize that the specific IgE is of maternal origin. Although it has been hypothesized that some of the fetal antibodies could be produced endogenously due to pathogen antigen transfer, no IgE-producing cells have been identified thus far in the tissue samples or following ex vivo stimulation.

Another protective function of IgE and MCs could be increased host resistance to certain venoms or toxins, including those of insects, reptiles, or bacteria [133, 320]. This is primarily based on work using different murine models deficient in MCs, specific MC proteases, or IgE-deficient animals [133]. IgE-MC activation can mediate protection via proteolytic degradation and absorption inhibition from the local injection site due to oedema formation [140, 321]. In the case of honeybee venom, the initial exposure can promote IgE formation [322], with the resulting IgE significantly enhancing resistance to a subsequent high venom dose exposure [323] by promoting the MC efficacy in venom inactivation [139]. Analogous protective effects of acquired IgE and MC-mediated immunity were demonstrated in mice during secondary exposure to viper venom [324]. In humans, there is a large discrepancy between the prevalence of venom- or toxin-specific IgE detection in serum, which is much higher than the proportion of subjects who manifest any allergic symptoms [325–327]. This may suggest that the anti-venom IgE is beneficial due to its protective effect. Maternal IgE might potentially confer advantage to offspring against insults that require rapid Th2 response induction for efficient protection. However, evidence of such effects in humans remains to be identified.

Finally, IgE-mediated allergic mechanisms have been theorized to serve as a food quality control system [328]. A pair of recent studies used mouse models of egg Ova allergy to show that drinking sugar water containing Ova triggered behavioral avoidance in the sensitized animals within minutes of allergen intake [329, 330]. Amounts of allergen consumption sufficient to trigger avoidance were below the threshold of those required to manifest outward food allergy symptoms or gastrointestinal inflammation based on tissue analysis. Ovalbumin aversion behavior required antigen-specific IgE-mediated intestinal MC activation [329, 330]. The reflex involved MC production of cysteinyl leukotrienes [329] and growth differentiating factor 15 (GDF15) peptide secretion from intestinal cells [330]. These signals communicated allergen detection to the CNS, resulting in neuronal signaling in the nucleus tractus solitarius, parabrachial nucleus, and amygdala brain areas [330]. GDF15 has been previously shown to be involved in nausea and emesis in humans and anorexia in mice [331, 332]. Similar IgE-MC-neural axis-mediated aversion preceding lung inflammation and involving overlapping brain regions may be present in an inhaled allergen avoidance mouse model [333]. Thus, the IgE-MC module can trigger both behavioral defense at low allergen doses, while a higher dose induces MC-mediated protective intestinal reflexes (i.e., mucus production and motility increase to promote the triggering substance expulsion) [334].

Maternal IgE transfer could potentially allow the transmission of acquired memory of maternal encounters with noxious dietary components. This could enable offspring protection without requiring an initial exposure or enhance their detection sensitivity in the post-weaning period. It is currently unknown if analogous neuro-immune mechanisms contribute to childhood food avoidance, picky eating, or anxiety. Food-allergic children report more pain [335], food anxiety [336], and long-term behavioral feeding difficulties [337]. Interestingly, GDF15

has been implicated in chemotherapy-induced nausea [331], which can develop in children in an anticipatory manner and be triggered by food stimuli, resulting in behavioral aversion development to those food items in the affected subjects [338]. Whether avoidance could result from maternal food allergen-specific IgE transfer remains to be tested in animal models.

8 | Factors Influencing the IgE Transfer or Functionality

IgE content in neonatal cord blood, a proportion of which is probably maternally derived, has been investigated by many past studies for use as a predictive risk marker in pediatric allergic disease development. However, this has proven difficult due to the results often being mixed. A positive association between cord blood IgE levels and future allergic disease was identified in some studies [339–343]. However, other studies found either no significant relationship [344, 345] or found an association with elevated total or specific IgE levels in later life but not with overt allergic disease [343, 346–348]. Thus, cord blood IgE levels are often associated with subsequent atopy or specific IgE development, but the sensitivity as a predictor for disease is too low. There are similarities in the observed allergen-specific IgE detection rates in populations across different regions, where its presence is a major risk factor for allergic disease that only manifests clinically in a minority of sensitized individuals [349–351].

The discrepancies between maternal and cord blood IgE, or neonatal IgE and allergen reactivity may arise from many different sources. Technical aspects of IgE serology [352, 353], definitions of positivity [285], or genetics [354] may partially contribute. Importantly, effector cell degranulation by IgE is affected by the total and allergen-specific IgE antibody concentration in an individual, its affinity, and the diversity of epitopes recognized on an allergen by the IgE repertoire [355]. These parameters could be modulated by numerous factors along the maternal-fetal IgE axis. For example, simultaneous transfer of allergen-specific IgG and IgA antibodies, or IgG-allergen immune complexes, may protect the offspring from allergic disease [10].

8.1 | IgE Regulation by Endogenous IgG Anti-IgE Antibodies

Interestingly, anti-IgE auto-antibodies are detectable in most individuals under physiological conditions and are known to be increased in allergic disease patients; however, little is known about their function [356]. Some studies suggest their function is to inhibit IgE [357]. Others have shown they could be pro-inflammatory by causing IgE cross-linking [358], although this may be due to the specific technical aspects of the experiments performed in vitro. Interestingly, IgG anti-IgE autoantibodies purified from the sera of HDM-allergic asthmatic patients could induce an inflammatory skin hypersensitivity reaction when injected into healthy subjects [359]. IgE-binding IgG have also been purified from commercial therapeutic human intravenous immunoglobulin (IVIG) preparations, further confirming its common occurrence. The IVIG anti-IgE could stimulate Th2 cytokine release from human donor basophils without inducing their degranulation [360, 361]. Thus, the discrepancy of observed anti-IgE IgG effects is on relative concentrations used for experiments, as the content was very low in IVIG [361].

Animal model-derived evidence supports an anti-inflammatory function of auto-IgG anti-IgE [40]. This may be because the anti-IgE IgG elicited in these studies targeted the same glycan residues shown to be required for IgE binding to FcεR1 (Figure 1A,B) [41]. This may not necessarily be the case with all anti-IgE antibodies. Additionally, the extent to which anti-IgE epitope depends on the method of its induction in animal studies has not been systematically investigated, as it could be influenced by the type of allergen and adjuvant used. This may be important because different allergens could potentially bias towards different anti-IgE binding specificities. In a model of allergen oral tolerization in mice previously sensitized to HDM, allergen consumption was associated with anti-IgE IgG generation in an allergen-specific manner [362]. Mice sensitized to *D. pteronyssinus* produced anti-IgE IgG, while animals allergic to *B. tropicalis* dust mite species did not [362]. Whether anti-IgE contributed to the reduction of disease severity was not determined. Induction of non-inhibitory anti-IgE is supported by data derived from human clinical samples. An analysis of anti-IgE IgG isolated from human patients identified both IgE Cε2 and Cε4 binding sites (Figure 1B) [39]. The Cε2-specific IgE will interfere with FcεR1 ligation, while the Cε4-binding species may not, as it is distal from the receptor binding sites (Figure 1) [86]. Maternal IgG anti-IgE thus may have distinct effects on IgE in different individuals depending on the past exposures.

Anti-IgE that does not block FcεR1 binding may still be beneficial to the mother by promoting IgE clearance from circulation by FcγR-mediated mechanisms [40]. However, this IgG binding probably does not interfere with its placental transport. An analysis of serum samples of newborns and their mothers showed that both contained IgG-IgE complexes [199]. Most of the cord blood IgE was natively bound in a complex with IgG, consistent with FcRn-mediated transport [199]. Our study corroborated the preservation of maternally transferred IgE FcεR1-binding capacity even after forming complexes with natively present anti-IgE in pregnant mouse dam blood [104].

Lastly, in addition to facilitating IgE transport, free anti-IgE IgG could potentially contribute to the antigen-independent influence of IgE on offspring MCs. Auto-IgG antibodies capable of binding two separate IgE antibodies were able to promote MC survival in vitro [363]. However, this has not been verified in vivo, following maternal IgG transfer into the offspring.

To summarize, maternal anti-IgE IgG that may normally act as a sink to reduce pro-inflammatory IgE, which may in turn mediate increased trans-placental passage of allergen-specific IgE to the offspring during early life. There are different anti-IgE forms, with the Cε4 domain-binding ones retaining the capacity of transferred IgE to bind offspring FcεR1 receptors.

8.2 | IgE Regulation by Its Glycosylation During Allergy and Pregnancy

A distinct feature of IgE immunoglobulins is their heavy glycosylation. Human and mouse IgE contain seven and nine Fc

domain glycosylation sites respectively (Figure 1A) [96]. The highly complex sugar chains can comprise 12% of the molecular weight [96]. Glycosylation can affect antibody function and receptor binding [96, 364] but this area remains understudied for IgE. For example, specific glycans in the IgE Cε3 domain (N394) are obligatory for FcεR1 binding and anaphylaxis initiation (Figure 1A) [365]. Others are crucial for maintaining IgE serum half-life in vivo, as hypoglycosylated forms get cleared 10 times faster in mice [366]. Although the specific factors affecting antibody glycosylation are not well understood and are probably complex, age, gender, or the specific cytokine environment all contribute [364].

There is evidence for IgE glycosylation differences in human allergy. Peanut-allergic individuals exhibit elevated IgE sialylation, compared to increased galactose residues in non-allergic subjects [367]. Sialic acid removal attenuated the IgE-mediated MC activation in vitro and inhibited the severity in a mouse model of passive anaphylaxis [367]. The specific mechanism is unclear but does not involve changes in FcεR1 binding [368].

It is currently not known if IgE glycosylation changes may happen in pregnant women and what the functional impacts may be. However, IgG1 antibody glycosylation changes have been demonstrated in a mouse model of maternal allergic airway inflammation during pregnancy induced by Ova [369]. Allergen challenge in sensitized dams led to a shift in both maternal and offspring allergen-specific IgG1 glycans, inflammation-associated profile [369]. This led to an increase in airway disease severity following offspring allergen inhalation [369]. There is clinical evidence that IgG glycosylation is modified during human pregnancy [370] and by allergen exposure during desensitization immunotherapy [371]. Thus, it may be reasonable to hypothesize that glycosylation of IgE could also shift under these conditions. It may be interesting to verify if the maternal and neonatal serum IgE glycosylation correlate.

8.3 | Glycan-Mediated IgG–IgE Interactions Along the Maternal-Fetal Axis

Apart from promoting allergic reactivity, glycans constitute a major avenue of IgG-IgE interactions that are crucial for IgE activity modulation. Mice immunized with IgE-feline allergen immune complexes developed endogenous anti-IgE IgG antibodies specific for IgE glycan epitopes that inhibited the severity of their anaphylaxis (Figure 1B) [40]. This could represent a potential negative feedback mechanism under high allergen exposure resulting in increased IgE-allergen complex formation. However, glycan-mediated IgG binding could potentially result in increased FcRn-mediated IgE transcytosis across the placenta during gestation.

In addition to determining the immunogenicity of IgE-autoantibodies, IgE glycosylation patterns may also be important for assessing the efficacy of IgE-neutralizing therapeutic antibodies. Omalizumab, the only widely used therapeutic antibody in the clinic, has been shown to require IgE to be glycosylated to exert its neutralizing activity [372]. Omalizumab is also being tested for safety in allergic women with high-risk pregnancies [373]. Thus, it may be important to validate that anti-IgE treatment does not promote maternal allergen-specific IgE transfer during gestation.

Lastly, glycosylation patterns do not only influence IgG binding to IgE but have also been shown to affect interactions with FcRn. Changes in IgG glycosylation have been shown to modulate its placental transcytosis rate [374, 375]. Such changes can potentially result in response to maternal inflammation during pregnancy. For example, SARS-CoV-2 infection of pregnant women during the 3rd trimester led to the production of anti-SARS-CoV-2 IgG with altered glycosylation [375]. Although these changes reduced the FcRn-mediated transfer, there was evidence of increased FCGR3 transport [375]. Whether similar effects can be induced by Th2-type inflammation following allergen exposure during pregnancy remains to be determined.

8.4 | Endogenous Offspring IgE and Its Modulation by Maternal Signals

The effects of maternal IgE could be influenced by the endogenous natural IgE levels in the offspring. As mentioned previously, natural IgE induction can be protective in mice during anaphylaxis [276], potentially due to FcεR1 occupancy. Glucocorticoids represent a potential pathway of natural IgE modulation by maternal signals during pregnancy, as they have been shown to enhance circulating natural IgE levels in naïve mice [275]. Glucocorticoid signals could be endogenous, as they are stress hormones, and human maternal stress during pregnancy has been linked to childhood allergy risk [376]. They could also be exogenous, as the use of antenatal steroids is a long-established therapy in women expecting premature birth, with the drug transferring across the placenta to boost fetal lung development [377].

Maternal steroid drug treatment has been shown to promote offspring disease in murine models of allergic asthma, but mechanisms involving IgE remain understudied. In one murine model, maternal steroid treatment enhanced HDM allergy in the sensitized offspring, but their IgE levels were not significantly different [378]. In another murine study, the maternal effect was mediated via glucocorticoid-induced programming of offspring respiratory ILC2 cells to increase their responsiveness [379]. In both cases the offspring allergen sensitization was done at the age of 4–7 weeks, removing the maternal steroid influence during offspring IgE development. In the final study, exposure of pregnant dams to stress-induced or administered glucocorticoids enhanced offspring allergy following suboptimal Ova sensitization starting day 4 after birth [380]. It is unknown whether glucocorticoid stimulation promoted allergen-specific IgE class switching in these animals, as the authors did not quantify the offspring IgE levels. Human epidemiological studies also investigated an association between gestational steroid use and offspring asthma development. There was a positive association in some cohorts [381, 382], but not in others [383, 384]. Defining steroid effects is challenging, both due to their pleiotropic nature and the uncertain direction of causality in the epidemiological studies, which can both introduce significant confounding effects.

In summary, the transfer of antigen-specific IgE takes place against the background of numerous immunological processes. Thus, its presence in the offspring alone may not be sufficient to allow allergic inflammation or facilitate sensitization. Furthermore, the properties of maternal IgE itself (e.g., glycosylation) could influence its capacity for translocation into the offspring, offspring receptor binding, or escaping inhibitory factors (e.g., anti-IgE IgG). This complexity of interactions, together with other non-IgE-dependent mechanisms, may partly explain why the detection of allergen-specific IgE and allergic disease manifestation do not always coincide within the same individual.

9 | Conclusion

Early life is a time when the immune system undergoes critical development, with maternal factors influential in shaping immune responses. Among these factors, maternal IgE has emerged as a likely contributor to allergy disease risk. While IgE, particularly when produced endogenously, is well established to promote allergic diseases, its broader immunological functions—including its effects on neonatal and early life immunity—remain poorly understood, with respect to both IgE that is endogenously produced or maternally derived.

The growing evidence that maternal IgE can be detected in fetal circulation raises important questions about its role in neonatal immune priming. Maternal IgE may predispose infants to allergic reactions upon initial allergen exposure, potentially contributing to the early onset of allergic diseases. Additionally, maternal IgE may influence Th2 polarization, shape dendritic cell function, and modulate cytokine environments, all of which could enhance allergic disease susceptibility. Furthermore, the role of IgE extends beyond allergen-specific antibodies, as natural IgE, which is produced independently of specific antigen exposure, may contribute to homeostasis and tissue repair. While natural IgE may offer protective benefits against infections or anaphylaxis, allergen-specific IgE has been implicated in the onset and persistence of allergic diseases. This highlights the complexity and context-dependent roles of IgE in early life.

Despite these insights, significant gaps remain in understanding how maternal IgE affects neonatal immunity and allergy development. Studies investigating cord blood IgE as a predictive marker for allergy risk have yielded inconsistent findings, emphasizing the complexity of IgE function and its interactions with other immune components. Factors such as maternal autoantibodies, IgE glycosylation patterns, and the broader maternal immune environment are likely to modulate IgE activity and its impact on offspring. As allergic diseases continue to rise globally and no curative therapies exist, further research into IgE's dual roles—both as a driver of pathology and a potential immune regulator—is essential. Given these contrasting functions, and the evolutionary conservation of IgE across mammalian species, further research is also needed to clarify and validate the presumed beneficial effects of early-life IgE in protection against pathogens, venoms, and toxins. A deeper understanding of maternal IgE transfer, its mechanisms, and its long-term effects on immunity could inform the development of novel approaches to allergy prevention and treatment.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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