

REVIEW ARTICLE

IgE in the human placenta: why there?

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Abstract

Immunoglobulin E (IgE) antibodies are key effector molecules in the allergic inflammatory response and are also involved in the protection against extracellular parasites. Allergic symptoms often develop early in life, and the intrauterine environment has been proposed to play an important role in affecting the risk of later allergy development. The placenta constitutes a selective barrier between the maternal and foetal circulation. Recently, we reported that maternal IgE antibodies are present on foetal macrophages in the villous tissue of the human placenta irrespective of maternal allergy status. This review discusses the presence of IgE antibodies in the human placenta and its possible roles in normal and pathologic pregnancy. It also deals with the relationship between placental IgE and development of allergy during childhood. A better understanding of the role of IgE in placenta could give us clues on how to prevent allergy development in the future generations.

Immunoglobulin E (IgE) is an important effector molecule in the allergic reaction and is also involved in the defence against extracellular parasites. IgE antibodies have been demonstrated to be present within the placenta, co-localized with Hofbauer cells, the placental macrophages (1). Placental IgE originating from the mother would be intriguing, because it is commonly believed that IgG is the only antibody class that can pass the placental barrier from the mother to the child. There is also the possibility that placental IgE is produced by cells within the placenta or by the foetus. It has been reported that foetal B cells have the capacity to produce IgE from as early as week 12 of gestation (2). Transfer of maternal IgE into the placenta might educate the immune system of the neonate and affect the risk of allergy development. Therefore, it is important to know how IgE is transported across the placental barrier and what role it fulfils within the placenta. This review aims to describe what is known about IgE in the human placenta. We discuss the possible roles for IgE within the intrauterine milieu and which questions future research should address.

IgE

In the late 1960s, IgE was discovered as a new class of antibody capable of transferring sensitivity to allergens (3, 4). IgE antibodies are involved in allergic inflammatory processes such as anaphylaxis, allergic rhinitis, asthma and

atopic dermatitis/eczema. IgE antibodies have also been associated with the protection against parasitic infections. *In vitro* studies published in the 1980s demonstrated that IgE is involved in cell-mediated killing of schistosomes (5). Later, epidemiological studies in a Gambian population revealed that there was an association between high levels of parasite-specific IgE and resistance to reinfection (6).

IgE is the least abundant antibody class in serum, with a normal concentration of 50–200 ng/ml in nonallergic individuals (7). The half-life of IgE in serum is 3 days; however, much of the IgE is sequestered in tissues (8). In contrast to serum IgE, IgE that is receptor bound on the surface of cells has a half-life of several weeks (9). The expression of IgE requires heavy-chain switching from IgM, often via IgG, to IgE by somatic recombination of the germline genes in B cells. Switching to IgE production is induced by type-2 cytokines (IL-4, IL-5, IL-9 and IL-13) produced by Th2 cells (10, 11). Structurally, IgE is built up similarly to antibodies of other classes, with two identical heavy chains and two identical light chains with variable and constant regions consisting of Ig domains (Fig. 1). In contrast to the IgG antibody, which has three constant domains on the heavy chain, the IgE antibody has four and no hinge region, making it less flexible. IgE also has a higher content of glycosylation sites compared to IgG (12).

Three IgE receptors have been identified in humans to date. Within the human body, most of the IgE is bound to

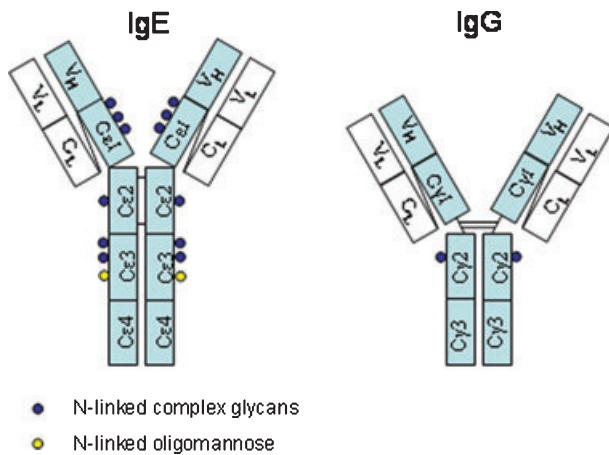


Figure 1 Glycosylations on IgE and IgG antibodies. Modified from Arnold et al. 2007. V = variable and C = constant regions. H = heavy and L = light chain.

its high affinity receptor, FcεRI, mainly present on mast cells and basophils (7), but also found on antigen-presenting cells such as Langerhans cells (13). FcεRI is built up of four chains in mast cells and basophils [FcεRI(αβγ₂)] and of three chains in monocytes, macrophages and neutrophils [FcεRI(αγ₂)] (14). Crosslinking of FcεRI via IgE activates mast cells and basophils to release pro-inflammatory mediators such as histamine, leukotrienes and cytokines (11). It also triggers upregulation of additional FcεRI. The low affinity IgE receptor CD23 (FcεRII) is expressed on several cell types including B cells, activated T cells, monocytes, eosinophils, platelets, follicular dendritic cells (DCs) and some thymic epithelial cells. Upon binding of IgE together with antigen, CD23 facilitates antigen presentation to T cells. It also acts as a negative feedback on the regulation of IgE production (7). There is also a third IgE receptor originally named ε-binding protein, now known as galectin-3 (15). This receptor has been reported to be present on neutrophils where it has a role in activating the cells (16) and is also expressed on trophoblast cells in the placenta (17). In mice, a fourth IgE receptor named FcγRIV has been described. Because of high sequence homology, the human FcγRIIIA was first suggested to be its human equivalent (18). Recent studies however suggest that the human equivalent of this receptor is FcεRI(αγ₂) (19).

Placenta

The placenta is a foetomaternal organ, and one of its main functions is to facilitate transfer of nutrients, oxygen, waste products and immunological factors between mother and foetus. It is a highly vascularized tissue, where the foetal blood flows through the capillary network of the umbilical vessels situated within the branched terminal chorionic villi, and the maternal blood flows through the intervillous space without participation of a capillary network (Fig. 2). The develop-

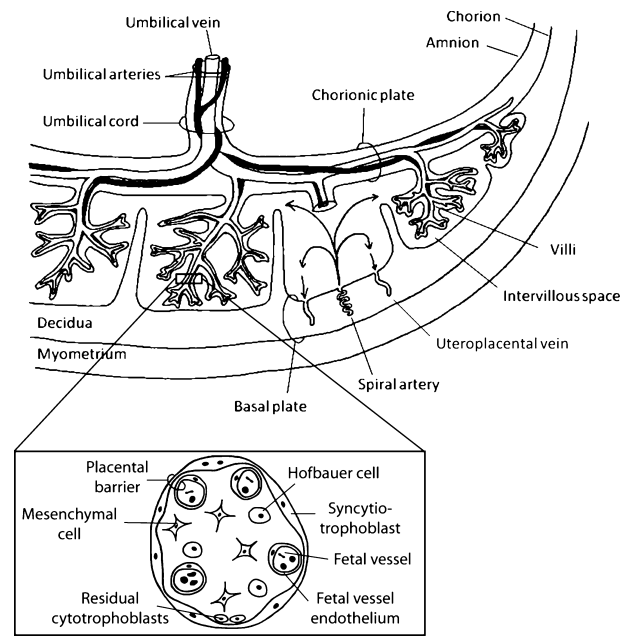


Figure 2 Schematic picture of the placenta and a cross-section of the villous tissue.

ment of the placenta starts with the implantation of the blastocyst into the endometrium, which is termed decidua during pregnancy. Extravillous trophoblast cells invade maternal blood vessels in the decidua, and lacuna starts to develop, which will later fuse to form the intervillous space. The decidua contains approximately 40% immune cells, and these are crucial for the development of the placenta. The major decidual leukocyte subpopulations are uterine natural killer (uNK) cells, macrophages, DCs, T cells and natural killer T cells (NKT cells) (20). Both CD4⁺ and CD8⁺ T cells are present in the decidua (21). Some of the CD4⁺ decidual T cells are Foxp3 expressing regulatory T cells, and these are believed to be important for maintaining the foetomaternal tolerance (22). The induction of tolerance by regulatory T cells might be generated via decidual DCs. One mechanism that has been proposed is the induction of DCs to express indoleamine 2,3-dioxygenase (IDO) (23).

The external trophoblast cell layer covering the villi (syncytiotrophoblast) is the principal site of exchange of nutrients and gases between the maternal blood stream and the foetus, and together with the foetal blood vessel endothelium, it constitutes the placental barrier (Fig. 2) (24). Because this trophoblast cell layer is a syncytium, it can only be passed transcellularly. Within the villi, transport easily takes place paracellularly by diffusion. From the villi and into the foetus, transport takes place paracellularly or transcellularly across the endothelium of the foetal blood vessels. Apart from the foetal vessels and trophoblast cells, the villi also contain mesenchymal cells and foetal macrophages called Hofbauer cells, as well as small amounts of fibroblasts, myofibroblasts and mast cells. In contrast to the decidua, the villi normally contain very few lymphocytes (25).

Presence of IgE in the placenta

Interestingly, IgE antibodies have been revealed to be present within the villous parenchyma of the human placenta (1) (Fig. 3). We demonstrated by double immunofluorescence stainings for IgE combined with human leukocyte antigen (HLA)-DR or CD68 that the placental IgE is bound to Hofbauer cells (1, 26). Presence of IgE in the placenta has only been investigated during second and third trimester, and it has not been studied in the endometrium. More IgE was found to be present in the placenta during second trimester, and then it decreased until term (26). This is probably related to the fact that the number of Hofbauer cells decreases with gestational age (27).

As for the origin of the placental IgE, *in situ* hybridization revealed that very few epsilon transcripts are present in the placenta (1). Thus, it is unlikely that cells within the placenta produce IgE. The foetal B cells have the capacity to produce IgE from as early as week 12 of gestation demonstrated in cultures with addition of IL-4 and anti-CD40 antibodies (2). A study of mRNA expression in foetal liver cells has shown that these cells can produce VDJε transcripts from 20 weeks of gestation, although IgE-producing cells in the blood are rare until 9 months after birth (28). Elution of placental IgE and determination of its specificity with ImmunoCAP® (Phadia, Uppsala, Sweden) demonstrated that the levels and the allergen specificity correlated well with maternal serum IgE but not with cord blood IgE, indicating maternal origin of the placental IgE (29). A previous study from Faulk et al. also found that immunoglobulins in placental eluates are of maternal origin (30). They did however not detect any IgE in their placental eluates using double diffusion Ouchterlony analysis.

The receptor responsible for binding IgE within the placenta has not yet been identified. Immunohistochemical analyses of high and low affinity IgE receptors after eluting IgE to free the receptors for detection showed no FcεRI⁺ cells and only a few scattered CD23⁺ cells, indicating that neither of these receptors is involved in binding the placental IgE (1). There was, however, an overlapping staining pattern for IgE and FcγRI in the placenta. The Hofbauer cells, which are binding the placental IgE, express all FcγRs (31). DC-SIGN/CD209 is another receptor expressed on Hofbauer

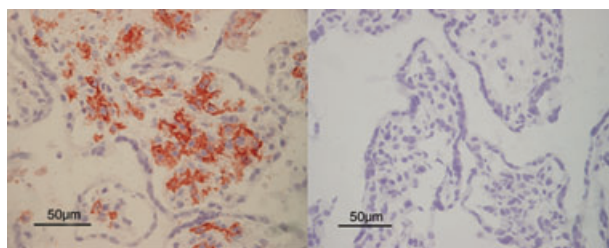


Figure 3 Immunohistochemical staining of IgE in a second trimester human placenta. Left picture: positive cells (red staining) are found within the villi. Counterstaining was performed with Mayer's haematoxylin. Right picture: isotype control staining.

cells in term placentas (32). DC-SIGN is a C-type lectin, which can function as a pathogen recognition receptor inducing diverse immunological responses depending on the pathogen (33). Furthermore, DC-SIGN has been shown to bind distinct carbohydrate structures such as mannose-containing glycoconjugates (34). We therefore speculate that IgE might bind to DC-SIGN on Hofbauer cells via mannose-containing glycans in a similar way as 2,6-sialylated Fc of IgG has been shown to bind to DC-SIGN expressing chinese hamster ovary (CHO)-cells (35).

Transfer of IgE into the placenta

The generally accepted dogma is that only IgG can cross the placental barrier from mother to foetus and that all other antibody isotypes are blocked from transfer across the placenta (36). This seems true for IgA, IgD and IgM in healthy placentas. However, in case of an intrauterine infection, IgA and IgM can also pass the placental barrier and be found within the villi (37). The transfer of IgE was, however, not analysed within this study. Transfer of IgG across the pla-

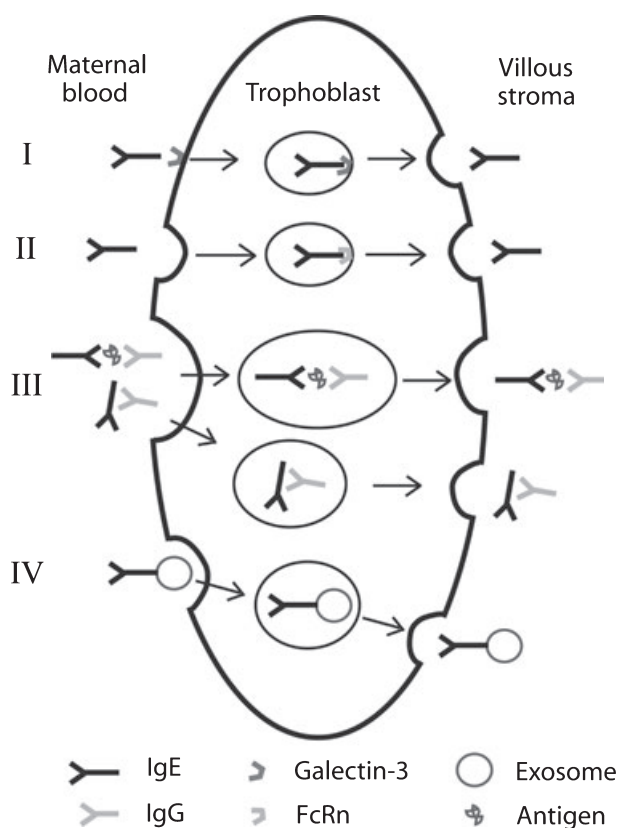


Figure 4 Schematic picture of possible transport mechanisms for placental IgE. Maternal IgE could be transported into the villous stroma of the human placenta via binding to galectin-3 (I), via endocytosis and binding to FcRn inside the endosome (II), via hitchhiking with IgG (III) or with the help of exosomes (IV). Hitchhiking with IgG could occur via a common antigen or direct binding between IgG and IgE.

centa involves passage through trophoblast cells, villous stroma and finally through the foetal vessel endothelium (31). The first step is believed to be achieved via fluid-phase endocytosis internalizing the IgG into the trophoblast cells. Inside the endosome, the IgG will bind to FcRn, and transcytosis takes place. Transport through the villous stroma can take place by diffusion. The mechanism of transfer across the foetal vessel endothelium is not fully known; however, FcγRIIb has been proposed to be involved (38). For IgE, it is probably only the initial transport across the trophoblast into the villous parenchyma that takes place.

There are several possible ways for IgE to cross the trophoblast barrier (Fig. 4):

(I) Transport of IgE via binding to galectin-3, which is expressed on the villous trophoblast cells (17). The final fate of glycoconjugates bound by galectins seems to be different depending on the glycosylation as shown for binding to galectin-8 (39). Our preliminary results suggest lower levels of α2,6 sialylation of placental IgE compared to plasma IgE (unpublished observation). Therefore, we speculate that galectin-3 on the placental trophoblast cells can bind the maternal IgE and that this IgE, depending on the glycosylation, can be sorted into different cellular compartments. Thereafter, the IgE might be recycled back to the plasma membrane and the maternal blood/intervillous space, or transcytosed to the villous stroma.

(II) Endocytosis of IgE in a similar fashion as IgG and binding to FcRn inside of the endosome. The fact that we do not find any IgE staining on trophoblast cells might indicate an uptake via endocytosis.

(III) Transport of IgE across the trophoblast by hitchhiking with IgG as an immune complex. This could be via direct binding by IgG or via a common antigen. This is supported by the fact that IgG–IgE immune complexes and anti-IgE IgG antibodies are present in plasma (40–42). Transfer of maternal immune complexes across the placenta has been shown for complexes of IgG and hepatitis B antigen (43) or animal insulin (44).

(IV) Transport of IgE across the placenta via exosomes. Exosomes are 30–100 nm membrane vesicles that can be produced and released extracellularly by different immune cells and also by epithelial cells (45). Exosomes have been reported to contain galectin-3, as shown with proteomic analysis, and this receptor might be responsible for binding IgE to exosomes (46). Pregnant women have more exosomes in their plasma compared to nonpregnant women (47); however, their ability to cross the placental barrier has not been investigated.

What is the role of IgE in the placenta?

Because IgE is present in the placenta, at least from second trimester and onward, regardless of maternal allergy or plasma IgE levels (26), it might affect the pregnancy outcome. Women with reproduction failure have been reported to have a lower production of IL-4 by peripheral CD4⁺ T cells and a lower frequency of elevated total and allergen-specific IgE compared to controls (48). The repro-

duction failure might however not be an effect of the IgE itself, but rather a disturbed Th1/Th2 balance. An increased Th1 response during pregnancy has been proposed to be associated with recurrent miscarriage (49). This could indicate an importance for IgE for a successful pregnancy outcome. On the other hand, there is, to our knowledge, no report in the literature of problems with fertility in patients with IgE hypogammaglobulinemia (50). It has also been shown in mice that maternal immunoglobulin production is not essential for successful pregnancy (51). Anti-IgE treatment with omalizumab is sometimes used to treat severe allergic asthma (52). Animal studies of omalizumab treatment during pregnancy have not shown any adverse effects. However, human data are lacking, and omalizumab treatment during pregnancy is therefore only given if the benefits to the pregnant woman outweigh any possible risks to the unborn child (personal communication with Novartis).

We have demonstrated IgE to be present within the placenta independently of maternal allergy, malaria infection or chorioamnionitis (1, 26). Malaria during pregnancy has been demonstrated to be more severe and more frequent than in nonpregnant women (53). Typically, the malaria parasites sequester in the placenta, and placental parasitemia is often higher than that seen in the peripheral blood. We did however not see any differences in the amount of IgE in malaria-affected placentas compared to nonaffected placentas (26). Chorioamnionitis, defined histologically as inflammatory infiltration of the foetal membranes and foetal vessels, is in general believed to represent a proxy for amniotic sac infection of bacterial origin. The infiltrate is composed mainly of neutrophilic granulocytes. An eosinophilic inflammatory component, often found at other sites of the body in connection to IgE-related allergic disease, is rarely seen in placental inflammation. The exception is a very uncommon inflammatory condition in the placenta, termed eosinophilic T-cell vasculitis (54), where eosinophilic granulocytes predominate together with mature T cells in foetal vessel walls; the aetiology and significance of the lesion remain unknown, and there is no apparent association with allergic disease. Evidence for an eventual relationship between the presence of IgE in placenta or foetal tissues and intrauterine infection is lacking in the literature. Association between chorioamnionitis and maternal allergic disease, i.e. asthma, or allergic manifestations in the offspring have been reported, although the issue is largely unexplored (55).

Trapping of IgE immune complexes on Hofbauer cells in the placenta might be a mechanism to protect the foetus from harmful allergens/antigens in the same manner as IgG immune complexes are absorbed in the villous stroma (56). Some of the placental IgE might also be directed against foetal HLA haplotypes inherited from the father or other paternal antigens and therefore trapped in the placenta. It has been demonstrated for IgG antibodies directed against paternal antigens that they are trapped in the placenta to protect the foetus (57, 58). Alternatively, IgE might have a homeostatic function in prolonging Hofbauer cell survival, as demonstrated for IgE bound to murine mast cells (59) and human lung mast cells (60).

Placental IgE and allergy development

The prevalence of allergic diseases has increased during the past decades, particularly in Western industrialized countries (61). However, there is some recent evidence that the prevalence rates are stabilizing (62, 63). The increase has most likely been caused by changes in environmental exposures (64). A small but growing body of literature provides evidence for a relationship between intrauterine exposure and later predisposition to asthma and allergy (65–67). The adaptive immune system of the foetus responds to allergens, as demonstrated by the detection of IgE specific to allergens (68) and T-cell responses to allergen stimulation in cord blood (69–71). Allergens have been demonstrated to be able to cross the placental barrier by detection in an *ex vivo* placental perfusion model (72) and also by direct measurement in cord blood and amniotic fluid (73). Jones et al. have also reported the presence of IgE in amniotic fluid (74). The simultaneous presence of maternal IgE and low concentrations of allergens may lead to IgE-mediated antigen focusing via high affinity IgE receptor (FcεRI) on foetal antigen-presenting cells (74, 75). IgE bound to FcεRI on antigen-presenting cells serves as allergen-focusing structures and increases the antigen-presenting capacity of a low concentration of allergen to allergen-specific T cells (75). This could represent a route of priming of the foetal immune system to allergens. Binding of allergens and IgE on placental cells might also lead to a local production of cytokines, which affects the development of the foetal immune system. Depending on the amount of IgE and allergen present, some fetuses might be primed for allergy development later in life. The presence of allergen-specific IgE in cord blood and the cord blood T-cell responses to allergens has, however, been debated (76). Some researchers claim that the origin of cord blood allergen-specific IgE is maternal contamination (77) and that the T-cell response is immature and unspecific (78). We have not been able to detect any allergen-specific IgE in the cord blood samples we have investigated (29).

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The idea that the intrauterine environment affects the development of allergic disease is supported by the finding that infants of allergic mothers are more susceptible to the development of allergies than the infants of allergic fathers (79, 80). Presymptomatic differences in the immune response in cord blood of children who later develop allergic disease have also been demonstrated (81, 82). It has also been suggested that the increased prevalence of allergy is caused by environmental factors influencing the epigenetic inheritance of 'allergy genes' (83, 84). Interestingly, environmental and lifestyle factors, such as exposure to animals, dust or food, can influence DNA methylation and thus gene expression (85). We have analysed gene expression differences in placenta in relation to lifestyle and allergic status of the parents (86) and are currently investigating the methylation status of the genes that were demonstrated to be differentially expressed.

Concluding remarks

The role of IgE in the placenta remains unknown. IgE is bound to Hofbauer cells in the villous tissue and present irrespective of maternal allergy status (1). It has been demonstrated that the placental IgE is of maternal origin and that it can be allergen specific (29). How the IgE is transported into the placenta and what function it has there are, however, still unsolved questions. Further characterization of the specificity and function of the placental IgE might lead to new insights into the immune mechanisms behind development of allergy. This might help us understand how allergy can be prevented or lead to development of more efficient treatments.

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