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REVIEW ARTICLE

Immunoglobulin E response in health and disease beyond allergic disorders

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Abstract

Immunoglobulin E is the latest discovered of immunoglobulin family and has been long associated with anaphylaxis and worm expulsion. Immunoglobulin E, along with mast cells, basophils, and eosinophils, is also a hallmark of type 2 immunity which is dysregulated in numerous diseases such as asthma, rhinitis, atopic dermatitis, and eosinophilic esophagitis in addition to anaphylaxis as aforementioned. However, recent advances have shed light on IgE regulation and memory explaining the low level of free IgE, the scarcity of IgE plasma cells that are mainly short live and the absence of IgE memory B cells in homeostatic conditions. Furthermore, IgE was implicated in inflammatory conditions beyond allergic disorders where IgE-mediated facilitated antigen presentation can enhance cellular and humoral response against autoantigens in systemic lupus or chronic urticaria leading to more severe disease and even against neoantigen facilitating tumor cell lysis. At last, IgE was unexpectedly associated with allograft rejection or atheromatous cardiovascular diseases where precise mechanisms remain to be deciphered. The purpose of this review is to summarize these recent advances in IgE regulation, biology, and physiopathology beyond allergic diseases opening whole new fields of IgE biology to explore.

KEYWORDS
CD23, facilitated antigen presentation, FcεRI, IgE, type 2 immunity

Abbreviations: Ag, Antigen; AID, Activation-induced cytidine deaminase; Aka, Also known As; APE1, APurinic-apyrimidinic Endonuclease 1; BSA, Bovine serum albumin; CDx, Cluster of differentiation n°x; CSR, Class switch recombination; DMBA, 7,12-dimethylbenz[a]anthracene; FAP, Facilitated antigen presentation; FcεRI, Receptor I for constant chain of immunoglobulin E; FcεRII, Receptor II for constant chain of immunoglobulin E; GC, Germinal center; GF, Germ free; GLTs or I_x, Germline transcript; IDO, indole-2,3-diamine oxygenase; IgE, Immunoglobulin of isotype E; IgG, Immunoglobulin G; IgND, Immunoglobulin not determined; IgY, Immunoglobulin Y; MALT, Mucosal-associated lymphoid tissues; MHC, Major histocompatibility complex; PBMC, Peripheral blood mononuclear cells; PID, Primary immune deficiency; SHM, Somatic hypermutation; SLO, Secondary lymphoid organs; srIg, Self-reactive immunoglobulin; TCR, T-cell receptor; Tfh, T follicular helper cell; Tfr, Follicular regulatory T cell; TNP, Trinitrophenyl; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UNG, uracil-DNA glycosylase.

1 | INTRODUCTION

Immunoglobulins of isotype E (IgE) were initially reported as a "reagin" in the early 1920s by Coca and Cooke who worked on a classification of "the phenomena of hypersensitiviness".[1] Little work occurred on "reagin" from the 1920s until the 1960s, until newer techniques to better detect proteins were developed. In 1966, Kimishige and Teruko Ishizaka described an anti-serum that was able to block type 1 hypersensitivity and called this molecule γE-globulin.[2] This globulin did not bind complement nor induced a precipitin reaction like other immunoglobulins. Simultaneously, Bennich and Johansson discovered a paraprotein in a patient affected by myeloma that did not belong to any of the known immunoglobulins. He called it "Immunoglobulin Not Determined" (IgND) and found that it had similar properties to reagin.[3] Both IgND and γE-globulin initiated the Prausnitz–Kustner test (i.e., passive cutaneous anaphylaxis) and the authors discovered that "reagin," IgND and γE-globulin were finally the same immunoglobulin.[4] In 1968, γE-globulin and IgND were officially named Immunoglobulin E by the World Health Organization International Reference Center for Immunoglobulins.[5]

Phylogenetically talking, IgG and IgE are thought to have emerged from a reptilian common ancestor called immunoglobulin Y (IgY).[6] On one hand, IgE and IgG share similarities. Both are monomeric immunoglobulins composed of two identical heavy and light chains ending with same variable domain. They adopt a 3D structure depending on their FC receptors binding profiles and thus on their biological function. They exert their effector functions through interactions with Fc receptors.[7] On the other hand, IgG and IgE evolved differently on several points in mammals. Indeed, they are, respectively, the most and the least abundant immunoglobulin classes in human serum. IgE heavy chain is longer than IgG with 4 constant domains and contains seven N-linked glycosylation sites (three on Cε1, one on Cε2, and three on Cε3) while a single N-linked glycosylation site is present in IgG.[7,8] This high glycosylation rate may contribute to increase its solubility whereas deglycosylated IgE had a tendency to aggregate.[8]

To date, IgE is mostly known as an anaphylactic immunoglobulin and studied in allergic diseases such allergic rhinitis & asthma and food allergy where specific IgE-allergen complex plays a major part in the physiopathology both in acute and chronic phases of allergic inflammation.[9] The main mechanism relies on allergen cross-linking with specific IgE bound on effector cells (mast cells, eosinophils, basophils) via its high-affinity receptor, FcεRI, inducing secretion of inflammatory cytokines and mediators such as histamine, heparin, tryptase, and prostaglandins.[4]

Beyond allergic inflammation and related diseases, specific IgE secretion is a soluble mediator and also a hallmark of "type 2 immunity" along with eosinophil, mast cell, and basophil infiltration in inflamed tissue and peripheral blood. So-called "type 2 immunity" or "type 2 response" is triggered by a large panel of microbial (virus, bacteria, parasite) and non-microbial (venom, allergens, synthetic or natural adjuvants) stimuli ranging from nanometer to several meters long suggesting a multiples variants of type 2 responses either protective or pathologic where the precise roles of IgE remain poorly understood.[10] However, several advances in recent years have begun to shed light on IgE regulation and memory, on its role in homeostatic and inflammatory conditions beyond allergic disorders such as helminth infection, neoplasia, autoimmunity/autoallergy, vascular disease, and solid organ transplantation. The purpose of this review is to summarize these advances in IgE physiopathology.

2 | IMMUNOGLOBULIN E REGULATION

Concentrations of free serum IgE are ~50–200 ng per ml of blood in healthy humans without any atopic background compared with around 1–10 mg per ml of blood for other immunoglobulin isotypes.[11] In addition, the serum half-life of IgE is the shortest of all immunoglobulin isotypes in human to ~2 days compared to 20 days for IgG.[11] Of note, IgE half-life is markedly prolonged around 9–12 weeks when bound to its high-affinity receptors on mast cells and basophils (FcεRI).[12] At last, IgE production can occur at a locoregional level.[13,14] These observations suggest that IgE production is tightly regulated at low levels under homeostatic condition to avoid potential life-threatening condition such as anaphylaxis or deleterious type 2 hyperresponsiveness.

Intrinsic regulation of IgE.

2.1 | IgE class switch recombination

Class switch recombination (CSR) occurs in naive B cells (CD19+, CD24+, CD38+, IgM+, and IgD+) in secondary lymphoid organs (SLO) such as lymph nodes, spleen or mucosal-associated lymphoid tissues (MALT) under BCR activation, CD40 ligation, and cognate CD4+ T cell help at the T-B zone before organizing into germinal centers.[15] CSR is an intrachromosomal rearrangement of the immunoglobulin heavy-chain locus resulting in isotype switching from IgM-IgD to either IgG_{1-4} or IgA or IgE that differ in effector functions without altering the specificity for the antigen.[16] CSR relies on activation of several key enzymes such as activation-induced cytidine deaminase (AID), uracil-DNA glycosylase (UNG), and APurinic-apyrimidinic Endonuclease 1 (APE1) that bind to specifically intronic regions called donor and acceptor switch regions (S_d and S_a, respectively).[17-19] DNA recombination between S_d and S_a as well as the transcription of germline transcript (GLTs aka I_x) which are crucial regulators of CSR via specific transcription factor binding sites[20] under the dependence of super-enhancer 3'RR.[21] Selection of IgE isotype is driven by cytokine micro-environment, IL-4, IL-13, and IL-9.[22]

IgE CSR has unique features. On a first hand, Sε structure is shorter (around 2kb) than other S region making more difficult DNA recombination all the more so chromatin is condensed according to epigenetic information.[23,24] On a second hand, IgE CSR can occur

directly from Sμ to Sε or indirectly from Sμ to Sγ1 and from Sγ1 to Sε.[25] Recently, a probabilistic model suggested that direct CSR occur more frequently with a low activation threshold generating low-affinity IgE[26] mostly from naive B cells in SLO[27] whereas indirect CSR would be more frequently associated with high-affinity-specific IgE[26,28] (Figure 1).

2.2 | *IgE BCR impacts on B-cell fate*

IgE BCR itself induces B-cell fate toward short life. First of all, IgE mRNA transcript lack the canonical polyadenylation tail and thus a lower ratio of IgE BCR at the cell membrane.[29] Moreover, IgE B entry in germinal center (GC) is impaired due to lower mobility preventing memory B cells or long-live plasma cell differentiation all the more so recent findings have revealed that CSR occurs preferentially before GC formation.[15] At last, membrane IgE BCR induces a suicide locus conferring to IgE+B cells a higher propensity to apoptosis.[30] Those observations argue that IgE+B cells are fragile, prone to apoptosis and to become short-live plasma cells consistent with low but not null IgE secretion (Figure 1).

3 | EXTRINSIC REGULATION OF IgE

3.1 | IgE CSR is tightly regulated in SLO

As aforementioned, indirect class switch recombination results more frequently in high-affinity IgE.[26,28] Though for a same rate of somatic hypermutation, IgE affinity remains lower compared to IgG1 affinity suggesting that T follicular helper cells (Tfh) regulate IgE CSR and affinity maturation in SLO. A new population of Tfh, "Tfh-13," was described in several mice models of food allergy and allergic asthma promoting high-affinity IgE maturation compared to non-allergic or helminth-infected mice.[31] These particular Tfh expressed canonical master genes for type 2 inflammation (GATA3) and follicular polarization (Bcl-6). They also expressed high amount IL-4 and IL-13 and low amount of IL-21 leading to indirect CSR. Indeed, IL-21, IFN-γ, and IL-10 are known to restrain IgE CSR all the more so they act in synergy.[32-34] At last, Tfh-13 are associated with IgG1 memory B cells that held IgE memory.[31] Clement et al described a novel follicular regulatory T cells (Tfr) producing neuritin that were able to constrain IgE-CSR and Tfh-13 formation preventing IgE high-affinity maturation.[35,36] Of note, human IgE repertoire was shown to have

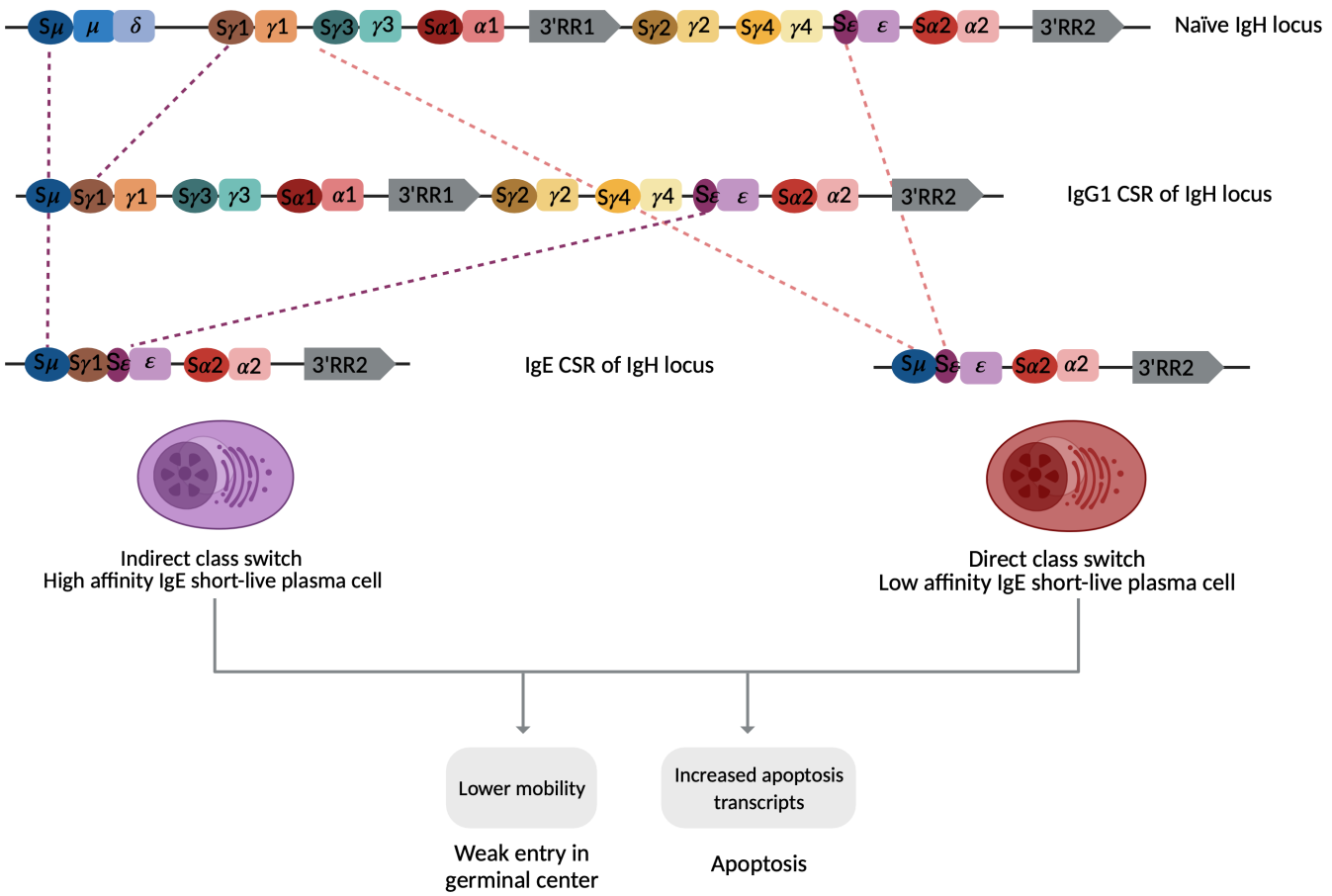


FIGURE 1 Intrinsic regulation of IgE. Class switch recombination (CSR) to IgE is regulated by the size of the ε acceptor region (Sε), which is smaller than all the others making more difficult to access for transcription factors. Furthermore, CSR can occur either directly from μ to ε or indirectly from μ to γ1 to ε. In both cases, the expression of IgE BCR leads to an increase rate of apoptosis and a lower mobility to germinal centers. This figure was created with BioRender.com

less SHM in healthy individuals.[37,38] Furthermore, Shade et al demonstrated that several glycosylation patterns on IgE correlated with its function. More precisely, N384-linked oligomannose on Cε3 was essential to enhance FceRI binding[39,40] whereas a higher number of sialic acid residues on N168 (Cε1) and N265 (Cε2) was essential to promote mast cell degranulation in food allergic patients.[41] Those modification were probably acquired after affinity maturation in the germinal center.[42] IgE binds a C-type lectin domain on its low-affinity receptor (CD23 or FcεRII; Kd ~0.1–1 μM).[43] Interestingly, IgE binding on its monomeric form (soluble or membrane-anchored) acts as a negative feedback loop on B cells, suppressing IgE synthesis when interacting with CD21.[44(p21),45]

Taken together, those observations suggest that, in SLO, IgE production and memory are constitutively constrained at low level with a relative low affinity to their cognate antigen. This is mostly due to Tfr balancing with Tfh-13 and CD21/CD23-mediated negative feedback loop. These concepts are summed up in Figure 2.

3.2 | IgE function is actively constrained out of SLO and in peripheral tissues

In 2018, Shan et al described an novel mechanism constraining IgE-driven basophil degranulation in epithelia and inflamed tissues via IgD and galectin 9. Briefly, in an ovalbumin (OVA)-sensitized mice model, OVA-specific IgD could bound basophils via galectin 9 and CD44 preventing their degranulation and enhanced type 2 inflammation. Galectin 9 could also bind IgE subsequently inhibiting FcεRI mast cell degranulation.[46] Finally, no intrinsic defect in activating nor regulatory signals were found in human basophils either from allergic patients or healthy volunteers.[47] These data strongly suggest that anaphylactic IgE are tuned down even when type 2 immunity is triggered.

FcεRI (aka high-affinity receptor—Kd ~ 1 nm) is found as a tetramer, αβγ2, on mast cells and basophils, and as a trimer, αγ2, on other cells such as monocytes, dendritic cells, eosinophils, and platelets. FcεRI interacts with IgE through Cε3.[48-50] A mathematical modelization of immunoglobulin metabolism found that IgE undergoes substantial catabolism at extravascular sites related to IgE/FcεRI interaction in the peripheral tissues.[51] This prediction was confirmed in vitro (human dendritic cells/monocytes) and in vivo (transgenic mice humanized with human trimeric form of FcεRI). Briefly, IgE is quickly endocytosed in a FcεRI-dependent manner promoting serum IgE clearance and participate in IgE homeostatis.[52]

At last, $IgG_{1\text{-}4}$ autoantibodies against IgE were described in atopic/allergic diseases and auto-immune disorders and healthy volunteers.[53-55] Those anti-IgE auto-IgG are able to recognize free and FcεR-bound IgE in contrast to Omalizumab that can bind only free IgE.[54,56] Recently, Chan et al showed that anti-IgE auto-IgG could either activate or inhibit in vitro basophil degranulation test to grass pollen recombinant protein[57] suggesting an inhibitory role preventing type 2 inflammation though mechanism is still unclear.

Altogether, those data highlight that in peripheral tissues, IgE function is constitutively tracked down by active mechanisms (IgD-mediated inhibition of basophil degranulation +/- inhibitory

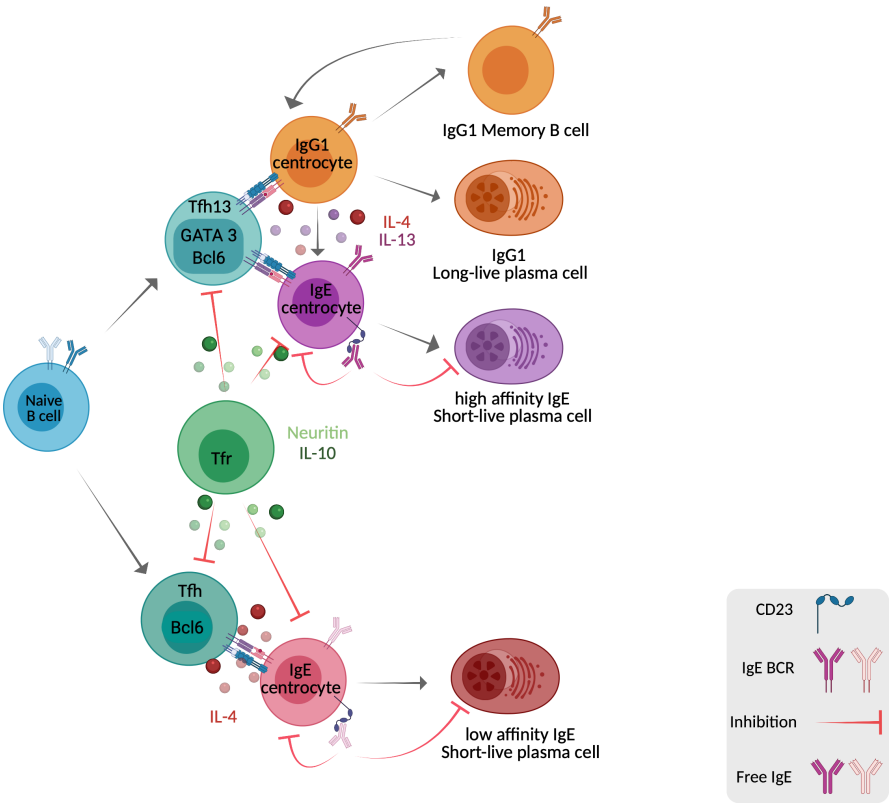


FIGURE 2 Extrinsic regulation of IgE in secondary lymphoid organs. When a naive B cell commits into IgE CSR (direct or indirect), there are two main mechanisms limiting the appearance of IgE long-live plasma cells. The first one is the presence of IL-10 or neuritin secreted by regulatory follicular helper cells (Tfr). The second mechanism is the negative feedback loop by IgE itself via monomeric CD23 (low-affinity receptor) binding on centrocyte or on plasma cell. This figure was created with BioRender.com

auto-IgG against IgE and constant IgE catabolism) in addition to previously detailed mechanisms in SLO (Figure 3).

3.3 | IgE production is a basal trait of mucosal and imbalanced immunity

More systemic and integrative hypothesis of IgE homeostasis arose from germ-free (GF) mice studies and monogenic primary immunodeficiencies in humans (PID). Such deficiencies result in hyper-IgE and atopic/allergic-like clinical manifestations along with susceptibility to infections and/or auto-immune manifestations. Those PID could affect either regulatory T-cell compartment (FoxP3 mutation loss of function), TCR/cytokine signaling (ZAP-70 hypomorphic mutation loss of function as an example), TCR repertoire (restrained oligo-clonal repertoire), glycosylation protein pathway (phosphoglucomutase 3 deficiency), transduction pathways (STAT3 or DOCK8 deficiency), or even barrier function (Netherton syndrome caused by SPINK5 mutation loss of function).[58] Despite precise mechanisms leading to hyper-IgE are still poorly understood, a common mechanism would be that the imbalanced/impaired type 1 or type 17 immunity unmask type 2 immunity.[59]

Indeed, a high amount of IgE in GF mice occurred early in life (before 5 weeks of age) in secondary lymphoid structure at mucosal sites. It was dependent on IL-4 produced by CD4+ T cells which precise lineage is not known. IgE production could be abolished by neonatal microbiota colonization or (before 5 weeks of age) by fecal microbiota transplantation from conventional-housed mice whereas in adults the process was stabilized.[60] In addition, food antigens in non-sensitized GF mice induced sustained specific IgE production at mucosal site but also in SLO. The IgE synthesis was dependent on CD40L+ ICOS+Tfh in secondary lymphoid structures.[61] In both studies, GF mice developed aberrant Ag-specific IgE bound to mast cells that could induce anaphylactic symptoms after second Ag exposure.

Taken together, these data suggest that IgE production (Tfh dependent) is set by default either at mucosal sites in absence of physiological microbiota colonization and/or by an imbalanced type 1 and/or type 17 immunity during early life. This makes an echo to

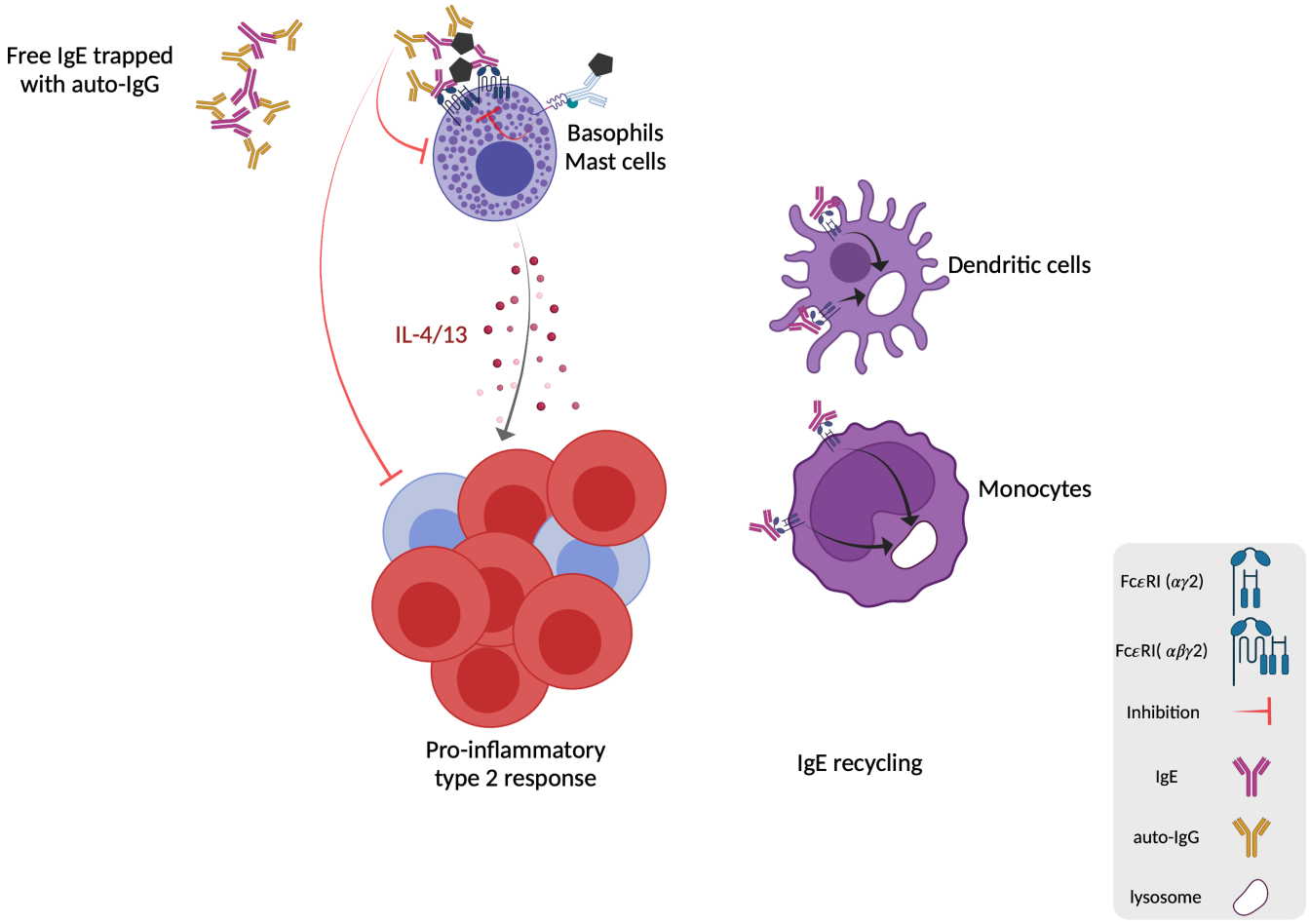


FIGURE 3 Extrinsic regulation of IgE production in peripheral tissue. Under homeostatic condition, IgE binds his high-affinity receptor (FcεRI) on mast cells and monocyte without antigen leading to a rapid internalization of IgE and its receptor to lysosomes. Under inflammatory condition, basophils/mast cell degranulation due to IgE cross-linking with antigen is constrained 1) by the antigen/IgD complex binding to its receptor (CD44 and galectin 9) and 2) by the autoreactive IgG against IgE under its soluble and bound form. This figure was created with BioRender.com

birth-delivery mode that impact on neonatal gut microbiota colonization and diversity leading to miseducation of immune system. Indeed, neonates with low gut microbiota diversity have a higher risk to develop atopic/allergic diseases consistent with IgE dysregulation[62,63] (Figure 4).

4 | IMMUNOGLOBULIN E BIOLOGY

4.1 | Does natural IgE production exist?

Several mechanisms are at play to tune down IgE production. Though, IgE titer is not null under homeostatic condition suggesting that a natural secretion of IgE does exist despite the absence of long-lived IgE plasma cells. One hypothesis would stand that IgE memory is kept by IgG1 memory B cells.[64(p1)] Thus, constant IgE secretion would suggest a low-to-intermediate affinity to avoid uncontrolled type 2 inflammation and a constant/regular stimulation by (auto-) antigens that remain to be determined. Another hypothesis relies on the secretion of natural IgE independent of major histocompatibility complex (MHC) cognate T-cell help in secondary lymphoid structures in a GF and T-cell-deficient mice models. Those IgE had a low rate of SHM suggesting a low-to-intermediate affinity for antigens. At last, no evidence of deleterious type 2 activation was observed.[65]

Whatever their origin, the role of natural IgE remains poorly understood. An hypothesis comes from old clinical observations where tissular damages (burns or in immediate post-operative period) resulted in a rapid polyclonal increase of circulating IgE without deleterious type 2 inflammation.[66,67] A recent study by Crawford et al demonstrated that a carcinogenic environmental xenobiotic called 7,12-dimethylbenz[a]anthracene (DMBA) triggered a strong polyclonal IgE response with self-reactivity when applied on skin. This IgE response, which was dependent on FcεRI binding, prevented epithelial damage.[68] Although their exact specificities remain to be determined, those IgE could be implied in maintaining immune tolerance to self-antigens from damaged tissues.[10] This is supported by two recent studies in mice humanized for FcεRI alpha subunit which demonstrated anti-inflammatory properties of IgE-FcεRI activated dendritic cells. Platzer et al showed that antigen/specific IgE complex dampened systemic inflammation in an allergic asthma

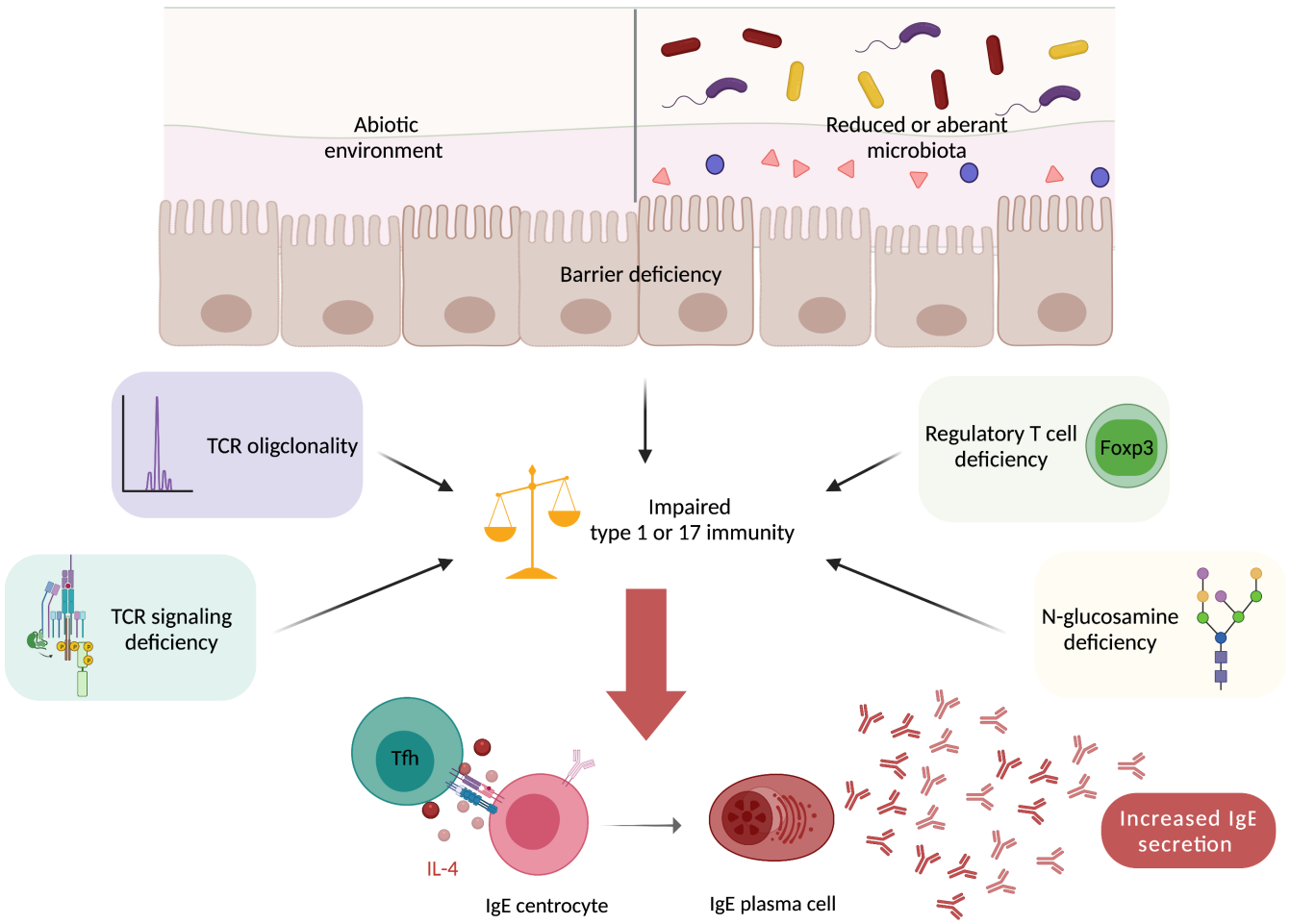


FIGURE 4 Loco-regional IgE secretion at mucosal sites. Loco-regional IgE secretion is a basal trait at mucosal sites in case of impaired type 1 or 17 immunity which can occur in case of 1) abiotic or aberrant microbiota leading to barrier deficiency (i.e., leaky epithelium); 2) TCR signaling or restrained repertoire; 3) tolerance impairment (mainly regulatory T cells); and 4) deficient or aberrant N-glycosylation. This figure was created with BioRender.com

mice model in a FcεRI-dependent manner.[69] Baravalle et al showed that monovalent antigen covalently bound to IgE first induced CD4+ T-cell proliferation, quickly followed by a systemic clonal deletion of the antigen-specific CD4+ T cells.[70] In addition, IgE-FcεRI activated DC promoted a IL-10 dependent retro-control loop leading to effector T-cell deletion and regulatory T-cell activation via indole-2,3-diamine oxygenase (IDO) activation.[71-73] A FcεRI soluble form was detected in human serum[74] and exhibited an inhibitory effect on mast cell degranulation.[75] Altogether, those data argue for an immuno-modulatory role of natural IgE on innate immunity and indirectly on adaptative immunity. Of note, soluble form of FcεRs could be an add-on level of regulation. Yet, further investigations are needed to understand the complex inter-play between IgE, FcεRs, and immune tolerance (Figure 5).

4.2 | IgE facilitated antigen presentation—a pivotal role in unmasking IgE response/inflammation

IgE-mediated response/inflammation is somehow necessary.[10] The IgE facilitated antigen presentation (IgE-FAP) aka IgE antigen focusing plays a pivotal role in IgE inflammation. This process has been mainly studied in immediate allergic diseases where it set up and amplified the allergic inflammation against allergens.[76]

In 1993, Heyman et al showed that the rate of IgG anti-bovine serum albumin (BSA) and BSA-specific IgG+B cells was higher when mice were immunized with trinitrophenyl (TNP)—BSA and TNP-specific IgE.[77,78] Another description of IgE-FAP came from the "toxin hypothesis" that stood a protective role of IgE against venom.[79] Later, it was demonstrated that bee-venom immunized mice were more resistant to IgE-mediated anaphylaxis when re-challenged with a lethal dose of bee or viper venom.[80] In the same line, a recent study demonstrated that a pre-existing IgE sensitization against *Staphylococcus aureus* (SA) toxin enhanced SA IgG immunization and infection clearance in a mice model of pulmonary infection.[81] These data suggest that one role of IgE-FAP would be to enhance humoral and cellular response against non-self-antigen.

There are two main mechanisms known so far for IgE-FAP implying either FcεRI or FcεRII. Multivalent antigen/IgE complexes were shown to activate dendritic cells[82] mostly toward a type 2 inflammation but not exclusively.[83] IgE-FAP-activated dendritic cells were also showed to boost specific CD4+ effector T cells via MHC-II presentation with a 100-fold to 1000-fold higher efficiency than canonical MHC-II presentation (low dose of antigen).[82] Moreover, IgE-FAP-activated basophils were more efficient at MHC-II cross-presentation than dendritic cells.[84,85] At last, FcεRI-driven IgE-FAP demonstrated in vitro a broad spectrum of action on human mast cells ranging from self-survival, pro-inflammatory cytokines

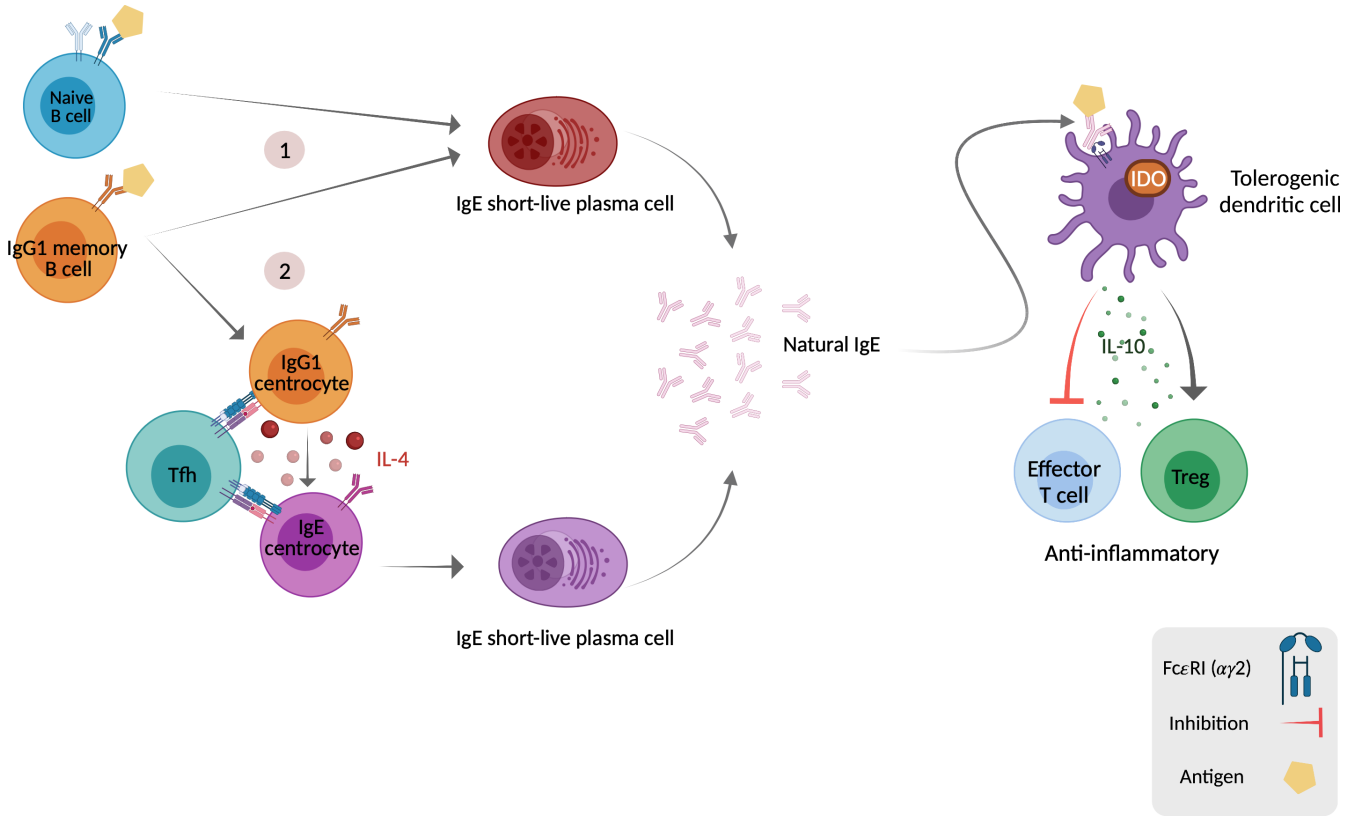


FIGURE 5 Natural IgE secretion. There are two main hypotheses to explain natural IgE secretion at steady state. 1) The first one consists of constant stimulation of naive or IgG1 memory B cells with (auto?)antigens without cognate T cells help leading to short live plasma cells. 2) The second one consists as well in constant stimulation of IgG1 memory B cells by (auto?)antigens with Tfh help in presence of IL-4 leading to shot live plasma cells. Those natural IgE could exert an anti-inflammatory role by promoting active mechanisms of peripheral tolerance (tolerogenic dendritic cells, regulatory T cells) but also preventing effector T-cell activation. This figure was created with BioRender.com

secretion to complete degranulation according to the nature of IgE and the antigen[86] (Figure 6A).

CD23 has three major known ligands: CD21, MHC-II, and IgE with different interaction sites, respectively,[87] especially with B cells and monocytes/macrophages.[88] Noteworthy, CD23 has two isoforms: CD23a is constitutively expressed and up-regulated after IL-4 stimulation whereas CD23b is expressed only after IL-4 stimulation.[89] Only CD23a under its trimeric form is implied in antigen processing whereas CD23b is more related to phagocytosis.[90] Conversely to FcεRI-driven IgE-FAP, several studies demonstrated that CD23a IgE-FAP enhanced humoral response (IgG and IgM) and the specific cellular response (CD4+ T cells) against a multivalent antigen (TNP-OVA) in mice models either adjuvanted with TNP-specific IgE or transgenic mice over-expressing CD23.[91,92] The magnitude of the response was higher with antigen/IgE complex and low dose of antigen.[92] Those data were confirmed in human by in vitro models where B cells from allergic patients expressed a high density of CD23 arguing for a trimeric form.[93,94] Trimeric soluble CD23 is also detectable in human serum which function seems to be identical to the membrane form[95] (Figure 6B).

Altogether, those data suggest another role of IgE-FAP which could be 1) the detection of low amount of antigen and 2) the onset of an adaptative type 2 immune response mainly but not exclusively. This suggests that IgE takes part to immuno-surveillance to non-self. As well, IgE-FAP seems to trigger an inflammatory response with multivalent antigens. This makes an echo to a recent study where the more the IgE interacting epitopes were numerous and close to each other the more the IgE complexes were able to cluster IgE receptors (FcεRI) and trigger mast cell activation.[96]

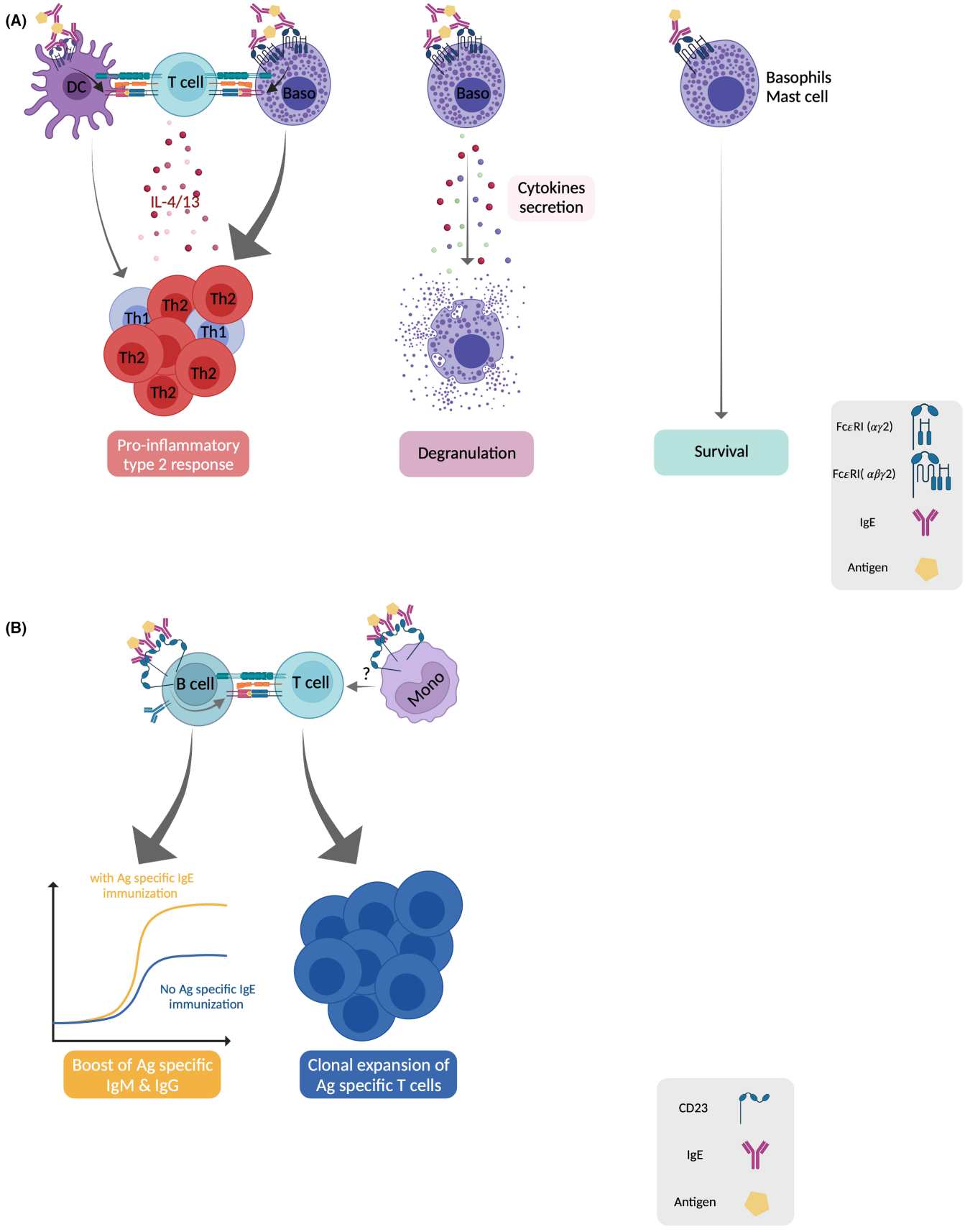
5 | POTENTIAL ROLES OF IMMUNOGLOBULIN E IN HEALTH AND NON-ALLERGIC DISEASES

5.1 | IgE and venom toxicity—a host defense mechanism?

The hypothesis that IgE could play a protective role against toxins after arthropods or reptile bite was proposed by James Stebbings in 1974[97] and Margie Profet in the early 1990s.[79] Since, important works from Stephen Galli's group have get credit to this hypothesis suggesting that IgE and its interaction with mast cells can enhance host resistance to venoms. More precisely, honeybee venom resistance to a lethal dose can be transferred to a naive mice by systemic serum therapy from a honeybee immunized mice.[80] This protective effect was lost either after depletion or inactivation of IgE in the serum or when FcεRI α or γ chain were knocked out in the naive recipient mice.[80,98] Those result suggested that IgE-mediated resistance to venom is linked to a FcεRI-IgE FAP on effector cells. Indeed, mice lacking mast cell and/or basophils were unable to acquire venom resistance after immunization.[99] Furthermore, local FcεRI-IgE FAP mast cell degranulation enhanced venom detoxification[99,100] thanks to proteases contained in their granule such as carboxypeptidase 3 and chymase,[101,102] which degrade venom peptides (sarafotoxin and helodermin, respectively) with structure similarity to endogenous mammalian peptide (endothelin 1 and vasoactive intestinal peptide, respectively).[103] Interestingly in those mice model of envenomation, mast cell, basophil, or even innate lymphoid cells type 2 were not required to induce IgG1 and IgE immunization against venom antigen.[98,99] Last but not least, previous IgE immunization against an irrelevant allergen added to venom resulted in enhanced resistance to the venom despite prior immunization.[99] Altogether, those data demonstrate that detoxification to a complex mixture of antigen such as venom involve specific IgE sensitization to a small fraction of antigen that induce the release of proteases due to FcεRI-IgE local degranulation of mast cells. Furthermore, those results suggest that venom itself induce specific IgE immunization independent of effector cells (Figure 7).

5.2 | IgE and helminth—who is protecting who?

High IgE titer is one hallmark of active helminthic infection with eosinophilia reflecting type 2 inflammation. In human, several studies associated resistance to (re)-infection to specific IgE against *Schistosoma mansoni or haematobium*[104,105] whereas the underlying mechanisms associated with IgE and parasite resistance remain unclear. So far, mice models of helminthic infection used to better decipher the role of IgE during helminthic infection in has led to conflicting results. An explanation, at least in part, could be the use of inadequate model to study IgE response such as AID-deficient mice, B-cell-deficient mice, or FcγR deficient (reviewed in[106]). Table 1 summarizes different studies that used IgE-deficient or FcεRI-deficient mice to better decipher their role during primary or secondary helminthic infections. Several interesting patterns draw according to worm burden mostly and to a lesser extent on granuloma in target organs. It is worth noticing that the time after infection inversely correlates with worm burden: The longer it is, the smaller the difference in worm burden is observed. In most studies, IgE or FcεRI deficiency is associated with an increased worm burden in the early phase (before 2 weeks) of the infection either during the first exposure (*Schistosoma mansoni*, *Strongyloides venezuelensis*, or *Brugia malayi*) or the second exposure (*Nippostrongylus brasiliensis* and *Heligmosomoides polygyrus*).[107-112] Interestingly, IgE or FcεRI deficiency was associated with a reduced specific IgG1 response during the first exposure.[110,112] The consequence of IgE or FcεRI deficiency in repeated exposures to helminths which can be modelized by the presence of granuloma in target tissue remains unclear. Though, IgE deficiency seems to be associated with smaller granuloma (i.e., smaller inflammatory infiltrate)[112,113] and FcεRI deficiency is associated with increased damages and inflammatory infiltrate in the target tissues.[108,114] Furthermore, basophil activation by IgE/worm antigens complexes were essentials for granuloma formation and limit tissue damages.[108,109] Altogether, those data suggest that IgE response might have different impact in helminthic infection. Upon acute exposure, IgE would



play a role in worm clearance 1) thanks to enhancement of specific IgG response, 2) FcεRI-driven IgE degranulation of effector cells such as mast cells, basophils, platelets, and eosinophils.[106,115] Upon repeated exposure (i.e., worm clearance failure), specific IgE and their interaction with FcεRI on basophils would take part in granuloma formation to constrain the worm, avoid target tissue

FIGURE 6 (A): Pivotal role IgE facilitated antigen presentation (IgE-FAP) via FcεRI. FcεRI IgE-FAP has a broad spectrum of effects on basophils (baso) or mast cells ranging from survival in case of cross-linking with a monovalent antigen to degranulation, cytokine secretion, or even amplification of type 2 response in case of multivalent antigen cross-linking (indirect presentation by class II major histocompatibility complex, (MHC-II)). FcεRI IgE-FAP with a multivalent antigen can also occur on dendritic cells (DC) where it enhances type 2 response thanks to indirect MHC-II presentation of the antigen. This figure was created with BioRender.com. (B): Pivotal role IgE facilitated antigen presentation (IgE-FAP) via FcεRII aka CD23. There are two main effects of trimeric CD23 IgE-FAP with multivalent antigen that can be mediated by B cells and probably by monocytes (Mono). The first one is to boost humoral response with specific IgM and IgG immunization. The second one is to enhance clonal expansion of antigen-specific T cells. This figure was created with BioRender.com

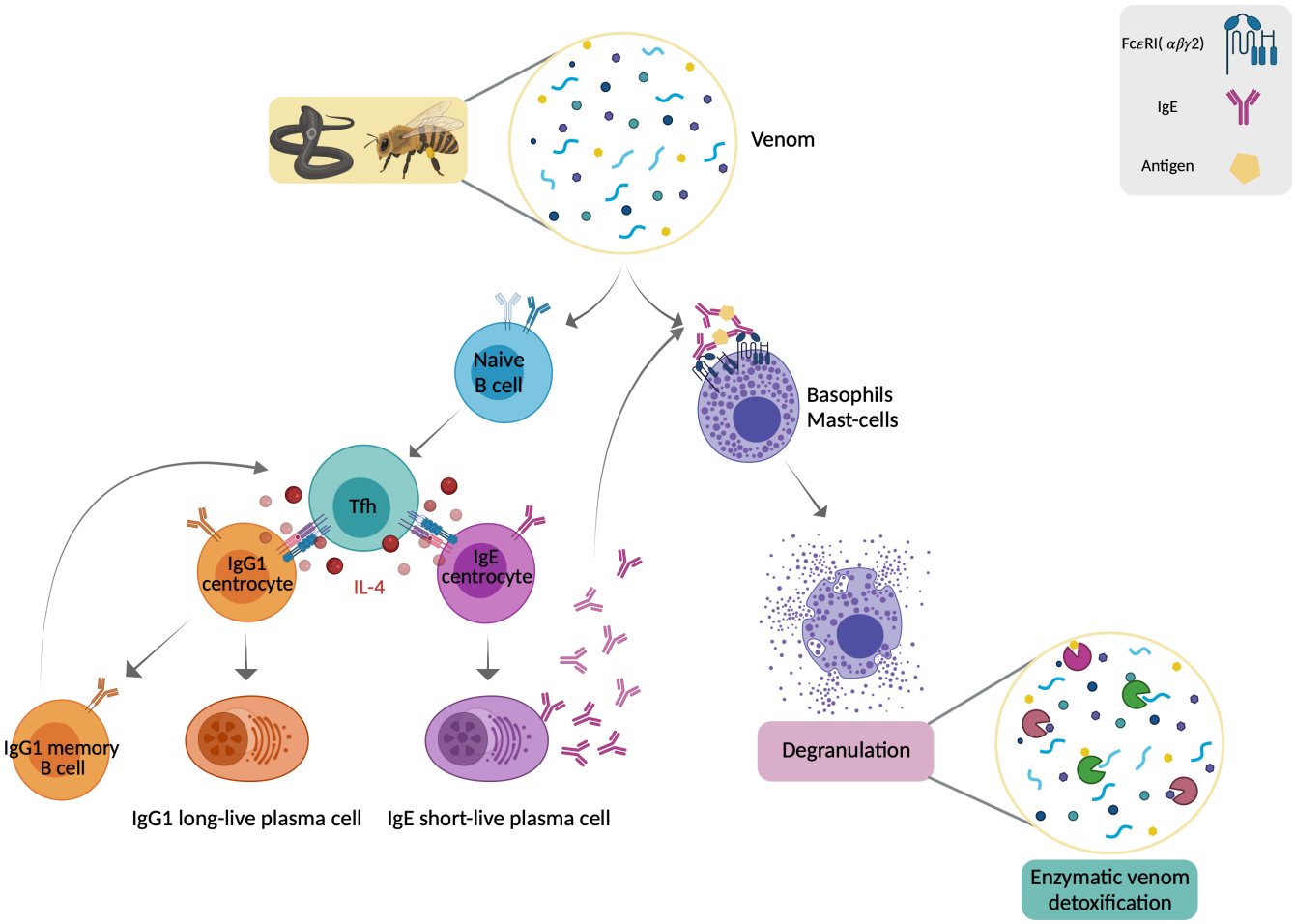


FIGURE 7 Role of IgE in venom detoxification. In case of venom inoculation, a specific IgG1 and IgE response will arise independently from basophils/mast cells against a small protein fraction of the venom. These venom-specific IgE will lead to basophils/mast cell degranulation releasing enzymes such as tryptase, chymase as example in the micro-environment that will cleave venom proteins with deleterious biological activity. The IgG1 memory against venom will warrant the specific IgE recall and venom detoxification in case of latter exposures. This figure was created with BioRender.com

damages[116] and tissue healing making an echo to the concept of natural IgE implied in tolerance.[65] Nevertheless, this latter point remains speculative since to date no clear role for IgE in wound healing has been documented (Figure 8).

5.3 | IgE in tumor immuno-surveillance—a kind friend?

Selective IgE deficiency is defined as total circulating IgE <2.5KU/L after excluding common variable immune deficiency.[117] Recently, three studies demonstrated either retrospectively or prospectively a significant association between selective IgE deficiency and the onset of malignant diseases in adult and children. Interestingly, the demographic data of neoplasm diseases were identical to the target population: solid organ cancer in adulthood and hematologic cancer in childhood.[118-120] These data suggest that IgE-FAP could play a role in tumor immune-surveillance. Indeed, a recent study by Crawford et al demonstrated that DMBA induced skin epithelial carcinogenesis triggered γδT cell activation and local self-reactive IgE production via IL-4 in mice. Those IgE took part in preventing epithelial carcinogenesis in a FcεRI dependent manner.[68] This

TABLE 1 Impact of IgE or FcεRI deficiency in mice models of helminthic infections based on time after infection, single or repeated exposure, worm burden, egg production, and the presence of granuloma (i.e., chronic exposure). ND = not determined

Name of the parasite	Mice model	Primary infection	Secondary infection	Evaluation (time after infection)	Worm burden	Eggs production	Granuloma (if applicable)	References
Trichinella spiralis	BALB/C IgE-deficient mice	Yes	No	1 week to 4 weeks	Increased compared to WT mice	ND	Increased compared to WT mice	107
	SJA/9 mice	Yes	Yes	4 weeks	No difference for both infection	ND	No difference for both infection	150
Angiostrongylus costariecensis	SJA/9 mice	Yes	Yes	6 weeks	No difference for both infection	ND	No difference for both infection	151
Nippostrongylus brasiliensis	SJA/9 mice	Yes	Yes	1 week & 2 weeks	No difference for both infection	ND	No difference for both infection	150
	BALB/C FcεRIα-deficient mice	No	Yes	2–5 days	No difference for the first infection; decreased in the skin and increased in the lung for the second infection compared to WT mice.	ND	Decreased number of granuloma in the skin and larger lung injuries compared to WT mice.	108
	BALB/C IgE-deficient mice	No	Yes	2 weeks	ND for the first infection; increased number in the small intestine compared to WT mice for the second infection	ND	ND	109
Heligmosomoides polygyrus	BALB/C IgE-deficient mice	No	Yes	2 to 3 weeks	No difference	ND	No difference	116
	BALB/C IgE-deficient mice	No	Yes	2 weeks	ND for the first infection; increased number in the small intestine compared to WT mice for the second infection	ND	ND	109
Strongyloides venezuelensis	FcεRI-/- mice	Yes	No	1,5 weeks	Increased compared to WT mice when FcγR are blocked	ND	ND	110
Brugia malayi	BALB/C IgE-deficient mice	Yes	Yes	2 to 6 weeks	Increased compared to WT mice in primary infection; no difference on secondary infection	ND	ND	111
Schistosoma mansoni	129/terSv IgE-deficient mice	Yes	Yes	8 weeks	Increased compared to WT mice in primary infection with lower specific IgG1 response; no difference on secondary infection	ND	Smaller granuloma in the liver than WT mice	112
	BALB/C FcεRIα-deficient mice	Yes	No	8 weeks	No difference	No difference	Larger granuloma with higher liver fibrosis than WT mice.	114
	SJA/9 mice	Yes	No	8 weeks	No difference for both infection	No difference	ND	152
Schistosoma japonicum	SJA/9 mice	Yes	No	8 weeks	No difference	No difference	Smaller granuloma in the liver than WT mice	113

assumption is supported by several observations in human where non-anaphylactic-specific IgE immunization against tumors could trigger specific cytotoxic responses in patients with colorectal, pancreatic, prostatic, and breast cancer[121-124] in a FcεRI-dependent manner.[125] On the opposite, two recent observations demonstrated a detrimental role of IgE in a mice model of skin cancer. More precisely, Taniguchi et al demonstrated that skin tumors were infiltrated with IL-33-induced FcεRI+ macrophages that promoted tumor growth suggesting a role of IgE on those tumor-infiltrating macrophages.[126] Also, Hayes et al demonstrated that tumor growth was promoted by an increase of polyclonal "natural" IgE after 12 -*O*-tetradecanoylphorbol-13-acetate (TPA) repeated applications. Tumor growth was also dependent on FcεRI IgE-FAP on basophils that infiltrated the tumor. Interestingly, selective IgE deficiency in those mice model abrogated tumor growth.[127] Altogether, those data suggest that IgE would prevent tumor growth in the early phase of carcinogenesis whereas IgE would promote tumor growth at an advanced stage (Figure 9). The distinct IgE repertoires induced by DMBA and TPA (self-reactive versus polyclonal natural, respectively) could explain, at least in part, the janus-faced role of IgE in cancer immunopathology despite type 2 immunity induction in both case.[68,127] In conclusion, further researches are needed 1) to consider selective IgE deficiency as a predictive biomarker of cancer onset[128] and 2) to better characterize the role of IgE at molecular (IgE repertoire, antigen identification, receptors) and cellular (CD8+ T cells, NK cells, γδT cells) levels in the tumor micro-environment

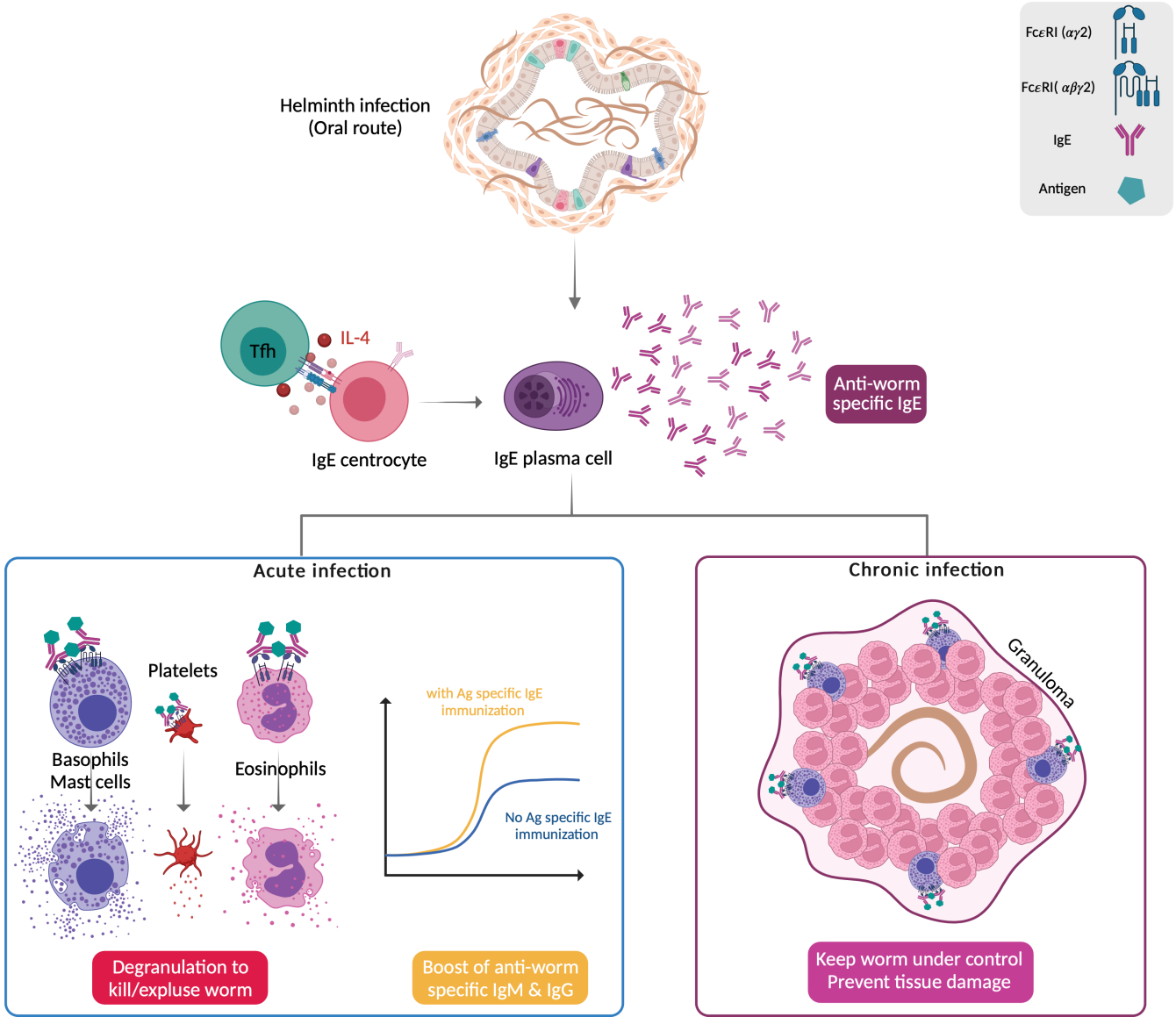


FIGURE 8 Role of IgE in anti-helminthic immunity. In case of helminthic infection (oral route mainly), the role of worm-specific IgE is different in case of acute or chronic infection. In case of acute infection, worm-specific IgE will lead to basophils/mast cells or eosinophils or platelets degranulation of cytotoxic molecules to kill and expulse worms. In parallel, a specific humoral immunity (IgM and IgG) will be boosted by worm-specific IgE. In case of chronic infection (i.e., failure of worm clearance), worm-specific IgE will take part in the creation of eosinophilic granuloma to constrain the worms and also prevent tissue damage. This figure was created with BioRender.com

(enhancing or preventing tumor growth) in order to achieve new add-on therapeutic strategies.[129,130]

5.4 | IgE self-reactivity: from autoallergy to autoimmunity—friend or foe?

The concept of autoallergy implies the presence of self-reactive IgE (srIgE) and was introduced by the end of 1950s[131,132] without any understanding of its role. To date, this concept has evolved into IgE autoimmunity with a growing spectrum of autoantigens identified in systemic erythematous lupus (double-strand DNA, SSA/B, RNP, nucleosome, acidic ribosomal P2 protein among others), chronic urticaria (thyroperoxidase, double-strand DNA, IL-24), bullous pemphigoid (BP180 or BP230), and atopic dermatitis (>140 autoantigens identified) mostly.[133] srIgE were associated with disease severity in systemic erythematous lupus,[134,135] bullous pemphigoid,[136] and chronic urticaria.[137] They are probably important in atopic dermatitis pathogenesis since a high percentage of patients have srIgE,[138,139] though the correlation between srIgE and disease severity remains debated requiring further investigations.[133] The cellular and molecular effects of srIgE were mainly deciphered in lupus where they enhance disease activity through two main pathways. On one hand, FcεRI-driven srIgE-FAP on plasmacytoid dendritic cells enhance srIgG/srIgE through B cells expansion and plasma cell differentiation in SLO in a TLR9-dependent manner.[134] On the other hand, MHC-II cross-presentation of autoantigen (double-strand DNA) via FcεRI-driven srIgE-FAP by activated basophils enhanced autoantibodies and B-cell differentiation through type 2 inflammation in SLO in a BAFF-dependent manner[140] (reviewed in[141]). In bullous pemphigoid, cellular and molecular effects of autoreactive IgE are not that well deciphered.[133] In chronic urticaria, the importance of auto-IgE has been strongly suggested by the great efficiency of omalizumab on disease activity[142] and also by passive anaphylaxis transfer with sera from patients with chronic urticaria.[143] Though, the precise mechanisms remain poorly understood.[133] In conclusion, the data strongly argue for a deleterious implication of srIgE through FcεRI-driven FAP. It also suggests that srIgE are of high affinity (indirect CSR) able to cross-link multivalent autoantigens and activate effector cells. Though, how autoreactive IgE and type 2 immunity are triggered leading to complex and different clinical features remains poorly understood.

5.5 | Unexpected associations between IgE and diseases

Implication of IgE was suggested in cardiovascular diseases thanks to mice models of aorta aneurysm where FcεRI alpha subunit knock-out partially protected from smooth muscle senescence,[144] neutrophils,

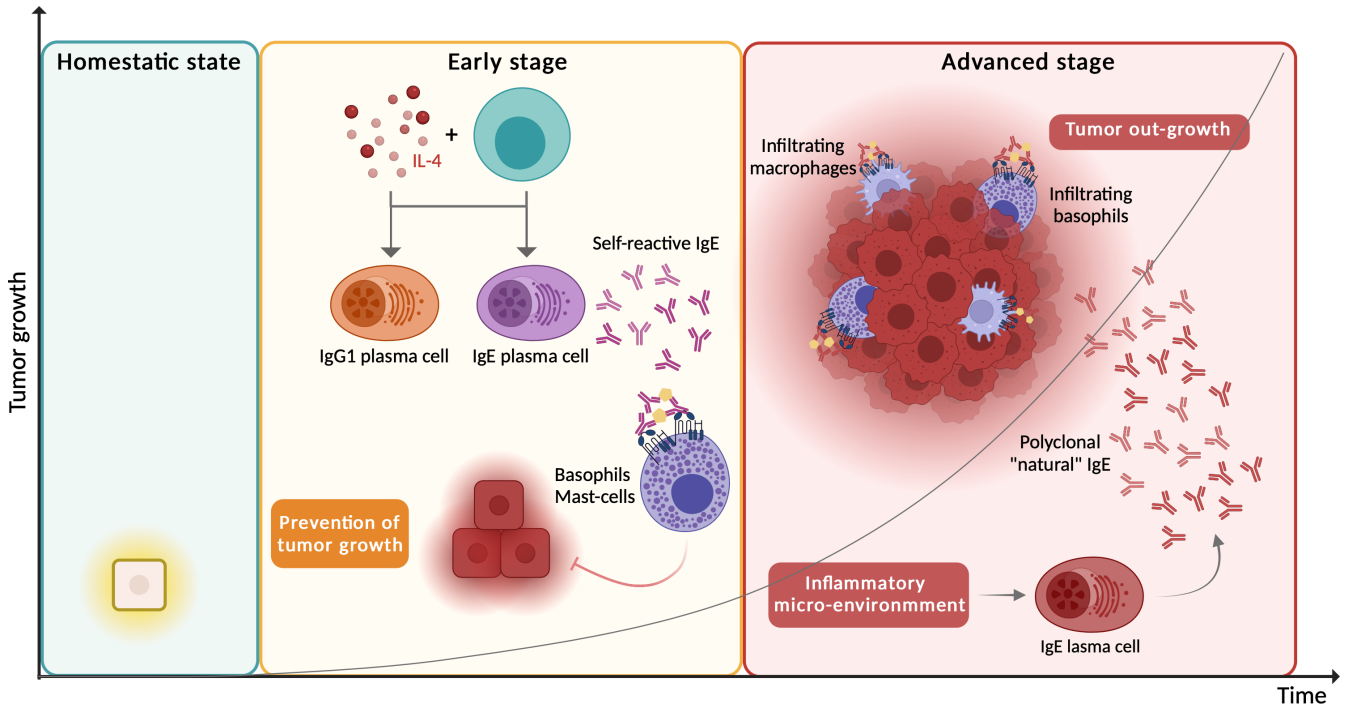


FIGURE 9 Janus-faced role of IgE in cancer immunopathology. In the early phase of cancer growth, self-reactive IgE will produced thanks to the help of IL-4 and resident γδ T cells. Those self-reactive IgE will activate the basophils thanks to FcεRI IgE-FAP that will prevent tumor growth and enhance anti-tumoral immunity. On the opposite at an advanced stage of cancer, the pro-inflammatory micro-environment will lead to the local secretion of polyclonal "natural" IgE that will enhance tumor out-growth thanks to FcεRI IgE-FAP on basophils and macrophages that infiltrate the tumor. This figure was created with BioRender.com

and macrophage infiltration and IL-6-mediated inflammation.[144,145] Yet, those results were not translated to human. Another observation suggested that IgE sensitization against alpha-gal oligosaccharide without any anaphylactic features was associated with a higher risk of coronary atheromatous disease at a younger age[146] which precise mechanisms remain to be determined. Altogether, those observations open a whole new field of IgE biology in cardiovascular homeostasis and disease.

Recently, functional anti-MHC IgE (i.e., inducing mast cell degranulation) was detected in mice models of skin and heart allograft serum. The author could also detect anti-HLA IgE in sera from kidney transplanted patients with high titers of donor-specific antibodies (n = 5).[147] Another recent study associated antibody-mediated rejection with anti-HLA IgE in the serum and IgE deposit colocalizing with mast cell/basophil in the kidney transplant.[148] Altogether, those data suggest that the HLA/IgE complex could interact with mast cell/basophils in the transplant and trigger deleterious type 2 immunity. It also questions about 1) the interaction of IgE with other cognate effector cells such as eosinophils[149]; 2) the triggers of allo-immune response in solid organ transplantation.[10]

6 | CONCLUSION

Since its characterization in 1966, IgE has been extensively studied in allergic diseases such as food or drug anaphylaxis, allergic rhinitis, and allergic asthma where it has a pivotal role. Furthermore, it would be finalistic to assume a simple pathological role for IgE especially since IgE is only found in mammals.[7] Some evidence argues for a constitutive secretion of IgE in the body fluids with homeostatic or even immune-modulatory properties. However, their precise roles and interactions with other immunoglobulins and immune cells remain to be determined. Some evidence also argues for a pro-inflammatory role of IgE when type 2 inflammation is triggered. In that case, IgE could enhance immune response against small amounts of antigen (IgE-FAP) with a wide spectrum of downstream responses modulated either by IgE affinity and/or receptor binding (FcεRI or FcεRII) and/or the target cell (basophils, mast cells, eosinophils, or even platelets). However, further studies are needed to decipher how these responses are finely tuned. Additionally, breakthrough works have unraveled some physiological roles of IgE such as resistance and detoxification to venom, worm clearance during acute infection, prevention of tissue damage in case of helminthic chronic infection. More surprising, there is a janus-faced role in cancer immunopathology where IgE seems to take part in tumor clearance/immuno-surveillance at an early stage. On the opposite, IgE seems to enhance tumor out-growth at an advance stage suggesting a diversion of IgE response which mechanisms remain unclear to date. Last but not least, IgE was unexpectedly implicated vascular disease or even rejection in solid organ transplantation where immunopathological mechanisms remain to be determined. Altogether, those interesting developments argue for a role of IgE response as an immunological adaptor to complex environmental changes which better characterization will lead to the development of innovating therapeutic strategies.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by allergy.

AUTHOR CONTRIBUTION

LC conceptualized, wrote the original draft, reviewed, and edited. AM and SB reviewed and edited the manuscript.

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