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1 **Immunoglobulin E response in health and disease beyond allergic**
2 **disorders**

3

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23

24 **Lists of 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 ^o 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	Germ Line 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
TPA	12- <i>O</i> -tetradecanoylphorbol-13-acetate
TCR	T cell receptor
Tfh	T follicular helper cell
Tfr	Follicular regulatory T cell
TNP	Trinitrophenyl
UNG	uracil-DNA glycosylase

25

26 **Running title:**

27 IgE involvement in health and non-allergic diseases

28

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47

48 **Abstract:**

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

64

65 **Key words:** IgE, Type 2 immunity, Facilitated-antigen presentation, FcεRI, CD23

66 INTRODUCTION

67

68 Immunoglobulins of isotype E (IgE) were initially reported as a “reagin” in the early
69 1920’s by Coca and Cooke who worked on a classification of “the phenomena of
70 hypersensitiveness”¹. Little work occurred on “reagin” from the 1920’s until the 1960’s, until
71 newer techniques to better detect proteins were developed. In 1966, Kimishige and Teruko
72 Ishizaka described an anti-serum that was able to block type 1 hypersensitivity and called this
73 molecule γ E-globulin ². This globulin did not bind complement nor induced a precipitin
74 reaction like other immunoglobulins. Simultaneously, Bennich and Johansson discovered a
75 paraprotein in a patient affected by myeloma that did not belong to any of the known
76 immunoglobulins. He called it “Immunoglobulin Not Determined” (IgND) and found that it
77 had similar properties to reagin³. Both IgND and γ E-globulin initiated the Prausnitz-Kustner
78 test (i.e., passive cutaneous anaphylaxis) and the authors discovered that “reagin”, IgND and
79 γ E-globulin were finally the same immunoglobulin ⁴. In 1968, γ E-globulin and IgND were
80 officially named Immunoglobulin E by the World Health Organization International Reference
81 Center for Immunoglobulins ⁵.

82 Phylogenetically talking, IgG and IgE are thought to have emerged from a reptilian
83 common ancestor called Immunoglobulin Y (IgY)⁶. On one hand, IgE and IgG share
84 similarities. Both are monomeric immunoglobulins composed of two identical heavy and light
85 chains ending with same variable domain. They adopt a 3D structure depending on their FC
86 receptors binding profiles and thus on their biological function. They exert their effector
87 functions through interactions with Fc receptors⁷. On the other hand, IgG and IgE evolved
88 differently on several points in mammals. Indeed, they are respectively the most and the least
89 abundant immunoglobulin classes in human serum. IgE heavy chain is longer than IgG with 4
90 constant domains and contains seven N-linked glycosylation sites (three on C ϵ 1, one on C ϵ 2

91 and three on Cε3) while a single N-linked glycosylation site is present in IgG^{7,8}. This high
92 glycosylation rate may contribute to increase its solubility whereas deglycosylated IgE had a
93 tendency to aggregate⁸.

94 To date, IgE is mostly known as an anaphylactic immunoglobulin and studied in allergic
95 diseases such allergic rhinitis & asthma and food allergy where specific IgE-allergen complex
96 plays a major part in the physiopathology both in acute and chronic phases of allergic
97 inflammation⁹. The main mechanism relies on allergen cross-linking with specific IgE bound
98 on effector cells (mast-cells, eosinophils, basophils) via its high affinity receptor, FcεRI,
99 inducing secretion of inflammatory cytokines and mediators such as histamine, heparin,
100 tryptase, prostaglandins⁴.

101 Beyond allergic inflammation and related diseases, specific IgE secretion is a soluble mediator
102 and also a hallmark of “type 2 immunity” along with eosinophil, mast-cell and basophils
103 infiltration in inflamed tissue and peripheral blood. So called “type 2 immunity” or “type 2
104 response” is triggered by a large panel of microbial (virus, bacteria, parasite) and non-microbial
105 (venom, allergens, synthetic or natural adjuvants) stimuli ranging from nanometer to several
106 meters long suggesting a multiples variants of type 2 responses either protective or pathologic
107 where the precise roles of IgE remains poorly understood¹⁰. However, several advances in
108 recent years have begun to shed light on IgE regulation and memory, on its role in homeostatic
109 and inflammatory conditions beyond allergic disorders such as helminth infection, neoplasia,
110 auto-immunity/auto-allergy, vascular disease and solid organ transplantation. The purpose of
111 this review is to summarize these advances in IgE physiopathology.

112

113 IMMUNOGLOBULIN E REGULATION

114

115 Concentrations of free serum IgE are ~50–200 ng per ml of blood in healthy humans
116 without any atopic background compared with around 1–10 mg per ml of blood for other
117 immunoglobulin isotypes¹¹. In addition, the serum half-life of IgE is the shortest of all
118 immunoglobulin isotypes in human to ~2 days compared to 20 days for IgG¹¹. Of note, IgE
119 half-life is markedly prolonged around 9-12 weeks when bound to its high affinity receptors on
120 mast-cells and basophils (FcεRI)¹². At last, IgE production can occur at a loco-regional
121 level^{13,14}. These observations suggest that IgE production is tightly regulated at low levels under
122 homeostatic condition to avoid potential life-threatening condition such as anaphylaxis or
123 deleterious type-2 hyperresponsiveness.

124

125 **Intrinsic regulation of IgE**

126 *IgE class switch recombination*

127 Class switch recombination (CSR) occurs in naive B cells (CD19+, CD24+, CD38+,
128 IgM+ and IgD+) in secondary lymphoid organs (SLO) such as lymph nodes, spleen or mucosal
129 associated lymphoid tissues (MALT) under BCR activation, CD40 ligation and cognate CD4+
130 T cell help at the T-B zone before organizing into germinal centers¹⁵. CSR is an
131 intrachromosomal rearrangement of the immunoglobulin heavy-chain locus resulting in isotype
132 switching from IgM-IgD to either IgG₁₋₄ or IgA or IgE that differ in effector functions without
133 altering the specificity for the antigen¹⁶. CSR relies on activation of several key enzymes such
134 as Activation Induced cytidine Deaminase (AID), uracil-DNA glycosylase (UNG) and
135 APurinic-aprimidinic Endonuclease 1 (APE1) that bind to specifically intronic regions called
136 donor and acceptor switch regions (S_d and S_a respectively)¹⁷⁻¹⁹. DNA recombination between
137 S_d and S_a as well as the transcription of germ line transcript (GLTs aka I_x) which are crucial

138 regulators of CSR via specific transcription factor binding sites²⁰ under the dependence of
139 super-enhancer 3'RR²¹. Selection of IgE isotype is driven by cytokine micro-environment, IL-
140 4, IL-13 and IL-9²².

141 IgE CSR has unique features. On a first hand, S ϵ structure is shorter (around 2kb) than
142 other S region making more difficult DNA recombination all the more so chromatin is
143 condensed according to epigenetic information^{23,24}. On a second hand, IgE CSR can occur
144 directly from S μ to S ϵ or indirectly from S μ to S γ 1 and from S γ 1 to S ϵ ²⁵. Recently, a
145 probabilistic model suggested that direct CSR occur more frequently with a low activation
146 threshold generating low affinity IgE²⁶ mostly from naive B cells in SLO²⁷ whereas indirect
147 CSR would be more frequently associated with high affinity specific IgE^{26,28} (Figure 1).

148

149 *IgE BCR impacts on B cell fate*

150 IgE BCR itself induces B cell fate toward short life. First of all, IgE mRNA transcript lack the
151 canonical polyadenylation tail and thus a lower ratio of IgE BCR at the cell membrane²⁹.
152 Moreover, IgE B entry in germinal center (GC) is impaired due to lower mobility preventing
153 memory B cells or long-live plasma-cells differentiation all the more so recent findings have
154 revealed that CSR occurs preferentially before GC formation¹⁵. At last, membrane IgE BCR
155 induces a suicide locus conferring to IgE+ B cells a higher propensity to apoptosis³⁰. Those
156 observations argue that IgE+ B cells are fragile, prone to apoptosis and to become short-live
157 plasma cells consistent with low but not null IgE secretion (Figure 1).

158

159 **Extrinsic regulation of IgE**

160 *IgE CSR is tightly regulated in SLO.*

161 As aforementioned, indirect class switch recombination results more frequently in high affinity
162 IgE^{26,28}. Though for a same rate of somatic hypermutation, IgE affinity remains lower

163 compared to IgG1 affinity suggesting that T follicular helper cells (Tfh) regulate IgE CSR and
164 affinity maturation in SLO. A new population of Tfh, “Tfh-13”, was described in several mice
165 models of food allergy and allergic asthma promoting high affinity IgE maturation compared
166 to non-allergic or helminth-infected mice³¹. These particular Tfh expressed canonical master
167 genes for type 2 inflammation (GATA3) and follicular polarization (Bcl-6). They also
168 expressed high amount IL-4 and IL-13 and low amount of IL-21 leading to indirect CSR.
169 Indeed, IL-21, IFN- γ and IL-10 are known to restrain IgE CSR all the more so they act in
170 synergy^{32–34}. At last, Tfh-13 are associated with IgG1 memory B cells that held IgE memory³¹.
171 Clement et al described a novel follicular regulatory T cells (Tfr) producing neuritin that were
172 able to constrain IgE-CSR and Tfh-13 formation preventing IgE high affinity maturation^{35,36}.
173 Of note, human IgE repertoire was shown to have less SHM in healthy individuals^{37,38}.
174 Furthermore, Shade et al demonstrated that several glycosylation patterns on IgE correlated
175 with its function. More precisely, N384-linked oligomannose on C ϵ 3 was essential to enhance
176 Fc ϵ RI binding^{39,40} whereas a higher number of sialic acid residues on N168 (C ϵ 1) and N265
177 (C ϵ 2) was essential to promote mast-cell degranulation in food allergic patients⁴¹. Those
178 modification were probably acquired after affinity maturation in the germinal center⁴². IgE
179 binds a C-type lectin domain on its low affinity receptor (CD23 or Fc ϵ R2 ; Kd ~ 0.1–1 μ M)⁴³.
180 Interestingly, IgE binding on its monomeric form (soluble or membrane-anchored) acts as a
181 negative feedback loop on B cells, suppressing IgE synthesis when interacting with CD21
182 ^{44(p21),45}.

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

187

188 *IgE function is actively constrained out of SLO and in peripheral tissues.*

189 In 2018 Shan et al described a novel mechanism constraining IgE-driven basophils
190 degranulation in epithelia and inflamed tissues via IgD and galectin 9. Briefly, in an ovalbumin
191 (OVA)-sensitized mice model, OVA-specific IgD could bound basophils via galectin 9 and
192 CD44 preventing their degranulation and enhanced type 2 inflammation. Galectin 9 could also
193 bind IgE subsequently inhibiting FcεRI mast-cells degranulation⁴⁶. Finally, no intrinsic defect
194 in activating nor regulatory signals were found in human basophils either from allergic patients
195 or healthy volunteers⁴⁷. These data strongly suggest that anaphylactic IgE are tuned down even
196 when type 2 immunity is triggered.

197 FcεRI (aka high affinity receptor - Kd ~ 1nM) is found as a tetramer, αβγ2, on mast cells and
198 basophils, and as a trimer, αγ2, on other cells such as monocytes, dendritic cells, eosinophils,
199 and platelets. FcεRI interacts with IgE through Cε3⁴⁸⁻⁵⁰. A mathematical modelisation of
200 immunoglobulin metabolism found that IgE undergoes substantial catabolism at extravascular
201 sites related to IgE/FcεRI interaction in the peripheral tissues⁵¹. This prediction was confirmed
202 in vitro (human dendritic cells/monocytes) and in vivo (transgenic mice humanized with human
203 trimeric form of FcεRI). Briefly, IgE is quickly endocytosed in a FcεRI-dependent manner
204 promoting serum IgE clearance and participate in IgE homeostasis⁵².

205 At last, IgG₁₋₄ auto-antibodies against IgE were described in atopic/allergic diseases and auto-
206 immune disorders and healthy volunteers⁵³⁻⁵⁵. Those anti-IgE auto-IgG are able to recognize
207 free and FcεR-bound IgE in contrast to Omalizumab that can bind only free IgE^{54,56}. Recently,
208 Chan et al showed that anti-IgE auto-IgG could either activate or inhibit in vitro basophil
209 degranulation test to grass pollen recombinant protein⁵⁷ suggesting an inhibitory role
210 preventing type 2 inflammation though mechanism is still unclear.

211 Altogether, those data highlight that in peripheral tissues, IgE function are constitutively
212 tracked down by active mechanisms (IgD mediated inhibition of basophils degranulation +/-

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

215

216 *IgE production is a basal trait of mucosal and imbalanced immunity.*

217 More systemic and integrative hypothesis of IgE homeostasis arose from germ-free
218 (GF) mice studies and monogenic primary immunodeficiencies in humans (PID). Such
219 deficiencies result in hyper-IgE and atopic/allergic-like clinical manifestations along with
220 susceptibility to infections and/or auto-immune manifestations. Those PID could affect either
221 regulatory T cell compartment (FoxP3 mutation loss of function), TCR/cytokine signaling
222 (ZAP-70 hypomorphic mutation loss of function as an example), TCR repertoire (restrained
223 oligo-clonal repertoire), glycosylation protein pathway (phosphoglucomutase 3 deficiency),
224 transduction pathways (STAT3 or DOCK8 deficiency) or even barrier function (Netherton
225 syndrome caused by SPINK5 mutation loss of function)⁵⁸. Despite precise mechanisms leading
226 to hyper-IgE are still poorly understood, a common mechanism would be that the
227 imbalanced/impaired type 1 or type 17 immunity unmask type 2 immunity⁵⁹.

228 Indeed, a high amount of IgE in GF mice occurred early in life (before 5 weeks of age)
229 in secondary lymphoid structure at mucosal sites. It was dependent on IL-4 produced by CD4+
230 T cells which precise lineage is not known. IgE production could be abolished by neonatal
231 microbiota colonization or (before 5 week of age) by fecal microbiota transplantation from
232 conventional-housed mice whereas in adults the process was stabilized⁶⁰. In addition, food
233 antigens in non-sensitized GF mice induced sustained specific IgE production at mucosal site
234 but also in SLO. The IgE synthesis was dependent on CD40L+ ICOS+ Tfh in secondary
235 lymphoid structures⁶¹. In both studies, GF mice developed aberrant Ag-specific IgE bound to
236 mast-cells that could induce anaphylactic symptoms after second Ag exposure.

237 Taken together, these data suggest that IgE production (Tfh dependent) is set by default
238 either at mucosal sites in absence of physiological microbiota colonization and/or by an
239 imbalanced type 1 and/or type 17 immunity during early life. This makes an echo to birth-
240 delivery mode that impact on neonatal gut microbiota colonization and diversity leading to
241 miseducation of immune system. Indeed, neonates with low gut microbiota diversity have a
242 higher risk to develop atopic/allergic diseases consistent with IgE dysregulation ^{62,63} (Figure 4).
243

244 **IMMUNOGLOBULIN E BIOLOGY**

245

246 **Does natural IgE production exist?**

247 Several mechanisms are at play to tune down IgE production. Though, IgE titer is not
248 null under homeostatic condition suggesting that a natural secretion of IgE does exist despite
249 the absence of long lived IgE plasma cells. One hypothesis would stand that IgE memory is
250 kept by IgG1 memory B cells^{64(p1)}. Thus, constant IgE secretion would suggest a low-to-
251 intermediate affinity to avoid uncontrolled type 2 inflammation and a constant/regular
252 stimulation by (auto-)antigens that remain to be determined. Another hypothesis relies on the
253 secretion of natural IgE independent of major histocompatibility complex (MHC) cognate T-
254 cell help in secondary lymphoid structures in a GF and T-cell-deficient mice models. Those IgE
255 had a low rate of SHM suggesting a low-to-intermediate affinity for antigens. At last, no
256 evidence of deleterious type 2 activation was observed⁶⁵.

257 Whatever their origin, the role of natural IgE remains poorly understood. An hypothesis comes
258 from old clinical observations where tissular damages (burns or in immediate post-operative
259 period) resulted in a rapid polyclonal increase of circulating IgE without deleterious type 2
260 inflammation^{66,67}. A recent study by Crawford et al demonstrated that a carcinogenic
261 environmental xenobiotic called 7,12-dimethylbenz[a]anthracene (DMBA) triggered a strong
262 polyclonal IgE response with self-reactivity when applied on skin. This IgE response, which
263 was dependent on FcεRI binding, prevented epithelial damage⁶⁸. Although, their exact
264 specificities remain to be determined, those IgE could be implied in maintaining immune
265 tolerance to self-antigens from damage tissues¹⁰. This is supported by two recent studies in mice
266 humanized for FcεRI alpha subunit which demonstrated anti-inflammatory properties of IgE-
267 FcεRI activated dendritic cells. Platzer et al showed that antigen/specific IgE complex
268 dampened systemic inflammation in an allergic asthma mice model in a FcεRI-dependent

269 manner⁶⁹. Baravalle et al showed that monovalent antigen covalently bound to IgE first induced
270 CD4+ T cell proliferation, quickly followed by a systemic clonal deletion of the antigen specific
271 CD4+ T cells⁷⁰. In addition, IgE-FcεRI activated DC promoted a IL-10 dependent retro-control
272 loop leading to effector T-cell deletion and regulatory T cell activation via indole-2,3-diamine
273 oxygenase (IDO) activation⁷¹⁻⁷³. A FcεRI soluble form was detected in human serum⁷⁴ and
274 exhibited an inhibitory effect on mast cell degranulation⁷⁵. Altogether, those data argue for an
275 immuno-modulatory role of natural IgE on innate immunity and indirectly on adaptative
276 immunity. Of note soluble form of FcεRs could be an add-on level of regulation. Yet, further
277 investigations are needed to understand the complex inter-play between IgE, FcεRs and
278 immune tolerance (Figure 5).

279

280 **IgE facilitated antigen presentation – a pivotal role in unmasking IgE** 281 **response/inflammation**

282 IgE-mediated response/inflammation is somehow necessary¹⁰. The IgE facilitated
283 antigen presentation (IgE-FAP) aka IgE antigen focusing plays a pivotal role in IgE
284 inflammation. This process has been mainly studied in immediate allergic diseases where it set
285 up and amplified the allergic inflammation against allergens⁷⁶.

286 In 1993, Heyman et al showed that the rate of IgG anti-bovine serum albumin (BSA)
287 and BSA-specific IgG+ B cells was higher when mice were immunized with trinitrophenyl
288 (TNP) – BSA and TNP-specific IgE^{77,78}. Another description of IgE-FAP came from the “toxin
289 hypothesis” that stood a protective role of IgE against venom⁷⁹. Later, it was demonstrated that
290 bee-venom immunized mice were more resistant to IgE-mediated anaphylaxis when re-
291 challenged with a lethal dose of bee or viper venom⁸⁰. In the same line, a recent study
292 demonstrated that a pre-existing IgE sensitization against *Staphylococcus aureus* (SA) toxin
293 enhanced SA IgG immunization and infection clearance in a mice model of pulmonary

294 infection⁸¹. These data suggest that one role of IgE-FAP would be to enhance humoral and
295 cellular response against non-self-antigen.

296 There are two main mechanisms known so far for IgE-FAP implying either FcεRI or
297 FcεRII. Multivalent antigen/IgE complexes were shown to activate dendritic cells⁸² mostly
298 toward a type 2 inflammation but not exclusively⁸³. IgE-FAP activated dendritic cells were also
299 showed to boost specific CD4+ effector T cells via MHC-II presentation with a 100 to 1000
300 fold higher efficiency than canonical MHC-II presentation (low dose of antigen)⁸². Moreover,
301 IgE-FAP activated basophils were more efficient at MHC-II cross presentation than dendritic
302 cells^{84,85}. At last, FcεRI-driven IgE-FAP demonstrated in vitro a broad spectrum of action on
303 human mast cells ranging from self-survival, pro-inflammatory cytokines secretion to complete
304 degranulation according to the nature of IgE and the antigen⁸⁶ (Figure 6a).

305 CD23 has three major known ligands: CD21, MHC-II and IgE with different interaction
306 sites respectively⁸⁷ especially with B cells and monocytes/macrophages⁸⁸. Noteworthy, CD23
307 has two isoforms: CD23a is constitutively expressed and up-regulated after IL-4 stimulation
308 whereas CD23b is expressed only after IL-4 stimulation⁸⁹. Only CD23a under its trimeric form
309 is implied in antigen processing whereas CD23b is more related to phagocytosis⁹⁰. Conversely
310 to FcεRI-driven IgE-FAP, several studies demonstrated that CD23a IgE-FAP enhanced
311 humoral response (IgG and IgM) as well as the specific cellular response (CD4+ T cells) against
312 a multivalent antigen (TNP-OVA) in mice models either adjuvanted with TNP-specific IgE or
313 transgenic mice over-expressing CD23^{91,92}. The magnitude of the response was higher with
314 antigen/IgE complex and low dose of antigen⁹². Those data were confirmed in human by in
315 vitro models where B cells from allergic patients expressed a high density of CD23 arguing for
316 a trimeric form^{93,94}. Trimeric soluble CD23 is also detectable in human serum which function
317 seems to be identical to the membrane form⁹⁵ (Figure 6b).

318 Altogether, those data suggest another role of IgE-FAP which could be 1) the detection
319 of low amount of antigen and 2) the onset of an adaptative type 2 immune response mainly but
320 not exclusively. This suggests that IgE takes part to immuno-surveillance to non-self. As well,
321 IgE-FAP seems to trigger an inflammatory response with multivalent antigens. This makes an
322 echo to a recent study where the more the IgE interacting epitopes were numerous and close to
323 each-other the more the IgE complexes were able to cluster IgE receptors (FcεRI) and trigger
324 mast cell activation⁹⁶.

325 **POTENTIAL ROLES OF IMMUNOGLOBULIN E IN HEALTH AND NON-**
326 **ALLERGIC DISEASES**

327 **IgE and venom toxicity – a host defence mechanism?**

328 The hypothesis that IgE could play a protective role against toxins after arthropods or reptile
329 bite was proposed by James Stebbings in 1974⁹⁷ and Margie Profet in the early 1990's⁷⁹. Since,
330 important works from Stephen Galli's group have get credit to this hypothesis suggesting that
331 IgE and its interaction with mast cells can enhance host resistance to venoms. More precisely,
332 honeybee venom resistance to a lethal dose can be transferred to a naive mice by systemic serum
333 therapy from a honeybee immunized mice⁸⁰. This protective effect was lost either after
334 depletion or inactivation of IgE in the serum or when FcεRI α or γ chain were knocked out in
335 the naïve recipient mice^{80,98}. Those result suggested that IgE-mediated resistance to venom is
336 linked to a FcεRI-IgE FAP on effector cells. Indeed, mice lacking mast cell and/or basophils
337 were unable to acquire venom resistance after immunization⁹⁹. Furthermore, local FcεRI-IgE
338 FAP mast cell degranulation enhanced venom detoxification^{99,100} thanks to proteases contained
339 in their granule such as carboxypeptidase 3 and chymase^{101,102}, which degrade venom peptides
340 (sarafotoxin and helodermin respectively) with structure similarity to endogenous mammalian
341 peptide (endothelin 1 and vasoactive intestinal peptide respectively)¹⁰³. Interestingly in those
342 mice model of envenomation, mast cell, basophil or even innate lymphoid cells type 2 were not
343 required to induce IgG1 and IgE immunization against venom antigen^{98,99}. Last but not least,
344 previous IgE immunization against an irrelevant allergen added to venom resulted in enhanced
345 resistance to the venom despite prior immunization⁹⁹. Altogether, those data demonstrate that
346 detoxification to a complex mixture of antigen such as venom involve specific IgE sensitization
347 to a small fraction of antigen that induce the release of proteases due to FcεRI-IgE local
348 degranulation of mast cells. Furthermore, those results suggest that venom itself induce specific
349 IgE immunization independent of effector cells (Figure 7).

350

351 **IgE and helminth – who is protecting who?**

352 High IgE titer is one hallmark of active helminthic infection with eosinophilia reflecting type-
353 2 inflammation. In human, several studies associated resistance to (re)-infection to specific IgE
354 against *Schistosoma mansoni* or *haematobium*^{104,105} whereas the underlying mechanisms
355 associated with IgE and parasite resistance remain unclear. So far, mice models of helminthic
356 infection used to better decipher the role of IgE during helminthic infection in has led to
357 conflicting results. An explanation, at least in part, could be the use of inadequate model to
358 study IgE response such as AID-deficient mice, B cell deficient mice or FcγR deficient
359 (reviewed in¹⁰⁶). Table 1 summarizes different studies that used IgE-deficient or FcεRI-
360 deficient mice to better decipher their role during primary or secondary helminthic infections.
361 Several interesting patterns draw according to worm burden mostly and to a lesser extent on
362 granuloma in target organs. It is worth noticing that the time after infection inversely correlates
363 with worm burden: the longer it is, the smaller the difference in worm burden is observed. In
364 most studies, IgE or FcεRI deficiency is associated with an increased worm burden in the early
365 phase (before 2 weeks) of the infection either during the first exposure (*Schistosoma mansoni*,
366 *Strongyloides venezuelensis* or *Brugia malayi*) or the second exposure (*Nippostrongylus*
367 *brasiliensis*, *Heligmosomoides polygyrus*)^{107–112}. Interestingly, IgE or FcεRI deficiency was
368 associated with a reduced specific IgG1 response during the first exposure^{110,112}. The
369 consequence of IgE or FcεRI deficiency in repeated exposures to helminths which can be
370 modeled by the presence of granuloma in target tissue remains unclear. Though, IgE
371 deficiency seems to be associated with smaller granuloma (i.e smaller inflammatory
372 infiltrate)^{112,113} and FcεRI deficiency is associated with increased damages and inflammatory
373 infiltrate in the target tissues^{108,114}. Furthermore, basophils activation by IgE/worm antigens
374 complexes were essentials for granuloma formation and limit tissue damages^{108,109}. Altogether,

375 those data suggest that IgE response might have different impact in helminthic infection. Upon
376 acute exposure, IgE would play a role in worm clearance 1)thanks to enhancement of specific
377 IgG response, 2)FcεRI-driven IgE degranulation of effector cells such as mast cells, basophils,
378 platelets and eosinophils^{106,115}. Upon repeated exposure (i.e, worm clearance failure), specific
379 IgE and their interaction with FcεRI on basophils would take part in granuloma formation to
380 constrain the worm, avoid target tissue damages¹¹⁶ and tissue healing making an echo to the
381 concept of natural IgE implied in tolerance⁶⁵. Nevertheless, this latter point remains speculative
382 since to date no clear role for IgE in wound healing has been documented (Figure 8).

383

384 **IgE in tumor immuno-surveillance – a kind friend?**

385 Selective IgE deficiency is defined as total circulating IgE < 2.5KU/L after excluding common
386 variable immune deficiency¹¹⁷. Recently, three studies demonstrated either retrospectively or
387 prospectively a significant association between selective IgE deficiency and the onset of
388 malignant diseases in adult and children. Interestingly, the demographic data of neoplasm
389 diseases were identical to the target population: solid organ cancer in adulthood and
390 hematologic cancer in childhood^{118–120}. These data suggest that IgE-FAP could play a role in
391 tumor immune-surveillance. Indeed, a recent study by Crawford et al demonstrated that DMBA
392 induced skin epithelial carcinogenesis triggered $\gamma\delta$ T cell activation and local self-reactive IgE
393 production via IL-4 in mice. Those IgE took part in preventing epithelial carcinogenesis in a
394 FcεRI dependent manner⁶⁸. This assumption is supported by several observations in human
395 where non anaphylactic specific IgE immunization against tumors could trigger specific
396 cytotoxic responses in patients with colorectal, pancreatic, prostatic and breast cancer^{121–124} in
397 a FcεRI-dependent manner¹²⁵. On the opposite, two recent observations demonstrated a
398 detrimental role of IgE in a mice model of skin cancer. More precisely, Taniguchi et al
399 demonstrated that skin tumors were infiltrated with IL-33 induced FcεRI+ macrophages that

400 promoted tumor growth suggesting a role of IgE on those tumor-infiltrating macrophages¹²⁶.
401 Also, Hayes et al demonstrated that tumor growth was promoted by an increase of polyclonal
402 “natural” IgE after 12-*O*-tetradecanoylphorbol-13-acetate (TPA) repeated applications. Tumor
403 growth was also dependent on FcεRI IgE-FAP on basophils that infiltrated the tumor.
404 Interestingly, selective IgE deficiency in those mice model abrogated tumor growth¹²⁷.
405 Altogether those data suggest that IgE would prevent tumor growth in the early phase of
406 carcinogenesis whereas IgE would promote tumor growth at an advanced stage (Figure 9). The
407 distinct IgE repertoires induced by DMBA and TPA (self-reactive versus polyclonal natural
408 respectively) could explain, at least in part, the janus-faced role of IgE in cancer
409 immunopathology despite type 2 immunity induction in both case^{68,127}. In conclusion, further
410 researches are needed 1) to consider selective IgE deficiency as a predictive biomarker of cancer
411 onset¹²⁸ and 2) to better characterize the role of IgE at molecular (IgE repertoire, antigen
412 identification, receptors) and cellular (CD8+ T cells, NK cells, γδT cells) levels in the tumor
413 micro-environment (enhancing or preventing tumor growth) in order to achieve new add-on
414 therapeutic strategies^{129,130}.

415

416 **IgE self-reactivity: from autoallergy to autoimmunity – friend or foe?**

417 The concept of autoallergy implies the presence of self-reactive IgE (srIgE) and was introduced
418 by the end of 1950's^{131,132} without any understanding of its role. To date, this concept has
419 evolved into IgE autoimmunity with a growing spectrum of autoantigens identified in systemic
420 erythematous lupus (double strand DNA, SSA/B, RNP, nucleosome, acidic ribosomal P2
421 protein among others), chronic urticaria (thyroperoxidase, double strand DNA, IL-24), bullous
422 pemphigoid (BP180 or BP230) and atopic dermatitis (> 140 autoantigens identified) mostly¹³³.
423 srIgE were associated with disease severity in systemic erythematous lupus^{134,135}, bullous
424 pemphigoid¹³⁶ and chronic urticaria¹³⁷. They are probably important in atopic dermatitis

425 pathogenesis since a high percentage of patients have srIgE^{138,139}, though the correlation
426 between srIgE and disease severity remains debated requiring further investigations¹³³. The
427 cellular and molecular effects of srIgE were mainly deciphered in lupus where they enhance
428 disease activity through two main pathways. On one hand, FcεRI-driven srIgE-FAP on
429 plasmacytoid dendritic cells enhance srIgG/srIgE through B cells expansion and plasma cell
430 differentiation in SLO in a TLR9-dependent manner¹³⁴. On the other hand, MHC-II cross-
431 presentation of autoantigen (double strand DNA) via FcεRI-driven srIgE-FAP by activated
432 basophils enhanced autoantibodies and B cell differentiation through type-2 inflammation in
433 SLO in a BAFF-dependent manner¹⁴⁰ (reviewed in¹⁴¹). In bullous pemphigoid, cellular and
434 molecular effect of autoreactive IgE are not that well deciphered¹³³. In chronic urticaria, the
435 importance of auto-IgE has been strongly suggested by the great efficiency of omalizumab on
436 disease activity¹⁴² and also by passive anaphylaxis transfer with sera from patients with chronic
437 urticaria¹⁴³. Though, the precise mechanisms remains poorly understood¹³³. In conclusion, the
438 data strongly argue for a deleterious implication of srIgE through FcεRI-driven FAP. It also
439 suggests that srIgE are of high affinity (indirect CSR) able to cross-link multivalent
440 autoantigens and activate effector cells. Though, how autoreactive IgE and type 2 immunity are
441 triggered leading to complex and different clinical features remains poorly understood.

442

443 **Unexpected associations between IgE and diseases**

444 Implication of IgE was suggested in cardiovascular diseases thanks to mice models of aorta
445 aneurysm where FcεRI alpha subunit knock-out partially protected from smooth muscle
446 senescence¹⁴⁴, neutrophils and macrophage infiltration and IL-6 mediated inflammation^{144,145}.
447 Yet, those results were not translated to human. Another observation suggested that IgE
448 sensitization against alpha-gal oligosaccharide without any anaphylactic features was
449 associated with a higher risk of coronary atheromatous disease at a younger age¹⁴⁶ which

450 precise mechanisms remain to be determined. Altogether, those observations open a whole new
451 field of IgE biology in cardiovascular homeostasis and disease.

452 Recently, functional anti-MHC IgE (ie. inducing mast cell degranulation) was detected in mice
453 models of skin and heart allograft serum. The author could also detect anti-HLA IgE in sera
454 from kidney transplanted patients with high titers of donor specific antibodies (n=5)¹⁴⁷. Another
455 recent study associated antibody-mediated rejection with anti-HLA IgE in the serum and IgE
456 deposit colocalizing with mast cell/basophil in the kidney transplant¹⁴⁸. Altogether, those data
457 suggest that the HLA/IgE complex could interact with mast cell/basophils in the transplant and
458 trigger deleterious type 2 immunity. It also questions about 1)the interaction of IgE with other
459 cognate effector cells such as eosinophils¹⁴⁹; 2)the triggers of allo-immune response in solid
460 organ transplantation¹⁰.

461

462

463 **CONCLUSION**

464 Since its characterization in 1966, IgE has been extensively studied in allergic diseases such as
465 food or drug anaphylaxis, allergic rhinitis and allergic asthma where it has a pivotal role.
466 Furthermore, it would be finalistic to assume a simple pathological role for IgE especially since
467 IgE is only found in mammals⁷. Some evidence argues for a constitutive secretion of IgE in the
468 body fluids with homeostatic or even immune-modulatory properties. However, their precise
469 roles and interactions with other immunoglobulins and immune cells remain to be determined.
470 Some evidence also argues for a pro-inflammatory role of IgE when type 2 inflammation is
471 triggered. In that case, IgE could enhance immune response against small amounts of antigen
472 (IgE-FAP) with a wide spectrum of downstream responses modulated either by IgE affinity
473 and/or receptor binding (FcεRI or FcεRII) and/or the target cell (basophils, mast cells,
474 eosinophils or even platelets). However, further studies are needed to decipher how these
475 responses are finely tuned. Additionally, breakthrough works have unraveled some
476 physiological roles of IgE such as resistance and detoxification to venom, worm clearance
477 during acute infection, prevention of tissue damage in case of helminthic chronic infection.
478 More surprising, there is a janus-faced role in cancer immunopathology where IgE seems to
479 take part in tumor clearance/immuno-surveillance at an early stage. On the opposite, IgE seems
480 to enhance tumor out-growth at an advance stage suggesting a diversion of IgE response which
481 mechanisms remains unclear to date. Last but not least, IgE was unexpectedly implicated
482 vascular disease or even rejection in solid organ transplantation where immunopathological
483 mechanisms remain to be determined. Altogether, those interesting developments argue for a
484 role of IgE response as an immunological adaptor to complex environmental changes which
485 better characterization will lead to the development of innovating therapeutic strategies.

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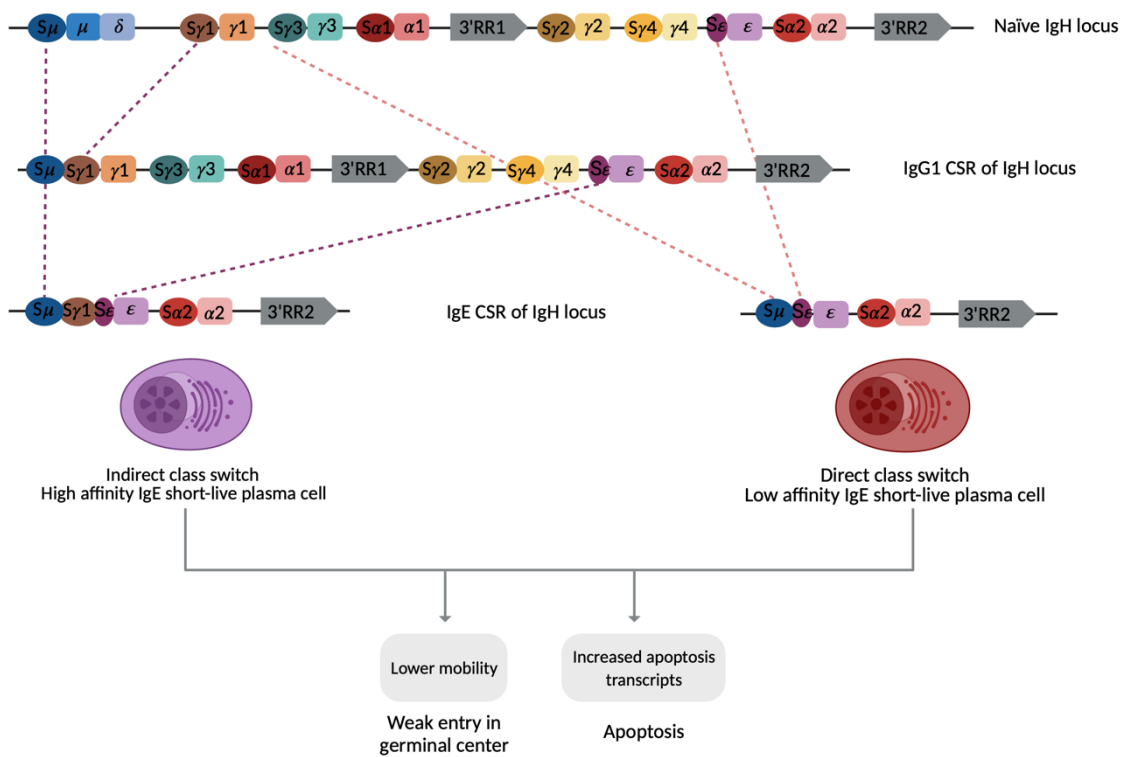
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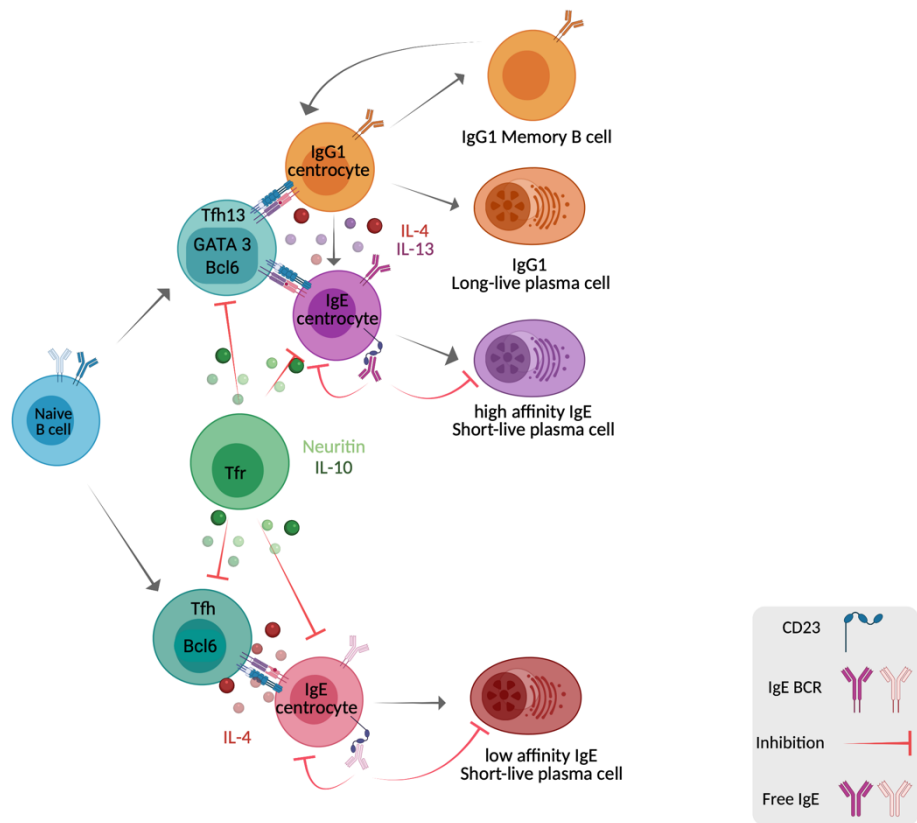
923 FIGURES & TABLES

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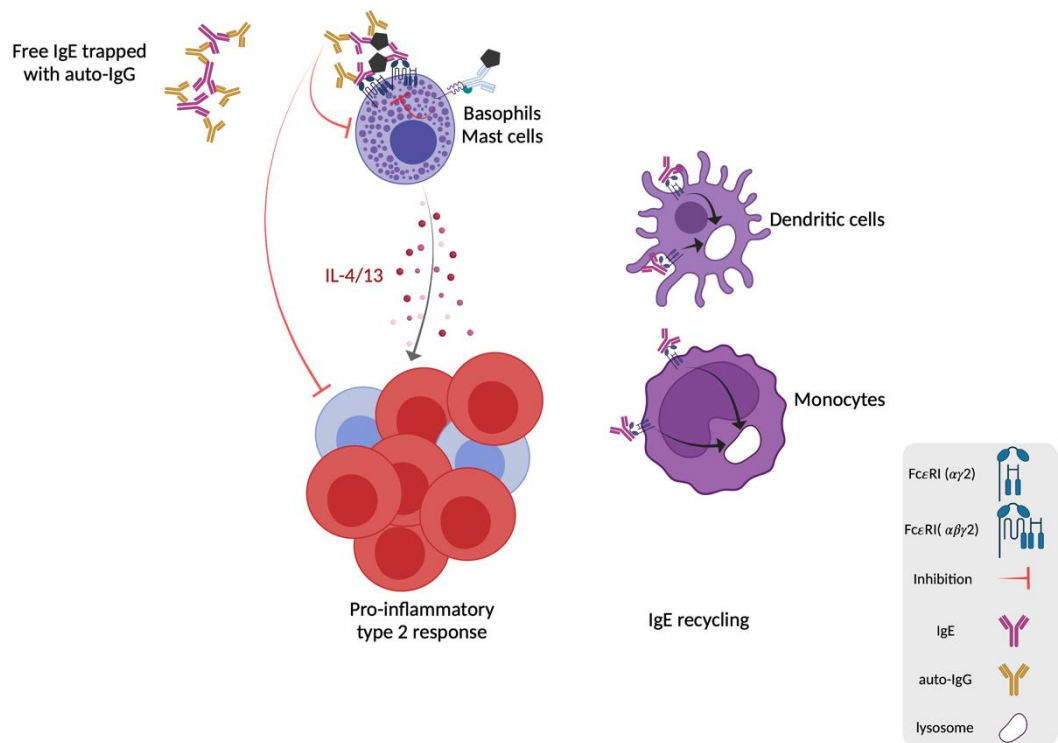
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926 Figure 1: Intrinsic regulation of IgE. Class switch recombination (CSR) to IgE is regulated by
 927 the size of the ϵ acceptor region ($S\epsilon$) which is smaller than all the others making more difficult
 928 to access for transcription factors. Furthermore, CSR can occur either directly from μ to ϵ or
 929 indirectly from μ to $\gamma 1$ to ϵ . In both case, the expression of IgE BCR leads to an increase rate
 930 of apoptosis and a lower mobility to germinal centers. This figure was created with
 931 BioRender.com.



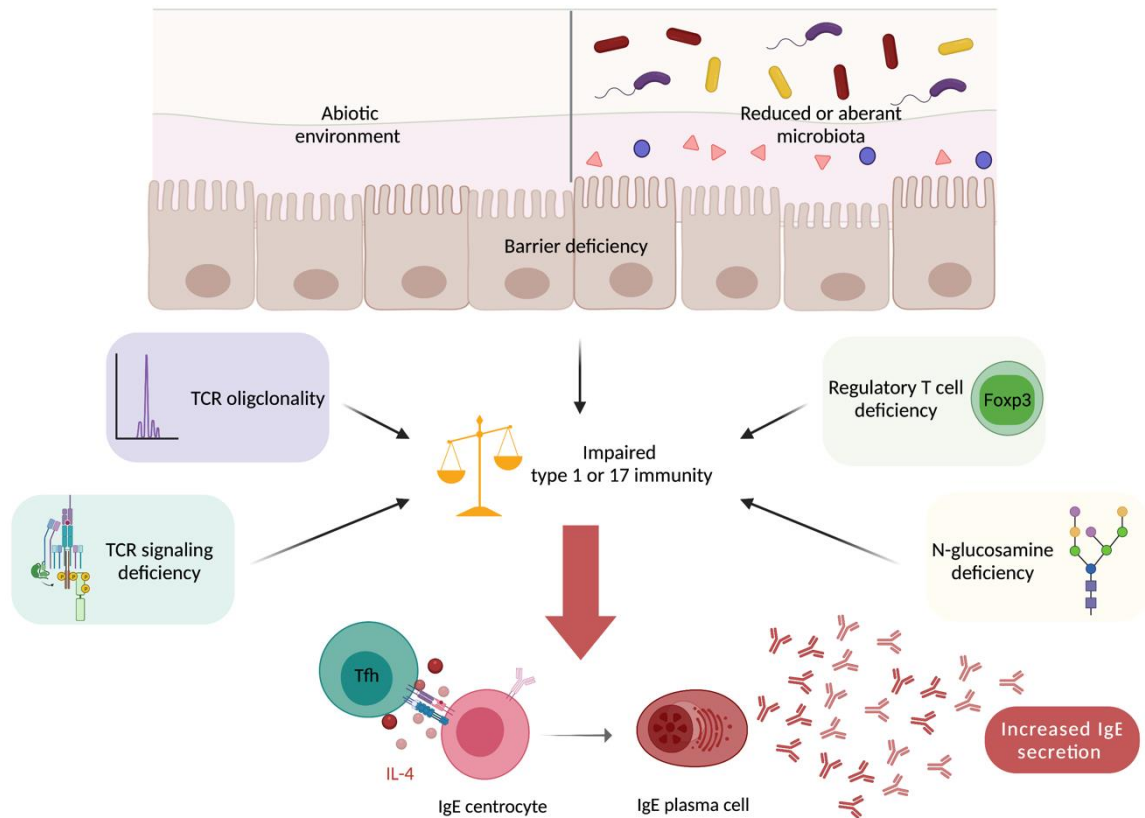
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933 Figure 2: Extrinsic regulation of IgE in secondary lymphoid organs. When a naïve B cell
 934 commits into IgE CSR (direct or indirect), there are two main mechanisms limiting the
 935 appearance of IgE long-live plasma cells. The first one is the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



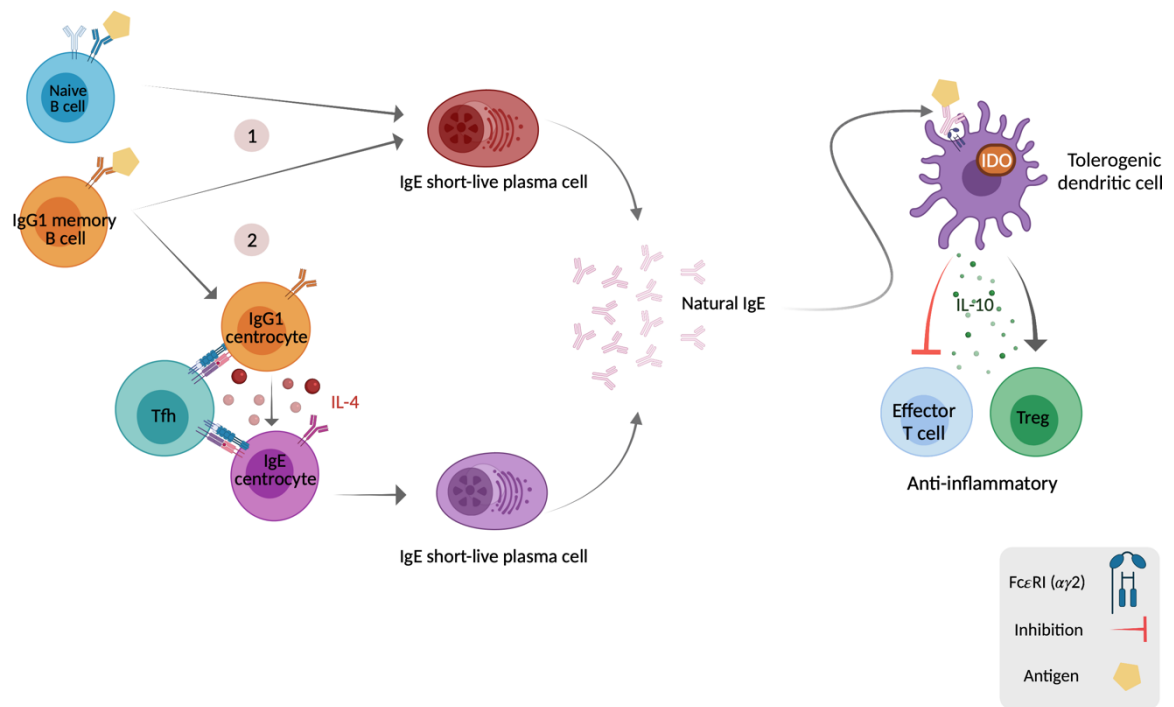
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940 Figure 3: Extrinsic regulation of IgE production in peripheral tissue. Under homeostatic
 941 condition, IgE binds his high affinity receptor (FcεRI) on mast cells and monocyte without
 942 antigen leading to a rapid internalization of IgE and its receptor to lysosomes. Under
 943 inflammatory condition, basophils/mast cell degranulation due to IgE cross-linking with
 944 antigen is constrained 1)by the antigen/IgD complex binding to its receptor (CD44 and galectine
 945 9) 2)by the auto-reactive IgG against IgE under its soluble and bound form. This figure was
 946 created with BioRender.com.



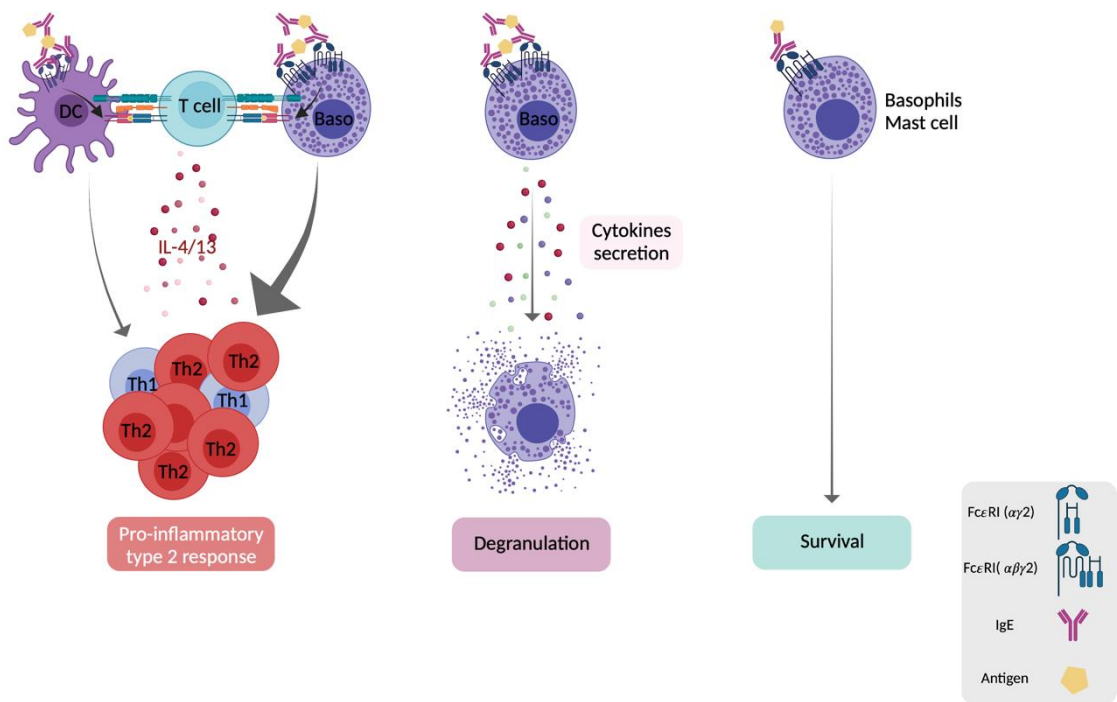
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948 Figure 4: Loco-regional IgE secretion at mucosal sites. Loco-regional IgE secretion is a basal
 949 trait at mucosal sites in case of impaired type 1 or 17 immunity which can occur in case of 1)
 950 abiotic or aberrant microbiota leading to barrier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



953

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



962

963 Figure 6a: The pivotal role IgE facilitated antigen presentation (IgE-FAP) via FcεRI. FcεRI

964 IgE-FAP has a broad spectrum of effects on basophils (baso) or mast cells ranging from survival

965 in case of crosslinking with a monovalent antigen to degranulation, cytokine secretion or even

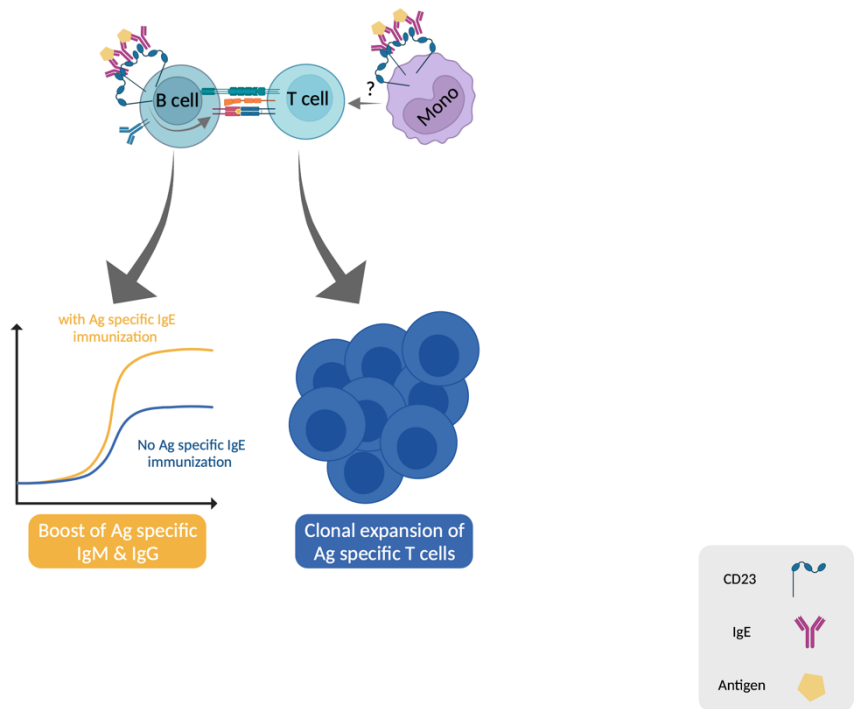
966 amplification of type 2 response in case of multivalent antigen cross-linking (indirect

967 presentation by class II major histocompatibility complex, (MHC-II)). FcεRI IgE-FAP with a

968 multivalent antigen can also occur on dendritic cells (DC) where it enhances type 2 response

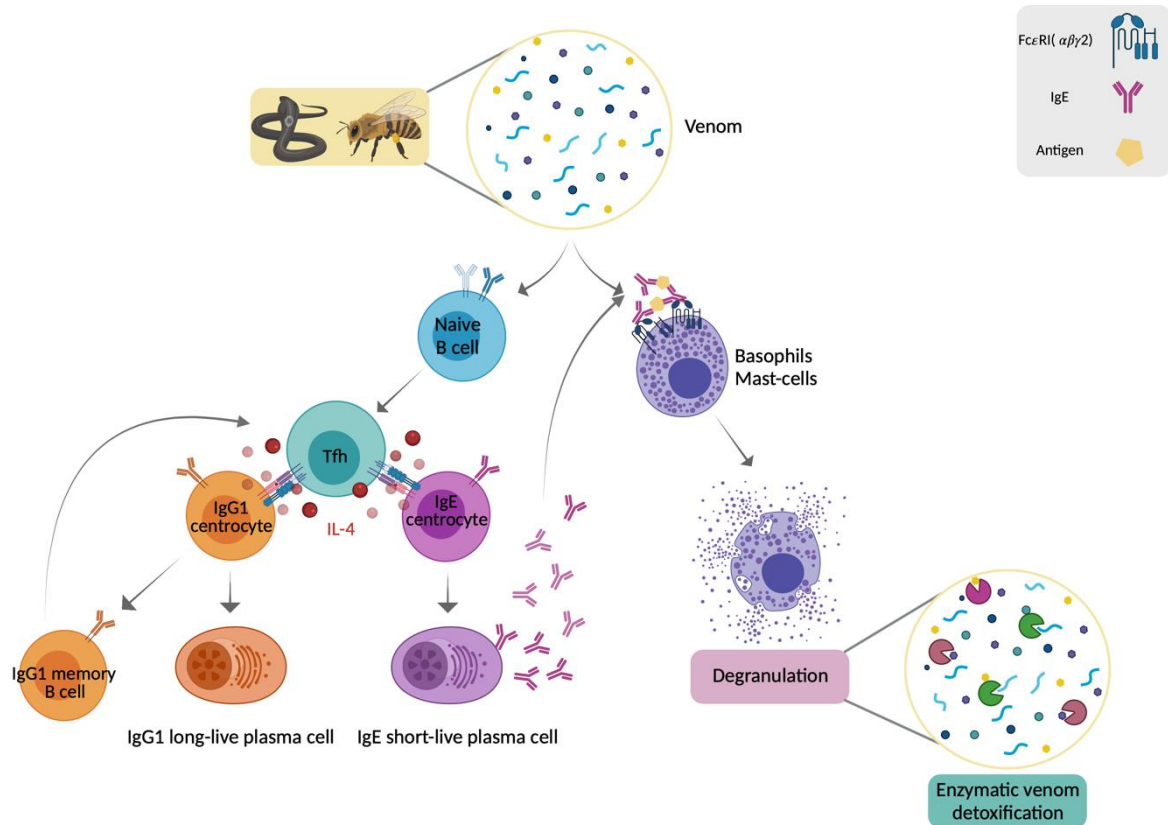
969 thanks to indirect MHC-II presentation of the antigen. This figure was created with

970 BioRender.com.



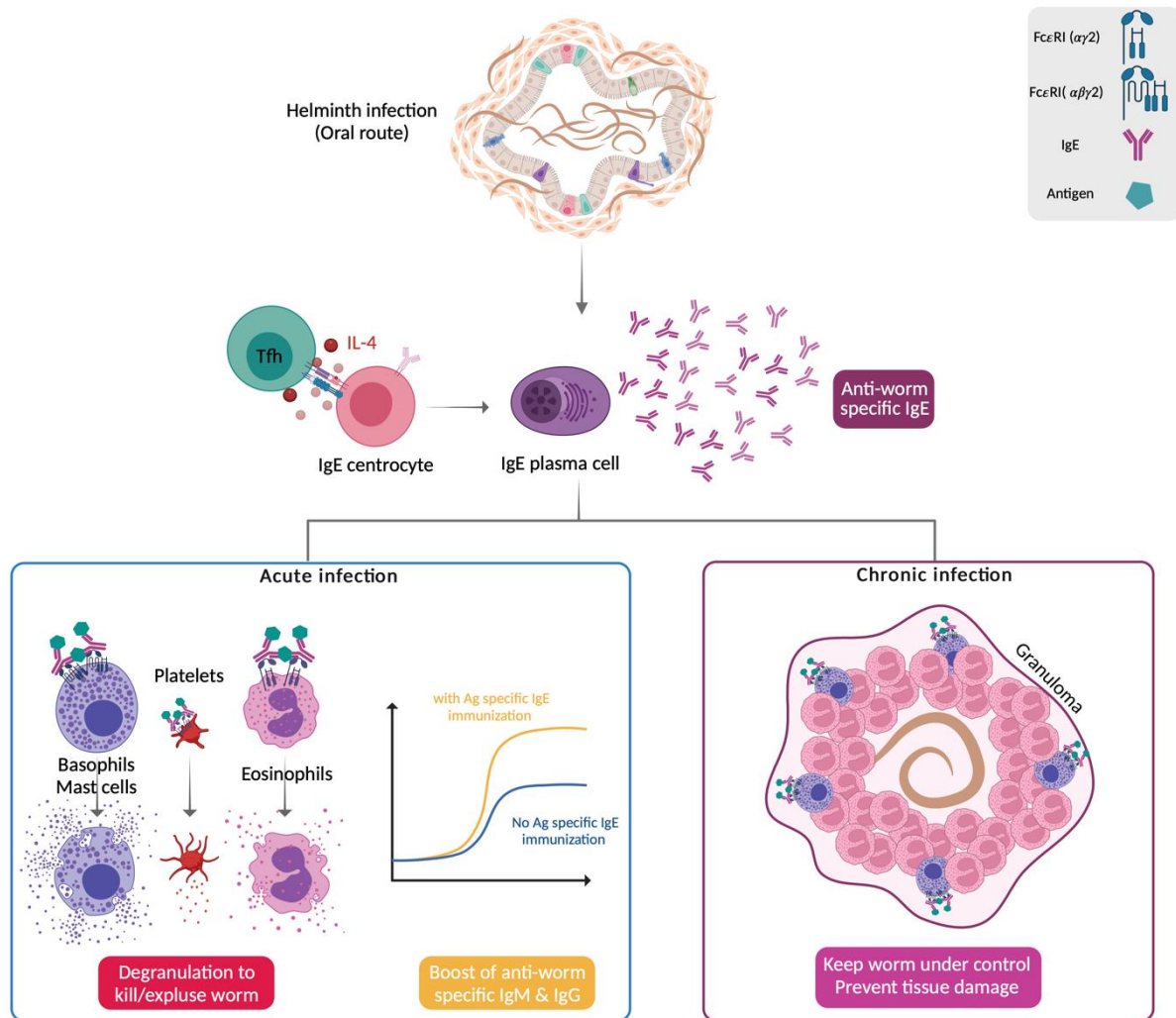
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972 Figure 6b: The pivotal role IgE facilitated antigen presentation (IgE-FAP) via FcεRII aka
 973 CD23. There are two main effects of trimeric CD23 IgE-FAP with multivalent antigen that can
 974 be mediated by B cells and probably by monocytes (Mono). The first one is to boost humoral
 975 response with specific IgM and IgG immunization. The second one is to enhance clonal
 976 expansion of antigen specific T cells. This figure was created with BioRender.com.



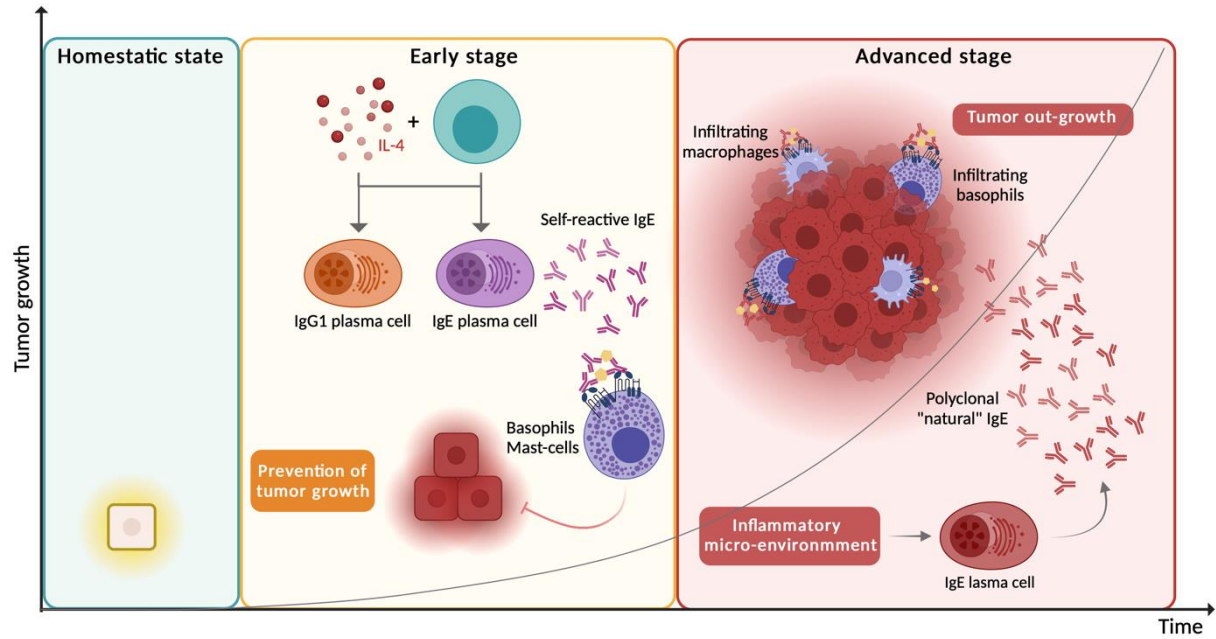
977

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



985

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



994

995 Figure 9: The janus-faced role of IgE in cancer immunopathology. In the early phase of cancer
 996 growth, self-reactive IgE will produced thanks to the help of IL-4 and resident $\gamma\delta$ T cells. Those
 997 self-reactive IgE will activate the basophils thanks to Fc ϵ RI IgE-FAP that will prevent tumor
 998 growth and enhance anti-tumoral immunity. On the opposite at an advanced stage of cancer,
 999 the pro-inflammatory micro-environment will lead to the local secretion of polyclonal “natural”
 1000 IgE that will enhance tumor out-growth thanks to Fc ϵ RI IgE-FAP on basophils and
 1001 macrophages that infiltrate the tumor. This figure was created with BioRender.com.

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1003

1004 Table 1: Impact of IgE or FcεRI deficiency in mice models of helminthic infections based on
 1005 time after infection, single or repeated exposure, worm burden, egg production and the presence
 1006 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 costaricensis	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 & increased in the lung	ND	Decreased number of granuloma in the skin and larger lung injuries compared to WT mice.	108

					for the second infection compared to WT mice.			
	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	ND	ND	109

					infectio n			
Strongyloide s venezuelensi s	FcεRI- /- mice	Yes	No	1,5 weeks	Increas ed compar ed to WT mice when FcγR are blocke d	ND	ND	110
Brugia malayi	BALB/ C IgE deficie nt mice	Yes	Yes	2 to 6 weeks	Increas ed compar ed to WT mice in primar y infectio n ; No differe nce on second ary infectio n	ND	ND	111
Schistosoma mansoni	129/ter Sv IgE- deficie nt mice	Yes	Yes	8 weeks	Increas ed compar ed to WT mice in primar y infectio n with lower specific IgG1 respons e ; No differe nce on	ND	Smaller granulo ma in the liver than WT mice	112

					secondary infection			
	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

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1009 **DISCLOSURE STATEMENT:**

1010 The authors of this manuscript have no conflicts of interest to disclose as described by Allergy.

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