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Review Article

The ontogeny of IgE forming cells

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Abstract

The origin and fate of IgE forming cells has commanded attention for more than 50 years largely because they drive allergic diseases that plague a third of the world's most economically privileged populations. Ontogeny studies began in the early1980s with the expressed intent of locating these cells so that IgE production might be turned off at the source, at the level of the IgE forming B cell. They continue to the present day. The technological revolution at the turn of the last century neatly divides efforts. From the outset, IgE seemed unlike other isotypes. IgE forming cells did not appear to clone in germinal centers like other B cells, but to arise rapidly and transiently within gut after stimulation. Long-lived memory seemed to reside in the periphery, in spleen and bone marrow. Even those early ontogeny studies hinted at isotype switching. As the century turned, advances in flow cytometry and the creation of transgenic mice synergized to allow the reliable detection of vanishingly rare cells. New technologies allowed genetic analysis of even single cells. With resolution unimaginable 20 years before, IgE forming cells were found to arise from direct and indirect isotype switching, from IgM and IgG precursors, potentially in all organs, including thymus and perhaps any tissue exposed to allergen. Armed with new tools, future work may one day soon make good on the old vision of turning off IgE responses at their source, at the level of the IgE forming cell.

Keywords: Allergy, B-lymphocytes, Immunoglobulin E, Isotype switching, Neonatal immunity, Plasma cells

Introduction

Allergy affects 30% of the world's population with increasing prevalence, especially in children [1]. In developed countries, IgE responses cause allergic diseases, like hay fever, rhinitis, asthma, atopic dermatitis, and forms of chronic urticaria [2]. In rare instances, such as IgE-mediated anaphylaxis, it can prove fatal [3]. Almost simultaneously with its description by Kimishi and Teruko Ishizaka in the mid-1960s [4], work of Dame Bridget Ogilvie established a crucial role in fighting helminthic gut worms [5]. Helminths remain a grave global health threat affecting 20% of the world's population [6]. Thus, IgE responses have commanded significant attention for over 50 years.

IgE is one of the more enigmatic immunoglobulins. Serum levels are very low in health, elevated in allergy and AIDs [7] and high only in rare disorders like Hyper-IgE syndrome, also known as Job's syndrome or Buckely's Disease [8,9]. While other immunoglobulin classes like IgG and IgM have far higher serum levels and broader functions, IgE is primarily associated with parasitic infestations and allergy [10], although it may also have roles in antigen presentation [11] and even cancer [12]. Most exists bound to mast cells, basophils, and eosinophils [13].

This review is not intended to cover IgE regulation, isotype switching or B cell development. These are each very large, deeply nuanced topics, far beyond the scope of this focused review. Indeed, in various contexts, they have recently been reviewed separately [14–16]. Instead, this work aims at a high-level summary of literature published over the last 50 years, relevant to questions of where IgE forming cells come from and where they go. Here, "IgE forming cells" means either B cells that make surface IgE or plasma cells that secrete IgE. These are distinct from cells decorated with cytophilic IgE.

Early Work: The 1980's and 90's

Germ free rats

Early studies by Durkin *et al.* suggested gut as a source of IgE producing cells. Working in germ free (bacteria free) rats, using specific antisera and emergent techniques of fluorescence labeling, they found IgE+ cells (~20%) in Peyer's patches, fewer (<10%) in blood, spleen, mesenteric and other lymph nodes and none in bone marrow or in normal rats. IgA+ cells were also threefold higher while IgM+ cells were reduced (23 vs 4% respectively). 50% of IgE+ cells also expressed IgA. High numbers in Peyer's patches suggested commitment to IgE production occurred there. Reduced IgM+ cells in the presence of IgE+/IgA+ cells hinted that IgE forming cell origins and fates involved isotype switching [17].

The very presence of IgE forming cells in gut suggested bacteria as potential "natural" IgE regulators. Indeed, Durkin et al reported that germ-free rat Peyer's patches were converted to those resembling conventional animals within hours after feeding unautoclaved chow. Histology confirmed that IgE formation occurred without cell division, germinal centers or mitotic figures, again suggested isotype switching. Attempts to identify specific bacterial products controlling IgE responses also reinforced isotype switching in response to gut flora signals [18]. This was consistent with the "hygiene hypothesis" [19,20], the idea that increased incidence of allergy was related to reduced bacterial exposure.

Parasite infested rodents

In the middle of the decade Urban *et al.* studied IgE responses in helminth infested rodents [21]. Using a fluorescence activated cell sorter and affinity purified antisera, they found IgE staining cells in the mesenteric lymph nodes rising from undetectable to about 30% to 50% weeks after infestation and persisting for months. However, cells with intracellular IgE never rose above 2%, suggesting that the vast majority were lymphocytes with cytophilic IgE. This, along with vastly differing kinetics depending on nematode species, casted doubts on the model's relevance to allergic disease [22].

Hapten specific responses

The early 1990s saw the development of the first isotype specific monoclonal antibodies. This allowed the indirect detection of IgE forming cells via flow cytometry, immunohistochemistry and a novel adaptation of the enzyme linked immunosorbent spot (ELISPOT) assay [23]. Auci *et al.* reported hapten specific IgE producing cells arose first in murine Peyer's patches and mesenteric lymph nodes [24]. Peak levels were observed (5-10% for IgE staining cells and about 200 per 10^7 lymphocytes for antibody forming cells), within 8-18 days of immunization, respectively. These cells abruptly disappeared from gut within weeks but were found for 70 days in bone marrow and spleen. Boosting increased numbers in bone marrow and spleen but not in gut. Strikingly, IgE/CD23 immune complexes appeared in gut tissue following the appearance and preceding the disappearance of IgE producing cells, one of the earliest suggestions of IgE regulation by soluble CD23. CD23 is the low affinity IgE receptor. Significant cytophilic IgE was not reported.

This early work suggested that commitment to IgE expression was a transient event quickly following antigenic stimulation. Memory, in contrast, seemed to resided in bone marrow and spleen. A few additional observations standout. First is the discovery of IgE/CD23 immune complexes, now known to be intimately associated with IgE regulation [25,26]. Second, histological analysis never detected IgE producing B cells cloning in germinal centers. These observations have since been confirmed, if not cited, by many groups.

Modern Rodent Studies: The 21st Century

As the 20th century closed, myriad strains of transgenic mice appeared, including animals bearing monoclonal populations of B and T lymphocytes specific for influenza virus hemagglutinin (HA) and chicken ovalbumin (OVA), respectively [27]. Initially, this model was used to elucidate IgE regulation, but five years later, in 2006, the model was used alongside helminth infestation to study ontogeny [28]. Several relevant findings stand out from that work, including a lack of IgE forming cells in germinal centers. This was reported as an 'unexpected' finding, despite similar observations by Durkin nearly two decades earlier. Response kinetics (peaks at approximately 8-10 days after immunization, followed by rapid disappearances) as well as peak numbers (about 10% of lymphocytes) were also similar to reports by Durkin *et al.* Improvements in immunohistochemistry and related reagents allowed the identification of IgE+ cells in the marginal zones and outside germinal centers. Cell staining and transcript analysis identified double bearing IgG1+/IgE+ cells and isotype switching as their likely source. Despite the failure to visualize these cells in germinal centers, this was where the actual switch to IgE expression was thought to have occurred. FACs analysis suggested their fate involved rapid differentiation into short-lived IgE forming plasma cells.

Table 1. Early rodent studies.

Model	Induction	Results	Reference
Germ Free Rat	Diminished gut bacteria	IgE forming cells observed in Peyer's Patches not Bone Marrow, potential involvement of isotype switching.	Durkin *et al.*, 1981 [17]
Germ free rat	Feeding unautoclaved chow	Histological evidence that IgE formation occurred in the absence of cell division, germinal centers or mitotic figures again suggested isotype switching.	Durkin *et al.*, 1989 [19]
Parasite infested Rodents	Various helminth worms	IgE staining cells in the mesenteric lymph nodes weeks after infestation, persistence for months. Widespread cytophilic IgE.	Katona *et al.*, 1985 [22]
BPO-KLH sensitized mice	Immunization with BPO-KLH alum.	Rapid and transient appearance of IgE forming cells in gut associated lymphoid tissue, followed by long term (memory?) production in spleen and bone marrow. Low cytophilic IgE Discovery of IgE/CD23 immune complexes in B cell dependent areas of gut associated lymphoid tissue.	Auci *et al.*, 1992 [24]

Another 5 years later, in 2012, Yang and colleagues constructed another transgenic fluorescent reporter mouse strain to track IgE-expressing B cells *in vivo* [29]. These mice had been genetically modified, linking B cell IgE expression to the production of a brightly fluorescent protein called Venus. This meant that all B cells expressing IgE were also labeled with Venus fluorescence. In addition, these authors used more refined flow cytometry, capable of detecting extremely rare cells at incidences far lower than 1%. Vanishingly rare IgE producing cells with germinal center cell markers were found in draining lymph nodes beginning 5 to 8 days after the s.c. immunization. The body of flow cytometry and histology data indicated that IgE forming cells with germinal center and antibody forming cell markers appeared quickly after immunization and disappear within two weeks. It was quite clear that IgE producing cells did not clone but rather arose through isotype switching. Strikingly, IgE forming cells were never found in bone marrow in this model. Rather, the preponderance of evidence presented suggested that IgE+ forming cells underwent reduced affinity maturation and were short-lived residents of draining LNs.

In the next year, an even clearer picture emerged with studies from He and colleagues. They used a new reporter mouse for the isotype switch to IgE, improved methods to functionally study IgE producing B cells *ex vivo* and *in vivo*, and novel *in silico* modeling.[30] The reason why IgE forming cells didn't clone in germinal centers was explained. They were found to have an impaired B cell receptor function leading to apoptosis. Importantly, the group demonstrated that different kinds of isotype switching were linked to distinct IgE forming cell populations with different fates. In the initial phase of the response, direct switching from IgM+ cells generates a transient wave of IgE forming germinal center cells. Another population of IgE forming plasma cells was generated at least in part through sequential switching from IgG1 committed cells.

As reviewed by Davies, the concept had emerged for a dual origin of IgE forming cells [31]. They could arise from immature (ie, IgM) B cell or from a mature antigen-experienced class-switched IgG+ B cell. These 2 routes to IgE are now referred to as direct (IgM to IgE) and indirect switching (IgM, IgG to IgE). Important findings from these reporter mouse studies were in some ways presaged by the early work of Durkin and colleagues, including similar kinetics and isotype switching. Similar kinetics were also found in studies of parasite infested mice published a few years later [32]. This group confirmed that IgE class switching did not require germinal center formation.

Only a few years ago, early in 2022, Kwon and colleagues published a stunning report of thymus as the source of homeostatic, or steady state, serum IgE levels [33]. Their results, from extensive FACS, ELISA and single cell mRNA paired with B cell receptor repertoire analysis, suggested an IL-4 dependent development of IgE-producing cells in the murine thymus. Cell surface marker analysis and transplantation studies indicated that these cells were thymic residents, not recent migrants, and had developed after birth from BM precursors. It is important to note that unlike IgE produced during allergic reactions, which is typically associated with antigen exposure, thymic cells produce IgE under normal, steady-state conditions. The relevance of these cells to allergic disease in humans will undoubtably be the subject of future studies, however, it is interesting to note that IgE forming B cells were reported in thymus of HIV infected children in the late 1990s [34].

Last year, Vecchione *et al.* used yet another transgenic mouse to characterize IgE plasma cells [35]. Animals expressed fusion proteins allowing the fluorescent detection of IgE formation and plasma cell differentiation. Chronic intranasal allergen (dust mites) exposure resulted in high IgE responses. Short-lived IgE plasma cells emerged in lung draining lymph nodes 1-3 weeks after exposure from isotype switching. Long-lived IgE plasma cells began to accumulate in the bone after 7 weeks. These were extremely rare cells, never exceeding 2% of total plasma cells in draining lymph nodes, or 0.5% of plasma cells in bone marrow.

These studies are summarized in **Table 2**. It is perhaps important here to note that long-lived IgE forming plasma cells are indeed found in human bone marrow, especially in the context of chronic allergen

Table 2. Modern rodent studies.

Model	Induction	Results	Reference
Transgenic mice	Cross-linked OVA-HA antigen	High IgE production and cells that could be identified with FITC and biotin conjugated antibodies.	Curotto de Lafaille *et al.,* 2001 [27]
Transgenic and helminth infested mice	Cross-linked OVA-HA antigen and helminth infestation	Lack of IgE forming cells in germinal centers, rapid appearance and disappearance in gut associated lymphoid tissue. Isotype switching as the likely source of IgE producing cells.	Erazo *et al.* 2007 [28]
Transgenic Venus reporter mouse	NP-KLH in Alum s.c.	Vanishingly rare IgE producing cells with germinal center cell markers in draining lymph nodes beginning 5 to 8 days after immunization. No cloning. Reduced affinity maturation, short-lived residents of draining LNs after the subcutaneous sensitization.	Yang *et al.* 2012 [29]
Reporter mouse for class switch recombination.	OVA-HA in alum s.c.	Different kinds of isotype switching were linked to distinct IgE forming cell populations with different fates. direct switching from IgM+ cells generates a transient wave of IgE forming cells; indirect switching from IgG1+ cells leads to IgE forming plasma cells.	He *et al.*, 2013 [30]
Various mutated and wild type mice	NP-OVA in alum s.c.	Transitional, mature, memory B cells and plasma cells arise in thymus and contribute to steady state IgE production.	Kwon *et al.*, 2022 [33]
Reporter mice expressing fusion proteins allow the fluorescent IgE detection.	Intra nasal house dust mite allergens (chronic exposure)	Rare, short lived IgE forming cells first arising in draining lymph nodes and then migrating to bone marrow as long-lived plasma cells.	Vecchione *et al.*, 2024 [35]

exposure and were thought to give rise to serological memory [36]. This leads us to the next topic of discussion: The origin and fate of human IgE forming cells. Studies of the origin and fate of human IgE forming cells were even more challenging, not only because of the low frequency of cells, but also because of the difficulty in obtaining scare tissue samples.

Early Human Studies. The 1980s and 1990s

Patterson and colleagues used autopsy samples, goat anti-human IgE antiserum and novel electron microscopy techniques to firmly establish human IgE forming plasma cells in gut lamina propria, a hotly debated question at the time [37]. Later, as reagents began to improve, autopsy tissue was fortuitously obtained by Durkin *et al.*, from a single patient with Buckley's disease within a few hours after his death (20) and analyzed using affinity-purified antisera by flow cytometry and immunohistochemistry on paraffin and frozen sections. One of the most striking findings upon gross and histological analysis was a complete lack of Peyer's patches. Cytophilic IgE appeared widespread. Blood contained two distinct IgE+ subpopulations, brightly IgE staining, CD21+ and CD23+ and dimmer, CD21- and CD23- cells. The source was likely mesenteric lymph node, the only organ with high numbers (~35%) of these cells. They were located in the thymus-dependent areas. IgE secreting plasma cells were not detected in any organ. Interestingly, most follicles in both mesenteric lymph nodes and spleen stained intensely for intercellular IgE and CD23.

By the mid-1990s, it was well known that serum IgE levels were high in HIV patients [7]. Durkin *et al.* analyzed autopsy samples from two HIV+ children, one with and one without Peyer's patches [34]. Thymus and MLN of the HIV+ child without Peyer's patches contained IgE+ (34% and 41%, respectively) and CD19+ cells (32% and 28%, respectively). In contrast, in the HIV+ child with Peyer's patches, IgE+ cells were detected in all organs, except bone marrow. The thymus of this child contained fewer CD19+ cells (7%). Thus, synthesis of IgE might occur in any organ. Widespread cytophilic IgE was observed in both children.

These observations **(Table 3)** were among the first rare glimpses of human IgE forming cells. While they strengthened the association of human IgE responses with gut, they also suggested they might occur in any organ. Further, the demonstration of IgE/CD23 complexes suggested a role in human IgE regulation as was indeed elucidated decades later [25].

Modern Human Studies: The 21st Century

In 2016, Looney *et al.*, analyzed Ig heavy chain gene rearrangements in blood of allergy patients [38] and suggested indirect isotype switching from IgG+ cells as a primary source of IgE.

A year later Ramadani *et al.*, [39] using cultured tonsil B cells (induced with IL-4 and anti-CD40) elucidated three distinct phenotypic stages of IgE forming cell development: (i) germinal center B cell-like, (ii) plasma cell-like 'plasmablasts' and (iii) plasma cells. Other important observations included that both direct and indirect isotype switching pathways gave rise to IgE forming plasma cells. Importantly, the survival of human IgE forming cells depended upon expression of elongated membrane IgE. These cells produced the high-affinity IgE antibodies important to allergic diseases. This was confirmed a year later by another group working with peripheral blood B cells isolated from food allergy patients. They also reported impaired membrane IgE expression that compromised memory [40].

A year after that, Eckl-Dorna *et al.*, summarized the then current knowledge of human IgE forming cells [41]. Although IgE production was observed in the peripheral blood and locally in tissues, the original site remained elusive. Important differences between humans and mice included two different processes governing human IgE production, one that continuously replenishes serum IgE and another inducible upon allergen contact. They speculated that sites of allergen exposure might contain IgE memory cells, which could be antigen activated, whereas long-lived plasma cells in bone marrow were responsible for continuous, stead state IgE production.

At the beginning this decade, Zghaebi *et al.* published a new protocol using Alexa Fluor 647 conjugated omalizumab for the exclusive staining of true IgE forming cells [42]. Double-staining with omalizumab and labelled birch pollen allergen estimated that allergen specific IgE forming cells in blood of patients averaged less than 1% of CD19+ B cells. These cells were not detected in non-allergic patients, or in patients without allergen.

In that same year, Corrado *et al.* performed sophisticated analysis of human samples by flow cytometry, ELISPOT, and RNA expression [43]. They described a novel mechanism for generation of IgE forming cells at the nasal mucosa, whereby activated IgD+ naïve B cells locally undergo both direct and indirect isotype switching to IgE. Importantly, IgE forming cells were detected by ELISPOT assay in nasal polyps (~1000 per million cells), peripheral blood (~50 per million) and bone marrow (~100 per million) of allergic patients (n=8), although there appeared to be great variability between individuals.

All these human studies are summarized in **Table 4.**

Table 3. Early human studies.

Model	Induction	Results	Reference
Autopsy samples	N/A	IgE forming plasma cells found in gut lamina propria	Patterson *et al.*, 1981 [37]
Hyper IgE syndrome Autopsy	Hyper IgE syndrome	Lack of Peyer's patches, IgE forming cells in mesenteric lymph nodes, not in germinal centers but in the thymus-dependent areas and in the medulla. None in bone marrow. two types of IgE forming cells in blood, high and low staining. Widespread cytophilic IgE. IgE/CD23 immune complexes in B cell dependent areas.	Durkin *et al.* 1989 [19]
AIDs Autopsy	HIV infection	IgE forming cells in the mesenteric lymph nodes and thymus. Widespread cytophilic IgE; IgE staining cells in all organs except bone marrow.	Auci *et al.* 1997 [34]

Table 4. Modern human studies.

Model	Induction	Results	Reference
Peripheral blood samples from allergic and non-allergic patient	Allergy	Indirect isotype switching of mutated IgG1-expressing B cells was the likely the primary source of IgE in humans,	Looney *et al.,* 2016 [38]
Cultured tonsil B cells	IL-4 and anti-CD40	Three distinct phenotypic stages; both direct and indirect isotype switching; indirect isotype switching produces the high-affinity IgE antibodies thought to be particularly important in allergic diseases.	Ramadani *et al.* 2017 [39]
Allergy	Tissue samples	At the nasal mucosa, activated IgD+ naïve B cells locally undergo both direct and indirect (through IgG and IgA) IgE class switching. IgE forming cells detected in bone marrow of allergy patients	Corrado *et al.* 2021 [43]

Discussion

From its first discovery it was clear that IgE was unlike other immunoglobulin isotypes. Vanishing serum levels and functional activity restricted to gut worms and allergy, set IgE apart. Central questions included where did the IgE response come from and where it go? It would be decades before adequate tools and animal models would be developed that could even begin to answer those questions.

Many of the early IgE ontogeny investigations, especially in mice, were incentivized not just for scientific curiosity, but also with a view to discovering pharmaceutical opportunities to control the responses. From those early studies, it seemed that IgE forming cells were rare, transient denizens of gut that arose rapidly after stimulation and then seeded other organs with memory cells. They did not arise in bone marrow or clone in germinal centers like other B cells. That, along with the speed of the responses, suggested only a minimal opportunity for affinity maturation. Lymphocytes bearing multiple isotypes along with what was already known about B cell genetics and development, all together, suggested that isotype switching was likely involved in the origin and fate of murine IgE forming cells. Little was known about their human counterparts, aside from a single case study of the rare, poorly understood hyper-IgE syndrome and a pair of children who had died of AIDs.

As the last century closed, transgenic mice, refined reagents, new flow cytometry hardware and software along with sophisticated nucleic acid analysis brought these extremely rare cells into sharp focus. It was possible to detect them and to confirm that they didn't clone in germinal centers but instead arose from both direct and indirect isotype switching. The former accounted for rapidly arising, short-lived transient responses, whereas the latter for long lived plasma cells capable of secreting high affinity IgE.

Many of these rodent observations apply to human allergic responses. Like rodents, human IgE forming cells do not appear to arise in bone marrow or to clone in germinal centers but instead arise primarily from indirect isotype switching from IgG1-expressing B cells. Both direct and indirect isotype switching pathways can give rise to human and murine IgE forming cells and impaired membrane IgE seems to determine whether cells become long lived IgE forming plasma cells or die from apoptosis. Unlike mice, human IgE production involves two different memory processes, one that continuously replenishes the IgE pool and another inducible upon allergen contact.

Recent work indicates that IgE forming cells and a form of IgE memory, may reside in tissues, locally, as IgG1+ cells poised to switch to IgE production [44]. Key inducers may be activated allergen specific CD8+ T cells [45]. New frontiers may arise from these intriguing findings that could have significant implications for the old dream of locating IgE responses and turning them off at the source, at the level of the IgE forming cell.

Conclusions

Early work suggested gut as origin of IgE responses and a potential target for strategies to limit them. However, the rarity of IgE forming cells, crude reagents, and scarcity of tissue samples, long hampered progress. Nevertheless, a few laboratories produced data suggesting that unlike other isotypes, IgE forming cells did not clone in germinal centers, but instead appeared to arise from isotype switching, near T cell dependent areas of gut associated lymphoid tissue, later to seed spleen and bone marrow. As the last century turned, development of more refined analytics, precise reagents and genetically engineered rodent models provided more definitive evidence that IgE forming cells indeed did not clone in germinal centers but arose from direct or indirect isotype switching, explaining how high affinity IgE was generated in the apparent absence of affinity maturation It now seems that human IgE memory, may reside locally in any tissue, as primed B cells poised to switch to IgE production under the direction of allergen specific T cells. New frontiers may include pharmaceutical targeting of these cells directly to turn off IgE responses at the source, at the level of the IgE forming cell.

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