



T follicular helper cells in IgE-mediated pathologies

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T follicular helper (Tfh) cells help orchestrate optimal humoral immunity by helping B cells to produce affinity-matured, class-switched antibodies in germinal centers. Recent studies have unveiled the complexity and heterogeneity in Tfh cell populations, particularly with respect to their cytokine production. These distinct Tfh cell subsets help tune the class, magnitude and quality of the immunoglobulins produced by B cells, thus shaping the course of humoral responses. The Tfh cell-B cell axis-dependent antibody production is mostly beneficial, but at times can go awry and result in the generation of pathologic antibodies that can harm the host. While IgE class of antibodies are infamous for their detrimental role in allergic diseases, emerging evidence is indicative of their pathologic roles in other dysregulated immune states. Here, we discuss the role of Tfh cell subsets in the regulation of pathologic IgE production in allergies and other immunopathologic conditions.

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transcription factor BCL6, and ultimately, their germinal center location [2,3]. In general, effector CD4 T cell response can be broadly classified as type 1 (Th1), type 2 (Th2), and type 3 (Th17) based on the CD4 effector T cell subsets elicited [4]. Indeed, millennia of natural selection have tailored immune responses to occur in distinct ‘flavors’, and thus the type of CD4 T cells and antibodies elicited, to best respond to specific insults; for instance, the nature of immune cells elicited to a virus (type 1 immunity) is distinct from anti-helminth responses (type 2 immunity). Much like the effector CD4 T cell type specialization, recent evidence shows that Tfh cells are heterogeneous and can be classified into the broad categories of type 1, 2, and 3 Tfh cells in mice and humans [5].

Tfh cells and humoral responses play a vital role in the success of vaccines and in protecting the host against a multitude of viral and bacterial infections. However, Tfh cells and antibody responses are not always beneficial. In immune dysfunction such as allergy or autoimmunity, Tfh cell-driven antibody responses can cause severe pathology in the host [2]. The class of antibody that is prototypically known to cause pathology in allergic diseases is IgE. Archetypal immunological insults that generate the IgE class of antibodies are helminth infections and allergic substances, both of which elicit type 2 responses. Although IgE antibodies may protect against certain helminth infections or toxins, they are quintessentially known for their involvement in the pathogenesis of allergy and asthma. Cross-linking of IgE molecules bound on surface of mast cells by allergens can lead to mast cell degranulation and in the most severe cases, systemic anaphylaxis [6,7]. Here, we discuss the recent developments that help our understanding of the role of Tfh cells in pathologic IgE antibody production.

Introduction

Distinct classes of antibodies with unique biological functions made by B lymphocytes are the cornerstone of the humoral arm of the adaptive immune response. Clonal selection, affinity maturation, class switching, and the generation of long-lived memory B cells and plasma cells are the foundation for an effective humoral immune response and are typically reliant on CD4 T cell help [1]. A key subset of CD4 T cells that aid B cells in achieving effective humoral immunity is T follicular helper (Tfh) cells. Tfh cells are distinct from other effector CD4 T cells by virtue of their surface markers (CXCR5, PD-1, ICOS), cytokine expression (IL-21), signature

Tfh cells, Tfr cells and allergic IgE

IgE-mediated allergies to environmental and food antigens have lately grown to epidemic proportions [8]. Antigen-specific IgE generation is dependent on CD4 T cell help and the cytokine IL-4 [9,10]. IL-4-expressing effector Th2 cells were originally thought to be the main drivers of the IgE response because early mouse models deficient in classic Th2 molecules such as IL-4, STAT6 or GATA3 showed lack of IgE induction to model allergens or type 2 immunizations [11–14]. However, recent studies, including ours, have revised this paradigm [15[•],16[•],17,18,19[•]]. Genetic models of Tfh cell deletion demonstrate that Tfh cells, but not Th2 cells, are critical

for allergen-specific IgE. Importantly, in these experiments, Th2-driven airway inflammation remained intact, underscoring the functional dichotomy between Th2 and Tfh cell subsets in allergen-induced asthma and pathologic IgE, respectively [15^{••},16[•]].

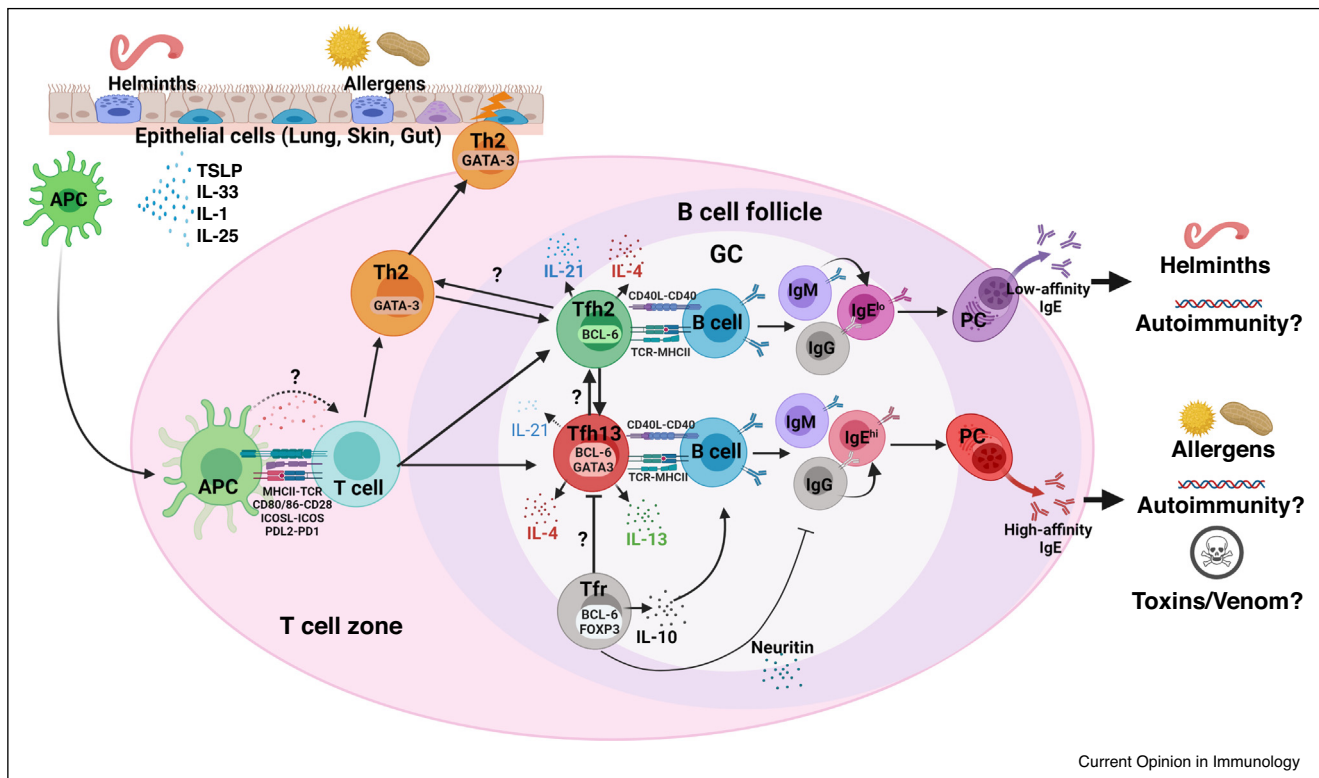
Tfh cells elicited in type 2 responses, often referred to as Tfh2 cells or type 2 Tfh cells, are distinguished by their ability to make abundant quantities of the cytokine IL-4 [5,15^{••},20–22]. Although IL-4 is considered as a canonical Tfh cell cytokine by some and was shown to be expressed in certain type 1 responses, the frequency of IL-4⁺ Tfh cells as well as the levels of IL-4 expression is modest in type 1 compared to type 2 responses [15^{••},23,24]. Isolated loss of IL-4 in Tfh cells during type 2 responses abrogates IgE production, signifying that Tfh cell-derived IL-4 is a critical factor for IgE induction [19[•]]. However, although IL-4⁺ Tfh cells are elicited in both helminth infections and in allergic sensitization, the nature of the IgE induced differs significantly (extensively reviewed elsewhere [6]). In contrast to many helminth infections, IgE elicited to allergens are typically high-affinity and anaphylactic, suggesting that additional signals derived from Tfh cells may be required for anaphylactic IgE in allergic sensitization. We recently found that allergens drive the differentiation of two distinct IL-4⁺ Tfh cell populations (Figure 1): a novel population of IL-4 and IL-13 co-producing Tfh cells in addition to the ‘classical’ IL-4⁺ Tfh2 cell subset [15^{••}]. Termed as Tfh13 cells, this subset expresses canonical transcription factors of both classical Tfh cells and Th2 cells, BCL-6 and GATA-3, respectively, and are transcriptionally distinct from Tfh2 and effector Th2 cells. The immunologic cues for Th13 cell subset specialization in allergic responses is unknown and warrants further study. Importantly, isolated loss of Tfh13 cells or IL-13 in Tfh cells results in poor induction of anaphylactic, high-affinity IgE to the model allergen *Alternaria* but modestly affects total or low-affinity IgE levels [15^{••}]. In a subsequent study, Tfh13 cells were also reported by Clement *et al.* in a model of house dust mite sensitization, and *in vitro* blocking of IL-13 by Tfh cells suppressed IgE production in Tfh-B cell co-cultures [25[•]]. IL-13 expression in Tfh cells has also been found in mouse models of peanut allergy [26[•]] and IL-33+ovalbumin sensitization [16[•]]. Tfh13-like cells are also found in humans [15^{••},27–29]. One of the earliest papers that characterized circulating CXCR5⁺Tfh-like cells (cTfh cells) in humans showed that CXCR3-CCR6⁺ cTfh cells can produce IL-13 and express GATA-3 [27]. Furthermore, we and others have observed the presence of cTfh13 cells in peanut-allergic and aeroallergen sensitive patients [15^{••},28]. How Tfh13 cells may promote anaphylactic IgE is unclear and warrants further study. Given that germinal center environments poorly support IgE production [30], Tfh13 cells may help overcome these constraints by promoting the survival of IgE GC B cells,

enhance sequential switching of IgG1 B cells to IgE B cells, and/or amplify IgE plasma cell output.

Yet another key regulator of antibody responses including that of IgE is the canonical Tfh cell cytokine IL-21 [7,31,32]. In contrast to IL-4 and IL-13, IL-21 seems to work as a broad negative regulator of IgE responses through the phosphorylation of STAT3 to block IgE class switching [33,34[•],35]. Indeed, Tfh cells abundantly express this cytokine in type 1 immunizations (where IgE is seldom made) compared to type 2 responses [15^{••}], and loss of IL-21 results in IgE augmentation [34[•],36,37]. Previous studies in mice had shown that isolated loss of IL-21R or *Stat3* in B cells results in increased IgE responses [35,36,37]. However, one conundrum in the field has been that, in contrast to mouse models, IL-21 seemed to promote IgE secretion in human B cells in some studies [38–40]. The IgE promoting role for IL-21 in human cells mainly stemmed from measuring IgE levels in culture supernatants as a surrogate for IgE switching with *in vitro* cultured circulating B cells. However, a recent paper by Allen and colleagues has revisited the suppressive role of IL-21 for IgE in both humans and mice [34[•]]. In mice, Tfh cell-specific loss of IL-21 resulted in IgE augmentation and parallel studies with primary B cells from human tonsils also showed that IL-21 impedes CD40+IL-4 mediated IgE class switching [34[•]]. Importantly, this negative effect of IL-21 on IgE switching was more pronounced on conditions where CD40 signaling was limited. Intriguingly, Tfh13 cells that promote anaphylactic IgE have reduced IL-21 which may be an additional mechanism by which these cells promote allergic IgE [15^{••}].

If IgE can cause anaphylaxis reactions, why did such a seemingly dangerous Tfh cell-dependent anaphylactic IgE pathway evolve? One school of thought is that the principal beneficial function of IgE is to protect the host from helminth infections and at times the immune response is ‘misdirected’ to innocuous substances, including to food antigens [41]. The alternative school of thought, originally proposed by Margie Profet, is that allergic IgE could be a defense mechanism against toxins and envenomation [42–44]. The experimental support for this idea has been accumulating lately [45,46,47[•],48]. Recent studies have shown that IgE to honeybee and snake venom can help the host tolerate otherwise lethal amounts of the venom in mice [45,46,48]. This IgE conferred protection was antigen-specific, mast cell-dependent and FcεR1-dependent, and involved a local anaphylactic response [46]. Similar to the studies on venom, recently it was shown that IgE-mediated local allergic activity confers protection against the pathogenic bacteria *Staphylococcus aureus* in secondary infections and intriguingly, toxin-replete *S. aureus* induced Tfh13 cells and antigen-specific IgE, which was diminished in toxin-deficient *S. aureus* [47[•]]. Thus, it is tempting to speculate

Figure 1



Schematic overview of the Tfh cell differentiation and IgE induction: Immunogens such as allergens or helminths can activate antigen presenting cells and also elicit tissue damage. Cytokines such as TSLP, IL-33, IL-1, and IL-25 are released as a response to tissue damage caused by type 2 immunogens which skew the immune response to type 2. The activated APCs (primarily dendritic cells) migrate into the T cell zone in the lymph node and activate naïve T cells to adopt a type 2 differentiation program through mechanisms that are not completely clear. The activated T cells differentiate into Th2 cells and type 2 Tfh cells, which are involved in tissue inflammation and help B cells produce antibodies, respectively. In helminth infections, Tfh2 cells which produce IL-4 and IL-21 interact with germinal center B cells, to elicit low-affinity IgE antibodies, presumably via direct class switching from IgM to IgE. Allergens induce Tfh13 cells that make IL-4 and IL-13 to aid high-affinity IgE secreting cells. The Tfr cells may regulate this process by the neuritin-mediated suppression of antigen-specific IgE production, as well as through IL-10 mediated enhancement of IgE B cells.

Abbreviations: BCL6, B cell lymphoma 6 protein; GC, germinal centers; GATA3, GATA binding protein 3; FcεR, Fc epsilon receptor; ICOS, inducible T cell costimulator; IgE, Immunoglobulin isotype E; IL-(4,13,21,10), interleukin-(4,13,21,10); Tfh cells, T follicular helper cells; cTfh, circulating T follicular helper like cells; TSLP, thymic stromal lymphopoietin; STAT, signal transducer and activator of transcription.

that the 'natural' role for Tfh13 cells may be to promote IgE to toxins to protect the host, but when this happens to 'innocuous' substances, one may develop aberrant allergic responses to such antigens.

Distinct from Tfh cells, Tfr cells are a subset of T regulatory (Treg) cells that can gain access to the B cell follicle by virtue of their CXCR5 expression. Tfr cells regulate the quality and magnitude of antibody responses and also prevent aberrant auto-reactive antibody generation in the host [49–51]. Tfr cells express the signature transcription factors of both Tfh cells (BCL6) and Tregs (FoxP3). Several recent studies have assessed the role of Tfrs cells in allergic IgE production [25*,26*,52**]. Employing an inducible *in vivo* depletion model of Tfr cells, Clement *et al.* showed that acute loss of Tfr cells during house dust mite extract sensitization resulted in

increased IgE plasma cells and IgE titers [25*]. They further showed that Tfr cells suppress Tfh-derived cytokines IL-4 and IL-13 and IgE production in an *in vitro* Tfh-Tfr-B cell co-culture assay, indicating direct suppression of Tfh cell function by Tfr cells. However, whether the escalated IgE response with the loss of Tfr cells was due to the augmentation of Tfh13 cells *in vivo* is unclear. In a more recent study using constitutive Tfr cell knockout mice, Vinuesa and colleagues also showed elevated IgE production in type 2 immunization and food allergy models [52**]. In this study, Tfr cells did not seem to directly impact IL-4 or IL-13 production by Tfh cells but affected B cells directly. Mechanistically, a Tfr cell-derived neurotrophic factor, neuritin, resulted in inhibitory phosphorylation of adaptors of IL-4 and IL-13 signaling, thus constraining IgE B cells [52**]. Intriguingly and in contrast to these studies, Xie *et al.* showed

that Blimp-1-expressing Tfr cell-derived IL-10 promotes peanut-specific IgE responses in food allergy by enhancing GC responses [26^{*}], similar to what has been demonstrated in viral infections [53]. In the study by Xie *et al.*, constitutive loss of Tfr cells resulted in poor induction of antigen-specific IgE albeit with an increase in total IgE levels. The precise reasons for the discrepant conclusions from these studies are unclear. The study by Clement *et al.* used a novel inducible deletion model to acutely deplete Tfr cells [25^{*}] while the studies by Xie *et al.* and Gonzalez-Figueroa *et al.* used a FoxP3^{cre} Bcl6^{flox} approach to constitutively delete Tfr cells [26^{*},52^{**}]. Further, the immunization models and/or the regimen were also different in these studies. Overall, all the above discussed studies point out the complexities in the biology of Tfr cell and Tfh cell subsets in regulating the IgE response and further work is needed to fully understand the nuances of IgE regulation by these T cell subsets (Figure 1).

Tfh cells and IgE in other immune disorders

In addition to allergens, helminth infections, venom, and toxins, elevated IgE levels and IgE to self-antigens have been reported in diseases such as systemic lupus erythematosus (SLE), atopic dermatitis (AD), chronic urticaria and has been implicated in their pathogenesis [54]. Here we discuss the potential roles of Tfh cells and IgE in the pathogenesis of SLE and AD as two examples. SLE is a classical, systemic autoimmune disease typified by the production of antibodies to nucleic acids and nucleoproteins. Clinical data and experimental models of SLE suggest that IgM and class-switched IgG, IgA, IgE antibodies to self-antigens are formed in SLE [55]. Classical germinal centers and Tfh cell responses are critical for the disease in most mouse models [56]. The precise role of IgE remains perplexing in lupus. The incidence of anti-nuclear IgE in SLE patients is extremely variable. However, IgE levels to self-antigens seem to correlate with the severity of the disease [55,57,58]. A recent clinical trial with omalizumab conducted on a small cohort of lupus patients showed blocking IgE improved clinical symptoms, indicating its role in disease severity [59].

The relevance of IgE in SLE has been tested in certain mouse models of the disease. Mice lacking the Src family protein tyrosine kinase Lyn develop spontaneous lupus nephritis with an associated increase of IgE to self-antigens [60]. Lupus nephritis severity was reduced when these mice were crossed to IgE or IL-4, but not mast cell, deficient mice. In a different study, IgE deficiency improved lupus-like symptoms in FcγRIIB^{-/-} and FcγRIIB^{-/-}.Yaa lupus-prone mice [57]. However, in both these studies, anti-nuclear IgG responses were also impaired. Blocking IL-21, which typically amplifies IgG but inhibits IgE, effectively blunts SLE pathology in mice [61–63]. Thus, it is unclear whether IgE promotes pathogenesis directly or amplifies autoreactive IgG

production in SLE. The Tfh cells that drive IgE production in SLE seem to be IL-4-producing Tfh cells. In a recent study, mice with a T cell-specific deletion of ETS1 (ETS proto-oncogene 1) developed lupus-like disease with high levels of IgE autoantibodies [64]. In these mice, IL-4⁺ Tfh cell, but not Th2 cell, frequency correlated with IgE germinal center B cells and autoantibodies. In line with these findings, circulating Tfh2 cells are associated with disease severity in lupus patients [65,66]. Intriguingly, Tfh cells in ETS1 deficiency co-expressed cytokines IL-13 and IL-4 and transcription factors *Gata3* and *Bcl6*, not unlike the pathologic Tfh13 cells in allergy described above. Further, in the Roquin^{san/san} model of SLE, Tfh cells were sufficient to drive spontaneous GCs and autoantibodies and additional IL-21 deficiency in Tfh cells enhanced the IgE response further [67]. Thus, it appears that the regulation of IgE by Tfh cells in this disease may also be similar to allergic responses; Tfh-derived IL-4 and IL-13 promote, while IL-21 dampens, IgE.

AD, also known as eczema, is a chronic inflammatory skin disease that typically is established in early infancy and its cardinal manifestations are pruritus and skin lesions. Inherent Th2 bias, high IgE levels (in most cases) along with skin barrier disturbance are regarded as the central disease mechanisms, although other T cell subsets (Th17, Th1, Th22) and innate cells also contribute to the disease [68]. AD can manifest without augmented IgE concentrations, and this form of the disease is known as non-atopic or intrinsic AD [69]. AD is often thought to be the first event that results in the ‘atopic march’, the tendency to become sensitized to multiple environmental allergens over time. Interestingly, considerable levels of IgE made in AD are self-reactive or can be cross-reactive to environmental antigens, and disease severity correlates with the levels of IgE in some but not in other studies [69]. Although IgE-independent AD has been demonstrated in certain mouse models of the disease [70,71], meta-analyses of clinical trials in AD patients and a recent large clinical trial with pediatric AD patients show alleviation of symptoms with omalizumab treatment, suggesting that IgE may contribute to disease severity [72,73]. However, the precise mechanisms of IgE-mediated pathology induced in AD remains unclear and requires further inquiry. Although Tfh cells were shown to be induced in some mouse models of AD, the function of these Tfh cells remains to be well-characterized [74,75]. In a vitamin D3 analog MC903 driven model of AD, Tfh2 and Tfh13 cells were both induced, but it is currently unclear if any of these subsets contribute to the disease [74]. A study by Szabo *et al.* observed increased frequency of IL-21⁺ cTfh cells particularly in pediatric AD patients [76]. A different study analyzed Tfh1, Tfh2, and Tfh17 cell subsets in adult AD patients before and after omalizumab treatment. At baseline, AD patients demonstrated lower Tfh17 cell frequencies but no difference in overall Tfh

cells, and no significant changes in Tfh subsets were observed after the completion of the treatment [77]. Thus, with the existing data, it is unclear whether Tfh cells promote pathology in AD.

Conclusions and future directions

Recent research on the regulation of IgE responses has unveiled the heterogeneity in Tfh cell subsets in type 2 immunity and has identified key cell types and molecules that instruct B cells to generate pathologic IgE in allergic sensitization. Key areas that are of immense future interest are the following: 1) Understanding the role of Tfh cytokines within and outside germinal centers (GC): Recent evidence suggests that class switching to IgG during protein antigen immunization occurs infrequently in the GCs but primarily at extrafollicular sites [78^{••}]. Given that Tfh cells that make IgE-promoting cytokines are found both within the GCs and extrafollicular sites [15^{••},20,21,79], the roles for these cytokines in these distinct locations with respect to IgE remains to be clarified. 2) Tfh cell subset specialization and plasticity: Whether type 2 Tfh cell specialization predominantly occurs via a linear developmental trajectory from naïve CD4 T cells or if these cells are a result of a transient developmental state between Th2 cells and ‘canonical’ Tfh cells due to their proposed plasticity is unclear and if this distinction matters for the nature of the IgE induced is unknown. 3) Precise roles of Tfr cells in IgE response: Tfr cells have been shown to inhibit as well as promote IgE response. Spatiotemporal regulation of IgE and Tfh cells by Tfr cells is an important future area of study. 4) IgE in diseases other than allergy: Accumulating evidence argues for a detrimental role for IgE in the prognosis of several diseases, including AD and SLE. However, the nature of the IgE induced in these diseases (affinity, anaphylactic ability, glycosylation status, etc.), the precise mechanisms of how IgE regulates their pathogenesis, and if the regulation of IgE in such disease states follows the rules of IgE induction as in allergy remains to be examined further. Indeed, a deeper understanding of the nuances of Tfh cell differentiation into specialized subsets and their regulation of IgE at a molecular level is critical for developing future therapeutic interventions for IgE-mediated diseases.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Crotty S: **A brief history of T cell help to B cells.** *Nat Rev Immunol* 2015, **15**:185–189.
 2. Crotty S: **T follicular helper cell biology: a decade of discovery and diseases.** *Immunity* 2019, **50**:1132–1148.
 3. Vinuesa CG, Linterman MA, Yu D, MacLennan IC: **Follicular helper T cells.** *Annu Rev Immunol* 2016, **34**:335–368.
 4. Annunziato F, Romagnani C, Romagnani S: **The 3 major types of innate and adaptive cell-mediated effector immunity.** *J Allergy Clin Immunol* 2015, **135**:626–635.
 5. Eisenbarth SC, Baumjohann D, Craft J, Fazilleau N, Ma CS, Tangye SG, Vinuesa CG, Linterman MA: **CD4(+) T cells that help B cells – a proposal for uniform nomenclature.** *Trends Immunol* 2021, **42**:658–669.
 6. Gowthaman U, Chen JS, Eisenbarth SC: **Regulation of IgE by T follicular helper cells.** *J Leukoc Biol* 2020, **107**:409–418.
 7. Haase P, Voehringer D: **Regulation of the humoral type 2 immune response against allergens and helminths.** *Eur J Immunol* 2021, **51**:273–279.
 8. Pawankar R, Canonica GW, Holgate ST, Lockey RF: **Allergic diseases and asthma: a major global health concern.** *Curr Opin Allergy Clin Immunol* 2012, **12**:39–41.
 9. Finkelman FD, Katona IM, Urban JF Jr, Holmes J, Ohara J, Tung AS, Sample JV, Paul WE: **IL-4 is required to generate and sustain in vivo IgE responses.** *J Immunol* 1988, **141**:2335–2341.
 10. Katona IM, Urban JF Jr, Finkelman FD: **The role of L3T4+ and Lyt-2+ T cells in the IgE response and immunity to *Nippostrongylus brasiliensis*.** *J Immunol* 1988, **140**:3206–3211.
 11. Kopf M, Le Gros G, Bachmann M, Lamers MC, Bluethmann H, Kohler G: **Disruption of the murine IL-4 gene blocks Th2 cytokine responses.** *Nature* 1993, **362**:245–248.
 12. Shimoda K, van Deursen J, Sangster MY, Sarawar SR, Carson RT, Tripp RA, Chu C, Quelle FW, Nosaka T, Vignali DA et al.: **Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene.** *Nature* 1996, **380**:630–633.
 13. Takeda K, Tanaka T, Shi W, Matsumoto M, Minami M, Kashiwamura S, Nakanishi K, Yoshida N, Kishimoto T, Akira S: **Essential role of Stat6 in IL-4 signalling.** *Nature* 1996, **380**:627–630.
 14. Zhu J, Min B, Hu-Li J, Watson CJ, Grinberg A, Wang Q, Killeen N, Urban JF Jr, Guo L, Paul WE: **Conditional deletion of Gata3 shows its essential function in T(H)1-T(H)2 responses.** *Nat Immunol* 2004, **5**:1157–1165.
 15. Gowthaman U, Chen JS, Zhang B, Flynn WF, Lu Y, Song W, Joseph J, Gertie JA, Xu L, Collet MA et al.: **Identification of a T follicular helper cell subset that drives anaphylactic IgE.** *Science* 2019, **365**
 - This study describes a novel subset of Tfh cells (Tfh13 cells) induced to allergens and found in allergic patients. Tfh13 cells were absolutely required for the generation of anaphylactic IgE to allergens.
 16. Kobayashi T, Iijima K, Dent AL, Kita H: **Follicular helper T cells mediate IgE antibody response to airborne allergens.** *J Allergy Clin Immunol* 2017, **139**:300–313.e7
 - One of the first papers to describe that Tfh cells, but not Th2 cells, drive IgE and are dispensable for airway inflammation.
 17. Dolence JJ, Kobayashi T, Iijima K, Krempski J, Drake LY, Dent AL, Kita H: **Airway exposure initiates peanut allergy by involving the IL-1 pathway and T follicular helper cells in mice.** *J Allergy Clin Immunol* 2018, **142**:1144–1158.e8.
 18. Noble A, Zhao J: **Follicular helper T cells are responsible for IgE responses to Der p 1 following house dust mite sensitization in mice.** *Clin Exp Allergy* 2016, **46**:1075–1082.
 19. Meli AP, Fontes G, Leung Soo C, King IL: **T follicular helper cell-derived IL-4 is required for IgE production during intestinal helminth infection.** *J Immunol* 2017, **199**:244–252

This study showed that isolated loss of IL-4 in Tfh cells abrogates IgE production in helminth infections and thus Tfh derived IL-4 was critical for IgE induction.

20. Weinstein JS, Herman EI, Lainez B, Licona-Limon P, Esplugues E, Flavell R, Craft J: **Tfh cells progressively differentiate to regulate the germinal center response.** *Nat Immunol* 2016, **17**:1197-1205.
 21. Reinhardt RL, Liang HE, Locksley RM: **Cytokine-secreting follicular T cells shape the antibody repertoire.** *Nat Immunol* 2009, **10**:385-393.
 22. Olatunde AC, Hale JS, Lamb TJ: **Cytokine-skewed Tfh cells: functional consequences for B cell help.** *Trends Immunol* 2021, **42**:536-550.
 23. Yusuf I, Kageyama R, Monticelli L, Johnston RJ, Ditoro D, Hansen K, Barnett B, Crotty S: **Germinal center T follicular helper cell IL-4 production is dependent on signaling lymphocytic activation molecule receptor (CD150).** *J Immunol* 2010, **185**:190-202.
 24. Weinstein JS, Laidlaw BJ, Lu Y, Wang JK, Schulz VP, Li N, Herman EI, Kaech SM, Gallagher PG, Craft J: **STAT4 and T-bet control follicular helper T cell development in viral infections.** *J Exp Med* 2018, **215**:337-355.
 25. Clement RL, Daccache J, Mohammed MT, Diallo A, Blazar BR, Kuchroo VK, Lovitch SB, Sharpe AH, Sage PT: **Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses.** *Nat Immunol* 2019, **20**:1360-1371.
- This study used a novel Tfr cell depletion model to show that Tfr cells negatively regulate IgE production and type 2 cytokine production in Tfh13 cells.
26. Xie MM, Chen Q, Liu H, Yang K, Koh B, Wu H, Maleki SJ, Hurlburt BK, Cook-Mills J, Kaplan MH *et al.*: **T follicular regulatory cells and IL-10 promote food antigen-specific IgE.** *J Clin Invest* 2020, **130**:3820-3832.
- This study found an IgE promoting role for Tfr cells in food allergy. IL-10 produced by Tfr cells was required to boost GC responses and generate food antigen-specific IgE.
27. Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, Foucat E, Dullaers M, Oh S, Sabzghabaei N *et al.*: **Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion.** *Immunity* 2011, **34**:108-121.
 28. Wang W, Lyu SC, Ji X, Gupta S, Manohar M, Dhondalay GKR, Chinthrajah S, Andorf S, Boyd SD, Tibshirani R *et al.*: **Transcriptional changes in peanut-specific CD4+ T cells over the course of oral immunotherapy.** *Clin Immunol* 2020, **219**:108568.
 29. Chen JS, Grassmann JDS, Gowthaman U, Olyha SJ, Simoneau T, Berin MC, Eisenbarth SC, Williams A: **Flow cytometric identification of Tfh13 cells in mouse and human.** *J Allergy Clin Immunol* 2021, **147**:470-483.
 30. Yang Z, Robinson MJ, Allen CD: **Regulatory constraints in the generation and differentiation of IgE-expressing B cells.** *Curr Opin Immunol* 2014, **28**:64-70.
 31. Wade-Vallance AK, Allen CDC: **Intrinsic and extrinsic regulation of IgE B cell responses.** *Curr Opin Immunol* 2021, **72**:221-229.
 32. Moens L, Tangye SG: **Cytokine-mediated regulation of plasma cell generation: IL-21 takes center stage.** *Front Immunol* 2014, **5**:65.
 33. Suto A, Nakajima H, Hirose K, Suzuki K, Kagami S, Seto Y, Hoshimoto A, Saito Y, Foster DC, Iwamoto I: **Interleukin 21 prevents antigen-induced IgE production by inhibiting germ line C(epsilon) transcription of IL-4-stimulated B cells.** *Blood* 2002, **100**:4565-4573.
 34. Yang Z, Wu CM, Targ S, Allen CDC: **IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells.** *J Exp Med* 2020, **217**.
- This study demonstrated that Tfh cell derived IL-21 suppresses IgE switching, through Stat3 mediated inhibition. Further, it clarified that IL-21 was indeed a suppressor of IgE switching in human B cells as well.
35. Kane A, Lau A, Brink R, Tangye SG, Deenick EK: **B-cell-specific STAT3 deficiency: Insight into the molecular basis of autosomal-dominant hyper-IgE syndrome.** *J Allergy Clin Immunol* 2016, **138**:1455-1458.e3.
 36. Linterman MA, Beaton L, Yu D, Ramiscal RR, Srivastava M, Hogan JJ, Verma NK, Smyth MJ, Rigby RJ, Vinuesa CG: **IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses.** *J Exp Med* 2010, **207**:353-363.
 37. Zotos D, Coquet JM, Zhang Y, Light A, D'Costa K, Kallies A, Corcoran LM, Godfrey DI, Toellner KM, Smyth MJ *et al.*: **IL-21 regulates germinal center B cell differentiation and proliferation through a B cell-intrinsic mechanism.** *J Exp Med* 2010, **207**:365-378.
 38. Avery DT, Ma CS, Bryant VL, Santner-Nanan B, Nanan R, Wong M, Fulcher DA, Cook MC, Tangye SG: **STAT3 is required for IL-21-induced secretion of IgE from human naive B cells.** *Blood* 2008, **112**:1784-1793.
 39. Wood N, Bourque K, Donaldson DD, Collins M, Vercelli D, Goldman SJ, Kasaian MT: **IL-21 effects on human IgE production in response to IL-4 or IL-13.** *Cell Immunol* 2004, **231**:133-145.
 40. Pene J, Guglielmi L, Gauchat JF, Harrer N, Woisetschlager M, Boulay V, Fabre JM, Demoly P, Yssel H: **IFN-gamma-mediated inhibition of human IgE synthesis by IL-21 is associated with a polymorphism in the IL-21R gene.** *J Immunol* 2006, **177**:5006-5013.
 41. Artis D, Maizels RM, Finkelman FD: **Forum: immunology: allergy challenged.** *Nature* 2012, **484**:458-459.
 42. Profet M: **The function of allergy: immunological defense against toxins.** *Q Rev Biol* 1991, **66**:23-62.
 43. Galli SJ, Metz M, Starkl P, Marichal T, Tsai M: **Mast cells and IgE in defense against lethality of venoms: possible "benefit" of allergy.** *Allergo J Int* 2020, **29**:46-62.
 44. Florsheim EB, Sullivan ZA, Khoury-Hanold W, Medzhitov R: **Food allergy as a biological food quality control system.** *Cell* 2021, **184**:1440-1454.
 45. Marichal T, Starkl P, Reber LL, Kalesnikoff J, Oettgen HC, Tsai M, Metz M, Galli SJ: **A beneficial role for immunoglobulin E in host defense against honeybee venom.** *Immunity* 2013, **39**:963-975.
 46. Starkl P, Marichal T, Gaudenzio N, Reber LL, Sibilano R, Tsai M, Galli SJ: **IgE antibodies, Fc epsilon R1alpha, and IgE-mediated local anaphylaxis can limit snake venom toxicity.** *J Allergy Clin Immunol* 2016, **137**:246-257.e11.
 47. Starkl P, Watzkenboeck ML, Popov LM, Zahalka S, Hladiak A, Lakovits K, Radhouani M, Haschemi A, Marichal T, Reber LL *et al.*: **IgE effector mechanisms, in concert with mast cells, contribute to acquired host defense against Staphylococcus aureus.** *Immunity* 2020, **53**:793-804.e9.
- A recent paper that describes a beneficial role for IgE and anaphylactic response to protect the host from toxins.
48. Palm NW, Rosenstein RK, Yu S, Schenten DD, Florsheim E, Medzhitov R: **Bee venom phospholipase A2 induces a primary type 2 response that is dependent on the receptor ST2 and confers protective immunity.** *Immunity* 2013, **39**:976-985.
 49. Sage PT, Sharpe AH: **The multifaceted functions of follicular regulatory T cells.** *Curr Opin Immunol* 2020, **67**:68-74.
 50. Wing JB, Lim EL, Sakaguchi S: **Control of foreign Ag-specific Ab responses by Treg and Tfr.** *Immunol Rev* 2020, **296**:104-119.
 51. Lu Y, Craft J: **T follicular regulatory cells: choreographers of productive germinal center responses.** *Front Immunol* 2021, **12**:679909.
 52. Gonzalez-Figueroa P, Roco JA, Papa I, Nunez Villacis L, Stanley M, Linterman MA, Dent A, Canete PF, Vinuesa CG: **Follicular regulatory T cells produce neuritin to regulate B cells.** *Cell* 2021, **184**:1775-1789.e19.
- This study showed that Tfr cells dampen IgE responses by directly regulating B cells by producing a neurotropic factor neuritin that dampens type 2 cytokine signaling in B cells.

53. Laidlaw BJ, Lu Y, Amezcua RA, Weinstein JS, Vander Heiden JA, Gupta NT, Kleinstein SH, Kaech SM, Craft J: **Interleukin-10 from CD4(+) follicular regulatory T cells promotes the germinal center response.** *Sci Immunol* 2017, **2**.
54. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M: **Immunoglobulin E-mediated autoimmunity.** *Front Immunol* 2018, **9**:689.
55. Dema B, Charles N: **Autoantibodies in SLE: specificities, isotypes and receptors.** *Antibodies (Basel)* 2016, **5**.
56. Seth A, Craft J: **Spatial and functional heterogeneity of follicular helper T cells in autoimmunity.** *Curr Opin Immunol* 2019, **61**:1-9.
57. Dema B, Charles N, Pellefigues C, Ricks TK, Suzuki R, Jiang C, Scheffel J, Hasni S, Hoffman V, Jablonski M *et al.*: **Immunoglobulin E plays an immunoregulatory role in lupus.** *J Exp Med* 2014, **211**:2159-2168.
58. Henault J, Riggs JM, Karnell JL, Liarski VM, Li J, Shirinian L, Xu L, Casey KA, Smith MA, Khatri DB *et al.*: **Self-reactive IgE exacerbates interferon responses associated with autoimmunity.** *Nat Immunol* 2016, **17**:196-203.
59. Hasni S, Gupta S, Davis M, Poncio E, Temesgen-Oyelakin Y, Joyal E, Fike A, Manna Z, Auh S, Shi Y *et al.*: **Safety and tolerability of omalizumab: a randomized clinical trial of humanized anti-IgE monoclonal antibody in systemic lupus erythematosus.** *Arthritis Rheumatol* 2019, **71**:1135-1140.
60. Charles N, Hardwick D, Daugas E, Illei GG, Rivera J: **Basophils and the T helper 2 environment can promote the development of lupus nephritis.** *Nat Med* 2010, **16**:701-707.
61. Bubier JA, Sproule TJ, Foreman O, Spolski R, Shaffer DJ, Morse HC 3rd, Leonard WJ, Roopenian DC: **A critical role for IL-21 receptor signaling in the pathogenesis of systemic lupus erythematosus in BXSB-Yaa mice.** *Proc Natl Acad Sci U S A* 2009, **106**:1518-1523.
62. Choi JY, Seth A, Kashgarian M, Terrillon S, Fung E, Huang L, Wang LC, Craft J: **Disruption of pathogenic cellular networks by IL-21 blockade leads to disease amelioration in murine lupus.** *J Immunol* 2017, **198**:2578-2588.
63. Herber D, Brown TP, Liang S, Young DA, Collins M, Dunussi-Joannopoulos K: **IL-21 has a pathogenic role in a lupus-prone mouse model and its blockade with IL-21R.Fc reduces disease progression.** *J Immunol* 2007, **178**:3822-3830.
64. Kim CJ, Lee CG, Jung JY, Ghosh A, Hasan SN, Hwang SM, Kang H, Lee C, Kim GC, Rudra D *et al.*: **The transcription factor Ets1 suppresses T follicular helper type 2 cell differentiation to halt the onset of systemic lupus erythematosus.** *Immunity* 2018, **49**:1034-1048.e8.
65. Le Coz C, Joubin A, Pasquali JL, Korganow AS, Dumortier H, Monneaux F: **Circulating TFH subset distribution is strongly affected in lupus patients with an active disease.** *PLoS One* 2013, **8**:e75319.
66. Choi JY, Ho JH, Pasoto SG, Bunin V, Kim ST, Carrasco S, Borba EF, Goncalves CR, Costa PR, Kallas EG *et al.*: **Circulating follicular helper-like T cells in systemic lupus erythematosus: association with disease activity.** *Arthritis Rheumatol* 2015, **67**:988-999.
67. Linterman MA, Rigby RJ, Wong RK, Yu D, Brink R, Cannons JL, Schwartzberg PL, Cook MC, Walters GD, Vinuesa CG: **Follicular helper T cells are required for systemic autoimmunity.** *J Exp Med* 2009, **206**:561-576.
68. Langan SM, Irvine AD, Weidinger S: **Atopic dermatitis.** *Lancet* 2020, **396**:345-360.
69. Pellefigues C: **IgE autoreactivity in atopic dermatitis: paving the road for autoimmune diseases?** *Antibodies (Basel)* 2020, **9**.
70. Yagi R, Nagai H, Iigo Y, Akimoto T, Arai T, Kubo M: **Development of atopic dermatitis-like skin lesions in STAT6-deficient NC/Nga mice.** *J Immunol* 2002, **168**:2020-2027.
71. Konishi H, Tsutsui H, Murakami T, Yumikura-Futatsugi S, Yamanaka K, Tanaka M, Iwakura Y, Suzuki N, Takeda K, Akira S *et al.*: **IL-18 contributes to the spontaneous development of atopic dermatitis-like inflammatory skin lesion independently of IgE/stat6 under specific pathogen-free conditions.** *Proc Natl Acad Sci U S A* 2002, **99**:11340-11345.
72. Wang HH, Li YC, Huang YC: **Efficacy of omalizumab in patients with atopic dermatitis: A systematic review and meta-analysis.** *J Allergy Clin Immunol* 2016, **138**:1719-1722.e1.
73. Chan S, Cornelius V, Cro S, Harper JL, Lack G: **Treatment effect of omalizumab on severe pediatric atopic dermatitis: the ADAPT randomized clinical trial.** *JAMA Pediatr* 2020, **174**:29-37.
74. Ochiai S, Jagot F, Kyle RL, Hyde E, White RF, Prout M, Schmidt AJ, Yamane H, Lamielle O, Le Gros G *et al.*: **Thymic stromal lymphopoietin drives the development of IL-13(+) Th2 cells.** *Proc Natl Acad Sci U S A* 2018, **115**:1033-1038.
75. Spidale NA, Malhotra N, Frascoli M, Sylvia K, Miu B, Freeman C, Stadinski BD, Huseby E, Kang J: **Neonatal-derived IL-17 producing dermal gammadelta T cells are required to prevent spontaneous atopic dermatitis.** *eLife* 2020, **9**.
76. Szabo K, Gaspar K, Dajnoki Z, Papp G, Fabos B, Szegedi A, Zeher M: **Expansion of circulating follicular T helper cells associates with disease severity in childhood atopic dermatitis.** *Immunol Lett* 2017, **189**:101-108.
77. Trichot C, Fauchoux L, Karpf L, Grandclaude M, Pattarini L, Bagot M, Mahevas T, Jachiet M, Saussine A, Bouaziz JD *et al.*: **TH cell diversity and response to dupilumab in patients with atopic dermatitis.** *J Allergy Clin Immunol* 2021, **147**:756-759.
78. Roco JA, Mesin L, Binder SC, Nefzger C, Gonzalez-Figueroa P, Canete PF, Ellyard J, Shen Q, Robert PA, Cappello J *et al.*: **Class-switch recombination occurs infrequently in germinal centers.** *Immunity* 2019, **51**:337-350.e7.
79. Jandl C, King C: **Cytokines in the germinal center niche.** *Antibodies (Basel)* 2016, **5**.

This paper shows that class switch recombination to IgG is triggered before differentiation into GC B cells or plasmablasts and are greatly diminished in GC B cells.