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HOW T FOLLICULAR REGULATORY CELLS SHAPE AND RESTRICT IGE-DRIVEN ALLERGIC REACTIONS

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Alergen-specific immunoglobulin E (IgE) represents a central trigger of allergic reactions and a major contributor to the development of allergic diseases in humans. Thus, therapeutic strategies aimed at limiting or preventing IgE formation hold promise for reducing the global burden of allergy-associated conditions. Over recent decades, numerous studies have explored the mechanisms governing IgE regulation, identifying multiple cellular and molecular factors that influence the induction and amplification of IgE responses. One of the critical sites for the generation of IgE-producing B cells is the germinal center (GC), where B cells undergo somatic hypermutation and affinity selection. This process is tightly dependent on IL-4–producing T follicular helper (TFH) cells. High-affinity IgE generated within the GC greatly increases the likelihood of severe allergic manifestations, including anaphylaxis.

Within GCs, T follicular regulatory (TFR) cells coexist with TFH cells and contribute to controlling the selection and maturation of high-affinity IgE+ B-cell clones. This review synthesizes current findings on the involvement of TFR cells in IgE-mediated immunity. Experimental data obtained from animal models indicate that TFR cells can effectively suppress IgE responses associated with allergic airway inflammation; however, paradoxically, they can also enhance IgE production in the context of food allergies. Although human studies suggest an association between higher TFR levels and reduced allergic reactivity, direct evidence demonstrating in vivo suppression of IgE production by TFR cells remains limited. These findings highlight the therapeutic potential of targeting TFR cells but also underscore the importance of selectively promoting their suppressive rather than supportive activities.

Keywords: allergic airway inflammation, food allergy, IgE, T follicular regulatory cells

During the past several decades, the incidence of atopic and allergic diseases has reached unprecedented levels, particularly in industrialized nations. The primary mediators of immediate-type hypersensitivity reactions are IgE antibodies directed against environmental allergens. When mast cell–bound IgE molecules are cross-linked by allergens, rapid degranulation occurs, releasing inflammatory mediators capable of triggering life-threatening anaphylactic responses.The induction of IgE-producing B cells requires strong co-stimulatory signals via CD40 as well as IL-4 exposure. The GC reaction serves as the microenvironment where B cells undergo extensive somatic hypermutation and affinity maturation, ultimately generating IgE-switched B cells. The production of high-affinity IgE is particularly detrimental because of its potent ability to drive severe allergic reactions. Therefore, TFH cells that provide IL-4 play a pivotal role in orchestrating IgE-specific responses.

Regulatory T cells (Tregs), including Foxp3+ subsets, also contribute to shaping IgE immunity.

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Notably, Noval-Rivas et al. (2015) demonstrated that food-allergic conditions in both humans and mice prompt the differentiation of IL-4–producing Tregs, which were required for sustaining IgE responses.

Further work by the Vinuesa group revealed that TFR cells secrete the neuropeptide neuritin, which limits IgE class-switch recombination and interferes with plasma-cell differentiation. Using Bcl6FC mice, the same group confirmed that TFR cells suppress antigen-specific IgE responses after OVA-Alum immunization.

Despite consistent findings that TFR cells suppress IgE responses in systemic immunization and airway allergy models, results from a peanut-induced food allergy model contradicted this pattern. Xie et al. unexpectedly observed that TFR-deficient Bcl6FC mice exhibited markedly reduced levels of peanut-specific IgE, peanut-specific IgG1, TFH cells, and GC B cells. These observations indicate that the functional role of TFR cells varies depending on the immunologic environment and the type of allergic response. Distinctions between gut-associated and airway-associated immune responses likely shape whether TFR cells act as suppressors or facilitators of IgE production. Since diverse TFH phenotypes have been documented across type 2 immune responses, it is plausible that TFR cells likewise adopt specialized functions depending on their tissuemicroenvironment.

The cytokine milieu within the gastrointestinal tract may drive TFR cells toward an IgE-enhancing phenotype. Supporting this hypothesis, research from the Chatila laboratory showed that food-allergic conditions induce IL-4–producing Tregs in both humans and mice. Although the study did not explicitly examine TFR cells, the fact that many TFR cells originate from Tregs suggests that a subset of TFR cells may produce IL-4 and thereby contribute to IgE amplification in food allergy settings.

Human TFR cells remain more difficult to study than those in mice due to their localization in lymphoid tissues rather than in peripheral blood. Consequently, our understanding of TFR cell biology in human IgE regulation remains incomplete. Identifying human equivalents of GC-resident TFR cells has also proven challenging. In 2019, Vinuesa and colleagues identified a population of IL-10–producing CD25+ TF cells in human tonsils that display several TFR-like characteristics, including elevated expression of CTLA-4 and other Treg-associated genes; however, these cells lack Foxp3 expression. Intriguingly, the abundance of CD25+ TF cells in human samples inversely correlated with serum IgE levels. In vitro experiments revealed that CD25+ TF cells suppress IgE class-switch recombination through an IL-10–dependent mechanism. This result contrasts with the IL-10–mediated enhancement of IgE responses observed in mouse food allergy models, emphasizing the complex and context-dependent nature of IL-10 in immune regulation.

Allergen immunotherapy (AIT) introduces controlled, low doses of allergens to induce immune tolerance and shift antibody responses away from IgE. Despite being clinically effective, AIT outcomes vary, and the precise mechanisms underlying treatment success remain poorly characterized. Biomarkers that reliably predict clinical improvement are still needed. Recent studies indicate that increases in circulating TFR (cTFR) cells relative to circulating TFH (cTFH) cells correlate with favorable AIT outcomes. Yao et al. demonstrated that successful AIT in allergic rhinitis patients was accompanied by a significant rise in the cTFR/cTFH ratio.

While major progress has been made in elucidating the roles of TFR cells in IgE regulation, numerous questions remain unresolved. One fundamental issue concerns the context-dependent behavior of TFR cells in different allergic models. What tissue-specific cues determine whether TFR cells exert suppressive or supportive functions? Are B cells in certain microenvironments

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more sensitive to TFR-mediated regulation than others? Preliminary in vitro findings from our laboratory indicate that TFR cells derived from food allergy models can promote IgE+ B-cell expansion, whereas TFR cells from airway allergy models suppress IgE responses. Further investigation is required to dissect the mechanisms underlying these contrasting functions.

Additional questions include whether TFR cells employ distinct suppressor pathways to regulate IgE responses in allergic versus non-allergic contexts, and whether major species-specific differences exist between human and mouse TFR effector mechanisms. For example, IL-10 appears to enhance IgE survival in mouse food allergy models yet suppresses IgE class switching in human allergic rhinitis. These discrepancies may reflect differences in target cell populations, signaling pathways, or tissue-specific cytokine environments. IL-10 may initially promote IgE induction, while later acting as a suppressor once IgE responses are established. Moreover, the airway and gut immune systems may respond differently to identical regulatory signals.

In summary, a comprehensive understanding of TFR cell biology in both mice and humans is essential for developing innovative therapeutic strategies targeting allergic disease. Single-cell RNA sequencing of TFR cells across diverse tissues and allergic conditions will be instrumental in clarifying their functional heterogeneity. Continued research on TFR-mediated modulation of IgE responses will pave the way for novel interventions aimed at preventing or treating IgE-driven disorders.

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