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T FOLLICULAR REGULATORY CELLS CONTROL THE IGE RESPONSE

Anotatsion: One of the main mediators of allergic reactions and a primary cause of allergy illness in humans is allergen-specific IgE. It would be beneficial to reduce the prevalence of allergic illness by using therapies that block the formation of IgE. The regulation of IgE reactions has been the subject of extensive study, and a number of variables that encourage the synthesis of allergic IgE have been identified. The formation of IgE-producing B cells in the germinal center (GC) depends on T follicular helper (TFH) cells expressing IL-4. Anaphylaxis, a strong allergic reaction, is encouraged by high affinity allergen-specific IgE that is developed as a result of Ig somatic hypermutation and B cell selection in the GC. In the GC response, T follicular regulatory (TFR) cells are also present. They collaborate with TFH cells to select high affinity IgE + B cells. The literature on TFR cells and IgE reactions is reviewed in this study. TFR cells have been shown in animal studies to have a suppressive effect on IgE responses in allergic airway illness; yet, they also assist in the IgE response in food allergies. TFR cells have been linked in human studies to a reduced allergic reaction; nevertheless, there is insufficient data to support a direct suppressive function of TFR cells on IgE in vivo. TFR cells might be a novel target for allergy treatments, however care must be taken to encourage TFR cells' suppressor rather than their helper functions.\

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

Over the past 70 years, atopic and allergic disorders have increased to an epidemic level, and allergic diseases are now very common in the United States. 1, 2,

There is a great need for novel allergy treatments. The main mediators of the acute hypersensitivity allergy reaction are immunoglobulin E (IgE) antibodies that are unique to allergens. Allergens that cross-link mast cell-bound IgE cause a potent inflammatory response that can result in anaphylaxis.[1]

When activated B cells receive significant CD40 and IL-4 signals, IgE responses are developed.The germinal center (GC) reaction, which is the site of Ig somatic hyper-mutation and antibody (Ab) affinity selection, can give rise to IgE-switched B cells. IgE with a high affinity for allergens is harmful and encourages anaphylaxis. Thus, the GC plays a crucial role in the production of high-affinity pathogenic IgE. T follicular helper (TFH) cells that produce IL-4 both support and are necessary for the production of antigen-specific IgE. [2]

Foxp3+ Treg cells control the way that IgE reactions are expressed. Despite the fact that Tregs are primarily thought of as immune response suppressors, Noval-Rivas et al. (2015) demonstrated that food allergies in both humans and mice result in the development of IL-4-expressing Treg cells and that Treg IL-4 production was necessary for the IgE response.

The Vinuesa group showed that TFR cells produce the neuropeptide neuritin, which suppresses IgE production by inhibition of IgE class-switching.[4] Neuritin acts directly on B cells to suppress plasma cell differentiation. The Vinuesa study also used Bcl6FC mice to show that TFR cells suppress Ag-specific IgE responses following intraperitoneal Ova-Alum immunization.[3]

While the above studies showed that TFR suppress IgE responses following either systemic immunization or induction of allergic airway inflammation in mice, results with a mouse food allergy model showed a completely opposite result. Using a well-studied peanut-based food allergy model

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Xie et al. unexpectedly found that the titer of peanut-specific IgE was reduced in TFR-deficient Bcl6FC mice along with the level of peanut-specific IgG1, TFH cells and GC B cells. TFR cell function is dependent on the type of immune response, and the model system used to delete TFR cells is unable to account for the various functions of TFR cells. This is indicated by the fact that TFR cells can function as either helper cells or suppressor cells for the IgE response in the Bcl6FC mouse model. The distinct immunological settings (gut mucosa versus the airway mucosa) involved can be used to explain the opposing roles of TFR cells observed in the food allergy and airway allergy investigations. It would not be surprising if TFR cells varied based on the kind of allergy response, given that distinct TFH cell types have been seen in various type 2 responses. In fact, the kinds of suppressor genes that TFR expresses types of immune response. The reason why TFR cells develop into IgE helper cells in the gastrointestinal (GI) tract is not yet clear but likely depends on the unique cytokine environment in the gut mucosa. In this regard, work from the Chatila lab showed that IL-4–expressing Treg cells develop in food allergy in both human and mouse.[24] The Chatila study showed IL-4 production from Tregs was required for the IgE response in their food allergy study but did not specifically examine TFR cells. Since most TFR cells are derived from Tregs, a reasonable hypothesis is that TFR cells can also express IL-4 and that this can explain the helper effect of TFR cells on IgE in food allergy. [4]
Human TFR cells are more challenging to examine than mouse TFR cells, as they are found in lymphoid tissue rather than blood. In fact, human TFR cells have received less research attention than mouse TFR cells. Therefore, in comparison to mice, our understanding of how genuine TFR cells control IgE in humans is remarkably restricted. Identification of GC-resident TFR cell equivalents in humans has likewise proven challenging. The Vinuesa group identified a subgroup of IL-10-expressing T follicular cells in 2019 that they dubbed CD25+ TF (T follicular) cells instead of attempting to identify human TFR cells in the tonsil.

Certain traits of mouse TFR cells are displayed by CD25+TF cells, such as elevated expression of CTLA4 and other Treg genes. TF cells that are CD25+, however, do not express Foxp3. Curiously, there was an inverse correlation between the quantity of CD25+ TF cells and the IgE levels in human sera. Additionally, CD25+ TF cells suppress class-switching to IgE via an IL-10 dependent mechanism, as demonstrated by in vitro preparations of B cells and CD25+ TF cells.
This observation runs counter to IL-10's beneficial influence on the IgE response in the mouse model of food allergies.[6]
Small dosages of allergens are employed in allergen immunotherapy (AIT), which can be a successful treatment for allergic disorders by building tolerance to the allergens and diverting the Ab response from IgE. Even yet, there is room for improvement in the therapy's efficacy and success rate, as the mechanism underlying AIT's effectiveness remains little known. Additionally required are predictive biomarkers to show the effectiveness of AIT. According to recent research, the effectiveness of AIT is correlated with a relative rise in cTFR cells. Yao et al. therefore shown that the ratio of cTFR cells to cTFH cells rose after effective AIT treatment of AR.[7]The studies described above significantly advance our understanding of the role of TFR cells in the regulation of IgE and allergic disease. However, many questions remain unanswered. One of the main questions concerns studies of IgE regulation by TFR cells in mouse models of allergic diseases, which show that the functions of TFR cells are complex and context-dependent. What are the tissue-specific factors that promote these suppressive or supportive functions of TFRs? Are these functions simply controlled by programming?Are TFR cells or B cells located in different sites more sensitive to TFR-mediated suppression than B cells located in other tissues? Using in vitro cultures with TFH cells, TFR cells and B cells, we found that TFR cells isolated from our food allergy model could induce an increase in IgE + B cells, while TFR cells isolated from airway allergens suppress IgE responses (manuscript

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submitted for publication). Here are some further studies on the specific micanisms of these effectsvarious TFR functions. Another question is whether TFR cells responding in allergic disease use different suppressor factors to inhibit IgE responses than TFR cells use to suppress non-allergic B cell responses? Also are there major differences in TFR cell effector pathways between mouse and human? This review described how IL-10 is a helper factor for IgE responses in mouse food allergy whereas in human studies on AR, IL-10 is associated with suppression of IgE. One explanation for the discrepancy may be because in the food allergy model, IL-10 is acting specifically to promote the survival of IgE + GC B cells in vivo, a different pathway from the TFR, TFH and B cells interactions tested in the in vitro cultures. Additionally, IL-10 is known to play different functions in the immune response. IL-10 may be important initially for the induction of IgE responses, whereas IL-10 is suppressive to established IgE responses. Another factor may be whether IL-10 operates differently on IgE responses in the airway immune response versus the gut immune response.[8]

All things considered, more research is required to fully characterize TFR cells and TFR roles in both mice and human systems. Many of the problems raised here would be addressed with the use of single cell RNAseq investigations of TFR cells in various immunological conditions. It is necessary to conduct more study on the function of TFR cells in IgE modulation and allergic illness, as this will help develop treatments for these conditions.

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