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Ann Allergy Asthma Immunol. Author manuscript; available in PMC 2014 January 01.

Published in final edited form as:

Ann Allergy Asthma Immunol. 2013 January ; 110(1): 7–10. doi:10.1016/j.anai.2012.10.015.

The Identification of Potentially Pathogenic and Therapeutic Epitopes from Common Human Allergens

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Introduction

Herein we present a brief historical review of our approach to identify T cell stimulatory allergen epitopes relevant to allergic disease. The intent was to develop an approach to thoroughly map allergenic epitopes recognized by T cells, and phenotype the different cell types potentially involved in stimulating and inhibiting allergic responses. However, the number of allergen epitopes is extremely large and the studies required for mapping would be too complex. However, in order for allergen specific T cells to be activated, HLA molecules are required to form bimolecular complexes with the peptides derived from allergen molecules. In vitro binding assays and bioinformatic predictions can identify these peptides. A series of pivotal studies, described herein, delineates the feasibility of the approach to map the highly diverse repertoire of allergen epitopes recognizable to responsive T cells.

Rationale for large-scale allergen epitope identification

Allergic disease involves both adaptive and innate immunity, as recently highlighted in several excellent reviews [1, 2]. At the level of adaptive responses, a key component are IgE antibodies produced by allergen-specific B cells [3]. However, T cells also play a key role both as regulators of antibody responses as well as directly contributing to pathogenesis by secretion of various cytokines [4, 5]. Furthermore, several studies implicate T cell responses as a determinant [6, 7] of the clinical efficacy of SIT (Specific Immuno-Therapy).

Despite their importance, the exact molecular structures (epitopes) recognized by T cells specific for common allergens have not been thoroughly mapped. Mapping these epitopes is of importance, to allow the measurement and characterization of allergen specific T cell responses, to directly assess the phenotype of responding cells, monitor efficacy of therapeutic treatments and probe mechanisms orchestrating pathogenic events.

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Author's contribution: All authors contributed to the preparation and critical reviewing and editing of the manuscript.

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The need to broadly define specific epitopes recognized in the context of allergic disease was emphasized by a meta-analysis of allergy-related data from the Immune Epitope Database (IEDB). The IEDB is a NIAID-sponsored resource that catalogs all data related to immune epitopes associated with infectious diseases, autoimmunity, transplantation and allergy [8] and makes it freely accessible to the scientific community. The majority of allergy-related epitopes found in the database are recognized by B cells / IgE antibodies, and the number of T-cell epitopes recognized by CD4+ T cells in the context of HLA class II is relatively low. Overall, coverage of known allergens was sparse, with data available for only ~17% of all allergens listed by the International Union Immunological Society (IUIS) database. Thus, further research was required to provide a more balanced representation across different allergen categories.

The complex nature of T helper subsets in allergic disease

It is well appreciated that human T helper (Th) cell responses are mediated by several different cell subsets, each associated with distinct functions and phenotypes. A large body of research has been devoted to the characterization of these subsets, their function in different types of immune responses and the complex interplay that occurs between each subset. The classic Th1, Th2, Th17 and Treg (Tr1) subsets are defined on the basis of the patterns of cytokine production and expression of specific chemokine receptors. In addition to these cell subsets, more recent investigations have also described Th22 and Th9 subsets [9].

Th2 cells have a clear established role in allergies, characterized by the production of IL-4, IL-5 and IL-13, and promote production of IgE. The role of the other Th subsets such as Th1, Th17 and regulatory T cells is less clearly defined. Th1 cells in allergies and asthma [10, 11] are associated with the production of IFNg, which is antagonistic to Th2 responses, and therefore it has been speculated that Th1 responses may protect against allergy and asthma. Indeed, Th1 cells have been shown to inhibit the proliferation and development of Th2 cells [12] and even IgE production in some instances [13].

Th17 cells were first described as key mediators of inflammation and autoimmune disease [14, 15]. Though a role for IL-17 in allergy and asthma has been established, several conflicting reports exist regarding its involvement in the development and pathogenesis of allergic disease [16]. A number of studies have described IL-17 as playing a proinflammatory role in allergy and asthma, whereas other studies have assigned IL-17 a more protective role [17, 18].

IL-10 has been well characterized as a mediator capable of suppressing T cell activation [19, 20]. It is produced in large part by a subset of regulatory T cells known as Tr1s [21]. Tr1s are characterized by the expression of CD4, CD25 and Foxp3, and the presence of these cells in allergic and asthmatic patients is associated with suppression of symptoms [19, 22]. In fact, a number of studies suggest the presence or absence of Tr1s and/or IL-10 may contribute to seasonal exacerbations and efficacy of SIT [23-25].

Several observations highlight the complex interactions and plasticity of Th subsets [26]. A subset of Th2 cells in PBMC from allergic individuals stimulated with anti-CD3 [27] produces both Th17 and Th2 cytokines and is characterized by expression of CCR4 and CCR6. The production of IL-17 is induced from Th2 cells and Th2 cytokines synergize with IL-17 in inducing the production of various chemokines. Several studies suggest that Th17 cells have the capacity to transform into other lineages [26] or become dual IL-4/IL-17 producing cells [28]. Indeed the interplay between Th cells producing these two cytokines has been implicated in the heterogeneity of the pathology of severe asthma [29]. Similarly, several studies [30] suggest that Th1 polarizing stimuli can induce Th2 cells to produce IFNγ. Finally, besides the well-appreciated regulatory activity of IL-10 in terms of production from Tr1s

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and resulting in inhibition of other Th subsets, it has been suggested that Th1 and IFNγ producing cells regulate themselves by inducing IL-10 production [31, 32].

These reports highlight the plasticity and interplay of Th cell subsets producing different cytokines. However, the lack of information regarding the actual epitopes recognized by Th cells derived from common allergens severely limits our capacity to probe these interactions in more depth.

A broad approach to the study and characterization of HLA class II restricted epitopes

Clearly defined T cell epitopes are the basis for the study and characterization of the allergen-specific T cell population. To address this issue, we set out to investigate a large panel of common allergens and to identify their T cell epitopes [33].

CD4 T cells recognize a bimolecular complex of the specific epitopes bound to specific HLA class II molecules (HLA restriction). HLA class II molecules are encoded by three different loci, designated as HLA DR, DP or DQ. Each of these loci is extremely polymorphic. This complexity must be taken into account in the design of a general strategy for identification and characterization of T cell epitopes in allergens. As outlined in Figure 1, we first selected a comprehensive, yet manageable, set of HLA DR, DP, and DQ molecules, representative of the most frequently expressed variants in different ethnicities worldwide. A panel of 25 different HLA class II molecules was selected for the experiments described below.

The number of peptides that could be tested to define epitopes from common allergens is very large, which poses significant challenges in terms of amounts of patient derived blood samples required. One method to reduce the complexity is to rely on the fact that epitopes have to bind specific HLA molecules, and the binding specificity of these molecules can be predicted. Accordingly, for each of the selected HLA molecules we developed high throughput binding assays and derived detailed peptide binding motifs. While assays and motifs were generally already available for DR molecules [34-37], the efforts directed towards DP and DQ specificities were largely novel.[38,39].

Next, large panels of synthetic peptides were tested for binding to the various HLA class II molecules. This generated a dataset of over 40,000 HLA-peptide binding affinities for the various HLA DR, DP and DQ allelic variants. Utilizing this dataset, we generated prediction tools utilizing several machine learning algorithms and made them freely available to the scientific community through the IEDB website [40]. The large datasets of measured binding affinities were also utilized to develop a functional classification of HLA class II on the basis of shared binding repertoires. Seven different main “supertypes” (main DR, DR4, DRB3, main DQ, DQ7, main DP, and DP2) were defined, corresponding to groups of alleles associated with similar peptide binding specificities. These results indeed highlighted that in general a high degree of peptide binding repertoire overlap exists amongst the various different HLA class II molecules.

Identification of T cell epitopes in the Timothy grass (TG) system

In approaching the problem of defining T cell epitopes from common allergens we expected to encounter a significant degree of heterogeneity due to HLA polymorphism. However, because of the overlap in repertoire of peptides bound by different HLA molecules, we also anticipated that some allergen-derived peptides are capable of binding several different HLA molecules (promiscuous binding). Our general hypothesis was that promiscuous epitopes

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account for a large fraction of reactivities, and that such promiscuous epitopes could be identified based on predicted HLA class II binding affinities.

This hypothesis was tested in the context of responses from patients allergic to Timothy grass. We considered 10 different proteins (Phl p 1, 2, 3, 4, 5, 6, 7, 11, 12, 13), corresponding to well-described allergens previously shown to elicit IgE reactivity. A total of 687 overlapping peptides spanning the sequences of these allergens were synthesized and tested for reactivity with T cell lines obtained by *in vitro* restimulation of PBMC with TG pollen extract. These studies utilized a cohort of 43 donors that included 10 non-allergic, 25 allergic, and 8 TG SIT individuals. A total of 70 unique peptides, corresponding to 43 unique Phl p antigenic regions were recognized [41]. Hence, as expected, the repertoire of epitopes recognized by TG-specific T cell responses is highly diverse. This data is also consistent with several previous studies characterizing TG-derived T cell epitopes, which also highlighted a highly diverse repertoire [42, 43].

Validation of an approach for epitope identification based on bioinformatic prediction of promiscuous HLA binding

Next, the restricting HLA locus was identified using anti-DR, DP or DQ antibodies. Interestingly, we found that while most of the responses are DR restricted, DP and DQ also account for a significant fraction of total spot forming cells (SFCs). The actual allelic variant restricting the response was determined by the use of fibroblasts expressing a single HLA class II molecule, and/or matched and mismatched EBV transformed B cell lines.

A key issue for these validation studies was whether we could account for the majority of the responses with relatively few promiscuous regions. Analysis of the data relating to the response magnitude revealed that this was indeed the case. More specifically, the top 20 antigenic regions accounted for about 80% of the responses against the TG allergens considered. We further found that all of these most dominant antigenic regions are promiscuous in that multiple HLA class II molecules can bind and present them. This observation provides at least a partial explanation for their dominance. The next key issue for our validation studies was whether we would be able to predict the allergen epitopes *in silico*. We found that *in silico* bioinformatic prediction of promiscuous binding identified about half of the responses in individual donors [41].

Additional data supporting the validity of bioinformatic predictions to identifiy allergen-derived epitopes was recently provided in the Bla g (*Blattella germanica)* cockroach allergy system [44]. In those studies, analysis of Bla g 1, 2, 4, 5, 6, and 7 allergen sequences led to the identification of 25 unique T cell epitopes, with 5 epitopes accounting for over half of the total response. These studies determined that Bla g 5 was the most dominant allergen for T cell responses. SIT resulted in down-modulation of IL-5 production, without induction of IFN-γ Bla g derived peptides.

Overall, we concluded that our initial hypotheses that promiscuous epitopes account for a large fraction of reactivities, and that such promiscuous epitopes could be identified based on predicted HLA class II binding affinities were valid. Consequently, we concluded that the approach for identification of allergen epitopes based on HLA predictions could be implemented to address a larger scale screen of allergenic proteins.

Further large-scale identification of allergen-derived epitopes

Based on the results obtained in the TG system, we embarked on a large scale screen of airborne allergens derived from a variety of different allergen sources. For each allergen

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system, all available sequences were collected. It was apparent that in the case of certain allergen sources many (in excess of 10) sequences were available, while in other cases only few protein sequences were reported.

Next, the predictive strategy defined in the TG model system was utilized to identify promiscuous HLA class II binding peptides from the various allergen sources. As a result, a total of 1736 peptides were synthesized[33] and tested for recognition in allergic donor PBMCs (Figure 1). Allergen extracts effectively stimulated T cell responses in most donors, with an average of 95.3% positivity over the different allergen extracts considered. However, when the percent of extract response captured by pools of predicted epitopes was examined, we observed a significant degree of variability[33], which correlated with the number of allergen sequences available for each allergen extract. On average, in the case of allergen extracts for which only one defined protein sequence was available, the peptides accounted for only 4% of the total response observed with the extract. By contrast, in the case of allergen extracts for which 6 or more sequences were available, the peptides accounted for approximately 40% of the total extract response.

A total of 87 different antigenic regions were recognized in 2 or more donors. Further experiments characterized the phenotype and restriction of these antigenic regions. In many cases the epitopes identified were the first defined T cell epitopes for that particular allergen source. In other cases, where T cell epitopes were previously known, our analysis greatly enhanced the breadth of T cell epitopes available to the scientific community [33].

Discussion

The ultimate goal of the identification of allergen epitopes is to utilize these molecularly defined reagents to illuminate and probe the mechanisms underlying T cell responses in allergic disease. We have initiated studies aimed at characterizing different disease states and correlated them with different epitope specific responses. In particular, several reports from the literature suggest that distinct patterns of cytokine production are associated with allergic asthma. A body of data has implicated, beyond Th2 cytokines, roles for IFNγ, IL-17 and IL-10 in allergic reactions [10, 11, 17-19, 22-25, 46, 47]. Notably most reports have utilized mitogens or model antigens for stimulations. Since the actual T cell populations specifically responding to the allergen epitopes were not analyzed, this raises doubts regarding the physiological relevance of these stimulations. We anticipate that definition of the actual epitopes recognized from allergen specific T cells will allow probing the interplay of different Th cell subsets in allergic disease and improve the understanding of their effects on the disease profile and progression. Furthermore, we are in the process of characterizing T cell responses from patients undergoing the course of specific Immunotherapy to TG allergy by analyzing in detail the cytokines and functional phenotype of the allergen-specific T cells generated, and monitor for significant changes over the course of SIT.

Conclusion

Recent years witnessed a significant expansion of knowledge related to epitopes recognized in allergic disease, and to the complex interplay between different Th cell subsets. We anticipate that the combination of the advances in these two fields will yield new insights regarding the molecular mechanisms of disease, and thereby translate into potential novel intervention strategies, as well as novel ways to determine the magnitude and phenotype of allergen-specific responses for diagnostic purposes.

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Acknowledgments

Financial support: This work was supported by National Institutes of Allergy and Infectious diseases Contract HSN272200700048C (to A.S.) and Grant U19AI100275 (to A.S.)

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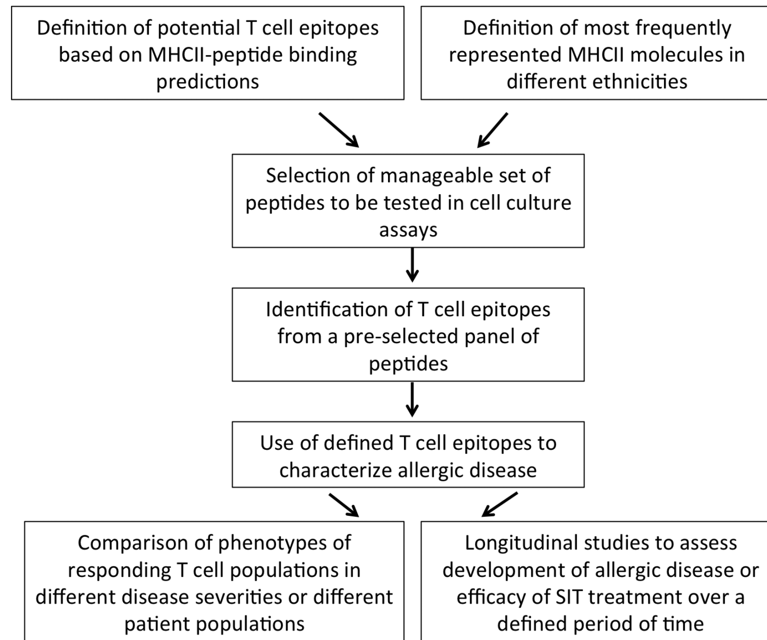

Figure 1.
A schematic overview of processes involved in large-scale T cell epitope identification from common allergens.