Main Submission

IgE+ B cells in the pathogenesis of allergic asthma: fundamental but often forgotten.

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Introduction

As of 2012 the World Health Organization had declared asthma as the most common, non-infectious disease among children (1). In addition to debilitating health concerns clinically manifested as recurrent episodes of breathlessness and wheezing, asthma also poses significant financial burdens and is estimated to cost Canadians $4.2 billion by 2030 (1). As such, asthma research is warranted not only by the clinical symptoms patients face but also by the economic consequences of the condition. Allergic asthma (AA) is a chronic inflammatory disorder hallmarked by airway eosinophilia, airway hyperresponsiveness, and reversible airflow obstruction (2). AA is further characterized as an IgE-mediated disease whereby inhaled allergens trigger type 2 inflammation by binding to membrane-bound IgE on the surfaces of mast cells and basophils. This induces the activation and release of inflammatory mediators and promotes clinical symptoms such as wheezing, coughing and shortness of breath (2; Figure 1). Consequently, this allergen-induced, IgE-mediated inflammatory response has also been shown to incite increased allergen-specific IgE in the airways of allergic asthmatics (3). Since B cells solely produce IgE it is evident that these cells play a crucial role in initiating asthma-related inflammatory processes. The aim of this article is to provide a brief overview of the B cell and allergic asthma literature. The role of B cells in the pathogenesis of allergic asthma will be highlighted and therapeutic implications for targeting IgE and IgE+ B cells will be explored.

Role of IgE and B cells in allergic asthma

Limited studies have documented the role of IgE and IgE+ B cells in the pathogenesis of AA. Here we summarize the current literature available reporting on the levels of IgE and relative frequencies of IgE+ memory B cell subsets in individuals with AA. Wilson et al. (4) observed significant increases in allergen-specific IgE in the bronchoalveolar lavage fluid of allergic asthmatics 24 hours after segmental allergen challenge. This trend was observed in the airways, suggesting localized accumulation of allergen-specific IgE (4). Similarly, Van de Pol et al. (3) observed an increase in allergen-specific IgE that persisted for at least 5 weeks after whole-lung allergen challenge. This increase in allergen-specific IgE levels was supplemented by findings of significantly increased production of type 2 cytokines (e.g., IL-4, IL-5, IL-13) pivotal to AA pathogenesis (3).

IgE has been established as an effective therapeutic target for the treatment of AA given its role in the pathogenesis of the disease; however the trafficking and relative frequencies of memory B cell subsets that produce IgE have been sparsely explored. Kidney et al. (5) initially reported on the importance of B cells within the airways of asthmatics when they found that asthmatic sputum had a larger proportion of B cells within the lymphocyte population when compared with non-asthmatics. More importantly, Kidney et al. (5) reported that sputum B cells positively correlated with sputum eosinophils, further highlighting the potential role of B cells in AA pathogenesis. This paper was published approximately 20 years ago, and since then, very limited research has been done to determine the role of B cells in allergic asthma. However, if there is a strong relationship between the frequencies of B cells and eosinophils, determining a functional relationship between these two cells would shed light on whether B cells play a role in asthma disease severity. More recently, Oliveria et al. (6) demonstrated that higher levels of IgE+ B cells were present in the sputum of allergic asthmatics (12.2% of airway lymphocytes) compared to healthy controls (5.6% of airway lymphocytes), suggesting localization of IgE+ B cells in the airways of asthmatics. The proportion of B cells between allergic asthmatics and healthy controls were comparable between Kidney et al. (5) and Oliveria et al.'s

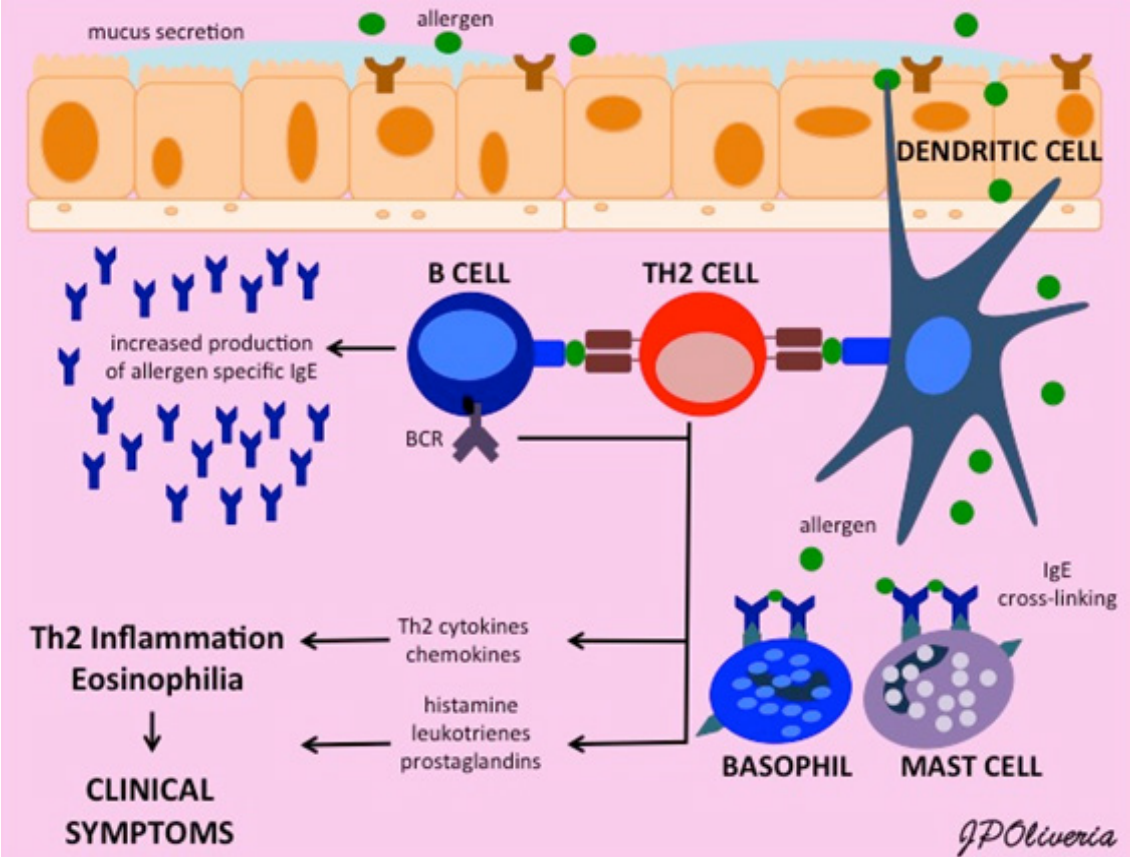

Figure 1: Pathogenesis of the allergic inflammatory cascade in asthma.

(6) studies. Oliveria et al. (6, 7) also showed that there were no changes in the frequency of IgE+ B cells in peripheral blood or bone marrow of allergic asthmatics following allergen inhalation challenge.

Wilson et al. (4) and Van de Pol et al. (3) both showed increases in allergen-specific IgE in the airways after allergen-induced exacerbations, implicating their relevance in disease manifestation and presence of clinical symptoms. Since B cells are the sole producers of IgE, further studies need to be done on characterization of B cells to determine their function in allergic asthma disease. Particularly, it is imperative to study the kinetics of IgE+ B cells following a whole-lung allergen challenge to determine whether changes to the IgE+ B cell population occur mainly in the airways. Considering currently published data, more studies also need to be conducted on the frequencies and function of IgE+ B cells and IgE in the airways of allergic asthmatics to delineate their role in AA pathogenesis. Specifically, characterizing the contribution B cells may add to local inflammation in the airways would further implicate their role in asthma pathogenesis.

Anti-IgE therapy - omalizumab and beyond

Having established the relative importance of B cells and IgE in the pathobiology of asthma, there is currently a focus on investigating treatments that specifically target IgE. Anti-IgE therapies have been efficacious in the treatment of moderate to severe AA, particularly in cases where inhaled corticosteroid therapy is ineffective. Omalizumab (Xolair®) is a humanized monoclonal antibody that binds to free, circulating IgE. This prevents IgE binding to high (FcεRI) and low affinity (FcεRII) IgE receptors on mast cells and basophils, thereby inhibiting the degranulation and release of inflammatory mediators (8). A systematic review by Rodrigo et al. (9) found that omalizumab therapy was able to reduce the rate of asthma exacerbations by up to 50% and significantly improve quality of life scores of allergic asthmatics (9). As an alternative to omalizumab, a new anti-IgE therapy being developed, ligelizumab, demonstrated an almost 50-fold increase in affinity to human IgE compared to omalizumab (10). Another alternative, quilizumab, which targets M1-prime (a protein specific to membrane bound IgE+ B cells), has been shown to reduce the production of IgE after allergen inhalation challenge (11). Despite the therapeutic potential of anti-IgE, major drawbacks of antibody therapies are their cost and that they must be

taken regularly for long-term treatment as their effects are known to wane following the termination of treatment (8). Additionally, anti-IgE therapies are prescribed to a small proportion of patients with moderate-severe allergic asthma. Thus ongoing research is being undertaken to explore the therapeutic effects of anti-IgE therapy in other diseases, including atopic dermatitis (itchy, sensitive skin) and chronic urticaria (rash, hives). It is important to explore the therapeutic effects of anti-IgE therapies due to the efficacy this therapy has shown in improving the quality of life of allergic asthma patients.

Conclusion

To date, limited research has alluded to IgE and B cells as integral components of the pathogenesis of AA, since targeting their depletion dampens disease manifestations. Although there are several anti-IgE treatments currently being developed in the treatment of asthma, including one already approved by Health Canada, there is still a long way to go before the development of a long-term therapy that can manage the diverse range of patients diagnosed with AA. In addition, further research on the function of B cells, particularly B cells located in the airways, needs to be conducted in order to gain a better grasp on the role of B cells in AA pathogenesis. This much-needed research will aid in anti-IgE and anti-B cell therapy development. However, beyond the search for new therapies, asthma-related research has vast potential to be translated into other domains of allergy and immunology, as well as the treatment of other IgE-mediated disorders. ■

List of Abbreviations

AA – Allergic asthma, FcεRI - high affinity IgE receptor, FcεRII - low affinity IgE receptor, IgE - Immunoglobulin E, IL - Interleukin

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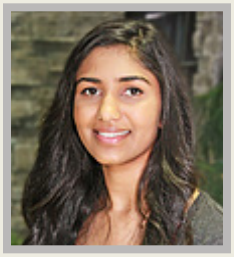

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