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Allergic Airway Inflammation

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1. Introduction

Allergic airway inflammation is one characteristic feature of asthma disease, with additional pathology including a reversible airway obstruction, airway hyperresponsiveness (AHR), infiltration of eosinophils and T-helper type 2 (Th2) cells into the airway submucosa, mucus hypersecretion, and airway remodeling (Agrawal & Shao 2010). Allergic airway diseases are inflammatory disorders in which aberrant immune regulation occurs and susceptible individuals mount allergen specific responses. Inflammatory cells are recruited to the asthmatic airways or are activated in situ. The inflammatory cells include mast cells, macrophages, eosinophils, T lymphocytes, dendritic cells, basophils, neutrophils, and platelets (Barnes et al. 1998). Structural cells may also be important sources of inflammatory mediators in asthma. Airway epithelial cells, smooth muscle cells, endothelial cells, and fibroblasts are all capable of synthesizing and releasing inflammatory mediators (Levine, 1995; Saunders et al. 1997; John et al. 1997). Moreover, these cells may become the major source of inflammatory mediators in the airway, which may explain how asthmatic inflammation persists even in the absence of activating stimuli. A majority of patients with asthma have an atopic, allergic background (Robinson 2000). The prevailing consensus in regards to these patients is that the immunological basis of atopic sensitization and allergic disease results from inappropriate Th2 cell responses to common environmental proteins termed allergens (Robinson 2009).

Here, we summarize recent findings regarding how immune response and inflammatory cells contribute to allergic airway inflammation and discuss recent progress in the regulation of these cells.

2. Immune mechanism

In general, airway inflammation involves the activation of pathogenic-specific inflammatory cells, modulation of transcription factors and release of inflammatory mediators (Barnes et al. 1998). Allergic asthma, classified as a type 1 hypersensitivity reaction, involves allergen-specific immunoglobulins of the IgE class bound to high-affinity Fcε receptors (FcεR) on the surface of basophils and mast cells present in the subepithelial layer of the airways. Cross-linking of the receptor initiates a coordinated sequence of biochemical and morphological events that results in exocytosis (figure 1) of secretory granules containing histamine or other pre-formed inflammatory mediators; synthesis and secretion of newly formed lipid mediators, such as prostaglandins and leukotrienes; and synthesis and secretion of

cytokines (Will-Karp et al. 1999). Many mediators are released in asthma, and it is clear that these mediators interact with each other in some way. Mediators may act synergistically to enhance each other's effects, or one mediator may modify the release or action of another mediator. Although the involved signaling pathways have been extensively studied, the precise sequence of events is still not well understood (Turner et al. 1999; Kim et al. 1997; Ali., et al. 2001; Ching et al., 2001; Siraganian 2003; Galli et al. 2008; Kim et al. 2008; Saini et al. 2009; Moran et al. 2010a,b; Colgan & Hankel 2010). The inflammatory mediators are capable of contracting airway smooth muscle cells, inducing edema and mucus secretion, which leads to narrowed, constricted airways. Furthermore, locally produced chemokines stimulate the recruitment of eosinophils, macrophages, neutrophils, and T lymphocytes (Broide 2001).

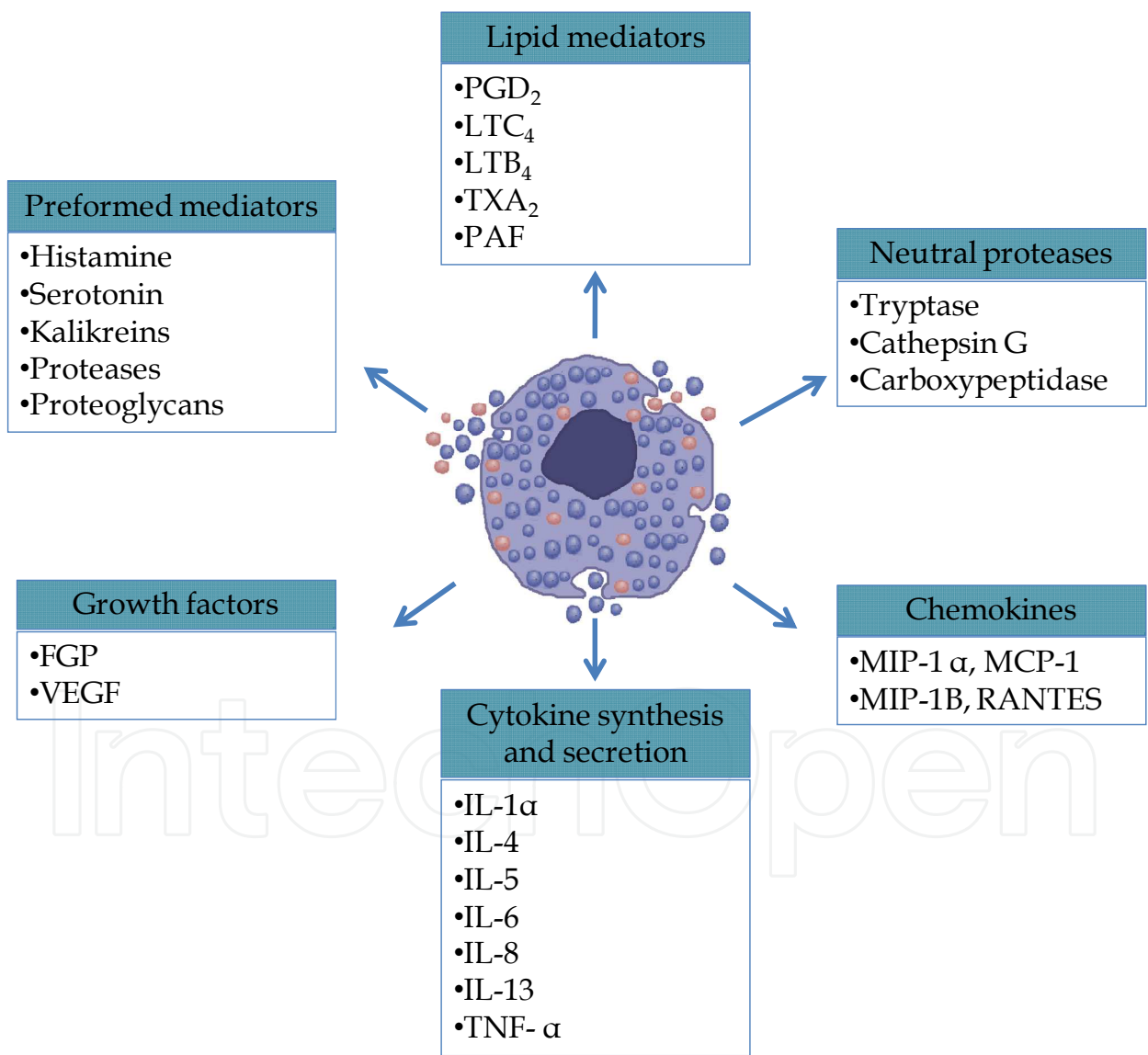


Fig. 1. Products of Mast Cells. PGD₂, prostaglandin D₂; LTC₄, leukotriene C₄; PAF, platelet-activating factor; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor, MIP; macrophage inflammatory protein; RANTES, regulated on activation, normal T-cell expressed and secreted MCP-1, monocyte chemotactic protein-1.

2.1 Role of T cells in airways allergy disease

T cells play an important role in the modulation of the immune response and are critical during allergy airway pathogenesis. Since 1986, the Th1/Th2 paradigm has dominated the understanding of the pathophysiology of asthma and allergic disease (Akbari et al. 2003). It is generally accepted that allergic respiratory disease in adults is associated with active T-cell immune responses to inhaled allergens that are skewed toward the Th2 phenotype, which is in contrast to a Th1-skewed immunity in healthy individuals (Agrawal and Shao 2010). Experimental animals model have been useful in the immunological delineation of the role of T cells and T cell-derived cytokines in the pathogenesis of airway allergy disease. In these animal models, sensitization with various allergens, such as ovalbumin, house dust mite, and aspergillus, induce a phenotype closely resembling that observed in human asthma (Hausding et al. 2008; Humar et al. 2008; Allen 2009; Bates et al. 2009; Qarcoo et al. 2009; Moran & Folch 2011).

Th2-associated cytokines such as IL-4 are important in driving IgE production to allergens and are essential in the initiation of an allergic airway response (Coyle et al. 1995). IL-5 contributes to the development, recruitment and activation of eosinophils at the site of the Th2 inflammatory response, which characterizes allergic disease. IL-9 is an important regulator of mast-cell activation. Studies suggest that IL-13 has an important role in the effector phase of the allergy response, specifically airway inflammation, bronchial hyperresponsiveness and mucus cell hypersecretion (Wills-Karps et al. 1998; Wills-Karps et al. 1999). The involvement of each the specific Th2 cytokines in atopic airway response has been demonstrated in studies in which IL-4, IL-5, IL-9 and IL-13 have been manipulated through either antibody blockade (Kung et al. 1995; Gavet et al. 1997) or gene targeting (Brusselle et al. 1995; Foster et al. 1996; Spergel et al. 1999). Additionally, IL-21 has been shown to be important in the development of Th2 immune response (Frohlich et al. 2007). Frohlich and colleagues (2007) suggest that although the mechanisms by which IL-21 regulates allergy inflammation are unknown, IL-21 may be important for Th2-cell survival or migration to peripheral tissues. On the other hand, Th1 cells are also pro-inflammatory, and the development of a Th1-associated inflammatory response can exacerbate asthma and allergic disease. IFN- γ is often present at sites of allergic inflammation and is thought to contribute to the disease. Th1 cells cross-regulate Th2 cells in some systems, and it was thought that Th1 cells downmodulated the effects of Th2 cells. However, recent advances in immunology have raised the possibility that other mechanisms may drive or co-exist with pathology in some patients with Th2-type allergy airway inflammation. New effector T-cell lineages have recently been identified. Th17 cells, which differentiate from naïve CD4⁺ T cells under the influence of IL-6/IL-21/IL-23 and transforming growth factor (TGF)- β via the signal transducer and activator of transcription 3 (STAT3)-ROR γ t pathway, are mainly responsible for neutrophilia in allergic severe asthma (Louten et al. 2009). Moreover, a variety of cytokines derived from epithelium, fibroblasts and other airway structural cells have recently been shown to have an important potential for interaction with Th1, Th2, Th17, eosinophil and mast cells. These cytokines include the following: proinflammatory cytokines [IL-1 β , IL-6, IL-11, tumor necrosis factor (TNF)- α , and granulocyte/macrophage colony-stimulating factor (GM-CSF)], which are involved in innate host defense; anti-inflammatory cytokines [IL-10, IFN- γ , IL-12, and IL-18]; growth factors [platelet derived growth factor (PDGF), TGF- β , fibroblast growth factor (FGF), and epidermal growth factor (EGF)]; and chemotactic cytokines or chemokines [RANTES, monocyte chemoattractant protein (MCP)-1-MCP-5, eotaxin, and IL-8] (Hamid and Tulic 2009).

Conversely, investigations into the contribution of cytotoxic CD8⁺ T cells towards the development of allergic airway inflammation are not well understood. The depletion of CD8⁺ T cells does not affect airway response to allergen challenge in mice (Gonzalo et al. 1996). However, a subset of CD8⁺ T cells, named *Tc2* cells, can produce Th2 cytokines such as IL-4, IL-5, and IL-13, which are increased in the bronchoalveolar lavage fluids (BALF) of allergic asthmatic patients in studies. This rise of cytokine production suggests that the immune responses to virus infections are characterized by an increase in the frequency of type 2 cytokine-producing T cells when they take place in an allergic environment in animal models (Coyle et al. 1995; Makela et al. 2003). Human studies show that CD8⁺ T cells from both normal and asthmatic subjects have the capacity to produce type 2 cytokines (Stanciu et al. 1996; Stanciu et al. 1997). In addition, the stimulation of CD8⁺ T cells from normal, healthy subjects in an IL-4 rich milieu significantly increased the number of IL-5-positive CD8⁺ T cells (Stanciu et al. 2001). Additionally, studies suggest that during a respiratory virus infection activated CD8⁺ T cells from asthmatic subjects may produce excess type 2 cytokines and may contribute to asthma exacerbation by augmenting allergic inflammation (Stanciu et al. 2005). These studies thus demonstrate that the frequency of airway CD8⁺ T cells producing type 2 cytokines are as great as those of airway CD4⁺ T cells are and that both are increased in asthma and are related to disease severity (Cho et al. 2005).

2.1.1 Transcription factors responsible for the Th1/Th2/Th17 cells and inflammatory mediators

Transcription factors are DNA-binding proteins that regulate the expression of inflammatory genes, including enzymes involved in the synthesis of inflammatory mediators as well as protein and peptide mediators (Barnes et al. 1998). Inflammation associated with hypersensitivity results from an exaggerated expression of inflammatory genes, and a number of researchers have explored the mechanisms implicated in inflammatory gene induction (Barnes and Karin, 1997; Barnes and Adcock, 1998). Many transcription factors are cell-specific and are crucial in cell differentiation and the regulation of specific cellular processes such as proliferation, enzymes, and cytokine expression. In animal models of airway diseases, such as atopic asthma, nuclear factor NF-(kB), activator protein-1 (AP-1), GATA-3, JunB and c-Maf play a central role in the control of airway inflammation (Finotto et al. 2001; Nguyen et al. 2003; Yamashita et al. 2007). In humans, there is evidence that NF-kB, AP-1 and GATA-3 expression is increased in asthmatic airways (Hart et al., 1998; Taha et al. 2003). Furthermore, these transcription factors are key downstream regulators of Th1/Th2/Th17 cytokine function and are phosphorylated/dephosphorylated in the asthmatic airway (Pernis and Rothman, 2002). The Th1 master regulator, T-box transcription factor (T-bet), is extensively expressed in polarized Th1 cells, and its expression and activity are induced by IL-12 via STAT4 or by IFN- γ via STAT1. IL-4 drives differentiation of IL-4-producing Th2 cells through STAT6, which is necessary and sufficient for the induction of the Th2 master regulator, GATA-3. Moreover, transcription factor c-Maf is selectively expressed in Th2 cells as a downstream effector of the IL-4/IL-4R/STAT6 signal transduction pathway, primarily regulating IL-4 expression in Th2 cells (Agrawal & Shao 2010).

2.1.2 Role of regulatory T cells in allergy airway diseases

As mentioned previously, allergic airway diseases show complex genetic associations and have a hereditary component (Cookson & Moffat 2004). However, the rapid and

geographically localized nature of the increase in the incidence of allergic diseases indicates compounding effects of recent changes in environment and lifestyle in the Western world. How these factors impact disease by promoting immune responses to allergens is a subject of considerable debate, which has led to the “hygiene hypothesis” (Wills-Karp et al. 2001; Liu & Murphy 2003). According to the theory, in its simplest iteration, the increase in hygienic living conditions and in the use of antibiotic and sterile food preparations resulted in the separation of the immune system from positive microbial exposure early in life (Martinez and Holt, 1999). The immunoregulatory mechanisms remain underdeveloped, and an imbalance in immune homeostasis predisposes to the development of T helper type 2-biased immune responses and, consequently, allergic disease (Feleszko et al. 2005).

Recent studies indicate that Th2 responses that are characteristic of allergic manifestations can be regulated by naturally occurring CD4⁺CD25⁺ regulatory T (nTreg) cells. These cells are a functionally mature T-cell subpopulation, which play key roles in the maintenance of immunologic self-tolerance and negative control of a variety of physiological and pathological immune responses (Sakagushi et al. 2006). They also constitutively express transcription factor forkhead box P3 (FoxP3), which prevents the deviation of Tregs into effector T cells (Burchill et al. 2007). These cells originate in the thymus, but inducible Treg (iTreg) cells, which have similar properties and characteristics, can also be induced in the periphery. Regulatory T cells appear to control the development of autoimmune disease and transplant rejection and may play a critical role in controlling asthma and allergy (Akdis et al. 2005). Several studies indicate that the function of naturally occurring Treg cells is impaired or altered in patients with allergies compared with normal healthy individuals. The adoptive transfer of antigen-specific CD4⁺CD25⁺ T-regs attenuates acute allergic airway inflammation, AHR, and airway remodeling. The capacity of Treg cells to inhibit the proliferation of naive T cells *in vitro* requires cell-cell contact (induction of an inhibitory signals on CD4⁺ and CD8⁺ T cells); however, *in vivo*, these cells can also function through induction of inhibitory cytokines (such as TGF- β and IL-10) and inhibition of antigen-presenting capacity (Zheng et al. 2006; Kearly et al. 2008). These data suggest that one potential treatment option would be to enhance CD4⁺CD25⁺ Tregs in addition to targeting decreased Th2 populations. An example of this therapeutic strategy would be allergen desensitization immunotherapy, which has been in use for almost a century and is one of the few specific immunomodulatory treatments that are commonly used for allergic asthma (Akbari et al. 2003; Kearly et al. 2008). Understanding the immune mechanisms that underlie successful allergen immunotherapy offers the potential to improve current allergen-immunotherapy regimens. Some authors suggest that this therapy might function, at least in part, to promote the generation of IL-10 and TGF- β -secreting regulatory T cells (Hawrylowicz & Garra 2005; Shevach et al. 2008).

3. Apoptosis regulation in allergy airway disease

Apoptosis is defined as a genetic program that eliminates unneeded, senescent, or damaged cells (Thompson 1995). Moreover, apoptosis is an important regulatory mechanism in the selection and containment of an immunocompetent T cell population, in T cell development and during immune responses. Dysregulation of apoptosis has been implicated in a range of diseases including tumors, neurodegenerative disorders, autoimmunity (Cohen 1999) and, perhaps, allergic asthma (Vignola et al. 1999; Woolley et al. 1996). Studies in human patients have demonstrated that reduced T cell apoptosis plays an important role in the pathogenesis

of allergic bronchial asthma (Cormican et al. 2001; Vignola et al. 1999; De Rose et al. 2004). These findings are also consistent in murine models of asthma (Jayaraman et al. 1999; Tong et al. 2006; Finotto et al. 2007). In addition, increasing lines of evidence suggest that changes in programmed cell death mechanisms in both mobile and resident cells of the airway may directly contribute to the development and clinical severity of allergy airway inflammation (Vignola et al. 2000).

Apoptosis has emerged as a major mechanism in the clearance of activated T cells during the resolution of an inflammatory response (Akbar and Salmon 1997). Inadequate T cell apoptosis in asthma patients appears to interfere with normal T cell elimination, resulting in T cell accumulation, which contributes to chronic inflammation and may be the major underlying cause for tissue damage, remodeling and repair (Müller et al. 2006; Vignola et al. 2000). Spinozzi et al. (1998) reported that pulmonary T cells isolated from the BALF of atopic asthma patients showed hypoexpression of Fas and FasL; this result may explain the low frequency of apoptosis in this group of patients. In contrast, horses with acute airway allergy have increased apoptosis of airway lymphocytes, which may partially explain the rapid resolution of the pathology once the allergen is removed in this allergy model (Moran et al. 2011). However, these authors suggest additional studies to examine apoptosis and cytokine profiles in other stages of the disease. In addition, basal levels of apoptotic activity were significantly lower in BALF lymphocytes from asthmatic subjects compared with peripheral blood lymphocytes from the same subjects. These data indicate that airway inflammation in asthma is associated with a reduced susceptibility to apoptosis, which may lead to enhanced survival of lymphocytes in the bronchial mucosa and prolonged inflammation (Müller et al. 2006). Other molecules are involved in the programmed cell death process, including members of the Bcl-2 gene family, which are known to inhibit apoptosis. Studies have shown that Bcl-2 expression is increased in lymphoid cells obtained from the airways of asthmatic patients and that neutralization of IL-10, an important inducer of Bcl-2, decreases Bcl-2 expression and apoptosis of cells from the respiratory tract of asthmatic patients (Hamzaoui et al. 1999a; Hamzaoui et al. 1999b).

4. Airway remodeling

Recently, airway remodeling has become a field of special interest in chronic asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and cystic fibrosis research as the process that causes patients to become largely resistant to medication and is an important factor in the development of irreversible airflow limitation (James et al., 1989; Lange et al., 1998; Jeffery et al., 2000; Kranenburg et al., 2002 Wegmann, 2008). In tissues from human with these diseases, remodeling changes include goblet cell and mucous gland hyperplasia, subepithelial fibrosis, neovascularization, airway smooth muscle (ASM) growth as well as increased deposition of extracellular matrix (ECM) proteins such as collagens, elastin, laminin, and proteoglycans around the smooth muscle and an overall thickening of the airway wall (Roche et al 1989; Laitinen et al., 1997; Davies et al., 2003). The molecular mechanisms that drive remodeling remain undefined, but many growth factors and cytokines, including fibroblast growth factor (FGF)-1, FGF-2, and transforming growth factor (TGF)- β 1, that are released from the airway wall have the potential to contribute to airway remodeling, revealed by enhanced ASM proliferation and increased ECM protein deposition (Parameswaran et al., 2006; Kariyawasam and Robinson 2007). TGF- β 1 is an important fibroblast chemotactic factor. Fibroblast numbers have been shown to correlate

with TGF- β 1 expression. TGF- β 1 also induces the differentiation of fibroblasts to myofibroblasts (Postlethwaite and Seyer, 1995; Vignola et al., 1997; Thannickal et al., 2003). Moreover, TGF- β 1 and FGF-1 stimulate mRNA expression of collagen I and III in ASM cells, suggesting their role in the deposition of extracellular matrix proteins by ASM cells in the airways of patients with chronic lung diseases. Furthermore, ECM proteins promote the survival, proliferation, cytokine synthesis, migration, and contraction of human ASM cells contributing to airway wall remodeling (Parameswaran et al., 2006)

5. Conclusion

Asthma allergy disease is multifactorial, characterized by allergy airway inflammation and increased bronchoconstrictory response to nonspecific stimuli. The current body of knowledge suggests that the inflammatory component of asthma results from a combination of elements from both the innate and adaptive immune responses. Expression of cytokine patterns consistent with Th1, Th2 and Th17 cell activation has been identified and determined to vary based on the chronic condition of the disease. Activation of transcription factors plays a pivotal role in regulating cellular signaling pathways through dynamic modulation of cytokines, chemokines, and similar molecules. The regulation of the apoptosis of inflammatory cells, fibroblasts, and myocytes through Bcl-2 expression contributes to the establishment of chronic disease and remodeling. Tregs seem to play a pivotal role in balancing tolerance versus immunologic response to allergens. Therapy with immunomodulators that enhance tolerance to allergens and increase Tregs would be most effective in the treatment of allergy airway disease.

6. Acknowledgment

The author acknowledges the support of Fondecyt grants (Chilean governments), 11100196.

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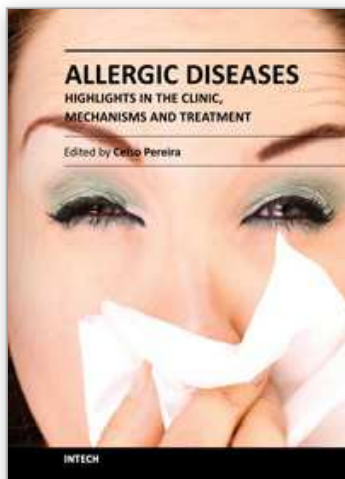
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Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment

Edited by Prof. Celso Pereira

ISBN 978-953-51-0227-4

Hard cover, 554 pages

Publisher InTech

Published online 14, March, 2012

Published in print edition March, 2012

The present Edition "Allergic diseases - highlights in the clinic, mechanisms and treatment" aims to present some recent aspects related to one of the most prevalent daily clinical expression disease. The effort of a group of outstanding experts from many countries reflects a set of scientific studies very promising for a better clinical care and also to the treatment and control of the allergy. This book provides a valuable reference text in several topics of the clinical allergy and basic issues related to the immune system response. The inflammatory reaction understanding in allergic disease is clearly evidenced, as well as new strategies for further researches.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Gabriel Morán, Claudio Henriquez and Hugo Folch (2012). Allergic Airway Inflammation, Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment, Prof. Celso Pereira (Ed.), ISBN: 978-953-51-0227-4, InTech, Available from: <http://www.intechopen.com/books/allergic-diseases-highlights-in-the-clinic-mechanisms-and-treatment/allergic-airway-inflammation>

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