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Vaccines against Allergies

Responsible series editor: Fritz Melchers

Springer

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ISSN 0070-217X
ISBN 978-3-642-20053-3 e-ISBN 978-3-642-20054-0
DOI 10.1007/978-3-642-20054-0
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2011936232

Cover design: Deblik, Berlin

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Current Strategies for Allergen-Specific Immunotherapy at its Centenary

We are celebrating this year the 100 years' anniversary of allergen-specific immunotherapy. In 1911 Leonard Noon published his seminal work "Prophylactic inoculation against hay fever" describing his attempts to achieve active immunity against "grass pollen toxin" by administering increasing doses of grass pollen extract before the grass pollen season to allergic patients. Although it was unknown at that time that allergy represents an immunological hypersensitivity disease, the treatment was effective and many observations made by Noon remained valid until today. Noon noted side effects and that initially increased sensitivity was followed by tolerance which lasted for approximately one year.

Today allergen-specific immunotherapy is well established as the only allergen-specific and disease-modifying treatment for IgE-mediated allergies and has long-lasting effects.

In fact, more than 25% of the population suffer from IgE-mediated allergies which therefore represent a major health burden of our society, particularly because untreated allergy often progresses to severe disabling forms of disease, such as asthma and sometimes kills sensitized people through anaphylaxis.

The pathomechanisms of allergy are meanwhile quite well investigated and the disease-causing allergens are characterized in great detail down to their molecular structures. We are thus beginning to see several new strategies for allergen-specific immunotherapy on the horizon, several of which are summarized in this issue. It thus seems that hundred years after the first experimental attempts to "desensitize" hayfever patients we are now capable of developing powerful and rational forms of immunotherapy which hold promise for curing allergy sufferers and

eventually may allow real prophylactic vaccination against allergy. It is thus quite possible that allergy may become eradicated similar as certain forms of infectious diseases through vaccination.

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Immunological Approaches for Tolerance Induction in Allergy

Melanie L. Conrad, Harald Renz and Kurt Blaser

Abstract Allergy is the consequence of an inappropriate inflammatory immune response generated against harmless environmental antigens. In allergic disorders such as asthma and rhinitis, the Th2 mediated phenotype is a result of loss of peripheral tolerance mechanisms. In cases such as these, approaches such as immunotherapy attempt to treat the underlying cause of allergic disease by restoring tolerance. Immunotherapy initiates many complex mechanisms within the immune system that result in initiation of innate immunity, activation of both cellular and humoral B cell immunity, as well as triggering T regulatory subsets which are major players in the establishment of peripheral tolerance. Though studies clearly demonstrate immunotherapy to be efficacious, research to improve this treatment is ongoing. Investigation of allergenicity versus immunogenicity, native versus modified allergens, and the use of adjuvant and modality of dosing are all current strategies for immunotherapy advancement that will be reviewed in this article.

Abbreviations

APC	Antigen presenting cell
Breg	B regulatory cell
CTLA4	Cytotoxic lymphocyte antigen 4

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Current Topics in Microbiology and Immunology (2011) 352: 1–26
DOI: 10.1007/82_2011_128

Published Online: 20 May 2011

DC	Dendritic cell
FoxP3	Forkhead box protein 3
NLR	NOD-like receptor
PBMC	Peripheral blood mononuclear cells
PRR	Pattern recognition receptor
SCIT	Subcutaneous immotherapy
SLIT	Sublingual immunotherapy
TCR	T cell receptor
Th	T helper
iTreg	Inducible T regulatory cell
TLR	Toll-like receptor
Treg	T regulatory cell
T_R1	Type 1 T regulatory cell
tTreg	Thymus derived t regulatory cell

Contents

1 Introduction

Allergy is based on a complex dysregulation of the immune system whereby harmless environmental antigens trigger an inappropriate immune reaction. Clinically, an allergy can manifest in many different forms including local reactions such as asthma, rhinitis and skin inflammation, as well as systemic reactions to

food, venom or drugs. These allergic phenotypes are complex and depend on many factors including genetic and environmental influences, the specific organs affected and the type and quantity of allergen (Larche 2006). Complicating matters further, exacerbations of current allergy are not only allergen driven but can also be brought about by infection (Tauro et al. 2008), pollutants (Riedl 2008) or non-specific stimuli (Gelardi et al. 2009).

In general, the development of an allergic response requires first that an individual be sensitized, a reaction involving the priming of specific CD4+ T-helper (Th) 2 cells, the production of the cytokine IL-4, isotype switching in B cells to produce IgE antibodies and binding of IgE antibodies to mast cells. After sensitization, secondary exposure to a specific allergen engages IgE coated mast cells which leads to mast cell degranulation and initiation of the allergic immune response. It is during secondary exposure to allergen that the complex clinical phenotype becomes apparent and it is well known that different mechanisms are responsible for the initiation of particular allergic phenotypes. For instance, patients that suffer from allergic asthma and allergic rhinitis exhibit mainly local Th2 type reactions (Pipet et al. 2009), atopic dermatitis patients exhibit an initial Th2 response that is converted to Th1 during the chronification of the disease (Leung and Bieber 2003; Novak et al. 2003; Werfel et al. 1996) and patients with food, drug and venom allergies often react by systemic anaphylaxis (Sicherer and Leung 2009). Due to the complexity of these different allergic responses, this review will concentrate specifically on two Th2 mediated allergic disorders, asthma and rhinitis (hay fever).

2 The Immune Response to Allergens is Regulated by T cells

Many immune mediators play important roles in the development of allergic disease, initiating pathways that cumulate in the differentiation of particular T cell subsets. In both healthy and diseased individuals, these subsets of effector T cells act to coordinate the entire immune system. Classically, Th cells were divided into two major subsets, Th1 and Th2, determined by cytokine profile and effector function. In the last 13 years however, T regulatory (Treg) cells have emerged as very important mediators of immune homeostasis, and are now at the forefront of research efforts. In recent years, still more T cell subtypes have been discovered such as Th17 (Burgler et al. 2009) and Th9 (Dardalhon et al. 2008a) both of which promote tissue inflammation.

The differentiation of naïve T cells to an effector subset is largely dependent on the cytokine milieu. Production of IL-12 and IFNγ by cells of the innate immune system stimulate the production of the transcription factor T-bet, Fig. 1. This results in the differentiation of Th1 cells that principally secrete IFNγ in response to intracellular pathogens. The Th2 cell lineage is generated in the presence of IL-4 due to activation of the transcription factor GATA3, Fig. 1. Th2 cells mainly utilize IL-4, IL-5 and IL-13 to regulate the clearance of extracellular

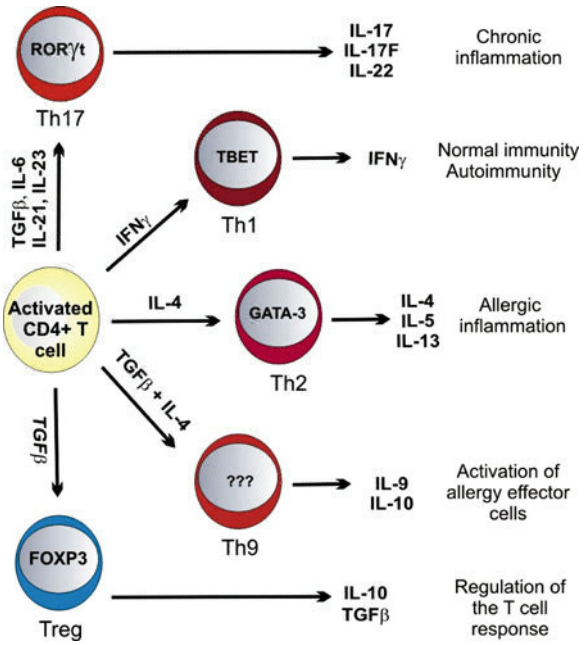

Fig. 1 Differentiation of T effector subsets from an activated CD4+ T cell

pathogens such as parasites. When a Th1 or Th2 response becomes dysregulated it leads to exaggerated inflammatory responses that are the foundation of autoimmunity and allergy, respectively (Dardalhon et al. 2008b).

Relatively new on the scene, Th17 cells are generated in the presence of both IL-6 and TGFβ; these cytokines initiate Th17 cell production by activation of the transcription factor RORγt, shown in Fig. 1. Th17 cells promote neutrophilic inflammation and appear to be responsible for eliminating both intra and extracellular pathogens through the secretion of cytokines IL-6, IL-8, IL-17A, IL-17F, IL-22, IL-26 and TNFα. Similarly to Th1 cells, an overabundance of the TH17 response leads to autoimmune disease and chronic inflammation (Schmidt-Weber et al. 2007). Finally, one of the most recent additions to the T cell subtype family is Th9. During an allergic response, the presence of IL-4 coupled with TGF-β leads to the differentiation of the Th9 cell which produces IL-9 and IL-10. Despite the abundant production of IL-10, Th9 cells do not have regulatory properties and instead act to promote tissue inflammation (Akdis and Akdis 2009; Dardalhon et al. 2008a, b; Veldhoen et al. 2008). While Th1, Th2, Th17 and Th9 subsets all generate inflammatory responses to various mediators, Treg cells act as a safeguard against unnecessary inflammation through immunosuppressive means. It is the complex interplay between these subsets that determines the health status of an individual.

Treg cells are indispensable for the maintenance of immune homeostasis and different subsets of these cells are defined by where they originate and what cytokines they secrete. Thymus derived Treg cells (tTreg, "natural" Treg), which were among the first lineage identified, are produced in the thymus, are

Table 1 Characteristics of T regulatory cell subtypes

	Thymus derived T regs	Induced T regs	
	"Natural"	TR1	Th3
Development			
Region	Thymus	Periphery	Periphery
Precursor	CD4+ precursor	CD4+CD25−	CD4+CD25−
Differentiation factors	?	IL-10, IFNα	TGFβ, IL-4
Markers			
CD4	+	+	+
CD25	+	+	+
CTLA4	+	+	+
FoxP3	+	/	+
Main mode of action	Cell contact suppression	Cytokine secretion	Cytokine secretion
Cytokines secreted			
IL-10	+	+++	+
TGF-β	+	+	+++

+ indicates expression or amount of secretion, /indicates not expressed

CD4+CD25+ and express the transcription factor forkhead box protein 3 (FoxP3), shown in Fig. 1 and Table 1 (Blaser 2008; Feuerer et al. 2009). The importance of this cell type is best exemplified by the Scurfy mouse, in which animals that fail to develop Treg cells acquire a rapidly fatal lymphoproliferative disease (Appleby and Ramsdell 2008; Brunkow et al. 2001; Khattri et al. 2001). Two additional Treg subsets, type 1 regulatory T cells (T_R1) and Th3 cells, have also been identified that can be induced in the periphery by IL-10 and TGFβ exposure, respectively, Table 1. Both tTreg cells and T_R1 cells secrete large amounts of IL-10 and TGFβ, whereas Th3 cells secrete primarily TGFβ (Workman et al. 2009).

Evidence for the regulatory capabilities of Treg cells is demonstrated by functional studies showing the suppression of both autoimmune and allergic responses by this cell type (Ozdemir et al. 2009; Walters et al. 2009). Treg cells have a major influence on both innate and adaptive immune cell types and are capable of suppressing the proliferation and differentiation of T cells as well as limiting the effector functions of B cells, NK and NK T cells, macrophages and dendritic cells (DC), shown in Fig. 2 (Ghiringhelli et al. 2005; Letourneau et al. 2009; Lim et al. 2005; Piccirillo and Shevach 2001). The role of Treg cells in the active suppression of inappropriate or excessive inflammatory responses is known as peripheral tolerance induction.

3 Tolerance

In order for the immune system to function properly there must be systems in place that allow for the discrimination of self versus non-self as well as harmless versus dangerous foreign molecules. There are several sophisticated mechanisms in the

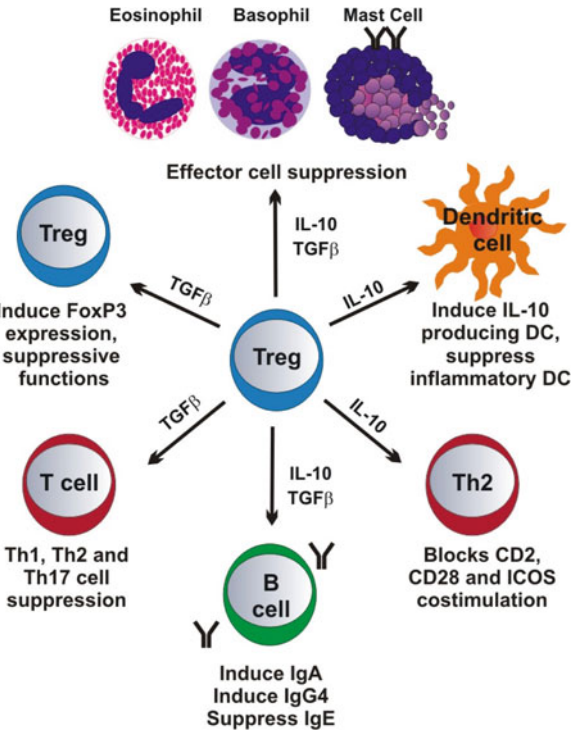

Fig. 2 The effects of Treg generated IL-10 and TGFβ on cells of the immune system

immune system that allow this interplay to occur including clonal deletion, anergy and immunoregulation. Regarding self versus non-self determination, clonal deletion (central tolerance) acts to delete self-reactive lymphocytes during development in the bone marrow and thymus before they mature into competent immune cells (Hogquist et al. 2005; McCaughtry and Hogquist 2008). In the periphery, tolerance mechanisms such as anergy and immunoregulation allow lymphocytes to distinguish between benign and harmful antigens after T cell development (peripheral tolerance). Anergy is a state of unresponsiveness that occurs when lymphocytes recognize an antigen in the absence of a secondary, co-stimulatory signal. Continual recognition of antigen in the absence of co-stimulation eventually results in the elimination of anergic lymphocytes via activation induced cell death (Wells 2009). Immunoregulation is a second system in the maintenance of peripheral tolerance in which Treg cells play an essential role in the control of immune homeostasis. In the context of allergy, dysregulated inflammatory responses are due to a failure of the immunoregulatory mechanisms that suppress reactions to harmless substances in the periphery. Hence, inducing peripheral tolerance to the offending allergen, possibly through the alteration of the Treg response, is the ultimate goal of allergy treatment.

4 Current Treatments for Allergy

Anti-inflammatory therapy and specific immunotherapy are the two present methods used to treat allergy that work in different ways. Anti-inflammatory therapy is an allergen unspecific treatment that involves using medications such as antihistamines, anti-IgE, epinephrine or corticosteroids, alone or in combination, to block the action of allergic mediators or generally suppress the immune system (Bjermer 2008; DuBuske and Kowal 2009; Pelaia et al. 2008). Though the use of medication is presently crucial for the control of allergy, this treatment provides only temporary results. Treatments involving more permanent methods that affect the underlying cause of the allergic disorder are highly desirable.

Immunotherapy differs from anti-inflammatory therapy by attempting to affect the cause of the allergy directly by inducing peripheral immune tolerance to a particular allergen. The earliest attempts to perform immunotherapy for allergy were initiated approximately 100 years ago when, in 1911, Leonard Noon and John Freeman immunized hay fever patients with subcutaneous injections of pollen extract. Though the underlying mechanisms of allergy and immunotherapy would not begin to be discovered for many years and the strategy was erroneously based on the idea that grass pollen was toxic, successful outcomes were seen to last up to one year after cessation of treatment. (Cohen et al. 2003; Noon 1955).

In the present day, allergen specific immunotherapy is recognized as a highly specific and effective method to treat certain types of allergy. Though not generally recommended for food or drug allergies, this therapy is proving particularly effective for patients with allergic rhinitis and allergic asthma (Abramson et al. 2003; Calderon et al. 2007; Pipet et al. 2009). Immunotherapy treatments are beneficial as they target the underlying cause of the disorder with long term results; disease remission is reported to last for 3–5 years after cessation of treatment (Durham 2008). In addition to this, immunotherapy is also extremely important in preventing the progression of allergic disease, for instance from rhinitis to asthma, and stopping the further development of new sensitizations against other allergens (Des Roches et al. 1997; Jacobsen et al. 2007). Though there are many protocol variations, the general treatment method consists of multiple administrations of an allergen vaccine with concentrations that increase in a step-wise manner until the maintenance dose is reached. The maintenance dose is then continued for a minimum of three years (Didier et al. 2007; Srivastava et al. 2009). The most common type of immunotherapy in use today, subcutaneous immunotherapy (SCIT), acts by inducing peripheral tolerance to the allergen vaccine administered.

5 Tolerance Induction

In the process of becoming tolerant, the immune system is modified in many different ways. Innate immune mechanisms are activated which, in turn, trigger the generation of specific T cell subsets. The subsequent cytokine secretion from these

activated T cells has wide ranging effects from reducing proinflammatory cell recruitment and activation, to modulating B cell antibody and cellular responses. Demonstrating this, many types of immune modulation have been documented after successful immunotherapy including direct suppression of antigen presenting cells (APC), induction of Treg subsets, altered IL-10 and TGFβ cytokine levels, suppression of mast cells and basophils and altered allergen specific antibody titres (Akdis et al. 1998, 2007; Francis et al. 2003).

5.1 The T Cell Response and Cytokine Secretion

Of the many T cell effector subsets, Treg cells have been acknowledged as critical players in allergy in both humans and mice. Lessons from mouse models have established the relevance of Treg cells in experimental asthma. Adoptive transfer of Treg cells into cockroach allergen sensitized and challenged mice resulted in improvement of airway reactivity and airway inflammation (McGee and Agrawal 2009). Furthermore, accumulation of Treg cells in the draining lymph nodes of mice is associated with the spontaneous resolution of chronic asthma (Carson et al. 2008). In patients with allergies such as asthma and rhinitis, accumulated evidence also suggests a strong association between allergy and a disruption of Treg cell function. Rhinitis patients have a decreased nasal FoxP3 expression compared with control subjects (Van Bruaene et al. 2008) and Treg cells from allergic subjects have a decreased ability to suppress cytokine responses in vitro (Ling et al. 2004). Dysregulated Treg cell function is associated strongly with allergy in both mouse models and human patients.

Considering immunotherapy, the induction of Treg cells is essential for the generation of immune tolerance. In adult patients who received successful immunotherapy, the frequency of FoxP3 Treg cells was increased in the nasal mucosa following SCIT with grass pollen allergen (Radulovic et al. 2008) and in PBMCs following sublingual immunotherapy (SLIT) with birch pollen allergen (Bohle et al. 2007). Upregulated Treg responses were also correlated with an increase in IL-10 expression. Interestingly, a recent pediatric study measuring the outcome of SLIT for patients treated with tree pollen allergens found correlations between FoxP3 mRNA expression and tolerance induction as well as IL-17 mRNA expression and poor therapeutic outcome (Nieminen et al. 2009). The fact that particular T cell subtypes can be associated with therapeutic outcome highlights the importance of ascertaining the mechanisms that generate T cell subtypes in successful immunotherapy.

Treg cells contribute to tolerance induction in immunotherapy both by cell–cell interactions and cytokine secretion. Concentrating for the moment on direct cellular interactions, cell contact suppression by Tregs is mediated by the constitutive expression of the cytotoxic lymphocyte antigen 4 (CTLA4). CTLA4 is a powerful suppressor of the immune response as evidenced by the lethal multi-organ inflammation observed CTLA4 knockout mice (Waterhouse et al. 1995). In the induction of peripheral tolerance, CTLA4 on allergen-activated Treg cells