

The Pathologic and Clinical Intersection of Atopic and Autoimmune Disease

Ankoor Shah

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Abstract Hypersensitivity reactions of the immune system have been broadly categorized into the atopic and autoimmune depending on whether the antigen triggering the reaction is endogenous (or self) or exogenous, the types of cellular and humoral components involved, and the clinical symptoms. Research into the pathophysiology of the resultant disease states has focused on a dichotomy between Th1 and Th2 T helper lymphocytes thought to govern autoimmune and atopic disease, respectively. Recent discoveries, however, have served to dispute this paradigm and have provided additional insight into the roles of Th17 cells, B-lymphocytes and T regulatory cells as well as the considerable communication and commonalities between the complex signaling pathways. Furthermore, clinical studies have served to challenge the idea that the presence of atopy and autoimmunity are mutually exclusive states. Finally, application of recent approaches to treatment—biologic targeted therapy in autoimmunity and induction of immune tolerance in atopic disease—to both disease states have shown mixed but promising results.

Keywords Atopy · Atopic disease · Autoimmunity · Autoimmune disease · Th1 · Th2 · Th17 · T regulatory cells · B regulatory cells · Thymic stromal lymphopoietin · IgE autoantibodies · Mast cells · Immunotherapy · Omalizumab

Introduction

While atopic (or allergic) disease and autoimmune disease are both thought of as immune-mediated processes, the co-

existence of both types of disorders in one individual has often been considered a rare event. It has been postulated that pathologic mechanisms governing these diseases tightly regulate each other in a delicate homeostatic balance, rendering overactivity of either process mutually exclusive. In this review, we will examine the intersection of autoimmunity and atopy, comparing and contrasting the pathophysiologic disease mechanisms, summarize the epidemiologic investigations into their coexistence, and discuss what implications increased understanding of the immunologic interplay may have on treatment.

Definition of Hypersensitivity, Atopy and Autoimmunity

How can one visualize the intersection of atopy and autoimmunity? The idea that both may fall under the umbrella of immune hypersensitivity is generally acceptable, but given this, are atopy and autoimmunity two completely separate pathologic and clinical entities? Perhaps there is a fundamental connection between the two, but if so, to what degree? Could it be possible that atopy is simply a form of autoimmunity, or vice-versa? Before delving into the literature that addresses these questions, it is critical to define the terms hypersensitivity, autoimmunity, and atopy.

For over 40 years, immunologists have used the Gell and Coombs schema to classify types of deleterious actions of the immune system into 4 distinct hypersensitivity categories (Table 1). The concept of allergy was first proposed by von Pirquet in 1906, while atopy was first described in 1923 with the observation of immediate hive formation with common allergens ascribed to heat-labile bodies called regains [1]. Further definitions were then proposed incorporating IgE antibodies (typically to an exogenous antigen) and clinical findings by Pepys in 1973 and Rocken in 1998 (see Table 2). Allergic reactions typically fall under a type 1 hypersensitivity

A. Shah (✉)
Duke University, Division of Rheumatology and Immunology,
Box 3874, Durham, NC 27710, USA
e-mail: ankoor.shah@duke.edu

Table 1 Gell and Coombs classification

Type	Name	Examples	Mediators
I	Allergy	Atopy Anaphylaxis	IgE, IgG4
II	Cytotoxic, antibody dependent	AIHA Goodpasture's	IgG, IgM Complement
III	Immune complex disease	Serum sickness Arthus reaction SLE RA	IgG
IV	Delayed type hypersensitivity	Contact dermatitis Chronic rejection PPD	T-cells (antibody independent)
	Cell mediated		

reaction. While allergic rhinitis and many allergic reactions fulfill these criteria, there are multiple examples of atopic diseases (such as some food and drug reactions as well as chronic atopic dermatitis and asthma) where there are no identifiable objective in vitro tests.

In terms of autoimmunity, Paul Ehrlich first described elements of the immune system that prevents an organism acting against itself and developing autotoxins, coining the term “horror autotoxicus” [2]. The concept of autoimmunity, however, took several decades to gain acceptance as evidenced by the fact that experimental autoimmune encephalomyelitis (the prevailing mouse model for multiple sclerosis) was originally coined autoimmune allergic encephalomyelitis [2]. A formal list of criteria, incorporating the need for an identifiable endogenous autoantigen, was then devised by Witebsky in a paper describing autoimmune thyroiditis [3•], later modified by Rose in 1993 (Table 3). As in atopic diseases, there are numerous conditions that behave as autoimmune disease, with no obvious autoantigen/autoantibody. Thus, these definitions have served as

guidance for categorization of diseases, but there is still no complete consensus as to what is atopic and what is autoimmune.

Common Underlying Mechanisms

The clinical definition of disease for autoimmunity and atopy has been complimented by a pathophysiologic one that helps elucidate the mechanism for immune system activation and tissue inflammation. In the 1980s the model of a balance between subsets of the CD4+ T helper cells—Th1 and Th2—rose to prominence. Both were defined primarily by the dominant cytokine profile. Th1 responses are controlled by antigen-presenting cells releasing Il-12 and Il-18 in response to intracellular pathogens or after stimulation of certain Toll-like receptor (TLR) pathways in turn activating the transcription factors T box expressed in T cells (Tbet), STAT1, and STAT4, ultimately leading to release of interferon gamma (IFN- γ), transforming growth factor (TGF)- β , tumor necrosis factor (TNF)- α , and other cytokines. Th2 responses, on the other hand, flourish in the absence of Il-18 and in the presence of Il-4. The transcription factor GATA3 is expressed and promotes further expression of Il-4, Il-5, and Il-10, and B cell-mediated humoral immunity. GATA3 activation also serves to repress IFN- γ secretion [4•].

Autoreactive Th1 cells are thought to play a crucial role in autoimmune disease such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune (or type 1) diabetes mellitus (T1DM), multiple sclerosis (MS) and autoimmune thyroid disease. TNF- α plays a crucial role in inflammation and disease progression in rheumatoid arthritis, and Th1 cell expansion (identified by the cell surface marker CD161 and production of IFN- γ) are found to be abundant in the synovium of the joints [5]. Th2 cells, on the other hand, classically drive the atopic response, including atopic dermatitis (AD), seasonal allergic rhinitis (AR), food and drug allergy and anaphylaxis. Elevated levels of Il-4, Il-

Table 2 Definitions of allergy/atopy

Pepys (1973)	Röcken et al (1998) [97]
Form of immunological reactivity of the subject in which reaginic antibody is readily produced in response to ordinary exposure to common allergens	- BOTH clinical symptoms of atopic disease (bronchial asthma, allergic rhinitis, atopic dermatitis) AND - at least two positive in vivo/in vitro parameters characteristic of atopy - increased serum levels of total IgE; - positive RAST to more than one environmental protein allergen; - positive skin prick test to more than one environmental protein allergen)

Table 3 Definitions of autoimmunity

Witebsky's postulates (1957) [3••]	Rose Modifications (1993)
1. The direct demonstration of free circulating antibodies OR of cell bound antibodies that are active at body temperature	1. Direct evidence from transfer of pathogenic antibody or pathogenic T cells
2. The recognition of the specific antigen against which this antibody is directed	2. Indirect evidence based on reproduction of the autoimmune disease in experimental animals
3. The production of antibodies against the same antigen in experimental animals	3. Circumstantial evidence from clinical clues
4. The appearance of pathological changes in the corresponding tissues of an actively sensitized experimental animal that are basically similar to those in human disease	

5 and IL-13 have routinely been discovered in the nasal mucosa of patients with allergic rhinitis [6] the bronchial epithelium of patients with asthma [7] and in skin lesions of patients with atopic dermatitis [8]. Furthermore these cytokines drive the production of allergen-specific IgE antibodies—a hallmark of atopic disease [9].

In addition to providing insight into the relevant cellular and humoral components involved in normal immune function and hypersensitivity responses, a paradigm emerged where diseases skewed towards a Th1-related process (such as autoimmune disease) inhibited Th2 cells and cytokines protecting a patient from atopic disease and vice versa. Many studies have served to support this notion. Recently, mouse models of lupus with active disease were found to have less severe AR compared to mice with inactive disease, a finding that correlated with an increase in splenic cell production of IFN- γ and decreased production of IL-4, suggesting counter-regulation [10••]. Conversely, helminth infection, which drives a Th2 response, has been demonstrated to downregulate Th1 pathways protecting from development of autoimmune disease [11, 12]. Although the concept of a balance between Th1 and Th2 is a useful framework for describing pathology and guiding treatment discovery, in more recent years, this paradigm is an incomplete model as Th1 responses have clearly been described in atopic disease and Th2 responses in autoimmunity.

Several atopic conditions refractory to treatment have been found to represent a Th1 or self-reactive environment as opposed to Th2-polarized. Groups of AD patients, defined by typical pruritic and morphological findings, have been demonstrated to have low IgE levels and significantly increased levels of IFN- γ with no differences between expression of IL-4 and IL-5 (although all higher than controls) [13]. This form of AD has been described as “intrinsic” as there is no increased prevalence of atopic disease nor evidence for sensitization to environmental or food allergens by skin or blood testing [14]. In several ways, the concept of intrinsic AD fulfills the definition of an autoimmune condition as well as it does an atopic disease. Additionally, it has been demonstrated that several human proteins cross-react with environmental allergen-specific IgE antibodies, particularly in

patients with a chronic intrinsic AD [2, 15]. For example, T cell lines from patients with AD and sensitized to the fungal protein Malassezia s 13 (from the fungus *Malassezia sympodialis*) cross-reacted to the homologous human thioredoxin protein. These T cells expressed both Th1 and Th2 phenotypes [16]. Finally, IgE antibodies have been demonstrated against the human protein α -nascent polypeptide-associated complex (α -NAC), with T cell clones from these patients predominantly producing IFN- γ in response to α -NAC stimulation [17]. IgE and IgG2 antibodies to both self and foreign α -NAC had previously been described in mouse models of asthma sensitized to only foreign α -NAC [18]. These findings provide further evidence against the mutual exclusivity of Th1/autoimmune and Th2/atopic responses.

In further contrast to the idea that diseases are driven purely by either Th1 or Th2 T cells, there is evidence for the importance of Th2 cells in autoimmune diseases. RA is a prototypical Th1-skewed disease with significant disease pathogenesis correlated with increases in Th1 cytokines, most notably TNF- α . While no studies have demonstrated Th2 dominance, RA synovial fibroblasts and peripheral blood T cell clones have been shown to express elevated IL-4 in early RA patients, decreasing with treatment or with long-standing disease [19]. It is not clear, however, if this finding represents either a true role for Th2 cytokines in early disease progression, or a counter-regulatory process of IL-4 in a disease imbalanced towards Th1 cytokine production.

Because a mutually exclusive inverse balance between Th1 and Th2 processes clearly does not explain the nuances of autoimmunity and allergy, other pathophysiologic pathways have been explored. A third type of T-effector cell, the Th17 cell, has received particular attention for its role in promoting inflammation. Th17 cells are defined by production of IL-17 and their differentiation is supported by IL-6, IL-21, and IL-23 [20]. Th17 cells were initially described in multiple sclerosis, when, in EAE mice, IL-23 (which preserves the function of IL-17-producing cells) was the main contributing cytokine leading to CNS inflammation [21, 22]. In rheumatoid arthritis, high levels of IL-23 and IL-17 are observed particularly in early disease, and promote

synovocyte proliferation and cartilage degradation [23]. Pathogenic roles for Th17 cells exist in other classic autoimmune disease such as type 1 diabetes [24], psoriasis [25], and lupus [26]. While the bulk of evidence regarding the role of Th17 cells has focused on autoimmune diseases, there is evidence for a presence in atopic disease. Significant upregulation of IL-17 has been demonstrated in patients with allergic nasal polyposis [27] and in the skin of patients with atopic dermatitis, with increased Th17 cells (both circulating and skin-residing) correlating with disease severity [28•]. IL-17 can also downregulate the expression of filaggrin mRNA, a gene critical for the maintenance of a functional epidermal barrier, that can be mutated in patients with atopic dermatitis [29]. Interestingly, filaggrin-deficient mice can have eczematous skin inflammation predominated by Th17 cells [30]. Similarly, in mouse models of allergic asthma, IL-17A can directly enhance airway smooth muscle contraction, whereas Th17-deficient mice were protected from bronchoprovocation with house dust mite sensitization [31]. Finally, patients with autosomal dominant Hyper-IgE syndrome, marked by chronic sino-pulmonary and skin infections, elevated IgE levels and eczematous skin inflammation, are noted to have significantly reduced Th17 cells [32]. Unsurprisingly, IL-17A has been shown to promote B cell class switching to produce IgE antibodies [33, 34].

The observation that healthy people have autoreactive T cells and autoantibodies indicates the presence of tolerance mechanisms to maintain homeostasis, key to the prevention of autoimmune and atopic disease. The discovery of CD4⁺CD25⁺FoxP3⁺ T cells, also known as T regulatory cells (Tregs), has initiated a wave of interest in their role of maintaining the balance between normal immune function and hypersensitivity. Absence of Tregs can lead to significant autoimmunity in animal models as well as in humans as evidenced by the eczematous dermatitis and autoimmune manifestations in a patients with immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), a disease marked by the lack of FoxP3 [35]. These patients also have abundant production of Th1, Th2, Th17 cytokine and IgE compared to healthy controls. A recent study attempted to elucidate their respective roles in autoimmunity, finding that, in mice with a deficiency of inducible Tregs (which develop in the periphery as opposed to the thymus), IFN- γ and IL-17 production were unaffected; however, Th2 cells were increased with marked elevation of IL-4, IL-5 and IL-13 in mesenteric lymph nodes and allergic inflammation of the intestine and airways [36]. These results imply that natural Tregs developed in the thymus may play a larger role in control of the Th1 response and autoimmunity. Conversely, the opposite was concluded in a study transferring both natural and inducible Tregs into mice with collagen-induced arthritis, finding that only the inducible Tregs were able to shift lymph node T cell predominance from Th17 to Tregs

[37]. These conflicting findings may certainly result from different mouse model systems, but also serve to highlight the complexity of the cross-talk between Th1, Th2, Th17 and Treg cells as well as the potential difficulty in translating mouse findings to human disease.

B-lymphocytes play a critical role in both atopic and autoimmune processes. They can act as antigen-presenting cells, driving the initial stages of the immune response and activate effector T cells. They also differentiate into immunoglobulin-producing plasma cells, able to produce both specific autoantibodies (typically of the IgG or IgM isotype) as well as allergen-specific IgE antibodies relevant to many atopic diseases. The presence of IgE antibodies, however, is not exclusive to atopic disease in spite of the classic definition. Specific IgE antibodies have been observed in autoimmunity: anti-cyclic citrullinated peptides in RA [38], anti-GAD65 antibodies in type 1 diabetes [39], anti-TSH receptor antibodies in Grave's disease [40], and anti-myelin peptides in multiple sclerosis [41], although the direct pathogenic role is largely unknown.

The term "intrinsic" asthma has been used to describe asthma without identifiable exogenous allergens [42]. Numerous studies have demonstrated the presence of autoantibodies in intrinsic asthma; however, their direct contribution to disease pathogenesis is generally unknown [43•]. Recently, autoantibodies, predominantly of the IgG isotype, directed specifically against the collagen V (ColV), have been described. The level of these autoantibodies correlates with disease activity as well as with inhaled corticosteroid dosage [43•]. ColV is an extracellular matrix protein in the bronchial basement membrane and may be thickened in asthmatics [44], providing some evidence for a specific role in causing this form of asthma.

The identification of IL-10-producing B regulatory (Breg) cells has also emerged as an important mechanism for control of inflammation. IL-10-deficient mouse models have significantly exacerbated antigen- and collagen-induced arthritis, autoimmune encephalitis, and inflammatory colitis [45–48]. More recent evidence has demonstrated that Bregs may exert control by promoting development of Tregs and suppression of both Th1 and Th17 cells [49, 50]. Despite the fact that IL-10 is considered a pro-Th2 cytokine, Bregs have also been shown to be important regulatory cells in models of allergic asthma [51], as well as of dermatitis secondary to non-IgE-mediated food allergy [52], although in the latter study it did appear that the Bregs predominantly produced TGF- β which may reflect the existence the multiple subtypes of Bregs. A recent study has identified a population of CD11b⁺B cells in healthy volunteers that produce IL-10 and suppress T cell activation [53]. These cells were selected based on the presence of the cell surface markers CD19 and CD20, which does raise the interesting question of the potential effect of B cell depleting therapy (such as rituximab) may have on Bregs.

Thymic stromal lymphopoietin (TSLP) is cytokine produced by epithelial cells, dendritic cells, and mast cells that has garnered interest as a master switch in promoting both allergic and, to a lesser extent, autoimmune inflammation, and may act as pathophysiologic link between the two sets of diseases [54]. TSLP is involved in stimulating the Th2 cytokine response and the expansion of CD4⁺ Th2 memory cells, particularly through Il-4 upregulation, ultimately leading to allergic inflammation [19, 55, 56]. Keratinocyte-induced TSLP activity has been demonstrated to be elevated in lesional skin from patients with atopic dermatitis [57] as well as in nasal polyps. Additionally, induction of skin TSLP in mice sensitized with house dust mite (HDM) had increased pulmonary inflammation as well as HDM-specific IgE and IgG1 [58]. Interestingly, in this experiment, levels of Il-17 (but not IFN- γ) were also increased, implying the role of a Th17 autoimmune response. Additionally recent observation that TSLP-deficient mice had decreased severity of experimental autoimmune arthritis while administration worsened joint inflammation, with significant increases in Il-17 and decreases in Il-10 and Il-13 [59•]. To add further complexity to this relationship is the demonstration that IL-17A and IL-17 F can specifically and significantly inhibit TSLP production in human skin explants as well as TSLP-mediated Th2 differentiation, suggesting that a major player in autoimmune inflammation has significant negative feedback and potentially inhibits Th2 allergic inflammation [60].

As evidenced above, the bulk of the literature regarding the pathologic players of autoimmune and atopic diseases have focused on the adaptive immune system. However, the innate immune system also plays a critical role in sustaining the immune response through antigen presentation or the production of cytokines and other inflammatory mediators. The mast cell, a key member of the innate immune system, has long been implicated in atopic disease. Activation leads to release of histamine, prostaglandins, leukotrienes, and other mediators of allergic inflammation in response to cross-linking of IgE receptors or by activated complement protein [61]. For example, bronchial epithelial mast cells have recently been demonstrated to release Th2 cytokines in response to Il-4 or double-stranded RNA (which can be produced by respiratory viral infections), a process dependent on TSLP [62].

Evidence has also been accumulating for a significant role of mast cells in autoimmunity. Increased mast cell numbers and elevated tryptase have, respectively, been identified in the central nervous system plaques and cerebrospinal fluid of patients with multiple sclerosis [63]. In addition, mast cell-deficient EAE models demonstrate significantly reduced disease severity [64], although their overall contribution to disease pathogenesis is still controversial [65]. In RA, mast cells are found in increased numbers in the synovium. They release histamine as well tryptase, a mast cell-

specific protease, leading to downstream production of TNF- α and Il-1 β and cartilage degradation [65]. In fact, mast cells have been found to be the major source of Il-17 in the synovium and synovial fluid [66•], with speculation that IgE anti-cyclic citrullinated antibodies cross-link IgE receptors on mast cells [67]. While IgE binding has been the predominantly studied mechanism for mast cell activation, particularly in allergic disease, IgG autoantibodies commonly found in autoimmune disease may also play a significant role. In mast cell-deficient EAE mouse models, reconstitution with IgG receptor (Fc γ R)-negative mast cells, reduced disease activity was observed [68], implying a role for IgG binding to mast cells in disease pathogenesis. Interestingly, a recent study demonstrated that Tregs can enhance mast cell production of Il-6 via TGF- β , which ultimately promotes a Th17 response [69]. This finding may lend support to the concept that shifting the T cell balance away from Th2 dominance can abrogate mast cell-dependent allergic reactions. Finally, IgG-Fc γ R activation on mast cells (as well as neutrophils) leads to degranulation and anaphylaxis, a process regulated by Lyn and Fyn kinases [70–72], which are critical to IgE-mediated mast cell activation. This pathway potentially represents a pathological intersection of the signaling system between autoimmune and atopic antibody-mediated disease.

Epidemiologic Studies

What is the evidence that classically defined autoimmune and atopic disease can coexist in the same patient? The prevailing thought, likely driven by the Th1/Th2 balance paradigm, was that there was also an inverse relationship between the incidence of autoimmune and atopic disease. One of the largest studies to date used the Third National Health and Nutrition Examination Survey (NHANES) database of 20,050 participants and found no statistically significant differences in history of autoimmune and atopic disease. In fact, they found that a history of autoimmune disease was associated with an increased risk of comorbid atopic disease, a relationship that was more significant with increased age and female gender [73•]. When looking at specific diseases such as RA, the data are mixed. O'Driscoll found no difference in atopic disease prevalence (defined by history or by positive skin prick test) in 40 patients with RA [74]. Others, on the other hand, found a significantly lower prevalence of allergic rhinitis in patients with RA compared to those without, also noting that those with comorbid disease had lower RA disease activity and decreased IFN- γ release from peripheral blood mononuclear cells [75, 76]. Similarly, a relatively large study of multiple sclerosis patients found that they were significantly less likely to have allergic rhinitis or respiratory disease compared to controls

[77]. Biases due to disease definition and patient recall strengthen the necessity for larger, prospective studies to fully address the clinical relationship between atopic and autoimmune disease.

Urticaria represents a unique intersection between atopy and autoimmunity. Acute urticaria manifests in the setting of type 1 hypersensitivity reactions such as food or drug allergy, and the pathophysiology is generally thought to be the result of IgE receptor cross-linking on mast cells and basophils leading to histamine and other inflammatory mediator release. Chronic idiopathic urticarial (CIU), which is defined as the presence of urticaria without an obvious trigger, is associated with IgG2 antibodies directed against the IgE receptor. A study of over 12,000 patients with CIU found that they were 17.3 times as likely to have rheumatoid arthritis, 16.3 times as likely to have SLE, and 17 times as likely to have Type 1 diabetes compared to healthy controls [78]. These findings support a Th1 environment in the pathogenesis of CIU. Furthermore, the presence of other atopic diseases is not increased in patients with CIU.

Two recent case reports have highlighted the fact in autoimmune disease may co-exist and in fact exacerbate atopic disease and vice versa. The first described 4 patients with comorbid Sjogrens syndrome (SS) and atopic dermatitis, finding that the abnormal sudomotor axon reflex (due to small fiber neuropathy associated with SS) accelerates the dryness of skin in atopic dermatitis, significantly contributing to pruritis and disease progression [79]. The second report described a patient with disseminated discoid lupus erythematosus (DLE) and comorbid atopic dermatitis. Here, the authors found decreased Treg and increased Th17 cells in skin lesions and related the triggering of the DLE from scratching due to the underlying hypohydrosis and xerosis stemming from atopic dermatitis [80].

Application to Treatment

Targeted treatment against products of the Th1 pathway, most notably TNF- α , have ushered in a new era of successful treatment of autoimmune diseases such as RA, psoriatic arthritis, and IBD. Significant decreases in peripheral blood mononuclear cell production of IFN- γ and IL-17-producing cells, coinciding with increased Tregs and a trend towards increased IL-4-producing cells have been observed in patients treated with 12 weeks of a TNF- α inhibitor [81]. Interestingly, one small study of treatment with TNF- α inhibitors in RA demonstrated a significantly higher rate of positive skin prick tests to specific allergens compared to RA patients not treated with TNF- α inhibitors and healthy controls [82]. Despite no apparent increase in allergic symptoms, these findings may give credence to a model of skewing towards a Th2 response with inhibition of Th1

cytokines. Despite its categorization as a classic Th1 cytokine, TNF- α has been shown to play some role in the pathogenesis of allergic rhinitis [83], and recently infliximab has been demonstrated to decrease nasal eosinophilic infiltration, specific IgE production, and IL-4 levels in mice sensitized to ovalbumin [84]. Results in use with atopic dermatitis have been mixed, with some reports of TNF- α inhibitor use promoting or exacerbating eczematous skin disease [85].

There is limited evidence supporting use of other successful targeted autoimmune disease therapy in atopic disease. The CD28/CD80 co-stimulatory signal (targeted by the biologic agent abatacept) activates effector T cells and has been shown to be important in the development of the autoimmune response. Inhibition in mice was unable to suppress IgE responses in mice sensitized with grass pollen, although basophil response to allergen as well as total immunoglobulin response was downregulated if co-stimulator blockade was given prior to sensitization [86]. Similarly, use of the anti-IL-6 biologic agent tocilizumab, approved for RA, did lead to over 50 % improvement in atopic dermatitis symptoms, but was complicated by staphylococcal skin infections in 2 out of 3 patients treated [87].

Agents targeting specific Th2 cytokines have had mixed but often disappointing results [88–90]. However, omalizumab, a monoclonal antibody directed against IgE, has proven to be very effective in the treatment of atopic asthma, and ongoing studies are being performed to clarify its role in the treatment of atopic dermatitis, allergic rhinitis and food allergy [91–93]. Despite the fact that IgE antibodies have been shown to be present in a number of autoimmune diseases, the use of anti-IgE therapy is limited, although there is abundant evidence for improvement in refractory chronic idiopathic urticaria [94].

While effective targeted biologic therapy is lacking for atopy, the holy grail of hypersensitivity treatment—developing immune tolerance—has been utilized to great effect in allergic diseases. Since its introduction in 1911, allergen and venom immunotherapy (IT) has grown into the mainstay of treatment of severe allergic rhinitis and insect venom hypersensitivity. Currently, patients undergo administration of increasing concentrations of allergens in a build-up phase until they reach a maintenance dosage. After 3–5 years of maintenance therapy, many patients can discontinue IT with minimal symptoms, indicating true immune tolerance. Interestingly, multiple studies have found response to IT is dependent on IL-10 production and a shift towards Tregs cells, although one recent study of house dust mite IT found lower basal FoxP3 level expression than untreated patients. This result may perhaps represent a tolerant steady-state. Additionally, IL-10 expression was not measured [95]. Unfortunately, IT using autoantigens has been less successful. The most promising results have involved coupling a self protein (for example, GAD65 in autoimmune diabetes), or

even a cytokine such as TNF- α , to a foreign protein to activate auto-reactive B cells [96]. One of the many challenges facing IT in autoimmunity is the need for the antigen used to account for antigen modification as it needs match the naturally processed antigen as bound to the MHC molecule.

Conclusions

Autoimmune and allergic diseases share fundamentally important features and the distinction between them is continually blurred. At their broadest definition, they both result from hypersensitivity to ostensibly harmless antigens; in autoimmunity, antigens tend to be endogenous whereas with atopy they are typically exogenous, although exceptions to this rule are observed. The pathophysiologic mechanisms that govern these processes, previously thought to be tightly controlled between two subsets of T cell responses, have far more complex regulatory mechanisms. While there is some convincing data that Th1 and Th2 pathways regulate each other, Th17, Tregs, mast cells, and B cells, as well as the specific antibodies (and autoantibodies) they produce, play a significant role in both autoimmune and atopic disease. Furthermore, epidemiologic studies have yet to clarify the coexistence of atopic and autoimmune disease on a population level, but there is certainly proof against exclusivity of disease, and, in examples such as intrinsic asthma and AD, chronic urticaria and others, there is obvious overlap. Finally, therapeutic strategies have diverged in that treatment of allergic disease has focused on immune tolerance and symptomatic relief with medications such as antihistamines, targeting the products of mast cells, whereas in autoimmune disease, treatment has successfully focused on targeting specific cytokines and cell signaling pathways to alleviate disease manifestations. There is obviously much to be learned from each field, and future approaches to treatment will continue on targeting specific cytokine and signaling pathways in the allergic diseases, and hopefully determining methods of inducing tolerance to autoantigens in autoimmune disease.

Disclosure No potential conflicts of interest relevant to this article were reported.

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