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Genetic evidence for the role of transforming growth factor-β in atopic phenotypes

Katherine A Weissler and Pamela A Frischmeyer-Guerrerio

New evidence in humans and mice supports a role for transforming growth factor-β (TGF-β) in the initiation and effector phases of allergic disease, as well as in consequent tissue dysfunction. This pleiotropic cytokine can affect T cell activation and differentiation and B cell immunoglobulin class switching following initial encounter with an allergen. TGF-β can also act on mast cells during an acute allergic episode to modulate the strength of the response, in addition to driving tissue remodeling following damage caused by an allergic attack. Accordingly, genetic disorders leading to altered TGF-β signaling can result in increased rates of allergic disease.

Address
Laboratory of Allergic Diseases, National Institutes of Allergy and Infectious Diseases, Bethesda, MD, USA

Corresponding author: Frischmeyer-Guerrerio, Pamela A (Pamela A)

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Introduction

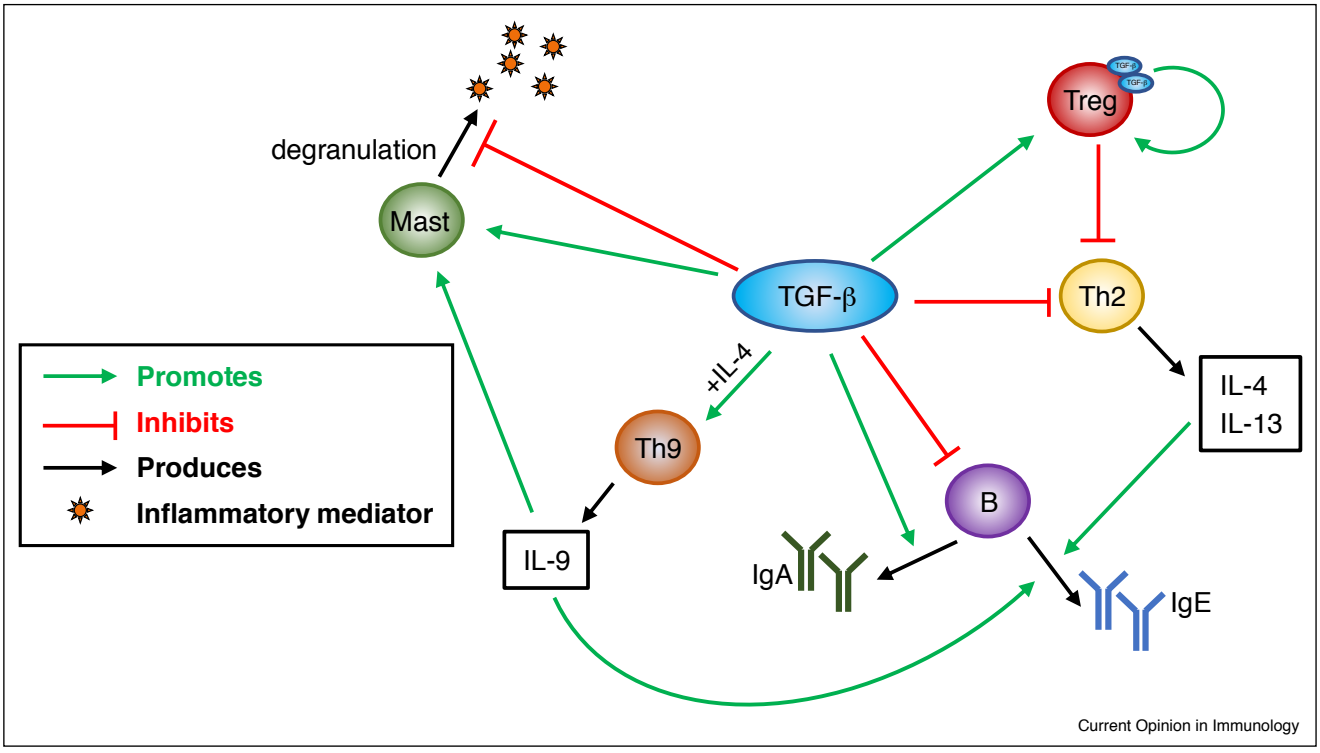
The transforming growth factor-β (TGF-β) family is a group of pleiotropic cytokines that have a variety of effects on a wide range of hematopoietic and non-hematopoietic cell types. Three known isoforms exist (TGF-β1, TGF-β2, and TGF-β3), although TGF-β1 is the predominant form involved in immune system homeostasis and activity and will be the focus of this review. TGF-β1 normally exists in an inactive form, in which association with latency associated peptide (LAP) prevents TGF-β1 from binding to its receptor. Removal of LAP allows TGF-β1 to bind to the heterotetrameric TGF-β receptor, which consists of TGF-β receptors I and II (TGF-βRI, TGF-βRII), and leads to phosphorylation and subsequent nuclear translocation of Smad proteins 2 and 3 where they modulate gene expression in conjunction with other transcriptional activators and repressors. TGF-β receptor signaling can also activate a variety of other 'noncanonical' signaling pathways (reviewed in Ref. [1]). Genetic association studies and observations of patients with single gene disorders have revealed a role for TGF-β in the pathogenesis of allergic disease. This review will discuss these studies and seek to understand possible mechanisms through which altered TGF-β signaling may impact the initiation and acute phase of an allergic reaction, as well as the ongoing tissue repair response (Figure 1).

Alterations in TGF-β signaling lead to atopy

A growing body of evidence suggests that alterations in TGF-β signaling can drive the development of allergic disease, in which immunoglobulin E (IgE) specific for usually innocuous substances is produced; IgE binds to the surface of mast cells, and crosslinking of IgE via allergen binding causes mast cell degranulation and allergic symptoms. Early indication of a role for TGF-β in atopy came from a study of 20 families with an asthmatic proband and 10 non-asthmatic families that revealed a polymorphism in the promoter of *TGFB1* (C to T at −509) that was present in homozygous form in 16 subjects and significantly associated with increased total IgE in a cohort of 47 unrelated individuals [2]. Subsequent studies involving larger cohorts found that the C to T polymorphism at −509 of *TGFB1* strongly correlated with an increased concentration of TGF-β1 in blood plasma [3,4], and was associated with the development of asthma [4–7]. Association with increased serum IgE was confirmed in some [4] but not all studies [5]. The C-509 polymorphism in TGF-β1 may also be a disease-modifying allele in patients with eosinophilic esophagitis (EoE), a condition characterized by excessive accumulation of eosinophils in the esophagus. EoE subjects with the TT genotype had higher numbers of TGF-β+ and tryptase+ cells in the esophagus, which was significantly increased in subjects with concurrent sensitization to food allergens [8,9]. These subjects were also less likely to respond to treatment with steroids [8]. A separate polymorphism in the *TGFB1* gene (915 G to C) was found to result in decreased TGF-β1 production by peripheral blood leukocytes, and was strongly associated with atopic dermatitis [10,11]. Studies in mice found that introduction of TGF-β-producing cell types reduced airway hyperreactivity (AHR) [12] as well as Th2 type cytokines in the lungs and IgE production [13] in two different asthma models.

More definitive proof that TGF-β plays an important role in the establishment of allergic disease came from a study

Figure 1



Summary of the cellular mechanisms by which TGF-β may both promote and inhibit allergic outcomes.
T regulatory cell = Treg; Mast cell = Mast; B cell = B; T helper 2 cell = Th2; T helper 9 cell = Th9.

of individuals with Loeys–Dietz syndrome (LDS), an autosomal dominant hypermobility disorder caused by mutations in the TGF-β receptor signaling pathway. The prevalence of food allergy, asthma, allergic rhinitis, and eczema were increased in a cohort of individuals with LDS relative to the general population [14]. Furthermore, levels of IgE and the allergy-associated type 2 cytokines IL-5 and IL-13 were all significantly higher in the group with LDS than in the control group. The majority of LDS-causing mutations occur in the kinase domains of *TGFBR1* and *TGFBR2* and are inactivating when transfected into HEK293 cells. However, levels of phosphorylated SMAD2/3, a direct target of TGF-β receptor kinase activity, are increased in several tissues from LDS patients including the aorta, bone, and thymus, suggesting that these mutations may result in paradoxically increased canonical TGF-β signaling in certain environments. Thus, it remains somewhat unclear whether the increased allergic phenotype is driven by decreased TGF-β signaling at the receptor level or by increased TGF-β signaling at the cellular level, or indeed if both possibilities contribute. Monogenic diseases caused by loss-of-function mutations in *STAT3* and *ERBB2IP* (the gene encoding ERBIN) also result in elevated serum IgE and increased rates of EoE [15,16]. STAT3 signaling induces ERBIN protein expression, and ERBIN then complexes with SMAD2/3 to prevent its nuclear localization and limit the transcriptional response to TGF-β signaling; PBMCs isolated from patients with *STAT3* or *ERBB2IP* mutations thus displayed increased nuclear SMAD2/3 when stimulated with TGF-β1. These studies underscore that a link exists between TGF-β and atopic disease with too much or too little TGF-β receptor signaling resulting in increased atopy in different contexts.

TGF-β contributes to regulatory T cell induction and function

Regulatory T cells (Tregs) are crucial in preventing unwanted immune activation in response to innocuous antigens. Mutations in *FOXP3*, the gene encoding the transcription factor necessary for Treg differentiation [17,18], cause immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, a fatal disorder characterized by widespread immune dysregulation and autoimmunity [18,19]. Some variations of IPEX present with severe allergic inflammation including atopic dermatitis, food allergy, elevated IgE levels, and peripheral eosinophilia [20,21], similar to what was observed in *Foxp3* mutant mice [22]. Furthermore, infants that went on to have a diagnosed food allergy at one year of age had lower percentages of Tregs at birth, and the *FOXP3* locus of these cells was less highly demethylated, indicating that they may be less well

differentiated [23]. Tregs with T cell receptors specific for self-antigens are thought to arise largely during T cell selection in the thymus, while those that recognize foreign antigens likely differentiate from circulating mature CD4+ T cells in the periphery. It is well established that exposure to TGF-β1 in the presence of T cell receptor stimulation induces FOXP3 expression and Treg differentiation in both mouse and human CD4+ T cells [24,25]. Mouse Tregs generated *in vitro* by addition of TGF-β1 were capable of suppressing an allergic response and limiting lung pathology and inflammatory cell infiltrate associated with house dust mite sensitization and challenge [24]. Similarly, Tregs generated *in vitro* using CD4+ T cells with transgenic allergen-specific T cell receptors significantly reduced the anaphylactic response following oral challenge in a model of food allergy, as well as limiting OVA-specific IgE and mast cell accumulation and degranulation [26]. *In vivo*, tissue-resident macrophages in the lungs and CD103+ dendritic cells in the gut present airborne or ingested antigen, respectively, to CD4 + T cells and induce their differentiation into Tregs in a manner dependent on TGF-β1 [27–29]. Tregs generated *in vivo* in response to orally administered antigen suppressed the production of IgE following immunization with the target antigen [30]. Induction of Foxp3 expression in response to TGF-β1 is dependent on an intronic *Foxp3* enhancer CNS1, and T cells from mice that lack CNS1 are significantly impaired in their ability to upregulate Foxp3 *in vitro* in response to TGF-β1 and *in vivo* in response to orally administered cognate antigen [31]. CNS1-deficient mice, which have normal thymically generated Treg development but diminished peripheral Treg differentiation, developed increased serum levels of IgE and IgA, increased reactivity of serum antibodies against mouse chow, and spontaneous Th2 inflammation in the gastrointestinal tract and lungs but did not exhibit symptoms of autoimmunity [31]. These studies show that TGF-β1 is a critical driver of CD4+ T cell differentiation into Tregs at mucosal sites, and that these Tregs normally suppress unwanted Th2 type inflammation. However, one study found that addition of TGF-β1 to cultures of naïve T cells stimulated in the presence of inflammatory cytokines actually suppressed production of IL-2, a cytokine critical for Treg survival and proliferation, and increased IL-4 production [23].

In addition to its role in promoting Treg differentiation, Tregs themselves produce TGF-β1, and TGF-β can attach to Tregs via binding of LAP to GARP on the cell surface [32–34]. Blocking TGF-β1 using an antibody in *in vitro* cultures abolished Treg-mediated suppression of T cell division in some [32] but not all reports [35]. Specific immunotherapy (SIT) for house dust mite allergy in human patients resulted in increased TGF-β production by peripheral blood mononuclear cells (PBMCs) and suppression of CD4+CD25− T cells by a population of CD4+CD25+ cells when stimulated with HDM, presumably by expanding the population of HDM-specific Tregs. Blockade of TGF-β limited the ability of CD4+CD25+ cells to suppress HDM-induced proliferation post-SIT and eliminated their suppression of inflammatory cytokine production (IFN-γ, IL-13, IL-5) in PBMC cultures [36]. This experiment suggests TGF-β is required for Treg-dependent suppression of the allergic response to HDM, but did not fully address the source of TGF-β or whether it is acting on the effector cells to suppress their activity or on the Tregs to enhance their stability or suppressive function. In support of a role for surface bound TGF-β in suppression of allergic disease, a polymorphism in *GARP* was found to associate with higher serum IgE levels [37]. Furthermore, T cells transferred into mice in which *Tgfb1* or *Garp* were specifically deleted in host Tregs or T cells, respectively, were less likely to convert into Foxp3+ Tregs in response to orally administered antigen, which strongly suggests that TGF-β on the surface of existing Tregs contributes to Treg induction *in vivo* [38]. While oral administration of antigen before immunization normally prevents the development of a delayed type hypersensitivity reaction, mice in which Tregs lacked the ability to produce TGF-β could not be tolerized in this manner, providing further evidence that Treg-derived TGF-β is crucial for oral tolerance [38].

Along with traditional Foxp3+ Tregs, a second population of suppressor T cells exists that is Foxp3− but that expresses LAP on the cell surface [39]. LAP+ T cells can be differentiated *in vitro* by addition of TGF-β, and *in vivo* by inhalation of antigen in a manner dependent on TGF-β [40] and by epicutaneous immunotherapy in a model of food allergy [41]. Transfer of LAP+Foxp3− T cells strongly reduced allergic lung inflammation in mice [40], in addition to suppressing mast cell activation during challenge of passively sensitized mice in a TGF-β-dependent manner [41].

TGF-β and T cell activation and differentiation

TGF-β is most well-known as an immunosuppressive cytokine and has been shown to inhibit the activity of many of the cell types responsible for driving allergic disease. Its immunosuppressive effects are evidenced by the observation that mice with a *Tgfb1* null mutation develop a wasting syndrome with mixed inflammatory cell infiltrate in multiple tissues and succumb to fatal autoimmunity within three weeks of birth [42,43]. Loss of *Tgfbr1* or *Tgfbr2* specifically in T cells similarly resulted in a lymphoproliferative disorder, increased T cell activation and differentiation, and fatal autoimmune disease by 3–5 weeks of age [44–46]. Furthermore, *Tgfbr2*-deficient T cells could not be controlled by *Tgfbr2*-sufficient Treg cells in mixed bone marrow chimeras, indicating that TGF-βR signaling is required to maintain T cell homeostasis and prevent unwanted T cell activation in a cell-intrinsic manner, and pathology is not solely a result of a

failure to produce or maintain Tregs [46]. The inhibition of T cell activation and proliferation by TGF-β signaling is highly dose-dependent; mice expressing a dominant negative version of TGF-βRII under a T cell-specific promoter in which TGF-β is severely reduced, but not absent, live normally for 3–4 months before eventually showing signs of wasting disease and immune cell infiltration into various organs [47]. These mice additionally showed increased accumulation of CD4+ T cells with an activated or memory phenotype that were capable of producing the Th1 cytokine IFN-γ or the Th2 cytokine IL-4. In contrast, complete loss of TGF-βRII in T cells resulted in increased percentages of CD4+ T cells making TNF-α and IFN-γ but no increase in IL-4 production [44,46]. CD4+ T cells act as coordinators of an immune response and can direct B cell activation and recruitment of additional immune cells through secretion of various cytokines. Inappropriate CD4+ T cell activation is hypothesized to play a key role in initiating allergic disease, with allergen-specific CD4+ T cells showing increased Th2 skewing in birch allergic [48], peanut allergic [49,50] and cow's milk allergic [51] individuals relative to non-allergic controls, and decreased or similar Th1 skewing.

More recently, TGF-β in combination with IL-4 has been shown to induce differentiation of Th9 cells [52] that produce IL-9, which likely plays a role in allergy pathogenesis by enhancing B cell production of IgE, acting as a growth factor and activator for mast cells, and indirectly leading to the recruitment of eosinophils [53–57]. Increased numbers of Th9 cells were found in the blood of individuals with pollen or house dust mite allergies relative to non-allergic controls, and the number of Th9 cells correlated with the amount of IgE in the serum [58]. Furthermore, serum IL-9 levels and the percentage of Th9 cells were elevated in atopic dermatitis patients and correlated with disease severity and IgE levels [59,60]. CD4+ T cells from atopic infants and adults cultured in the presence of IL-4 and TGF-β1 had higher levels of IL-9 expression [61,62]. These studies strongly suggest a role for Th9 cells in the pathogenesis of allergic disease. In a mouse model, transfer of Th9 cells before sensitization enhanced the allergic response to house dust mite, as shown by increased mast cell numbers and activation, increased eosinophil infiltration, and higher IgE levels. In contrast, blockade of TGF-β and its family member activin A together (but not alone) limited Th9 accumulation and allergic lung inflammation [58]. Given these observations, it is reasonable to hypothesize that effects on T cell activation and differentiation may be part of the mechanism by which alterations in TGF-β signaling affect the development of allergic disease.

TGF-β affects B cell activation and immunoglobulin production

While T cells are important in the initiation of an allergic response, allergy ultimately results from the production of allergen-specific IgE by B cells. Mice with a B cell-specific deletion of *Tgfbr2* exhibit increased B cell activation and proliferation, increased B cell accumulation and germinal center participation in the Peyer's patches, and increased levels of IgM and IgG (particularly IgG1) in the serum, which indicates that TGF-β normally acts on B cells to suppress their activity [63]. The B cell hyperplasia and increased germinal center activity in the Peyer's patches is particularly interesting in the context of food allergy given that B cells encounters with food antigen would likely occur in this location. *In vitro*, TGF-β decreased B cell activation in response to both Toll-like receptor-9 and IL-4 stimulation, but enhanced survival in stimulated B cells [64]. TGF-β is necessary for IgA class switching as shown by *in vitro* experiments [65,66] and by the observations that serum and mucosal IgA levels were significantly lower when B cells could not respond to TGF-β [63,67]. IgA is produced and secreted predominantly at mucosal surfaces, where it provides protection against pathogens and ingested substances and maintains gut homeostasis by limiting inflammation and restricting entry of commensals into the mucosal surface [68]. IgA is additionally believed to have a role in protection from allergy. Frequent atopic disease was noted in a cohort of IgA deficient patients as early as 1980 [69,70]. Among children who had serum IgA levels within the normal range, lower IgA levels correlated with more severe atopic disease and increased incidence of asthma in children and positive skin prick tests for common allergens [71], and low salivary IgA levels correlated with the development of allergic rhinitis between ages 2 and 4 years [72]. Low serum IgA levels were also identified as a risk factor for moderate to severe AHR in adult asthmatics [73]. Furthermore, successful immunotherapy for allergy was found to result in increased antigen-specific IgA. The amount of salivary peanut-specific IgA increased in peanut allergic individuals after undergoing sublingual immunotherapy and correlated positively with the amount of peanut the individual was able to consume in an oral food challenge after 12 months of treatment [74]. Similarly, individuals undergoing immunotherapy for grass pollen allergy had increased serum levels of anti-pollen IgA2 relative to controls who received placebo injections, and in this case the anti-pollen IgA2 level correlated positively with nasal TGF-β mRNA, perhaps suggesting that the higher TGF-β production might be responsible for the increased IgA2 [75]. While human results are by necessity largely correlative, mouse models have provided further evidence for a direct role of IgA in limiting allergy. In one study, immunization of neonatal mice with a cockroach antigen resulted in increased cockroach-specific IgA levels in the lungs after subsequent intratracheal sensitization in adulthood, as well as

decreased numbers of CD4+ T cells and eosinophils in the bronchoalveolar lavage fluid and lung parenchyma, and better lung function. However, in mice that could not produce IgA specific for the major cockroach antigen, immunization did not protect against cockroach allergy [76]. B cell produced TGF-β1 likely plays a role in B cell class switching in both humans and mice, and complexes of GARP and latent TGF-β1 can be found on the surface of human B cells after stimulation [77,78]. Given the importance of TGF-β in restraining B cell activity (particularly in the Peyer's patches of the gut) and in directing class switching to the protective IgA immunoglobulin isotype, it is likely that variations in TGF-β signaling could alter the B cell response to allergens.

TGF-β suppresses mast cell activity

TGF-β can act directly on mast cells to limit their release of inflammatory molecules that cause the symptoms of an allergic response. *In vivo* treatment with TGF-β at the time of challenge significantly reduced the mast cell-dependent 2 hour ear swelling response in mice passively sensitized by intravenous injection of monoclonal anti-TNP IgE antibody [79]. Pretreatment with TGF-β inhibited mast cell release of inflammatory mediators such as histamine, tumor necrosis factor-α (TNF-α) β-hexaminidase, and IL-6 in studies using rat [80], mouse [81], and human skin mast cells [82]. Several mechanisms have been proposed to explain how TGF-β inhibits mast cell activation including by downregulating surface expression of Kit, the receptor for stem cell factor that is necessary for mast cell growth and activity, and the high affinity receptor for IgE (FcεRI), and increasing rates of apoptosis upon activation [81–83]. More recently, TGF-β was found to suppress IL-33-induced murine and human mast cell activation and cytokine production [84]. One potential source of TGF-β for mast cells *in vivo* is Tregs; *in vitro* generated Tregs suppressed mast cell activation and cytokine production in mice with established contact hypersensitivity, but this suppression was abolished when Tregs were pre-treated with TGF-β1 siRNA [85]. Thus it seems likely that in a setting where TGF-β signaling is reduced, mast cells might release more inflammatory molecules, leading to a heightened allergic response. However, TGF-β may also promote mast cell differentiation in certain contexts, such as within the gut. Mouse mast cell protease-1 (mMCP-1) is only expressed by mucosal mast cells, and TGF-β1 promoted mMCP-1 expression and release in mast cells differentiated from bone marrow precursors *in vitro* [86]. A separate study showed that TGF-β promotes IL-6 production by mast cells [87], which could potentially lead to increased mast cell proliferation and differentiation, and enhanced degranulation [88]. In this case, decreased TGF-β signaling might result in fewer and less active mast cells, particularly within the gut, which might limit allergic reactions.

TGF-β and tissue dysfunction

Later stages of allergic asthma (reviewed in Ref. [89]), atopic dermatitis, and EoE are frequently characterized by tissue remodeling and fibrosis following multiple rounds of tissue injury and repair. TGF-β plays a role in wound healing and promotion of tissue fibrosis, and can induce fibroblast differentiation and deposition of extracellular matrix components such as collagen and fibronectin [89–91], as well as airway smooth muscle cell (ASMC) proliferation and migration [92,93]. In association studies, TGF-β1 expression was found to be increased in the lungs of individuals with chronic asthma [94,95], where it positively correlated with disease severity [96], in chronic skin lesions in individuals with atopic dermatitis [97], and in esophageal biopsies of children with EoE [98]. Eosinophils likely act as a major source of TGF-β1 leading to fibrosis within the lungs and skin [96,97,99], while TGF-β1 derived from both mast cells and eosinophils has been implicated in EoE [98,100]. ASMCs may also become more responsive to TGF-β as asthmatic disease progresses. One study found that ASMCs from mice sensitized for allergic airway disease displayed enhanced proliferation in response to TGF-β1 and expressed higher levels of TGF-βRII and Smad3 than ASMCs from control mice [101], while another study found that treatment of ASMCs with TGF-β1 *in vitro* increased expression of TGF-βRI [92]. Mice with established chronic allergic asthma that were treated with anti-TGF-β antibody experienced reduced extracellular matrix deposition and airway smooth muscle cell proliferation while Th2 cytokine production remained unchanged [102]. TGF-β can also promote epithelial-mesenchymal transition (EMT) in esophageal epithelial cells; the extent of EMT was significantly higher in EoE patients than in healthy controls or gastroesophageal reflux disease patients, and correlated with fibrosis and TGF-β staining in the esophagus [103]. Finally, TGF-β can induce smooth muscle contraction in both asthma and EoE, perhaps contributing to long-term dysmotility [100,104,105]. Thus, in established disease, overexpression of TGF-β1 likely increases fibrotic responses and leads to greater impairment of airway function, increased skin thickening and scarring, and tissue dysfunction.

Conclusions

A growing body of evidence supports a role for TGF-β in atopic disease. A number of single gene disorders and common polymorphisms in genes in the TGF-β pathway have been associated with allergic phenotypes. Because of its ability to modulate the activity of a wide variety of cell types, TGF-β likely affects allergy development at the initial stage of T cell differentiation, where it can suppress T cell activity and promote the development of Tregs, while also driving the differentiation of potentially pathogenic Th9 cells. TGF-β is additionally important in modulating the B cell response to an allergen, both by limiting B cell activity and germinal center formation

(particularly in the gut), as well as by promoting a protective IgA response. Upon exposure to an established allergen, TGF-β can limit mast cell degranulation and reduce the severity of an allergic episode, although conversely, it may promote mast cell differentiation in some contexts. Finally, TGF-β is important in the resolution of tissue damage following an allergic episode, and its continued presence can lead to fibrosis, which can worsen symptoms in asthma, atopic dermatitis, and EoE. The various and contradictory roles of TGF-β in allergy development and progression are summarized in Figure 1.

Timing of exposure to TGF-β and the regional microenvironment are likely important in determining its effect on allergic disease. For instance, naïve T cells stimulated through the T cell receptor in the presence of TGF-β alone likely develop into Treg cells. However, if IL-4 is also present within the environment, then these same cells may develop into pathogenic Th9 cells. Marfan syndrome, which is caused by mutations in fibrillin-1 leading to increased levels of TGF-β locally, phenotypically resembles LDS in terms of aortic enlargement and dissection, joint hypermobility, and kyphosis. However, allergic disease propensity does not appear to be altered in individuals with Marfan syndrome, possibly because the increased levels of TGF-β are restricted to areas where fibrillin-1 is expressed, mainly the muscles and soft tissues, and are less likely to be found at sites of environmental exposure (e.g. lungs, intestines, and so on) or adaptive immune priming (e.g. lymph node, spleen). Recent work on a mouse model of LDS has found that impaired responsiveness to TGF-β by secondary heart field-derived vascular smooth muscle cells leads to increased production of TGF-β1 and TGF-β3, which in turn drive increased phosphorylation of Smad2/3 in cardiac neural crest-derived vascular smooth muscle cells and subsequent aortic aneurysm, thus highlighting how regional the production of and response to TGF-β can be [106]. Although outside the scope of this review, it is worth noting that other TGF-β family members, including activins and TGF-β2 and 3, may also play roles in immune regulation and tissue fibrosis [107,108].

The progression of allergic disease, generally known as the atopic march, frequently begins early in life. There is evidence that higher levels of TGF-β in breastmilk may correlate with decreased rates of atopy [109–113], and it has been suggested that oral supplementation with TGF-β in young children may protect against atopic disease [114]. However, controversy remains regarding the link between TGF-β exposure during infancy and allergic disease, and given its role in both promoting and restraining allergic disease, more studies are needed before strategies to modulate TGF-β signaling as a prevention or therapeutic strategy for allergic disorders can be considered [112,115].

Conflict of interest statement

Nothing declared.

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