

REVIEW ARTICLE

Transforming growth factor-beta1 in inflammatory airway disease: a key for understanding inflammation and remodeling

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Abstract

Airway diseases such as chronic rhinosinusitis, asthma, and chronic obstructive pulmonary disorder are characterized by inflammation and remodeling. Among inflammatory and extracellular matrix regulatory cytokines, transforming growth factor-beta (TGF- β) stands central, as it possesses both important immunomodulatory and fibrogenic activities, and should be considered a key for understanding inflammation and remodeling processes. This review will briefly summarize the recent findings on the role of TGF- β 1, from the view points of inflammation and remodeling, and discuss the role of TGF- β in the upper and lower airway diseases. This may reveal new perspectives in the understanding of airway inflammation and remodeling processes and may open innovative treatment strategies for the regulation of TGF- β 1.

TGF- β 1 in inflammatory airway diseases

Chronic upper and lower airway diseases, often present as comorbidities (1), are common health problems with impaired airway function, low quality of life, and significant medical costs (2, 3). Although their mechanisms are not fully clarified, airway diseases may be associated with similar triggers such as bacterial products (4–7), and importantly, chronic rhinosinusitis with (CRSwNP) and without nasal polyps (CRSsNP), asthma, and chronic obstructive pulmonary disease (COPD) are similarly characterized by mucosal inflammation and remodeling. TGF- β 1, among others, is an important regulator in airway diseases and therefore merits specific attention (8–11). TGF- β 1 has been demonstrated to be up-regulated in CRSsNP and COPD, up-regulated or unchanged in asthma, and down-regulated in CRSwNP. Recent evidence suggests that TGF- β 1 is involved in very early events of respiratory disease as well as late persistent disease, in both the inflammatory and the remodeling component of airway disease (12).

This review aims to summarize recent findings in upper airway disease and compare that in lower airway findings, in order to illustrate the role of TGF- β 1 in the regulation of inflammation, including its effects on T-helper (Th) and T-regulatory (Treg) cells, and in remodeling processes, involving extracellular matrix (ECM) production and the regulation of the matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinase (TIMP) system. It becomes clear that TGF- β 1 is a key cytokine in the understanding of mucosal airway disease, identifying it as a target to therapeutic interventions that aim to up- or down-regulate its production or function.

The TGF- β activation and signaling pathway

The TGF- β superfamily, all showing a similar prodomain fold (13), consists of more than 33 members, including mainly TGF- β s, bone morphogenetic proteins (BMP), growth and differentiation factors (GDFs), activins, and inhibins. These

members act as multifunctional regulators of cell growth and differentiation (10). Among them, the TGF- β family has three different TGF- β isoforms in mammals: TGF- β 1, TGF- β 2, and TGF- β 3. They share 60–80% homology and have similar properties *in vitro* through the same cell surface receptors and have similar cellular targets, but are encoded by different genes (14). TGF- β 1, the most prevalent isoform, is almost ubiquitously found in mammalian tissues and implicated in a wide range of cell functions (15). TGF- β 1 is produced as an inactive latent complex that is targeted to the ECM and consists of the mature 25-kDa polypeptide dimer (TGF- β), latency-associated protein (LAP), and latent TGF- β -binding protein (LTBP). The release from pericellular matrices and the activation of TGF- β 1 from its latent complex are important mechanisms in several pathophysiologic conditions (16), including proteolysis, thrombospondin and integrin interactions, pH changes, and reactive oxygen species (17, 18). Recent studies showed that the activation of TGF- β 1 requires the binding of $\alpha(v)$ integrin

to a sequence in the prodomain and exertion of force on this domain, which otherwise is held in the ECM by latent TGF- β 1-binding proteins (13).

Biologically active TGF- β 1 has important functions through distinct signal transduction pathways including Smad-dependent and Smad-independent pathways (Fig. 1). The Smad-dependent pathway is the canonical signaling pathway for TGF- β 1, through the activation of the TGF- β 1 type I and II receptors, phosphorylation of the receptor-activated Smads (R-Smads, Smad 2, 3), subsequently forming complexes with the Co-Smad, Smad 4, and finally translocating to the nucleus to regulate gene transcription. Inhibitory Smad (I-Smad, Smad 7) can antagonize TGF- β signaling by binding to the type I receptor. Interestingly, Smad 7 expression is triggered by Smad 3, providing a negative feedback loop to limit TGF- β 1-mediated effects. Additionally, TGF- β 1 can also activate the Smad-independent pathway in a noncanonical fashion through the activation of all three known

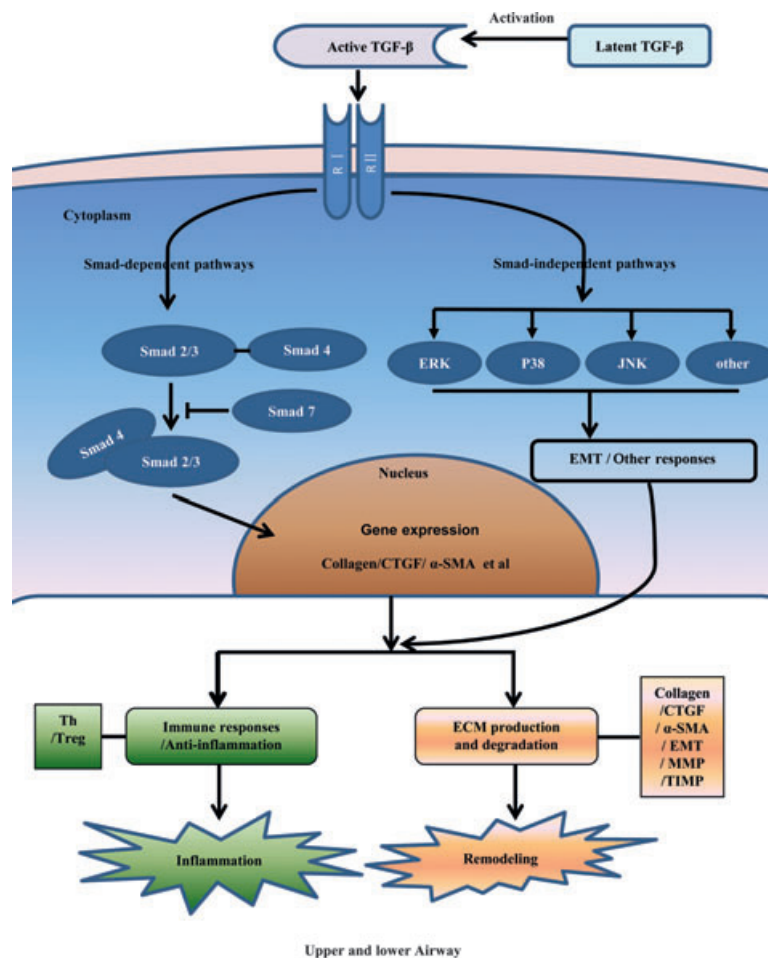


Figure 1 TGF- β signaling pathway and function. TGF- β 1 is a key for understanding inflammation and remodeling in airway diseases. TGF- β 1 plays a complex and intertwined role in inflammation through inducing Th17 and Th9, and anti-inflammation through inducing Treg. TGF- β 1 also takes a central role in remodeling by balancing extracellular matrix

production and degradation. α -SMA: α -smooth muscle actin; CTGF: connective tissue growth factor; EMT: epithelial-mesenchymal transition; JNK: c-Jun-N-terminal kinase; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinases; R: receptor; Th: T-helper cells; Treg: T regulatory cells; TIMP: tissue inhibitors of metalloproteinase.

mitogen-activated protein kinase (MAPK) pathways: extracellular signal-regulated kinase (ERK), p38 MAPK, and c-Jun-N-terminal kinase (JNK). Signaling through these pathways may further regulate Smad proteins and mediate Smad-independent TGF- β responses (19, 20).

TGF- β 1 is a pleiotropic and multifunctional growth factor with important immunomodulatory and fibrogenic characteristics (Fig. 1). Firstly, TGF- β 1 is a master regulator of immune responses and exerts powerful anti-inflammatory functions. On the one hand, TGF- β 1 has potent chemoattractive properties and can lead to the rapid accumulation of macrophages, granulocytes, and other cells at the site of inflammation. TGF- β 1 can also induce differentiation of Th17 cells, which secrete large amounts of IL-17 and sustain acute inflammation by promoting the secretion of other inflammatory cytokines and by recruiting granulocytes, and then amplify the inflammatory component (15, 21). Recent evidence indicates that TGF- β 1 is also involved in the generation of IL-9-producing T-helper (Th9) cells (22). On the other hand, TGF- β 1 exerts broad anti-inflammatory and immunosuppressive effects. For instance, TGF- β 1 inhibits the differentiation of immune cells (Th1 cells, Th2 cells, B cell, and CTLs) as well as cytokine production (IFN- γ and IL-2) (20, 23, 24). Furthermore, TGF- β 1 is shown as an important differentiation factor for some regulatory T cells that exert powerful and diverse immunosuppressive effects (25, 26). For example, TGF- β 1 is critical for the development and differentiation of FOXP3⁺ regulatory T cells (Tregs) (27, 28). TGF- β 1-deficient mice developed a multiorgan autoimmune inflammatory disease and died a few weeks after birth (29). In a word, with regard to the immune system, TGF- β 1 plays a complex and intertwined role in inflammation, T-cell lineage commitment, immune suppression, and tolerance (28).

Secondly, TGF- β 1 also takes a central role in remodeling, which is a dynamic process in both health and disease that balances ECM production and degradation. Fibrosis can be viewed as the result of a series of ECM changes that take place over time. TGF- β 1 has been implicated in fibrosis formation and is suspected to play a major role in the pathogenesis of fibrosis in kidney, liver, cardiovascular, and lung diseases (14). During the development of fibrosis, TGF- β 1 induces target genes, including connective tissue growth factor (CTGF), α -smooth muscle actin (α -SMA), collagen, plasminogen activator inhibitor (PAI), inducing proliferation and chemoattraction of fibroblasts and their differentiation into myofibroblasts to synthesize ECM proteins, such as fibronectin and collagen, which finally contract the ECM (30). Fibroblasts have a crucial role in regulating both fibrotic and immune responses in the lung depending on α v β 8-mediated activation of TGF- β 1 (31). The function of bronchial epithelial cells, a key player in coordinating airway wall remodeling, can be modulated by the underlying fibroblasts through TGF- β signal mechanism (32). TGF- β 1 can enhance ECM production and myofibroblast differentiation in pulmonary fibroblasts from individuals with COPD (33). TGF- β 1 can also induce myofibroblast differentiation and collagen production in nasal polyp-derived fibroblasts (NPDFs), which can be inhibited by simvastatin (34) and macrolides (35). However, partly due to the heterogeneity between nasal and

lung fibroblasts that have heterogeneous responsiveness to TGF- β 1, the pathological outcomes of inflammation in the upper and lower airways are different (36). Moreover, in several tissues including the lung, TGF- β 1 has been identified as a 'master switch' in the induction of the epithelial-mesenchymal transition (EMT), involving the conversion of differentiated epithelial cells into fibroblasts and myofibroblasts. Thus, EMT has been proposed as a mechanism for an increase in mucosal fibroblasts and myofibroblasts, as well as for collagen overproduction and fibrosis as observed in asthma and COPD. Lung alveolar epithelial cells, primary human bronchial epithelial cells (HBEs), and airway epithelial cells isolated from asthmatics have been demonstrated to undergo EMT *in vitro* upon TGF- β 1 stimulation via a primarily Smad 2/3-dependent mechanism (37, 38). Dysregulated repair processes involving TGF- β 1 and EMT may lead to fibrosis. In contrast, TGF- β 1 inhibitors such as Smad 7 or BMP 7 can inhibit EMT (30, 39). Little is known about EMT in the upper airways; this topic is ripe for future study.

Interestingly, TGF- β 1 impacts fibrosis formation also through the influence on ECM degradation. For example, TGF- β 1 influences the balance between MMPs and TIMPs, such as MMP-9/TIMP-1, in asthmatic airway remodeling (40, 41). Furthermore, TGF- β 1 is known to activate PAI-1, a fibrinolytic component, which can counteract the conversion of inactive promatrix metalloproteinases into active MMPs (42). A recent study found that the concentrations of TGF- β 1 correlated with increased PAI-1 in CRSsNP (43). In summary, the function of TGF- β 1 could be understood as a counter-regulatory cytokine to resolve inflammation and to initiate the repair processes, including remodeling.

Owing to the complexity of the TGF- β pathway as described before, only the simultaneous measurement of TGF- β 1 and its receptors and signal transduction molecules is able to provide a comprehensive understanding of the role of TGF- β 1 in pathologic conditions. This is an unmet need in the area of CRS research.

TGF- β 1 in chronic sinus disease

Chronic rhinosinusitis (CRS), a common health problem with an overall prevalence of 10.9% in Europe by symptom-based epidemiological EP(3)OS criteria (44, 45), is characterized by persistent inflammation and remodeling of the nasal and paranasal mucosal linings and is currently classified into two major subgroups: CRSwNP and CRSsNP (46). The term 'rhinosinusitis' implies that both the nasal and the sinuses are involved; this has recently been confirmed by a study illustrating that the inflammatory mediator profile in the nasal mucosa of patients with CRWwNP or CRSsNP followed the profile found in the sinus mucosa of the respective patient group. In CRSwNP, increased levels of IL-5 and ECP were observed in the ethmoidal and nasal inferior turbinate mucosal samples. In contrast, in CRSsNP, IFN- γ levels were up-regulated in both ethmoidal and nasal mucosa compared to control tissue (47).

Thus, CRSwNP and CRSsNP should be regarded as distinct clinical entities in Caucasian patients on the basis of different inflammatory mediator profiles (46). It has also been

demonstrated that there is a difference in the presence of Treg cells, with a deficit in FoxP3 expression and Treg cell numbers in CRSwNP, but not in CRSsNP (48). This may allow for a more severe inflammatory cell infiltration, the up-regulation of the Th2 transcription signal GATA-3, and B-/plasma cell activation in CRSwNP compared to CRSsNP (49). Both the Treg and inflammatory cell dysregulation in CRSwNP are coincident with significant down-regulation of TGF- β 1 expression and TGF- β -specific intracellular signaling (phosphor-Smad) events (26, 48). In contrast, CRSsNP demonstrates no deficit in Treg cell numbers and migration capacity (50) and displays a much less severe inflammatory mucosal reaction (26).

Interestingly, the hallmarks of low TGF- β 1 protein expression and deficit in Treg cell presence were also found in Asian patients, although only a minority of those polyps expressed a Th2-biased inflammation (48, 51). In contrast to the mostly eosinophilic inflammation in Caucasians, polyps in mainland Chinese patients demonstrated a neutrophilic type of inflammation in more than 80% of cases; the inflammation was characterized by a Th1/Th17 polarization (48), which again seemed not controlled by Treg cells (52). This suggests that the Treg dysfunction may precede inflammation. Certainly, other immunoregulatory cells, such as FoxP3-IL-10-producing iTregs, IL-10-producing B cells, and resident macrophages, may contribute to the immune regulation and need further to be studied in CRS.

In addition to being a key factor in the generation or the deficit of Treg cells, TGF- β 1 is also a critical factor implicated in the remodeling process in the upper airways. Histologically, CRSwNP is characterized by an intense edematous stroma with albumin deposition, formation of pseudocysts,

and subepithelial and perivascular inflammatory cell infiltration, whereas CRSsNP is characterized by fibrosis, basement membrane thickening, goblet cell hyperplasia, and mononuclear cell infiltration (26). A recent study reported that TGF- β 1 protein concentration, TGF- β 1 receptor II and III mRNA expression, and the number of activated pSmad 2-positive cells were significantly lower in patients with CRSwNP vs control subjects. In contrast, in patients with CRSsNP, TGF- β 1 and TGF- β 2 protein concentrations, TGF- β 1 receptor I and III mRNA expression, and the number of activated pSmad 2-positive cells were significantly higher when compared to control and CRSwNP subjects (42). Indeed, at the protein level, the down-regulation of the TGF- β 1 signaling pathway was reflected by edema formation and a lack of collagen production in patients with CRSwNP, and its up-regulation was reflected by excessive collagen deposition associated with fibrosis in patients with CRSsNP (53). The TGF- β 1 signaling pathway also contributed to the regulation of expression of MMPs and their natural TIMPs, the imbalance of which allows ECM degradation and albumin deposition, contributing to edema and remodeling. Compared to CRSsNP, patients with CRSwNP showed significantly lower expression of TIMP-1 and TIMP-4, failing to counterbalance MMP-7 and MMP-9 activity; this imbalance may be directly caused by decreased TGF- β 1 expression (54).

In contrast to the differences described for inflammatory patterns in Caucasian and Asian patients, the above-stated remodeling patterns in CRSsNP and CRSwNP are reasonably conserved all over the world (42, 54), indicating that TGF- β 1 protein and its signaling might be universally applicable markers to differentiate the distinct CRS entities (Fig. 2). In line with this, an up-regulation of TGF- β 1 and

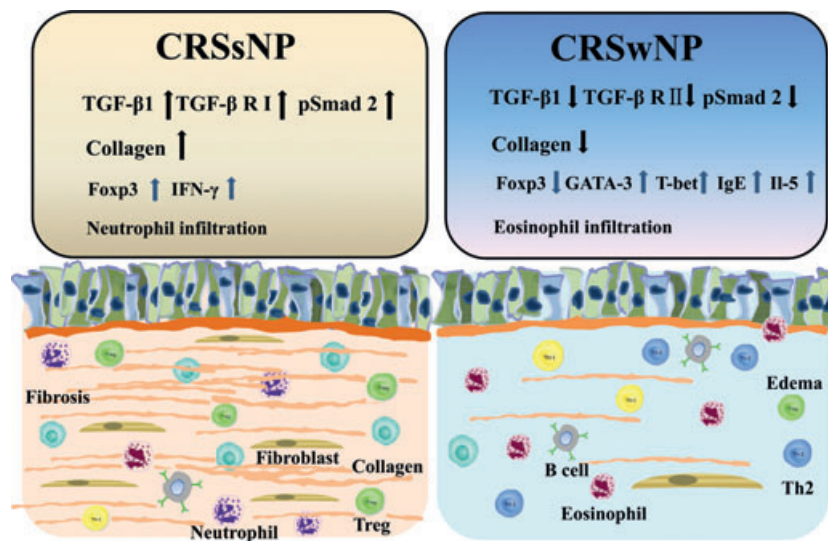


Figure 2 Regulation of TGF- β 1 in CRSsNP and CRSwNP from inflammation and remodeling. The differences between CRSsNP and CRSwNP base on inflammatory mediators and remodeling factors. CRSsNP is characterized by an enhanced TGF- β signaling and

no deficit in Treg cells, excessive collagen production and fibrosis; whereas CRSwNP is characterized by a low level of TGF- β signaling and a deficit in Treg cells, a lack of collagen and an intense edematous stroma.

an increase in collagen deposition in patients with early-stage CRSsNP without any sign of inflammation were recently observed in the region of the osteomeatal complex, the key access area for the ethmoidal and maxillary sinuses (12), indicating that remodeling processes could precede inflammation; whether the same is true for CRSwNP needs to be demonstrated. It was recently reported in a large Pan-European study that smoking is associated with CRSsNP (44). Cigarette smoke enhances OVA antigen-induced mast cell activation and exacerbates airway remodeling via the TGF- β 1/Smad signaling pathway (55). Further studies need to clarify this possible link.

Owing to its regulatory function in both inflammation and remodeling processes, TGF- β 1 represents an interesting therapeutic target for CRSsNP. Long-term, low-dose macrolide therapy is believed to have anti-inflammatory effects; for example, clarithromycin therapy has been shown to reduce cellular expression of TGF- β 1 in *in vitro* biopsies from CRS patients (56). *In vivo*, however, nasal biopsies taken before and after clarithromycin treatment for 3 months showed no differences in cellular expression of TGF- β 1. Further studies are needed to unravel possible therapeutic approaches based on the TGF- β 1 pathway in CRSsNP (11).

TGF- β 1 in asthma

Asthma is one of the most common chronic diseases affecting an estimated 300 million people worldwide (57). A recent survey in Europe (GA(2)LEN) found that self-reported asthma was associated with CRS (1). Like CRS, asthma is also a chronic disease characterized by inflammation and remodeling of the airways, with airway hyper-responsiveness and reduced lung function (58). Among the inflammatory mediators, TGF- β 1 again is believed to play an important role in inflammation and remodeling processes: It can either function as a pro- or anti-inflammatory cytokine on inflammatory cells, participating in the initiation and resulting in inflammatory and immune responses in the airways. It is also involved in the remodeling of the airway wall, epithelial changes, subepithelial fibrosis, airway smooth muscle remodeling, and microvascular changes in asthmatic patients (9, 59). Moreover, gene polymorphisms in the TGF- β 1 promoter have been associated with asthma development (60), and a recent meta-analysis suggested that the -509C/T polymorphism in the TGF- β 1 gene may be a risk factor for asthma susceptibility (61).

TGF- β 1 plays a key role in inflammation in asthma. Firstly, TGF- β 1 displays pro-inflammatory properties by being a potent chemotactic factor and activator for inflammatory cells. TGF- β 1 is produced in the airways by inflammatory cells infiltrated in the bronchial mucosa, such as eosinophils, lymphocytes, and macrophages, as well as by structural cells of the airway wall including fibroblasts, epithelial, endothelial, and smooth muscle cells. These different cells may release TGF- β 1 and thus contribute to the increased levels of TGF- β 1 observed in bronchoalveolar lavage (BAL) fluid from asthmatic patients (58, 59). In fact, increased TGF- β 1 expression has been attributed

predominantly to increases in eosinophils (62) and macrophages (63); BAL levels of TGF- β 1 are further increased following allergen challenge (64). In a murine asthma model, anti-TGF- β 1 antibody specifically inhibited monocyte/macrophage recruitment and reduced eosinophil and lymphocyte numbers in BAL (65). In addition, TGF- β 1 also induces the differentiation of T lymphocytes into pro-inflammatory Th17 and Th9 cells, which then amplify the inflammatory component (66, 67). Secondly, TGF- β 1 displays anti-inflammatory actions by regulating lymphocyte homeostasis, inhibiting Th1 and Th2 cell responses, and promoting the differentiation of Treg cells (68). Allergic asthma is characterized by chronic mucosal Th2 inflammation, and chronic Th2 responses to allergens are normally suppressed by CD4⁺ CD25⁺ Treg cells (69). For example, TGF- β 1 induces the peripheral expression of the transcription factor FoxP3, which promotes the generation of CD4⁺ CD25⁺ Treg cells and prevents house dust mite-induced allergic reactions in murine lungs (70). Administration of CD4⁺ CD25⁺ Treg cells reduced established lung eosinophilia, Th2 infiltration, and expression of IL-5, IL-13, and TGF- β 1 in a BALB/c mice model (71). Intratracheal delivery of TGF- β 1 also suppressed allergen-induced inflammation (72). In contrast, blocking TGF- β 1 signaling specifically in T cells resulted in enhanced airway hypersensitivity, airway inflammation, and increased Th2 cytokine production (73). Moreover, reduced expression of TGF- β 1 in experimental asthma was accompanied by a strikingly increased eosinophilic inflammation and increased levels of OVA-specific IgE in serum (74). Thus, the often severe Th2-biased inflammation in asthma is likely related to the deficit in Treg cells and the lack of sufficient TGF- β 1 protein, similar to CRSwNP.

Eosinophils are a hallmark of asthma and link inflammation to remodeling; studies demonstrated that eosinophils were the main source of TGF- β 1 in asthmatic airways and suggested that eosinophils may play an important role in airway remodeling (65, 75). In bronchial biopsies of patients with severe asthma, it was shown that 65% of TGF- β 1 mRNA-positive cells were eosinophils and 75% of eosinophils were positive for TGF- β 1 mRNA (76). Moreover, the degree of TGF- β 1 expression was significantly higher in patients with moderate-to-severe asthma compared with mild asthma (77). Patients with mild atopic asthma and with anti-IL-5 antibody (mepolizumab) treatment for 2 months consequently showed a reduction in tissue eosinophilia, lung TGF- β 1 expression, and ECM component deposition (75). Similarly, IL-5 knockout mice chronically exposed to allergic challenge showed a reduced number of TGF- β 1-positive cells in the peribronchial region and a reduced expression of TGF- β 1 in the whole lung (78).

According to these findings, a two-step model can be proposed: An initial deficit in TGF- β 1 expression leads to a lack of T-regulatory cells, allowing for the induction of airway inflammation orchestrated by Th2 cells; this then orchestrates an eosinophilic inflammation, which – if strong enough – also increases TGF- β 1 in the tissue predominantly derived from those migrating eosinophils, which may activate the EMT and myofibroblasts, and finally induces fibrosis. The

increase in TGF- β 1 may still fail to block the eosinophilic inflammation due to the persistent relative deficit of Treg cells and due to the fact that Tregs do not effectively suppress Th2-induced airway inflammation (79); further studies are needed to fully unravel these mechanisms.

TGF- β 1 has direct effects on remodeling in mouse models; instillation into mouse lungs and TGF- β 1 transgenic overexpression or adenoviral expression in the airway epithelium can induce airway collagen mRNA and protein deposition (80). Consequently, anti-TGF- β 1 antibody was effective in inhibiting pulmonary fibrosis and significantly reduced collagen deposition, smooth muscle cell proliferation, and goblet cell mucus production in an asthma model (81). The treatment of OVA-sensitized asthmatic mice with ISO-1, a macrophage migration inhibitory factor antagonist, significantly reduced TGF- β 1 mRNA levels in pulmonary tissue and its protein level in BAL and inhibited airway remodeling (82). Treatment with mepacrine, a synthetic antimalarial drug, could reduce TGF- β 1 and decrease the development of sub-epithelial fibrosis (83).

In summary, TGF- β 1 is one of the main mediators involved in many aspects of persistent inflammation and tissue remodeling in the asthmatic lung. High expression of TGF- β 1 in patients with eosinophil-rich asthma was reported, but TGF levels may be low in the beginning of the disease. Controversies remain whether the concentration of TGF- β 1 directly correlates with disease severity and what role TGF release from eosinophils plays in the suppression of airway inflammation and enhancement of remodeling. Therapeutic approaches modulating the TGF- β 1 pathway may target fibrosis in asthma.

TGF- β 1 in COPD

Chronic obstructive pulmonary disorder is a global health problem and is the fourth leading cause of death in the developed world (84). The prevalence is estimated to be about 1% worldwide. Its risk factors include tobacco smoke, genetic predisposition, occupational and environmental exposure, and asthma (85). Chronic obstructive pulmonary disorder is a chronic lung inflammatory disease, characterized by irreversible expiratory airflow limitation because of two main features: small airway disease (SAD), which includes airway inflammation and remodeling, and emphysema, which is characterized by airspace enlargement (10).

Like asthma, COPD develops as a result of the participation of a variety of structural and inflammatory cells and mediators (85). Among these, TGF- β 1 has recently evolved as an important regulator in the pathogenesis of COPD. First of all, some genetic studies have identified TGF- β 1 as a promising candidate gene related to COPD. Various studies identified several single-nucleotide polymorphisms (SNPs) of TGF- β 1, which may be related to COPD susceptibility, especially in Caucasians populations (86, 87) with some inconsistency in Asians (88). Three SNPs of TGF- β 1 were found to be associated with severe dyspnea in 304 white participants (89). A quantitative meta-analysis from 100 unique case-control comparisons identified that the TGF- β 1 variant

(rs1800470) was significantly associated with COPD susceptibility (90). Second, in line with these genetic associations, increased expression of TGF- β 1 was reported in COPD lungs and primary cells, such as epithelial cells, fibroblasts, or macrophages, isolated from COPD specimens, suggesting an impact of TGF- β 1 on the development and progression of COPD (10).

Chronic obstructive pulmonary disorder is a heterogeneous syndrome associated with abnormal inflammatory immune responses of the lung to noxious particles and gases and is recently considered a Th1/Th17 disease (91). Patients with COPD show systemic inflammation with an increased influx of Th1 and cytotoxic cells into the airway (92) and with an increased expression of Th1 (STAT4 and INF- γ) CD4⁺ T cells in lungs (93). In peripheral blood, an increase in Th17 cells was observed in patients with COPD compared with current smokers without COPD and healthy subjects. In bronchial biopsies of patients with COPD compared to control subjects, IL-17F immunoreactivity is significantly higher, and the absolute number of both IL-17A- and IL-17F-positive cells is increased in the submucosa. As compared to never smokers, a greater number of Tregs was found in lungs of healthy smokers, but fewer Tregs and less FOXP3 mRNA expression was found in lungs of smokers with COPD (94). Also (95) the proportion of Foxp3⁺ Tregs in peripheral blood of patients with COPD was significantly smaller than that in healthy subjects. However, increased Tregs were reported in COPD patients with acute exacerbations (96) and in the lungs of patients with emphysema (97); an up-regulation of FOXP3-positive cells in large airways but a down-regulation in small airways was also reported (98).

Cigarette smoke (CS) as well as concomitant smoke-induced inflammation has been shown to induce TGF- β 1 production and release. Correlated with the burden of cigarette smoking, the TGF- β 1 expression in airway epithelial cells from patients with COPD and smokers was increased (99). Increased TGF- β 1 expression correlated with the number of peribronchiolar fibroblasts and basal membrane thickness (10). Additionally, the report of decreased expression of the inhibitory Smad 6 and 7 proteins in bronchial biopsies of patients with COPD further suggests increased TGF- β signaling in COPD (100). Oxidants in cigarette smoke or released by smoke-evoked inflammatory cells may cause the activation of latent TGF- β on the airway epithelial cell, leading to increased collagen production. In addition, oxidative stress may activate MMP-9, which in turn can activate latent TGF- β (101). Altogether, these data support the idea that increased TGF- β 1, mainly secreted by airway epithelial cells, contributes to the development of SAD in humans.

Abnormal repair with increased TGF- β 1 may result in fibrosis of the airways and contribute to fixed airflow limitation in SAD; inadequate repair with decreased TGF- β 1 in the face of tissue injury may contribute to the development of emphysema. Thus, TGF- β 1 is an important regulator of inflammation and remodeling and may deliver new therapeutic strategies in COPD.

Conclusions

Inflammation and remodeling have both been identified as hallmarks of inflammatory airway diseases, such as CRSsNP, CRSwNP, asthma, and COPD. TGF- β 1, with important immunomodulatory and fibrogenic characteristics, has been implicated in inflammation and remodeling processes. After activation in ECM, through Smad-dependent and Smad-independent pathways, TGF- β 1 regulates cellular functions of a variety of cell types, such as Th2, TH17, especially Treg cells, and fibroblasts to change the inflammatory processes and to synthesize ECM proteins involved in tissue repair and remodeling. Thus, TGF- β 1 represents a master switch in inflammation and remodeling processes in both upper and lower airways and provides a key for understanding inflammation and remodeling. TGF- β 1 might be thought of as a double-edged sword, inhibiting T-cell activation and down-regulating inflammatory processes, but also initiating persistent epithe-

lial activation and structural remodeling. It is the balance between these two facets that will finally determine the end result.

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Conflict of interest

The authors declare that they have no conflict of interest writing this manuscript.

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