



Lung remodeling mechanisms in chronic lung diseases

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Purpose of review

To summarize the new knowledge on tissue remodeling in the context of lung diseases. Tissue remodeling includes changes in cells: differentiation; response to growth factors, hormones, or environmental factors; and composition of the extracellular matrix. So, can one trigger cause them all or are they independently regulated?

Recent findings

New evidence from clinical and experimental studies strengthened the view that a susceptibility to remodeling can be initiated in early life and be re-activated by environmental triggers later in life. Many studies further support the idea that TGF- β plays the central role in the pathogenesis of remodeling and fibrosis. However, the activation pathways and the end-effect of TGF- β activation seems to be distinctive of disease and effector cell specific patterns. The existing animal models do not properly reflect the human disease and thus have to be further improved.

Summary

The central role of TGF- β on pathological mechanisms leading to remodeling and fibrosis has been further confirmed. However, the questions of why TGF- β is activated as well as its disease and cell type specific mode of action remain to be answered. Based on clinical data redefining the term 'tissue remodeling' in a disease and cell type specific way should be considered.

Keywords

cellular signaling, chronic inflammatory lung diseases, remodeling

INTRODUCTION

Tissue remodeling in the airway wall was regarded to be the consequence of chronic inflammation, but recent data imply that this disorder develops independently [1]. Further evidence supports the existence of a mechanism that preconditions airways during embryogenesis and early childhood to become susceptible to chronic inflammatory airway diseases later in life [2]. Even eosinophilia, which was considered to result from inflammation, can occur in childhood asthma together with remodeling independent of the classical Th-2 cytokines being present [3^{***}]. However, the underlying mechanisms are not well understood and involve epigenetic gene regulation.

Tissue remodeling can occur in any organ and at any stage of a disease. The major problem with tissue remodeling is that the term describes several independent processes which lead to lasting disorders: increased proliferation of mesenchymal cells such as fibroblasts and muscle cells; epithelial-to-mesenchymal transition (EMT); infiltration of circulating

fibrocytes; the activation of tissue resident mesenchymal stem cells; or reduced apoptosis of resident cells; which all result in hyperplasia [3^{***},4–6]. Furthermore, a high level of cell activity can lead to increased cell volume, and hypertrophy; a process which is even less well studied and understood. In addition, tissue remodeling includes: over-production of one or more components of the extracellular matrix; increased or reduced degradation of the extracellular matrix; and each of these processes is controlled by more than one enzyme [6]. A further complication in understanding extracellular matrix metabolism is the fact that degrading and building factors are integrated into the extracellular matrix and are released when the extracellular matrix is

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Curr Opin Allergy Clin Immunol 2014, 14:69–76

DOI:10.1097/ACI.000000000000022

KEY POINTS

- Clinical data further supports the idea that tissue remodeling in the lung is a pathology that develops independently of or parallel to inflammation.
- The term 'remodeling' should be re-defined and be more specific for each disease since the different components of 'remodeling' do not change the same way in all diseases.
- Experimental studies underline the central role of TGF- β in remodeling, raising the question of whether inhibition of TGF- β can be achieved in a tissue or organ specifically for developing new therapies.
- In-vitro studies suggest an interaction of TGF- β with members of the Wnt-protein family in chronic inflammatory lung diseases.

modified. Therefore, their action cannot be easily monitored and controlled on the genetic level [6,7]. In this context especially, it is important to note that some degradation products of collagens, statins, have a feedback mechanism on tissue remodeling as it was reported for asthma [8,9].

CLINICAL STUDIES

In the following section we provide an overview of clinical studies that provided new aspects of the mechanisms that lead to the well known pathologies in asthma, COPD or fibrosis.

Asthma

A postmortem analysis of airways in 51 controls, 49 nonfatal asthma patients, and 55 fatal asthma patients confirmed that hypertrophy of airway smooth muscle cells is present in the large airways in all asthma patients, while hyperplasia occurred in small and large airways of fatal asthma patients only [4]. Independently of hyperplasia or hypertrophy the increase of basal membrane and sub-epithelial extracellular matrix deposition occurred in all asthma patients. Importantly, the duration of the disease had no effect on these tissue structure changes [4].

There is further evidence from airway biopsies obtained from 23 elite swimmers, 10 age-matched patients with mild asthma and 10 healthy controls that intensive swim training in chlorinated indoor pools causes airway structure changes similar to asthma [10¹¹]. In addition, the swimmers also had increased mucin secretion, which was however, independent of airway hyper-responsiveness.

Mechanic stretching of the airway wall as it occurs during exacerbations has been implicated earlier to contribute to airway remodeling, which was re-assessed in mechanically ventilated patients ($n = 16$) with and without acute lung injury and six matched ventilated controls. Acute lung injury patients had high airway pressure, lower end-expiratory lung volume, and higher strain than controls. No significant differences were found for: gas exchange, respiratory mechanics, or extracellular matrix remodeling deposition. However, in patients with high mechanical strain, concentrations of IL-6 and IL-8 were found to be at a four-fold increase in the bronchial lining fluid [11].

Genetic polymorphisms for extracellular matrix regulating enzymes including MMP-3, MMP-9, MMP-12 and TIMP-3 correlated with the susceptibility to severe airway injury in children with chronic bronchitis and recurrent pneumonia [12]. However, the mechanism behind this correlation remains to be investigated. There is no information demonstrating whether the resulting changes in genetic information leads to changed enzymatic activity in order to explain the increased susceptibility to airway injury.

Chronic obstructive pulmonary disease

TGF- β and B-cell receptor signaling were found to be most important in gene activity screening study [13¹⁴] in COPD tissue samples. Interestingly, treatment with the tri-peptide Gly-His-Lys (GHK) blocked most of the TGF- β dependent genes in isolated human lung fibroblasts. The role of TGF- β , angiotensin-1 and IL8 in COPD was investigated in 42 COPD patients and 10 healthy controls. COPD patients were grouped by COPD severity [14]. The results indicated that regardless of the severity in the expression levels of angiotensin-1, IL-8 and TGF- β_1 were statistically significantly different when comparing patients with acute to stable COPD. Increased angiotensin-1 levels correlated more than TGF- β_1 with FEV and FEV1 in more severe patients.

Disease specific patterns of airway wall remodeling have been shown in a comparative study [15] of small airway cross-sections obtained from 261 asthma and 348 COPD patients by high-resolution computer tomography. The results indicated thicker bronchial walls in asthma patients compared with COPD patients. Furthermore, airway wall thickness and lumen diameter correlated to disease severity in asthma, but not in COPD. In biopsies of steroid naive COPD patients having 30 months of steroid treatment increased collagen type-I density and postbronchodilator FEV1 ($R_s = 0.45$, $P = 0.04$), while

smoking had no effect on extracellular matrix composition [16]. The upregulation of Wnt4 and IL-8 correlated strongly in tissue samples obtained from COPD patients [17]. The action of Wnt4-activated p38 MAPK-c-jun signaling in epithelial and airway smooth muscle cells. Moreover, the effects of Wnt4 synergistically enhanced the inflammatory action of other pro-inflammatory factors such as IL-1 β [17].

New markers for collagen degradation in COPD and idiopathic pulmonary fibrosis have been reported [18]. Collagen degradation was highly upregulated in patients with COPD and idiopathic pulmonary fibrosis, which was reflected in significantly elevated serum markers C1M, C3M, C5M and C6M compared with controls. Furthermore, C3A and C4M were only elevated in COPD patients.

Idiopathic pulmonary fibrosis

In 23 patients with idiopathic pulmonary fibrosis and 15 healthy controls, it was shown by biopsy-based tissue analysis that low numbers of early endothelial precursor cells may account to reduced tissue repair suppressed repair and recovery, thereby driving pro-fibrotic events [19]. The increased vascular endothelial growth factor (VEGF) level that was observed may present a mechanism in order to increase endothelial precursor cells. A similar role of endothelial precursor cells in idiopathic pulmonary fibrosis was presented by others in biopsy material of 64 patients [20].

In another study [21], the low level of dehydroepiandrosterone and its sulfated form in patients with idiopathic pulmonary fibrosis has been reported. In male patients with idiopathic pulmonary fibrosis both forms of dehydroepiandrosterone were significantly reduced, while in women only the sulfated form was reduced. The reason for these sex-specific differences remained unknown. Furthermore, in-vitro dehydroepiandrosterone reduced fibroblast proliferation while it increased apoptosis and thus may control tissue homeostasis in the healthy lung.

In 34 surgical lung biopsies obtained from patients with idiopathic pulmonary fibrosis immunohistochemical analysis was used to determine the expression of telomerase, α -smooth muscle actin, and the tissue expression of inter IL-4, TGF- β , and basic fibroblast growth factor [22]. The study showed high telomerase expression in areas of early remodeling, while α -smooth muscle actin expression predominated later remodeling. The detailed mechanism of how basic fibroblast growth factor and IL-4 contributed to this phase specifically remains unclear.

EXPERIMENTAL LUNG REMODELING

Based on the clinical studies described in the previous section of this review we now present experimental studies which provide more detailed analysis of pathogenic mechanisms leading to asthma, COPD or fibrosis.

Asthma

Histamine challenge stimulated airway epithelial cells to produce the epithelial growth factor receptor ligands, amphiregulin and heparin-binding epidermal growth factor-like growth factor (HB-EGF), which were both also found in airway epithelial cells of asthma patients [23]. By this mechanism histamine induced the phosphorylation of the epithelial growth factor receptor, the up-regulation of goblet cell differentiation (CLCA1), and the proliferation and migration of human airway epithelial and smooth muscle cells. Thus histamines contribute to airway remodeling of the airway epithelium by increasing goblet cell formation and sub-epithelial hyperplasia. In a mouse model intra-tracheal instilled bone marrow derived eosinophils enhanced airway inflammation, EMT and fibrosis, as well as the levels of TGF- β ₁ with subsequent activation of its signal transducer Smad3 [24]. Pretreatment of animals with TGF- β ₁siRNA decreased airway wall EMT and fibrosis, suggesting an active role of lung infiltrating eosinophils to asthma associated fibrotic tissue changes and the release of cysteinyl leukotrienes by eosinophils might contribute to airway smooth muscle cell proliferation and extracellular matrix deposition [25]. Ovalbumin challenge of mice also induced TGF- β ₁ through aldose reductase activation [26]. TGF- β ₁ activated Smad 2/3 and IP₃K – Akt – GSK3 β . Only the latter pathway up-regulated E-cadherin, vimentin, occludin and MMP-2 in epithelial cells, while in fibroblasts it upregulated α -smooth muscle actin and fibronectin; both events contribute to fibrosis (Fig. 1). Furthermore, focal adhesion kinase (FAK) was essential to mediate airway smooth muscle proliferation and contractility, involving IP₃K and MEK [27]. Steroids might reduce smooth muscle cells contractility, and correct the deficiency of high molecular weight hyaluronic acid deposition in asthma [28,29].

In human airway smooth muscle cells the over-expression of the tumor suppressor PTEN inhibited the cells proliferation, downregulated Akt phosphorylation levels and cyclin D1, while it did not alter ERK1/2 MAPK activity [30]. Upregulating, p21^(Waf1/Cip1) expression PTEN arrested the cells in the transition from the G₀ into the S-phase of the

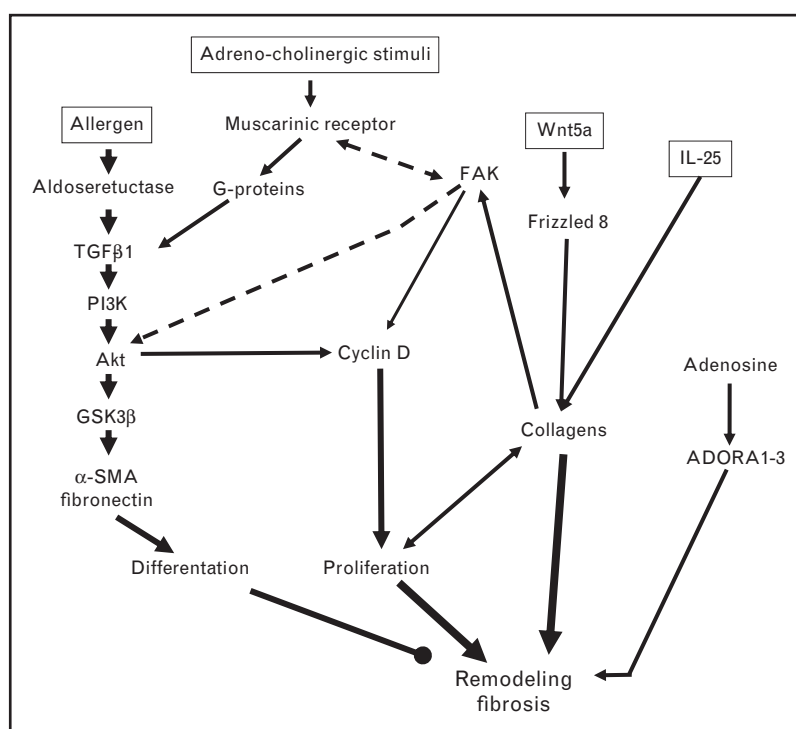


FIGURE 1. Remodeling regulating factor and intracellular signaling in mesenchymal lung cells (fibroblasts, myo-fibroblasts and smooth muscle cells). Dotted lines indicate indirect proven interactions.

cell cycle without inducing apoptosis and may present a method to control smooth muscle hyperplasia in asthma (Fig. 1). Another potential inhibitor for remodeling may be tri-arylmethane (TRAM)-34, a KCa3.1 blocker, which dose-dependently inhibited airway inflammation, Th2-type cytokines, sub-epithelial extracellular matrix deposition, goblet-cell hyperplasia, and airway hyper-responsiveness in ovalbumin-induced asthma in mice [31]. In the same cell type a cross talk between muscarinic receptors and TGF- β had been suggested as well as a regulatory role of Wnt5a and its receptor frizzled8 in extracellular matrix deposition [32,33].

In an allergen-driven asthma model in mice the blockade of IL-25 had only moderate inhibitory effects on airway eosinophilia and IL-5 and IL-13 levels. However, neutralization of IL-25 significantly reduced IL-33 and thymic stromal lymphopoietin, extracellular matrix deposition, airway smooth muscle hyperplasia and airway hyper-reactivity in house dust mite challenged and smad2-overexpressing mice. Interestingly IL-25 seems to directly act on human fibroblasts and induce collagen synthesis and may contribute to angiogenesis [34].

Mizutani *et al.* [35] introduced a mouse model for IgE-induced asthma leading to airway structural changes including goblet and fibroblast hyperplasia, and extracellular matrix deposition. As remodeling was found only after repeated IgE sensitization, the

underlying molecular mechanism remains unclear. In Fig. 1 we summarize the interactions in mesenchymal lung cells.

Chronic obstructive pulmonary disease

In the past years, several studies in primates and humans indicated clearly that prenatal or postnatal exposure to risk factors sensitizes the lungs to develop remodeling and/or fibrosis leading to COPD later in life [36]. This hypothesis had been tested in cigarette smoke exposed pregnant mice and their offspring; even so the authors' aim was to prove maternal imprinting for asthma by cigarette smoke in the F1-generation [37]. The results showed that $\alpha 7$ nicotine acetylcholine receptors, and therefore the adeno-cholinergic system, sensitized the lungs off the F1-generation to produce more TGF- β , IL-13 and collagens when stimulated with metacholine later in life. The same treatment led to functional and structural changes of the airway and lung tissue [38]. Importantly, remodeling aspects occurred in the absence of allergens and thus may represent a precondition for COPD as well. Further evidence of a role for adenosine in COPD was provided by Allen-Gipson *et al.* [39].

In COPD, a deregulation of TGF- β_1 signaling is assumed to result in lasting alveolar injury, emphysema, airway epithelial hyperplasia with fibrosis,

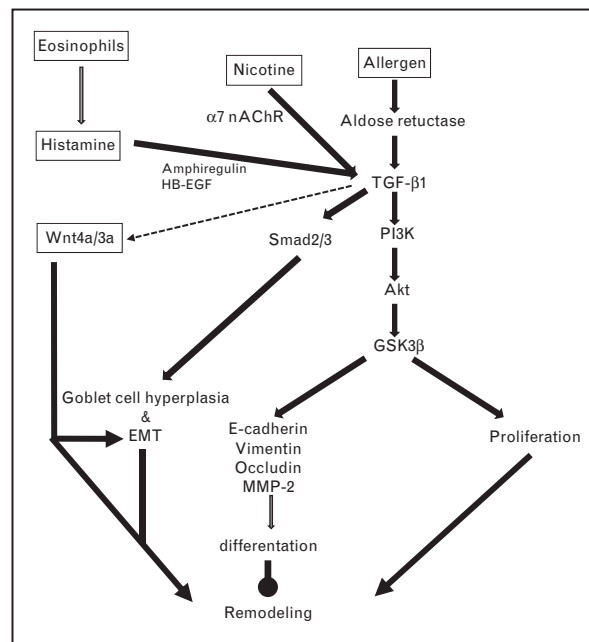


FIGURE 2. Remodeling regulation in epithelial cells. Dotted lines indicate indirect proven interactions.

and alveolar cell apoptosis, as well as oxidative stress, inflammation, metalloprotease activation and elastin in cigarette smoke-exposed mice [40]. All tissue structural changes were reduced when mice were treated with either neutralizing TGF- β_1 antibodies, or with an angiotensin receptor type 1 blocker (losartan); the latter may present a new target in COPD. In contrast, another mouse model did not confirm the stimulating effect of cigarette smoke on remodeling [41]. Based on gene activity studies the tri-peptide Gly-His-Lys (GHK) was identified as a possible inhibitor of COPD related and TGF- β_1 mediated activation of human lung fibroblasts [13^o].

In human lung fibroblasts vitamin D reduced PGE₂ independently of COX1 and COX2, but the detailed mechanism was not demonstrated [42]. It is noteworthy that vitamin D acts through its specific receptor, which acts, like the steroid receptor, as a transcription factor and forms a complex with PPAR- γ , another transcription factor that was suggested to be a novel therapeutic target in chronic inflammatory airway diseases [43]. Furthermore, vitamin D deficiency was previously linked to asthma and COPD.

The cell specific action of steroids was demonstrated in human lung fibroblasts, preventing both biglycan synthesis in airway and parenchymal fibroblasts, while reducing pro-collagen type I synthesis only in parenchymal cells [44]. Wnt4 and IL-8 upregulation correlated in biopsy material obtained from COPD patients and involved p38 MAPK – c-jun signaling in epithelial and airway smooth muscle

cells. Cell-type specific Wnt4 stimulated epithelial, but not airway smooth muscle cell growth [17]. Wnt3a signaling stimulated β -catenin in bronchial epithelial cells and induced EMT [45].

DNA methylation induced by cigarette smoke may precondition cells by an epigenetic mechanism, which consequently increases the susceptibility of embryos to develop chronic lung inflammation later in life, especially when they are again challenged by cigarette smoke. Thus, it is interesting that pharmacological modification of DNA methylation patterns and of HDAC2/SIRT1 and of their oxidative posttranslational modifications may offer novel therapeutic targets for COPD [46].

As EMT is an important factor in the pathogenesis of COPD, we summarized the interaction between the described factors on epithelial cell differentiation in Fig. 2.

Fibrosis

DNA methylation analysis highlighted similarities between carcinogenesis and the pathogenesis of idiopathic pulmonary fibrosis, suggesting that epigenetic changes in the genome account for the pathologies, while the disease specific differences remain to be elucidated [47]. In a bleomycin-fibrosis mouse model a correlation between the expression of the hepatocyte growth factor and the deposition of extracellular matrix, distal air space, and the surface area of alveolar epithelium was described. Interestingly, the expression of the hepatocyte growth factor by mesenchymal cell

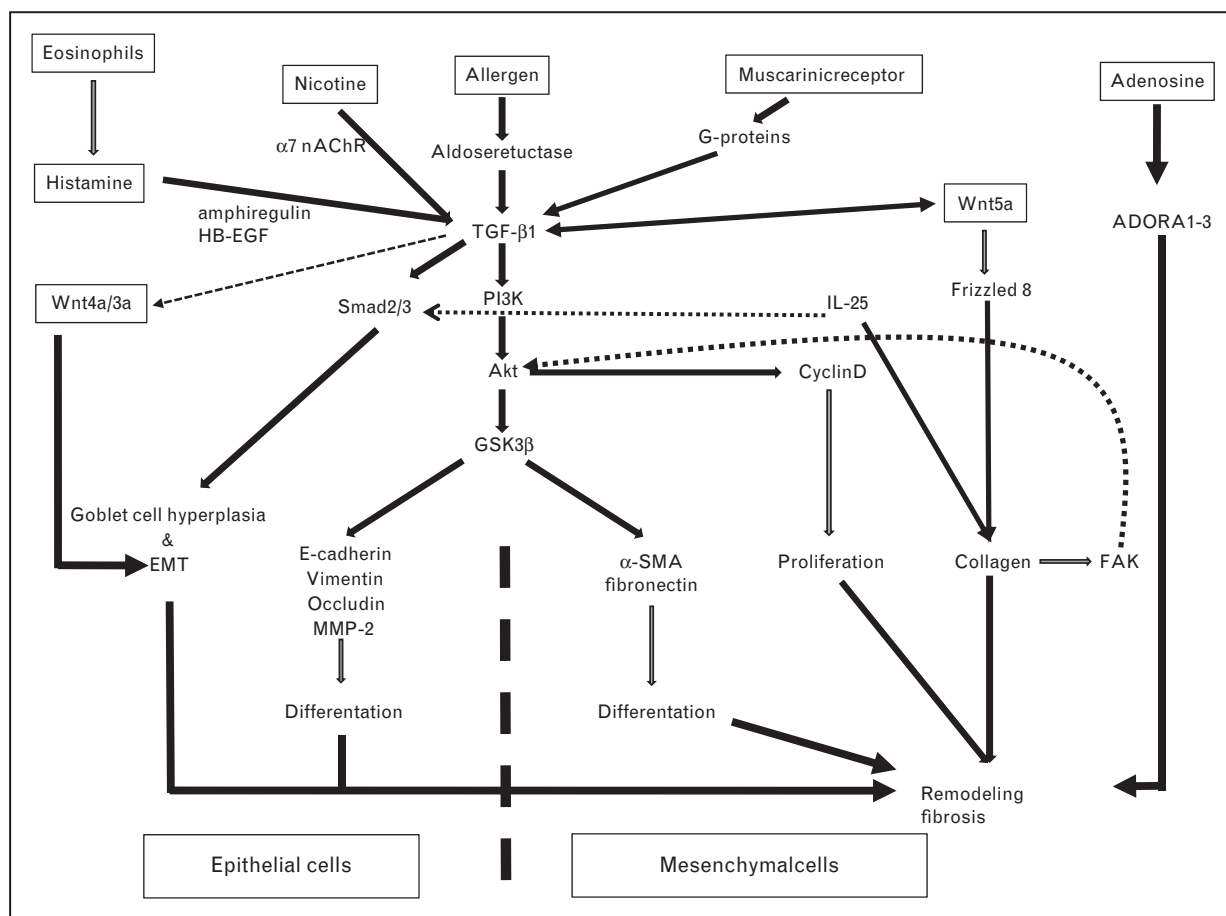


FIGURE 3. The interaction of remodeling regulating factors and their intracellular signaling pathways in the epithelial–mesenchymal–trophic unit. The left side of the black dotted line shows the regulatory pathway in epithelial cells, from both human and animal studies. The right side of the black dotted line presents signaling pathways related to remodeling and fibrosis in mesenchymal cells, which include fibroblasts, myo-fibroblasts, epithelial cell derived fibroblasts (EMT) and airway smooth muscle cells. Dotted lines indicate indirect proven interactions and the strength of the lines indicate the assumed contribution of the interaction to the subsequent step.

types led to remodeling of the connective tissue in the alveolar walls in the healthy lung [48]. However, it remains unclear if the hepatocyte growth factor plays a beneficial or a fibrosis triggering role in the lung.

Stem cell therapy is a relative novel therapeutic concept for idiopathic lung fibrosis. In a mouse model, amniotic fluid derived stem cells prevented bleomycin-induced fibrosis [49]. Amniotic fluid derived stem cells preferentially located to fibrotic lesions and increased MMP-2 levels in bronchus lining fluids in turn cleaving the pro-fibrotic cytokine CCL2.

Further links

Remodeling in activities of human lung fibroblasts have been shown to be triggered by mast cells in a co-culture system, while fibroblasts activated mast cells in a feedback mechanism [50]. Mast

cell-induced fibroblast activity was mediated through PAR-2 – PKC- α – Raf-1 – Erk1/2 MAPK leading to increased extracellular matrix synthesis, while proliferation was mediated by PAR-2 but not the subsequent signaling.

Finally, the role of protein belonging to the Wnt family, its receptors and antagonists in chronic inflammatory lung diseases has to be further investigated. Wnt proteins respectively the activation of their receptors can modify lung function, however to understand this system one has also to assess the presence of their natural occurring inhibitor [51]. There is evidence that Wnt and related proteins are released by tissue forming cells and thereby modify the action and activity of immune cells. *In vivo*, lung epithelial cells released sonic hedgehog protein upon exposure to allergens, which activated lung infiltration of T-cells [52].

CONCLUSION

Most data in humans implicated TGF- β_1 as the central factor stimulating remodeling and fibrosis in the human lung; however, general inhibition of it may lead to many unwanted side-effects due to its importance in tissue repair and homeostasis. Thus, new concepts, which are organ and cell-type specific, will have to be developed. Animal models will also have to be improved to reflect the full human disease, which needs to be mimicked before models can be used to investigate disease-specific pathogenesis and for finding treatment targets.

The question of whether inflammation precedes remodeling or vice versa, or if both events occur independently of each other, is controversially discussed and may never be clearly answered. Studying a single cell type or pro-inflammatory mediator will not answer the questions that will help us to develop new diagnostic tools and therapies. The many regulatory feedback loop-mechanisms that exist in chronic inflammatory lung diseases make it difficult to identify a single factor as the cause for a specific disease. Moreover, research in chronic inflammatory diseases has accumulated sufficient knowledge in which it should be possible to understand the complex networks that regulate cell–cell interaction between different cell types and the underlying intracellular signaling mechanisms. In regard to the above-described recent studies, we aim to provide such an overview in Fig. 3.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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