Characteristic Patterns in the Fibrotic Lung

Comparing Idiopathic Pulmonary Fibrosis with Chronic Lung Allograft Dysfunction

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Abstract

Tissue fibrosis, a major cause of death worldwide, leads to significant organ dysfunction in any organ of the human body. In the lung, fibrosis critically impairs gas exchange, tissue oxygenation, and immune function. Idiopathic pulmonary fibrosis (IPF) is the most detrimental and lethal fibrotic disease of the lung, with an estimated median survival of 50% after 3–5 years. Lung transplantation currently remains the only therapeutic alternative for IPF and other end-stage pulmonary disorders. Posttransplant lung function, however, is compromised by short- and long-term complications, most importantly chronic lung allograft dysfunction (CLAD). CLAD affects up to 50% of all transplanted lungs after 5 years, and is characterized by small airway obstruction with pronounced epithelial injury, aberrant wound healing, and subepithelial and interstitial fibrosis. Intriguingly, the mechanisms leading to the fibrotic processes in the engrafted lung exhibit striking similarities to those in IPF; therefore, antifibrotic therapies may contribute to increased graft function and survival in CLAD. In this review, we focus on these common fibrosis-related mechanisms in IPF and CLAD, comparing and contrasting clinical phenotypes, the mechanisms of fibrogenesis, and biomarkers to monitor, predict, or prognosticate disease status.

Keywords: idiopathic pulmonary fibrosis; oCLAD; rCLAD; fibrosis

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Because of a paucity of curative therapeutic regimens, many patients with end-stage chronic lung disease are listed for lung transplantation as a last therapeutic option. Idiopathic pulmonary fibrosis (IPF) is the most detrimental and lethal fibrotic disease of the lung, as such patients with IPF constitute one of the largest groups receiving lung transplants per year worldwide. Posttransplantation lung function, however, is compromised by short- and long-term complications, most importantly chronic lung allograft dysfunction (CLAD). CLAD, which affects up to 50% of all lungs transplanted after 5 years, is characterized by small airway obstruction with pronounced airway epithelial injury, aberrant wound healing, and subepithelial and interstitial fibrosis. Both IPF and CLAD share common disease features, such as extracellular matrix (ECM) deposition, architectural disruption, epithelial activation, or fibroblast hyperproliferation. To date, IPF is considered a predominantly "alveolar" disease, whereas CLAD mainly exhibits a "small airway" localization. Intriguingly, both diseases share common pathophysiological mechanisms that may provide deeper understanding of conserved mechanisms of fibrosis in the lung. Both conditions do exhibit similar survival curves: for both IPF and post–lung transplantation, median survival is about 3–5 years.

In this review, we thus focus on common fibrosis-related mechanisms in IPF and CLAD, comparing and contrasting clinical phenotypes, mechanisms of fibrogenesis, and biomarkers to monitor, predict, or prognosticate disease status. The purpose of this review is not to outline classification-related details, because this has been reviewed by Verleden and colleagues (1).

Definition and Clinical Features

Tissue fibrosis, a major cause of death worldwide (2), leads to significant organ dysfunction in any organ of the human body. In the lung, fibrosis critically impairs gas exchange, tissue oxygenation, and immune function (3). IPF is the most detrimental and lethal fibrotic lung disease (4); it develops predominantly in elderly

males with clinical symptoms occurring in the sixth and seventh decades of life, including a long and progressive history of shortness of breath and cough, a restrictive pattern in lung function (FEV_1/FVC ratio, <80%), and a decrease in the diffusing capacity of the lungs for carbon monoxide. Interstitial abnormalities, defined as a usual interstitial pneumonia pattern, are found on radiological and histological assessment and, after careful exclusion of other causes of diffuse parenchymal lung disease, a multidisciplinary consensus usually establishes the diagnosis of IPF when patients have already developed advanced lung remodeling (5). At present, two antifibrotic therapies are approved by the U.S Food and Drug Administration (FDA)/ European Medicines Agency (EMA) (nintedanib/Ofev [6] and pirfenidone/ Esbriet [7]), which have been shown to moderately decrease disease progression (8, 9).

Because these pharmacological regimens do not stabilize or cure IPF, lung transplantation remains the only definitive therapeutic alternative for advanced IPF and other end-stage lung diseases. Although transplantation prolongs survival of patients with end-stage IPF, acute and chronic rejection of the graft limit median posttransplantation survival to 55% (10). The processes that limit post-transplantation graft function and life expectancy include primary graft dysfunction, infections, large airway complications, thromboembolism, pleural effusions, and chronic graft rejection, among others (11). Importantly, patients with IPF and chronic obstructive pulmonary disease exhibit the worst median survival of all lung diseases, for which lung transplantation is performed (7). As such, understanding the mechanisms of chronic lung allograft dysfunction, in particular the mechanisms leading to the fibrotic processes in the engrafted lung, may ultimately contribute to increased graft function and survival using antifibrotic therapies.

To better understand and define chronic rejection processes after lung transplantation, the term "chronic lung allograft dysfunction" (CLAD) was introduced to account for the various manifestations of chronic allograft rejection (1). First, lung allograft dysfunction was identified on the basis of the FEV_1 response after treatment with the neomacrolide azithromycin and high bronchoalveolar lavage (BAL) fluid neutrophil counts (≥10% FEV_1 increase after a 2- to 3-mo treatment). Those patients were designated as having azithromycin-responsive allograft dysfunction (ARAD). However, only 35% of these patients showed an initial response. Patients not responding to azithromycin were designated as having CLAD, defined as a persistent decline in FEV_1 of at least 20% compared with the mean of the two best postoperative values (12). The CLAD definition has been extended to include restrictive CLAD (rCLAD; also named restrictive allograft syndrome, RAS) and obstructive CLAD (oCLAD; also called bronchiolitis obliterans syndrome, BOS). rCLAD (RAS) is characterized by a restrictive physiology; a persistent decline in VC and TLC, which is accompanied by a decline in FEV_1 of more than 20%; and a predominantly pleuroparenchymal pattern of fibrosis. In contrast, oCLAD is characterized by a strictly airway-related pathology (13). Importantly, rCLAD (RAS) exhibits poorer graft function after diagnosis compared with oCLAD (BOS) (median survival, 0.6–1.5 vs. 3–5 yr) (14), even if early-onset BOS limits prognosis for all posttransplantation patients (15). The mechanisms of airway fibrosis in CLAD are likely multifactorial, but have been extremely poorly studied up to now.

Mechanisms of Injury and Cellular Phenotypes in CLAD and IPF

Several studies have explored the pathomechanisms of CLAD. Those studies that have used and characterized human samples, in particular, have not been properly classified into the CLAD phenotypes known today. Therefore, this section summarizes data from those studies, although it remains unclear in many instances whether they included rCLAD or oCLAD phenotypes. It is also likely that other manifestations of CLAD, such as ARAD, were included in those studies. Thus, care should be taken when interpreting and extrapolating those studies to the new CLAD nomenclature.

Although IPF and CLAD clearly exhibit distinct disease origins, both syndromes have overlapping characteristics with respect to pathophysiology (Table 1). These pertain to epithelial cell injury and activation, increases in ECM production and deposition, immune cell activation, and fibroblast proliferation, albeit this partially occurs in different lung compartments. To date, IPF is characterized by alveolar epithelial injury, dysfunction, and hyperplasia, subepithelial accumulation of α-smooth muscle actin–positive fibroblastic foci, and increased deposition of ECM components, such as collagens or fibronectin (4). Similarly, oCLAD (BOS) is characterized by pronounced airway epithelial cell injury and dysfunction, aberrant wound healing with peribronchiolar leukocyte infiltration, and peribronchiolar fibroblast accumulation, remodeling, and fibrosis. Further, dysbalanced cellular mechanisms, such as growth factor dysregulation (16–18), protease–antiprotease imbalance (19, 20), endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) (21), and the epithelial-to-mesenchymal transition (22), contribute to the pathology of both IPF and CLAD.

ER Stress and the Unfolded Protein Response

The UPR is an evolutionarily conserved adaptive machinery of the ER reaction to a variety of cellular stressors. The UPR, which is highly conserved in mammals and other organisms, aims to clear unfolded proteins and restore ER homeostasis. When ER stress cannot be reversed, cellular functions are critically impaired, which often leads to cell death (23). Thus far, evidence of UPR has been documented in a large number of diseases, such as neurodegenerative disorders (24, 25), kidney diseases (26), and cancer (27, 28), thereby identifying this homeostatic pathway as an important therapeutic target in many diseases (29).

There is a growing body of evidence that an altered UPR represents a major contributor to alveolar injury and disease perpetuation in IPF (30). Initially, mutations in surfactant protein C (SP-C) in familial interstitial pneumonia have been associated with increased ER stress and UPR in alveolar epithelial cells (AECs) (30, 31). This is supported by data from mouse models expressing the mutant L188Q SFTPC exclusively in type II alveolar epithelium, which showed an exaggerated UPR and fibrotic response to bleomycin-induced fibrosis (21). Biopsies

Table 1. Pathomechanisms contrasting idiopathic pulmonary fibrosis and chronic lung allograft dysfunction

Pathomechanism	IPF	CLAD
Fibrosis/ECM deposition	Subpleural and interstitial	rCLAD: Pleural and parenchymal oCLAD: Small airway
Epithelial dysfunction	Hyperplastic and apoptotic alveolar and distal bronchial epithelium	Bronchial epithelium: EMT and regeneration failure
ER stress	SP-C mutations in AEC myofibroblast differentiation	HBECs: Hyaluronan induction

Definition of abbreviations: AEC = alveolar epithelial cell; CLAD = chronic lung allograft dysfunction; ECM = extracellular matrix; EMT = epithelial-to-mesenchymal transition; ER = endoplasmic reticulum; HBECs = human bronchial epithelial cell; IPF = idiopathic pulmonary fibrosis; oCLAD = obstructive CLAD; rCLAD = restrictive CLAD; SP-C = surfactant protein C.

of patients with sporadic IPF also demonstrated UPR activation in AECs lining areas of fibrotic remodeling, as evidenced by expression of apoptotic cleaved caspase-3 and ER stress markers (p50, ATF-6, ATF-4, CHOP, XBP-1) (32). Importantly, not only AECs, but also fibroblasts show signs of ER stress during fibrosis, for example, in fibroblast–myofibroblast differentiation induced by transforming growth factor (TGF)-β (33). Taken together, there are several lines of evidence that indicate that ER stress is a contributor to AEC injury in lung fibrosis.

To date, there is a paucity of data supporting a definitive role of ER stress in disease onset or progression of CLAD, or with respect to stratification to a specific CLAD phenotype (rCLAD or oCLAD). On the basis of the literature, ischemia–reperfusion injury and acute rejection episodes can induce ER stress in transplanted organs (34). *In vivo*, ER stress was detected in 40% of bronchial epithelia of patients with BOS and associated with subepithelial hyaluronan deposition (35). *In vitro*, bronchial epithelial ER stress led to the expression of lymphocyte-trapping hyaluronan (36). These limited data reinforce the need for more studies to better understand the role of ER stress in CLAD.

Epithelial Injury and Hyperplasia, Epithelial–Mesenchymal Transition

Epithelial injury, hyperplasticity, and epithelial-to-mesenchymal transition (EMT) on injury have been documented in multiple diseases (37), especially in cancer (38). Although the process and contribution of EMT to IPF remains a controversial topic to date, several groups have investigated the contribution of epithelial cells to the activated fibroblast pool and ECM production in the fibrotic lung (39). Fate mapping studies in mice have shown that about 30% of the $S100A4^+$ fibroblast pool is epithelial in origin in the multiple-hit bleomycin model (40). Importantly, subsequent studies using different mouse lines were unable to show contribution of the epithelium to the myofibroblast pool, but instead reported that mesenchymal cells, such as pericytes, are precursors of activated myofibroblasts after injury (41). In humans, immunohistochemical stainings of IPF tissue have shown that fibroblasts in fibroblast foci stained positive for epithelial markers (42), and epithelial-like cells lined fibrotic areas positive for fibroblast markers (43). Importantly, other groups have found no histological evidence of EMT in IPF (44). It is therefore critical to highlight that EMT is difficult to document *in vivo* in humans; nonetheless, there is substantial evidence that the hyperplastic epithelium contributes to fibrotic injury by secreting ECM components and soluble mediators that enhance fibroblast proliferation and survival.

There are numerous studies that document evidence of EMT in CLAD after lung transplantation. Here, isolation of primary bronchial epithelial cells from patients with BOS exhibit evidence of EMT (45). In detail, 15% of epithelial cells in biopsy sections from lung transplant recipients stained positive for S100A4 and matrix metalloproteinase (MMP)-7. Similarly, primary human bronchial epithelial cells from transplant recipients showed baseline expression of MMP-2, MMP-9, cytokeratin, and S100A4; coexpression of E-cadherin with vimentin and fibronectin in single cells was also detected (46, 47). Common injuries, such as infections with *Pseudomonas aeruginosa* (48) or graft ischemia (49, 50), may also induce EMT in bronchial epithelial cells.

Club cells (Clara cells) serve as progenitor cells capable of renewing the bronchial epithelium during injury (51). Many groups have shown that dysregulation of club cell secretory protein (CCSP) is associated with BOS development. Initially, Nord and colleagues (52) showed in a 2-year follow-up cohort that patients with BOS had significantly less CCSP in serum and BAL compared with control subjects (no BOS), which was later confirmed by others (53). Additional studies suggested that the decreased CCSP levels were due to a regenerative failure of club cells (54, 55). Bourdin and colleagues demonstrated that the reduced potential for club cell–related repair was related to an A38G single-nucleotide polymorphism (SNP) in the donor CCSP gene, which was associated with decreased CCSP levels early after lung transplantation and poor long-term outcome (56). Further, reduced expression of surfactant protein (SP)-A in tissue and BAL, as well as poor prognosis of BOS, was associated with an SP-A2 gene SNP (57).

The data summarized above highlight the pathogenic relevance of the bronchial epithelium in CLAD. Although these cells have been neglected for a long time in IPF, several studies have highlighted that dysregulation of bronchial-related secreted factors, in particular mucins, occurs in IPF. Data from the Schwartz laboratory have identified an SNP in the promoter region of an airway mucin gene (MUC5B), which was associated with increased production of MUC5B and IPF (58). Further work from the same group and others confirmed these associations (59), and uncovered other polymorphisms (e.g., TERT, TERC, FAM13A, DSP, OBFC1, ATP11A, and DPP9), which might also be associated with IPF. Importantly, the expression of cilium-associated genes was shown to identify a unique molecular phenotype of IPF, characterized by extensive honeycombing and higher expression of MUC5B and MMP-7 (60). The histological lesion termed "honeycombing" is

suggested to derive from the distal airway epithelium, which was defined as a pseudostratified mucociliary epithelium predominantly expressing MUC5B (61, 62). In summary, these novel data suggest that alterations in bronchial epithelial-related processes contribute, to a much greater extent, to altered repair mechanisms of the IPF lung than previously appreciated (63).

Clearly, the above-mentioned characteristics of the CLAD phenotypes ARAD, oCLAD (BOS), and rCLAD (RAS) vary in extent and magnitude (1). Therefore, comprehensive mechanistic studies are required to determine and understand the distinct cellular pathomechanisms in these entities. For instance, specific expression of alveolar alarmins was discovered on tissue damage and activation of the immune system (64), which may differentiate CLAD phenotypes. As published, BAL of patients with rCLAD (RAS) exhibited higher S100A9, S100A8/9, S100A12, S100P, and HMGB1 levels compared with patients with oCLAD (BOS) or control subjects, yet the functional consequence of these elevated alarmin levels remains to be elucidated (65). These data relate to similar findings of activated growth factors during lung fibrosis, such as TGF-β (16), hepatocyte growth factor (66), platelet-derived growth factor (67), or fibroblast growth factor (68). In CLAD, several reports detected an increase in BAL fluid of hepatocyte growth factor, a growth factor known to influence epithelial differentiation (45, 69). Moreover, high levels of TGF-β_1, the prototypic profibrotic growth factor, were detected in BAL and tissue of patients with BOS (17, 70).

Mesenchymal Cells and Myofibroblasts

Cells from the mesenchymal lineage play a prominent role in any fibrogenic process. Resident lung-specific mesenchymal stromal cells (MSCs) were initially detected in BOS tissue samples and demonstrated distinct proliferation, migration, and differentiation properties *in vitro* after isolation from BAL. These MSCs exhibited increased levels of α-smooth muscle actin, collagen I, and endothelin-1, as well as decreased SP-B levels (71, 72). An inhibitory effect was observed after treating MSCs with prostaglandin E_2, suggesting that an autocrine–paracrine mechanism exists (73). Lung-resident allograft-derived MSCs from BAL expressed forkhead/winged helix transcription factor forkhead box (FOXF) mRNA, which correlated with the number of MSCs detected in BAL. In addition, FOXF1 positively stained myofibroblasts of fibrotic lesions (71), suggesting that lung-resident MSCs can possibly give rise to myofibroblasts. Circulating fibrocytes of recipient origin may also be involved in the development of BOS, as higher fibrocyte numbers were reported in patients with BOS compared with control subjects (53, 74). Analysis of circulating precursor cells demonstrated that 15–30% of myofibroblasts were of recipient origin, which supports the idea of involvement of circulating precursor cells in the development of fibrotic lesions. Further, an increased number of fibrocytes and mesenchymal progenitor cells correlated with BOS development and severity; therefore, these cells may be used as a biomarker and/or potential therapeutic target in BOS (74–76). Several groups have discussed the role of neutrophils in BOS, because neutrophilia is a common finding in patients with BOS and is associated with a pronounced protease–antiprotease imbalance (70, 77).

Immune Cells and Mediators

Neutrophilia in stable recipients is reported to exhibit a predictive value to identify recipients at risk for BOS (78, 79). Lately, the role of neutrophilia in CLAD was analyzed in properly classified patients, where neutrophilia was associated with ARAD and persistent airway neutrophilia, but not with oCLAD or rCLAD (80). Evidence also suggested that BAL eosinophilia is a strong predictor for CLAD development (81), particularly rCLAD (82). Interestingly, high levels of eosinophils are also described in patients with IPF, where they are detected in BAL and tissue, and negatively correlate with lung function and survival rate (83, 84). The role of these immune cells therefore seems to be critical in CLAD pathogenesis, but clearly requires additional studies with patients with properly stratified CLAD to evaluate, in detail, the contribution of neutrophils and eosinophils in CLAD.

High levels of IL-1α, IL-1β, and IL-8 were previously related to BOS in general (70), to ARAD and persistent airway neutrophilia (80), but not to oCLAD or rCLAD. In contrast, the chemoattractant peptide proline-glycine-proline (PGP) was increased in the BAL of patients with BOS, and CXCR3 ligand was highly abundant during the phase of diffuse alveolar damage (85, 86). Interestingly, when cytokine expression levels were measured in preimplanted donor lungs, high IL-6 expression was predictive for posttransplantation CLAD (87). Furthermore, the chemokine CXCR2 seems to be important for early neutrophil influx and subsequent vascular remodeling in BOS (85, 88). Neutrophil recruitment leads to activation of proteases, mainly MMP-9 and -2 (89–91). Interestingly, increased levels of MMP-8, -9, and tissue inhibitor of metalloproteinase-1 were detected in BAL of posttransplantation patients, independent of infection or rejection (92).

In general, chronic rejection is characterized by fibrotic changes of the implanted organ parenchymal structure that affects graft function. This is thought to be initiated by a host anti-graft immune response, in an antigen-dependent or -independent manner, involving cell- and humoral-mediated immunity leading to graft dysfunction (93, 94). In the lung, a large body of evidence supports the idea that circulating donor-specific HLA antibodies are associated with BOS (95, 96). Autoimmune responses to autoantigens potentially exposed during injury and tissue remodeling were related to increased expression of proteases and ECM components in the lung microenvironment (89, 91, 92). In particular, type V collagen (97–99) and anti–K-α_1 tubulin have been shown to significantly contribute to the pathogenesis of BOS in animal models and clinical samples alike (100–102). Various cytokines have been related to CLAD, such as the CXCR3 ligands CXCL9, CXCL10, and CXCL11, which have been shown to be associated with the diffuse alveolar damage lesion in CLAD (85). A modulator of cytokine signaling and critical component of the lung ECM, hyaluronic acid, is localized within intraluminal fibrotic tissue in patients with BOS (35, 103, 104). Hyaluronic acid is increased in the BAL and blood of patients with BOS compared with control subjects, and mRNA levels of hyaluronan synthases 1 and 3 are detected in patients with end-stage BOS (105). Todd and colleagues also confirmed, using a murine orthotropic lung transplant model, that low-molecular-weight

hyaluronic acid triggers lung allograft rejection, via an increase in neutrophils and expansion of allogeneic $CD4^+$ T cells. This reaction is promoted by dendritic cell presentation of low-molecular-weight hyaluronic acid, which induced helper T type 1 and type 17 responses via a Toll-like receptor–mediated mechanism (105).

Monitoring and Phenotyping Disease: Biomarkers in IPF and CLAD

Biomarkers are useful in various situations: they can help stratify the risk for disease development, diagnose disease (sub)types, monitor treatment responses, and predict disease severity and/or outcome, among others (106). Whereas significant advances in biomarker discovery and validation, as well as therapeutic development (with two drugs for IPF approved by the FDA), have been achieved in IPF, these processes are currently underway in CLAD. Because CLAD has been categorized in subtypes, imaging and pulmonary function testing remain the main monitoring strategy available. Although potential targets that reflect ongoing rejection have been discussed, there are currently not enough data, using large cohorts with replication and validation approaches that support biomarkers, at this time for clinical use.

Two publications significantly increased our knowledge about lesion characteristics and physiological phenotyping of CLAD. Verleden and colleagues (107) have thoroughly described the obstructive airway lesion in CLAD in unprecedented detail: After lung transplantation, lesions are located in conducting airways and uniformly distributed within the lungs. These CLAD lesions develop in airways with a mean lumen diameter of 647 ± 317 μm, and the mean length of the obstructive lesion has been measured as $1{,}063 \pm 157$ μm. No lesions are observed in larger airways and terminal bronchioles, and the alveolar surface area usually remains unchanged. Histologically, lesions seem to be heterogeneous: obstructive, fibrous, and mostly rich in collagen. Several groups have shown that 30% of patients with CLAD have an FVC decline at CLAD onset, a feature associated with worse survival, which largely may be rooted in more fibrotic CLAD lesions (108, 109). It is important to note, however, that bringing biomarkers to clinical practice is a challenging task. Although an unprecedented body of literature has described and validated biomarkers for IPF diagnosis and outcome prediction in multiple cohorts and centers, none have yet entered the clinical arena. Ley and colleagues have comprehensively reviewed the available biomarker scenario in IPF (110), highlighting the limited number of biomarkers entering clinical practice in IPF. These include MUC5B genotyping (58) and peripheral blood measurement of MMP-7 (111, 112), which should by now be used throughout academic centers working in IPF.

Outlook

CLAD is a severe disease of patients who have undergone lung transplantation, affecting 50% of all patients, and it limits overall posttransplantation survival. In the last two decades, several studies have been performed to elucidate the pathomechanisms underlying CLAD; however, detailed knowledge is still limited and curative therapeutic approaches are not available. Several aspects in the study of CLAD are challenging: One aspect is the heterogeneity of the CLAD process, which has led to the new classification including restrictive CLAD (rCLAD; also named restrictive allograft syndrome, RAS) and obstructive CLAD (oCLAD; also called bronchiolitis obliterans syndrome, BOS). In early studies, the common terminology BOS prevailed, which is now a subcategory of CLAD. Therefore, many initial studies may have to be reconsidered/reevaluated in terms of inclusion criteria and subphenotyping. Moreover, the nature of the fibrotic process in CLAD and its subtypes is not fully understood yet, especially in the context of tissue remodeling and ECM deposition. A lack of knowledge also exists of the characteristic cellular phenotypes driving this process. Largely, cell types were generated from BAL or bronchial epithelial brushings, limiting the analysis of structural cell types and tissue composition. Although MSCs have been studied in detail, the role of other mesenchymal cells, such as fibroblasts or bronchial smooth muscle cells, has not been characterized thus far. As these cells, as well as alveolar epithelial cells, are of great importance in the context of ECM production and angiogenesis, their specific role in CLAD might be of special interest. Finally, the tissue microenvironment is influenced by immunomodulatory cells, such as macrophages, because the innate immune system contributes to the development of BOS. Therefore, including cell types of the immune system in great detail will be important in the future. Genetic studies of CLAD are rare because of limited patient cohort sizes, and although a pool of biomarkers is associated with CLAD or one of its subcategories, these will have to stand the test of time in large validation studies.

Importantly, the number of lung transplantations has continuously increased, and it will continue to do so in the future. Intensive research in CLAD will be necessary at this point to significantly improve the outcome of lung transplantation and push graft function to levels of other solid organs. Therefore, scientific approaches will have to lead to a better understanding of the cellular pathomechanisms driving the CLAD process and the identification of biomarkers helping to determine different CLAD phenotypes and outcome at early stages of the disease. In our view, using the lessons learned from a decade of world-class research in IPF may help to achieve these goals. ■

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