CHEST

Current Concepts in Pathogenesis, Diagnosis, and Management of Smoking-Related Interstitial Lung Diseases

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Tobacco exposure results in various changes to the airways and lung parenchyma. Although emphysema represents the more common injury pattern, in some individuals, cigarette smoke injures alveolar epithelial cells and other lung cells, resulting in diffuse infiltrates and parenchymal fibrosis. Smoking can trigger interstitial injury patterns mediated via recruitment and inappropriate persistence of myeloid and other immune cells, including eosinophils. As our understanding of the role of cigarette smoke constituents in triggering lung injury continues to evolve, so does our recognition of the spectrum of smoking-related interstitial lung changes. Although respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia, pulmonary Langerhans cell histiocytosis, and acute eosinophilic pneumonia have a well-established association with tobacco use, its role and impact on idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, and connective tissue disease-related interstitial lung diseases is still ambiguous. Smoking-related interstitial fibrosis is a relatively newly appreciated entity with distinct histopathologic features but with unclear clinical ramifications. Increased implementation of lung cancer screening programs and utilization of CT scans in thoracic imaging have also resulted in increased identification of "incidental" or "subclinical" interstitial lung changes in smokers, the ensuing impact of which remains to be studied.

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Cigarette smoking is implicated to varying degrees in a distinct but heterogeneous group of parenchymal lung diseases (smoking-related interstitial lung diseases [ILDs]) in addition to emphysema. Lung diseases in this spectrum can be grouped into those that likely have a causal association with tobacco exposure (respiratory bronchiolitis-interstitial lung disease [RB-ILD], desquamative interstitial

ABBREVIATIONS: AEC2 = type 2 alveolar epithelial cells; AEP = acute eosinophilic pneumonia; CPFE = combined pulmonary fibrosis and emphysema; CTD-ILD = connective tissue disease-related interstitial lung disease; DIP = desquamative interstitial pneumonia; GGO = ground-glass opacity; HRCT = high-resolution CT; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PDGF = platelet-derived growth factor; PH = pulmonary hypertension; PLCH = pulmonary Langerhans cell histiocytosis; RA = rheumatoid arthritis; RB = respiratory bronchiolitis; RB-ILD = respiratory bronchiolitis-interstitial lung disease; SRIF = smoking-related interstitial fibrosis; UIP = usual interstitial pneumonia

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pneumonia [DIP], pulmonary Langerhans cell histiocytosis [PLCH], and acute eosinophilic pneumonia [AEP]) and those in which smoking likely acts in conjunction with endogenous or exogenous factors but causality is yet to be established (idiopathic pulmonary fibrosis [IPF], combined pulmonary fibrosis and emphysema [CPFE], and connective tissue disease-related interstitial lung disease [CTD-ILD]). The present review discusses our current understanding of the manifold mechanisms by which cigarette smoke inhalation can trigger and propagate interstitial lung injury in smokers, as well as the key clinical features that differentiate these disorders. We also discuss the potential clinical ramifications of smoking-related interstitial fibrosis (SRIF) and the downstream impact of incidentally detected "subclinical" interstitial lung changes in smokers.

Mechanisms and Spectrum of Cigarette Smoke-Induced ILDs

Tobacco smoke is a toxic assortment of particulate matter and various chemicals that induce inflammatory, genotoxic, proliferative, and other stimuli to lung cells that extend from the conducting to the gas exchange zones. Reactive oxidant species, nicotine, and other toxins in cigarette smoke induce epithelial as well as endothelial cellular activation, often leading to secretion of a variety of inflammatory cytokines and chemokines that secondarily recruit immune cells into various lung compartments, including small and large airways and the lung parenchyma.[1,2] Emphysema, the more common parenchymal lung injury pattern associated with smoking, is associated with alveolar cell apoptosis and destruction accompanied by loss of lung scaffolding. Although morphologically very different compared with lesions observed in smoking-induced diffuse lung diseases, some of the mechanisms by which smoking induces emphysema are similar to those involved in fibrosis and distal lung remodeling.

One cell type that is likely central in the pathogenesis of both emphysema and lung fibrosis is the alveolar epithelial stem cell. In the lung, a subset of type 2 alveolar epithelial cells (AEC2) performs the function of new AEC2 progenitors as well as a source of new type 1 alveolar epithelial cells. In this context, certain pathogenic events such as telomere dysfunction and predisposition to cellular senescence may provide insight into the susceptibility of some smokers to develop either emphysema or fibrotic interstitial lung changes (or a combination of both). Telomerase is an enzyme system that performs the essential function of maintaining telomeres on the ends of chromosomes.[3] This cellular function is critical as evidenced by the predisposition of cells with abnormally short telomeres to develop a phenotype of senescence and apoptosis. Studies performed in telomerase knockout mice revealed an increased susceptibility to cigarette smoke-induced damage and development of emphysema.[4] This finding may be particularly relevant to understanding susceptibility to both emphysema and fibrosis because of the demonstration that up to 10% of patients with nonfamilial fibrotic idiopathic interstitial pneumonia (most of whom have IPF have abnormally short telomere lengths[5]). Although this study did not perform correlations between smoking history and telomere length, it does suggest a common mechanism by which certain smokers may develop a predisposition to alveolar epithelial cell senescence and an abnormal lung regenerative pathway that may lead to the phenotype of emphysema in some and fibrosis in others (or even both in some patients).

The induction of alveolar epithelial cellular senescence by cigarette smoke is potentially also pivotal for the development of either emphysema or interstitial changes and fibrosis in certain smokers. Cellular senescence, a state of replicative arrest brought on by cellular stressors (including cigarette smoke), results in emergence of the senescence-associated secretory phenotype.[6] The mediators secreted by these cells include a variety of cytokines, chemokines, matrix metalloproteinases, and growth factors that have been implicated in the pathogenesis of both emphysema and pulmonary fibrosis.[6] It is possible that the induction of senescent cells in the lungs of predisposed smokers may be sufficient to drive a subsequent inflammatory and tissue remodeling response, such that the ensuing inflammatory cell recruitment becomes a secondary phenomenon of the aberrant biology, rather than a primary driver of tissue injury, and may provide some insight into why antiinflammatory (corticosteroid or other immunomodulatory) therapy is generally lacking in therapeutic efficacy in at least some of the tobacco-induced lung diseases.

Cigarette smoke, or its constituents, can also directly induce profibrotic factors from lung cells.[7,8] Among the growth factors directly induced by cigarette smoke, transforming growth factor-beta 1 (TGF-β_1) and platelet-derived growth factor (PDGF)-A and -B are particularly relevant.[8,9] TGF-β_1 is essential for matrix generation (including collagen, fibronectin, and elastin)

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