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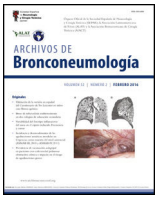

Editorial

Smoking and Interstitial Lung Damage/Effects: A Plausible Association?☆

Tabaco y alteraciones intersticiales: ¿una asociación plausible?

Inhaled tobacco smoke delivers multiple harmful particles that cause inflammatory, genotoxic, and proliferative changes in the entire lung anatomy from the airway to the parenchyma. Lung cancer and chronic obstructive pulmonary disease are the lung diseases most commonly associated with smoking, but today it is estimated that 8%–10% of smokers have some associated interstitial lung abnormalities.[1] This association is dose-dependent, i.e., the greater the exposure to tobacco smoke, the greater the risk.[1,2] As our knowledge of how tobacco injures the lung increases, so does our understanding of the heterogeneous breadth of the spectrum of smoking-related interstitial lung diseases (ILD). These pathologies primarily include respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia, pulmonary Langerhans cell histiocytosis, acute eosinophilic pneumonia, combined pulmonary fibrosis and emphysema, smoking-related interstitial fibrosis, and idiopathic pulmonary fibrosis.[3]

At the biological level, it is plausible that smoking-induced cell abnormalities associated with small airway changes and alveolar wall destruction also affect the interstitium. Pathogenic studies are still lacking, but ILD may be associated with mechanisms that parallel those of chronic obstructive pulmonary disease and lung cancer, primarily:

a) Immune response changes

Cigarette smoke can affect the immune system at different levels. It can chemically modify signaling pathways and extracellular matrix by acetylation, nitrosylation, carbonylation and oxidation, which can impact the survival, activation and differentiation of immune cells.[4] These immunological modifications can have two types of opposing consequences: they can either trigger a proinflammatory cascade, or they can have an immunosuppressive effect,[5] due to reduced macrophage phagocytic ability,[6] and decreased NK cell function, immunoglobulin activity, dendritic cell maturation, and lymphocyte function.[3] As a result of these mechanisms, pulmonary fibrosis is often characterized by elevated neutrophils, monocytes and macrophages that promote a moderate proinflammatory state with the production of cytokines IL-8, IL-6 and CCL2 and an increase in senescent T lymphocytes that produce Th2 cytokines, considered profibrotic.[7] Prasse et al.[8] demonstrated that osteopontine, a glycoprotein with cytokine-like properties, is increased in the extracellular matrix of bone as a result of chronic exposure to nicotine in patients with smoking-related ILDs, particularly in desquamative interstitial pneumonia and pulmonary Langerhans cell histiocytosis.

b) Oxidative stress

It is well established that tobacco causes oxidative stress due to the inability of endogenous pulmonary antioxidant mechanisms to combat the increased levels of free radicals caused by cigarette smoke. This process leads to increased transcription of inflammatory genes, among other mechanisms, which, through the release of cytokines and chemokines, perpetuate the inflammatory response and induce rapid lung aging by increasing the activity of proteases and other mediators (both in the large and small airways and the parenchyma).[9]

c) Premature aging

It has been associated with both COPD and idiopathic pulmonary fibrosis. In addition to oxidative stress, telomere shortening, cellular senescence, epigenetic changes (histone acetylation and hypermethylation), loss of proteostasis, mitochondrial dysfunction, and DNA damage are considered distinctive of the aging process.[10,11] Many of these mechanisms are associated with smoking: for example, smokers who develop pulmonary fibrosis show telomere shortening (present in the circulating leukocytes of smokers, and more pronounced the greater the cumulative exposure to tobacco smoke[12]). The aggression from cigarette smoke causes aging mesenchymal stem cells in the bone marrow to accumulate DNA damage and lose their response to soluble factors. This could impair their ability to repair damaged organs, which could increase susceptibility to the development of fibrosis.[10] Moreover, senescent epithelial cells produce numerous profibrotic mediators that, together with senescent fibroblasts, may favor pulmonary fibrosis.[13]

In conclusion, there is evidence that smoking plays a role in the pathogenesis of ILD that is not yet well established. Prevention and treatment of smoking are essential to treat such diseases, although in many cases cessation is not enough to prevent progression. It is therefore extremely important to characterize the cell pathways by which tobacco smoke induces different interstitial lung diseases, because understanding the relevant pathogenic pathways will help us develop new drugs

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aimed at specific targets and thus change the course of these diseases.

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