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COPD, IPF and tobacco: What are the common (immune) denominators?

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COPD, IPF and tobacco: What are the common (immune) denominators?

Chronic Obstructive Pulmonary Disease (COPD) and pulmonary fibrosis, including idiopathic pulmonary fibrosis (IPF), remain among the leading chronic respiratory diseases that represent major public health challenges worldwide. The physical, psychological and socioeconomic burden of both diseases is a major concern and, with the population ageing, their impact on patients and healthcare systems is expected to worsen significantly (1).

COPD and IPF are two severe chronic respiratory diseases which differ in their clinical manifestations and pathophysiology. COPD is characterized by a persistent airflow limitation, primarily marked by chronic airway inflammation, airway remodelling and destruction of the alveolar compartment (2). IPF is a progressive fibrotic interstitial lung disease of unknown aetiology, mainly characterized by aberrantly activated epithelial cells and fibrosis in the interstitial tissue (3). Despite these obvious differences, they do share, however, several common threads. COPD and IPF share some overlapping risk factors such as environmental exposures, age, genetic predisposition and respiratory infections, but probably the first and

most prominent risk factor that comes to mind is tobacco smoking (1). Although these diseases can occur independently of smoking, patients who actively smoke or have a history of smoking additionally experience greater accelerated loss of lung function, more severe decline in quality of life, higher risk of acute exacerbations and worse clinical outcomes (2, 3). Moreover, both diseases also share common underlying pathomechanisms such as lung tissue remodelling, immune dysfunction, accelerated ageing and oxidative stress (2-4). This editorial explores how these interconnected biological pathways converge focussing on how smoking influences COPD and IPF development and progression by altering adaptive immune cell function.

Tobacco smoke is a complex mixture of toxins and compounds that generate oxidative stress and trigger inflammatory responses in the lungs (5). Over time, chronic exposure results in tissue damage and impaired repair leading to distinct structural changes in COPD and IPF that probably relate to the complex interplay of environmental, genetic, immune and ageing-related factors in each individuum (2). The cumulative amount of chronic exposures, such as smoking, might act as the spark, while the individual background fuel the fire. Tobacco smoking not only contributes to mostly irreversible structural damage in the lung architecture but also intensifies the pathogenicity of co-exposed pathogens (5). This is best explained by the impact of cigarette smoking on the immune system. The balance and type of respiratory immune response might be a key determinant in “deciding” which lesions become more predominant and, consequently, which respiratory condition may develop. Thus, depending on how the immune system responds to harmful stimuli, if it is (over)activated or depressed and whether more innate or adaptive immune responses are triggered, different pathways of lung damage might be initiated. Which type of immune response is ultimately activated in response to tobacco smoke could be, in part, determined by the individual genetic background and the impriniting of life-long exposures on the individual immune shield. Of note, the prevalence of active smoking between COPD and IPF differs. This might be related to the time of diagnosis:

while COPD is typically diagnosed earlier (50-60 years) with many patients being active smokers, IPF is often diagnosed at the age of 60-70, when the proportion of active smokers tends to be lower (2, 3). These differences in the prevalence of active smoking and age of diagnosis may relate to differential control of damage by an aging adaptive immune system, highlighting the importance of understanding the relationship between lifespan exposures and age-related (immune) factors in the pathogenesis and progression of these diseases.

A hallmark paper only recently unravelled that innate immune activation by cigarette smoke is transient upon smoke cessation while the adaptive immune system mediates persistent effects on human health (6). Accordingly, activation of B cells is a prominent feature in smokers and COPD patients and observed in IPF patients (2, 7, 8). Moreover, T cells play a dual role in both COPD and IPF: they are crucial for orchestrating immune defenses against any pathogens or insults, but can also trigger disease exacerbations and progression when dysregulated. Smoking alters T cell phenotypes, leading to an imbalance in pro-inflammatory and anti-inflammatory signals, even after smoking cessation (6). Interestingly, the hyperactivation of $CD8^+$ (cytotoxic) T lymphocytes in COPD and IPF have increasingly gained attention due to their role in immune-mediated tissue damage (9). While the exact mechanisms of $CD8^+$ T cell activation in COPD and IPF are unresolved, it is well established that $CD8^+$ T cell receptors are activated in a major histocompatibility complex (MHC) class I-dependent manner involving peptide generation by the immunoproteasome (10). The Meiners lab recently demonstrated that both the immunoproteasome and MHC I antigen presentation are elevated in aberrant alveolar epithelial cells which is associated with $CD8^+$ T cell activation but also immune exhaustion in IPF lungs (11). Persistent immune activation by yet unknown antigens may thus result in T cell exhaustion causing ineffective immune responses which then facilitate disease progression. At the same time, this “exhausted” immune phenotype could also be seen as a form of “tolerance” aimed to prevent further damage (12). Similarly, the Jurkowska lab identified epigenetic reprogramming of alveolar epithelial cells isolated from COPD lungs

which resulted in elevated MHC I antigen presentation and immunoproteasome expression potentially driving $CD8^+$ T cell activation in COPD (13). Along these lines, a recent study demonstrated that cellular senescence upregulates MHC I antigen presentation and concomitant $CD8^+$ T cell activation (14). In contrast, cigarette smoke was shown to interfere with antigen generation and presentation via MHC I, impairing activation of virus-specific cytotoxic $CD8^+$ T cells thereby compromising the capacity of T cells to recognize and effectively respond to specific pathogens or infected cells. This may partly explain why smokers, COPD and IPF patients are more susceptible to viral infections (15).

Despite public health campaigns and anti-smoking regulations, smoking cessation continues to be challenging even in patients diagnosed with respiratory lung diseases due to nicotine addiction, psychological factors, and social influences. Moreover, the rising popularity of other forms of smoking (e-cigarettes and vaping devices) in recent years which fosters a false sense of "harmless alternatives" particularly among young people, adds a new layer of complexity and uncertainty to the field, as their long-term consequences are still to be determined. These facts manifest the importance of understanding the complex and heterogeneous biological processes that smoking triggers, which will shed light on new target strategies involving immune modulation therapies that can break the vicious cycle of tissue damage and help restore lung health.

None of the authors have any conflicts of interest.

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