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EDITORIAL

Adding (Viral) Insult to (Smoke) Injury may Prolong COPD Changes After Smoking Cessation

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The COVID-19 pandemic has made once again painfully clear that viral infections play an important adverse role in the life of COPD patients [1]. Viral infections are a risk factor for acute exacerbation of COPD [2] and are associated with a prolonged course of COPD exacerbation [3]. On the other hand, COPD patients are at increased risk for viral infections [2] and suffer from prolonged symptoms after viral infections; for example, COPD is a risk factor for persisting symptoms after COVID19 [4, 5]. Cigarette smoke dampens antiviral signaling in small airway epithelial cells by disrupting toll-like receptor signaling [6] and increases susceptibility to viral infection in lung epithelial cells by upregulating viral endocytosis [7]. Thus, viral infections and COPD are connected in a vicious cycle of mutual reinforcement and increased susceptibility.

Most research to date has focused on the acute impact of viral infections on COPD. Much less is known about the potential chronic impact of recurrent viral infections in COPD development and persistence. This gap is addressed by the work of Li et al., in this issue of *LUNG* [8]. The authors utilize a cigarette smoke/immune activation (through poly-I:C administration) model, to demonstrate that combination exposure exacerbates inflammatory and remodeling changes beyond what either exposure alone achieves. Furthermore, they demonstrate these effects to be more persistent in the case of co-exposure: in this model, inflammatory and remodeling changes persisted for several weeks even after smoke exposure and poly-I:C administration were stopped [8]. This is a significant finding which may have major implications in the prognosis of COPD patients even after smoking cessation.

There are obvious caveats in extrapolating findings of an animal study into the clinical arena. Mouse lungs do not share exact anatomical details with humans [9]. Furthermore, in this study the authors utilized a recurrent exposure to a TLR3 agonist (i.e., poly-I:C) as opposed to actual viral infection. Nevertheless, the results are intriguing and raise important questions about the impact of chronic or recurrent viral infections in the progression of COPD.

How can viral infections lead to progressive COPD? Chronic, low level viral infection leads to a persistent innate immune activation that in turn leads to chronic lung disease [10]. In fact, viral infections can lead to a decline in lung function even in the absence of an exacerbation [11]. In COPD, there is evidence that some patients may be harboring chronic viral infections [12, 13] although this is somewhat controversial [2]. Cigarette smoke exacerbates virus-induced pulmonary innate immune and remodeling responses [14] and may thus potentiate these effects in the case of COPD patients who are active smokers. Viral infections may also lead to weakening of antimicrobial defenses in COPD patients [2, 15] and thus induce changes in the lung microbiome, which may persist beyond the acute infection, thereby causing persistent inflammation. It is also possible that a combined exposure to cigarette smoke and viral infection potentiates airway remodeling to such extent [16, 17], that it prolongs or prohibits full functional recovery. Finally, chronic or recurrent viral infections may alter lung cellular metabolism to an extent that impacts regenerative capacity of the lung. This has been observed, for example, in patients with HIV infection, which is notoriously associated with COPD development [18].

In conclusion, viral infections may potentiate cigarette smoke-induced injury and significantly prolong inflammation and airway remodeling, even after smoking cessation. The paper by Li et al. (8) supports that viral infections in COPD patients can cause more than just a temporary setback. Perhaps it is time to focus more on the COPD lung

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virome and find ways to monitor and treat viral infections in these patients, in order to give their lungs a chance to heal.

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