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Reply to Li *et al.*

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From the Authors:

We thank Li and colleagues for responding to our recent review in the *Journal* (1). Indeed, unraveling the sequence of events within the pathophysiology of chronic obstructive pulmonary disease (COPD) is a challenge: do alterations manifest initially in the gastrointestinal (GI) tract or the respiratory tract?

Does intestinal microbiota dysbiosis precede COPD onset, either in the presence or absence of cigarette smoke exposure, and contribute to disease development and increased vulnerability? In the hypothetical scenario wherein dysbiosis occurs in the intestinal tract before smoking, alongside low-grade inflammation at local and systemic levels, cigarette smoke could constitute a secondary impact, potentially leading to heightened inflammatory responses within the lungs. Consequently, this dual impact may play a role in initiating or exacerbating susceptibility to COPD. There are indications that patients with inflammatory bowel disease (IBD) have an increased susceptibility to pulmonary manifestations (2), and animal studies have suggested that intestinal and systemic inflammation in colitis models would predispose these patients to lung pathologies (3, 4). Moreover, a disturbed gut microbiota was observed after cigarette smoke and particulate matter exposure (5–7). The disturbed gut microbiota may serve as one of the cofactors or, in other words, risk factors promoting COPD progression. In addition, there are fascinating data supporting a correlation between chewing tobacco (predominantly leading to exposure through the GI tract) and COPD incidence (8, 9).

However, it should be realized that the initiation of intestinal and pulmonary inflammation following cigarette smoke or particulate matter inhalation may occur simultaneously. Clinical studies have reported adverse effects of smoking on the upper pharyngeal-esophageal sphincter contractile reflex and pharyngeal swallowing reflex (10, 11), which may be due to swallowing of smoke particles. In addition, as mentioned in the review and above, smoking tobacco exposes the lungs to a variety of particles that will end up in the GI tract via mucociliary clearance. Chen and colleagues reported high levels of nicotine in ileocecal mucosal tissues of smokers and found accumulation of nicotine at greater than plasma concentrations in the ileum of mice exposed to smoke for 2 weeks, with levels of nicotine in the ileum comparable to the accumulation in the lungs (12). This evidence implies that the lungs and intestines are simultaneously exposed to cigarette smoke components during smoke inhalation. The gut microbiota composition changes after smoke inhalation, and the endogenous gut microbiota starts to metabolize nicotine from smoke (12). Notably, in the early stages of smoke exposure, local low-grade inflammation in the gut and lungs may occur, and this low-grade inflammation may promote immune system activation to alleviate local damage. A healthy GI tract may support the homeostasis of the lungs during smoke exposure via the release of antiinflammatory agents such as short-chain fatty acids that are produced by GI microbes (13). However, excessive intestinal and airway inflammation and accumulation of particles from smoke can disrupt the gut microbiota as well as immune homeostasis (6). The increased local and systemic inflammation and associated decreased intestinal epithelial integrity creates a vicious cycle between the gut and respiratory tract. Another reason why COPD may at least in part "originate" in the GI tract is that cigarette smoke induces not only systemic but also local hypoxia in the intestine (14). This phenomenon may also lead to intestinal dysbiosis, inflammation, microbiota alterations, and the disturbance of epithelial

integrity. However, it is unlikely that hypoxia in the GI tract alone may cause or increase the risk for COPD features. Again, a "second hit," cigarette smoke in the respiratory tract, will be a prerequisite to initiate the pathophysiological changes related to COPD.

It is clear from the abundant literature in recent decades that cigarette smoke can directly induce damaging effects on the lungs via a variety of pathways (15–18). In addition, evidence is growing that pathophysiological changes in the lung may affect homeostasis in the GI tract, as described in our paper (1).

As mentioned by Li and colleagues, we would also like to emphasize that the GI tract may, at least in part, hold promise as a therapeutic target for respiratory diseases (as also concluded in our review [1]). This is a serious gap in the literature. As add-on therapy for lung diseases, nutrition and pharmaceuticals directed to the intestine to suppress local inflammation and restore the microbiota might help patients with COPD (19). There is a close interaction between the lungs and the gut in COPD pathogenesis, and these organs may need each other to maintain homeostasis. ■

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Tacrolimus and the Treatment of Pulmonary Fibrosis

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To the Editor:

Idiopathic pulmonary fibrosis (IPF) is characterized by irreversible lung scarring; however, the precise role of vascular remodeling remains largely elusive. We read with great interest the article by Yanagihara and colleagues in the *Journal*, who explored the interplay between fibroblasts and vascular cells to elucidate a mechanistic connection between IPF and pulmonary hypertension (1).

We commend the authors for their diligent study of intercellular interactions. It is intriguing that the authors used animal models to measure T-cell count and proliferation, indicating that low doses of tacrolimus (TAC) have a minimal impact on the immune system. As a well-established immunosuppressant used in organ transplantation and autoimmune diseases, TAC inhibits the calcineurin pathway, thereby blocking the transcription of T-cell growth factors such as IL-2 (2). Furthermore, T follicular helper (Tfh) cells generated in the presence of TAC could not activate B cells effectively, and TAC has also been shown to prevent B cell–mediated humoral alloreactivity in transplantation patients by inhibiting B-cell proliferation (3).

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