To "Fe"ed or Not to "Fe"ed: Iron Depletion Exacerbates Emphysema Development in Murine Smoke Model

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death worldwide, with globally rising prevalence in developing and developed countries alike (1). Although COPD is generally considered to be predominantly a respiratory syndrome, patients with COPD often have many coexisting conditions ("multimorbidity"), affecting nearly every other organ system (2).

Although tobacco smoke exposure is accepted as the principal cause of COPD, only a fraction of smokers develop COPD, and a significant portion of patients with COPD are never smokers (2). This phenomenon has led to the exploration of other genetic and environmental factors that contribute to COPD pathogenesis and progression. Abnormal iron metabolism has been proposed as a candidate pathway linked to COPD susceptibility, with supportive evidence dating as far back as 30 years. Specifically, alveolar macrophages from smokers and patients with COPD appear to be loaded with iron and ferritin (3, 4), and sputum and BAL fluid from these subjects seem to be enriched for iron and a variety of iron-binding proteins (5, 6). More recently, a key regulator of iron metabolism, *IREB2* (iron-responsive element–binding protein 2), has emerged from multiple genome-wide association studies as a COPD susceptibility gene, and the deletion of IRP2 (the protein product of *IREB2*) protected mice in an experimental COPD model (7, 8). In that study, mice fed a low-iron diet or treated with an iron chelator had improved mucociliary clearance and reduced pulmonary inflammation in response to acute cigarette smoke (4 wk of exposure using a whole-body smoke exposure system) (8). Ferroptosis, a form of programmed cell death involving excessive lipid peroxidation requiring iron, has also been proposed as a downstream mediator of lung parenchymal destruction in COPD (9).

There is also a plethora of studies suggesting that it is iron deficiency, not overload, that accelerates COPD progression. In one longitudinal cohort study, subjects with elevated serum iron were protected against lung function decline from smoking (10). Anemia is a well-recognized comorbidity in COPD and is associated with worse outcomes, including mortality (11, 12). In addition, nonanemic iron deficiency in patients with COPD is associated with hypoxemia (independently of airflow limitation), and even without overtly low iron stores, many patients with COPD have functional iron deficiency, in which the iron supply is "normal" but inadequate to meet the needs of cellular function (13). Iron deficiency has been shown to exaggerate hypoxic pulmonary hypertension that is reversed by subsequent iron administration, and it is associated with higher pulmonary arterial pressures in patients with COPD with pulmonary hypertension (14). In this issue of the *Journal* (pp. 588–597), Sato and colleagues report on a series of experiments that shed more light on the relationship between iron deficiency and COPD (15). By administering mice an iron-deficient diet, the authors were able to significantly reduce systemic iron levels and induce anemia. These iron-depleted mice, upon exposure to cigarette smoke (8 wk of whole-body smoke exposure), responded with a more intense immune cell response in the airway, and, most important, they developed more severe emphysema and lung hyperinflation. Relevant to this model, cigarette smoke exposure resulted in iron accumulation in alveolar macrophages and the alveolar epithelium in control mice, and this effect was attenuated with the iron-deficient diet. As a potential mechanism of action, the authors propose that lowering cellular iron levels enhanced NF-κB phosphorylation, which was already induced by cigarette smoke.

These results are provocative, and it is indisputable that an impressive amount of emphysema was observed in the iron-deficient mice in this study after only 8 weeks of cigarette smoke exposure. Intriguingly, animals fed a control diet did not develop iron deficiency after 8 weeks of smoke exposure, and they actually had increased hematocrit, hemoglobin, and red blood cell counts; it was unclear if smoke alone, perhaps over a longer period of smoke exposure, would have been sufficient to induce iron deficiency in this model. It was also not clear how iron deficiency exacerbated smoke-induced lung damage, so more studies are needed to elucidate potential mechanisms. Iron is a vitally important element, indispensable for the synthesis of heme, hemoproteins, and iron sulfur clusters needed by all living cells and organisms. It is notable that in this study, an iron-deficient diet induced global iron depletion, and although only a moderate anemia was noted, lung total iron was reduced by half; the functional and metabolic effects of this significant reduction in iron were not shown, and it is possible that the various lung cell populations, such as immune, epithelial, and endothelial cells, were rendered severely dysfunctional from this treatment alone, such that reparative responses to a further insult such as cigarette smoke could not take place. In addition, the contribution of the bone marrow or the liver, both key organ systems in the regulation of iron metabolism, were not evaluated in this study or model system. Future experiments that create organ-specific iron deficiency or, better yet, target a specific lung cell population are needed to determine which lung cell is the most susceptible to iron depletion.

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Given the results of the experiments in this study and the abundance of data from previous human and murine studies, the link between iron dysregulation and COPD is undeniable. Demonstration of this connection in experimental COPD models has posed many challenges to researchers, not the least of which is the imperfect nature of the models themselves. The progression of human COPD is not linear but instead is characterized by punctuated events of rapid lung function decline that are termed "exacerbations"; the prevention of COPD exacerbations is an important aim of currently available pharmacotherapy (2). The predominant cause of COPD exacerbations is respiratory infections, and in this respect, local extracellular iron availability becomes a major factor promoting the growth of bacteria, both symbiotic and pathogenic species (16). In this study, total lung iron increased as a result of cigarette smoke, and it is worthwhile to consider whether systemic supplementation of iron, advocated by Sato and colleagues and already attempted in other studies (17), could exacerbate smoking-associated lung iron accumulation and increase the risk of infection and exacerbation in these patients. Additional research is clearly needed; nevertheless, iron remains a very attractive novel therapeutic target in COPD, and as the authors alluded to, in perhaps other respiratory diseases as well. ■

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