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Crucial role for lung iron level and regulation in the pathogenesis and severity of asthma

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ABSTRACT Accumulating evidence highlights links between iron regulation and respiratory disease. Here, we assessed the relationship between iron levels and regulatory responses in clinical and experimental asthma.

We show that cell-free iron levels are reduced in the bronchoalveolar lavage (BAL) supernatant of severe or mild–moderate asthma patients and correlate with lower forced expiratory volume in 1 s (FEV_1).

Conversely, iron-loaded cell numbers were increased in BAL in these patients and with lower FEV_1/forced vital capacity (FVC) ratio. The airway tissue expression of the iron sequestration molecules divalent metal transporter 1 (*DMT1*) and transferrin receptor 1 (*TFR1*) are increased in asthma, with *TFR1* expression correlating with reduced lung function and increased Type-2 (T2) inflammatory responses in the airways. Furthermore, pulmonary iron levels are increased in a house dust mite (HDM)-induced model of experimental asthma in association with augmented *Tfr1* expression in airway tissue, similar to human disease. We show that macrophages are the predominant source of increased Tfr1 and Tfr1$^+$ macrophages have increased *Il13* expression. We also show that increased iron levels induce increased pro-inflammatory cytokine and/or extracellular matrix (ECM) responses in human airway smooth muscle (ASM) cells and fibroblasts *ex vivo* and induce key features of asthma *in vivo*, including airway hyper-responsiveness (AHR) and fibrosis, and T2 inflammatory responses.

Together these complementary clinical and experimental data highlight the importance of altered pulmonary iron levels and regulation in asthma, and the need for a greater focus on the role and potential therapeutic targeting of iron in the pathogenesis and severity of disease.