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

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The relationship between iron and the pathogenesis of asthma remains unclear. Here it is shown for the first time that altered iron responses are a key feature of clinical and experimental asthma and may play important roles in disease.


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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 (FEV1).
Conversely, iron-loaded cell numbers were increased in BAL in these patients and with lower FEV₁/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.