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Iron deficiency has been linked to impaired humoral immunity to vaccines. In this issue of Med, Frost et al. demonstrate the importance of serum iron levels for lymphocyte function during vaccination and infection, pointing to iron supplementation as a strategy to boost vaccine efficacy, including against COVID-19.1

Iron deficiency is one of the most widespread nutritional deficiencies and the leading cause of anemia. Many studies have examined the role of iron in immunity with often inconsistent results.2 Anemia has been linked to impaired responses to some vaccines, but the precise role of iron in adaptive immunity is not fully understood. In this issue of Med, Frost and colleagues provide compelling evidence for a crucial role for serum iron levels in orchestrating T and B lymphocyte effector and memory function in response to vaccination and infection. The study points to a critical role for iron in vaccine efficacy and supports iron supplementation to improve vaccination outcome in people who are deficient in iron.

Iron is an essential micronutrient involved in numerous cellular processes including DNA synthesis and repair, mitochondrial function, and cell death.3,4 The authors blame the lack of consistency in studies on the role of iron in immunity on methodological differences and so undertook an analysis using multiple approaches and species. They first utilized a mimic of hepcidin (minihepcidin), which lowers serum iron. In mice, it was found to suppress antigen-specific CD8 T cell responses, as well as T follicular helper cell, germinal center B cell, and plasma cell responses, in an ovalbumin vaccination model. T cells from minihepcidin-treated mice were unable to synthesize interferon-γ and TNF. In mice with a mutation in the gene encoding the iron transporter Transferrin Receptor, the authors observed a defect in lymphocyte proliferation. In addition, the authors observed that multiple proteins that control iron homeostasis, including IRP1 and IRP2, are required in proliferating T cells. IRP1- and IRP2-deficient CD8 T lymphocytes have defective proliferation that can be restored with iron supplementation. The authors also show that iron is required for mitochondrial function, optimal metabolic activity, and cell cycle progression in T cells. In vivo, iron deficiency had a significant impact on the generation of central memory T lymphocytes upon ovalbumin vaccination.

The authors then examined piglets, which naturally become iron deficient unless sow’s milk is supplemented with iron, and observed that the pig pathogen Mycoplasma hyopneumoniae elicited an enhanced antibody response in piglets that had received iron. They then turned to humans with a genetic form of iron deficiency involving elevated hepcidin. Strikingly, there was an impaired antibody response in these subjects when vaccinated with Rubella, Hemophilus...
influenzae, or Streptococcus pneumoniae. Finally, in a model of influenza in mice, there was a major defect in T and B cell responses, and increased lung inflammation and pathology in mice treated with minihepcidin.

Taken together, these observations provide evidence for the importance of serum iron in regulating lymphocyte function during infection and vaccination (Figure 1). Iron is required for mitochondrial function in T cells during immunity, which in turn is essential for effector and memory responses. Iron supplementation in populations where iron deficiency is prevalent should therefore boost vaccine efficacy. Since hypoferremia was also shown to be a potential risk factor for the development of more severe inflammatory responses during influenza virus infection, dietary iron supplementation may improve outcomes in respiratory virus infection. IL-6 is a driver of hepcidin expression, therefore blocking IL-6 might have a therapeutic effect in part by boosting iron levels.

The authors highlight how this might have particular relevance to COVID-19, since low serum iron has been associated with worse outcome in patients. The beneficial effect of inhibiting IL-6 in COVID-19 might in part be due to a reversal of hypoferremia which in turn could boost anti-viral immunity. This study suggests that iron supplementation could be an important strategy to enhance vaccine efficacy when iron is deficient because of malnutrition or to enhance host defense during infection in the face of inflammation.

DECLARATION OF INTERESTS

The author declares no competing interests.

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