Ferroptosis regulates follicular helper T cell function

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Abstract

Follicular helper T (T_{FH}) cells are a specialized subset of $CD4^+$ T cells that essentially support germinal center responses where high-affinity and long-lived humoral immunity is generated. The regulation of T_{FH} cell survival remains unclear. Here we report that T_{FH} cells show intensified lipid peroxidation and altered mitochondrial morphology, resembling the features of ferroptosis, a form of programmed cell death that is driven by iron-dependent accumulation of lipid peroxidation. Glutathione peroxidase 4 (GPX4) is the major lipid peroxidation scavenger and is necessary for the survival of T_{FH} cells, which are otherwise susceptible to ferroptosis due to intensified TCR signals. The deletion of GPX4 in T cells selectively abrogated T_{FH} cells and germinal center responses in mice induced by protein immunization and vaccination. Selenium supplementation enhanced GPX4 expression in T cells, increased T_{FH} cell numbers and promoted antibody responses in mice and humans. Our findings reveal the central role of the selenium–GPX4–ferroptosis axis in regulating T_{FH} function, which can be targeted to enhance humoral immunity in infection and following vaccination.