

'DieT' control: how dietary fats make T cells die

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A recent study published in *Nature* by Wang *et al.* demonstrates that dietary fatty acid composition determines T cell susceptibility to ferroptosis through ACSL4-mediated incorporation of polyunsaturated fatty acids (PUFAs), thereby reshaping humoral and antitumor immunity and improving the efficacy of CAR-T cancer immunotherapy¹.

Ferroptosis, a programmed cell death driven by iron-dependent lipid peroxidation, has emerged as a critical regulator of peripheral T cell homeostasis². Unlike apoptosis, ferroptosis is promoted by oxidative chain reactions of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), compromising membrane integrity³. The central protective mechanism is known as the glutathione-glutathione peroxidase 4 (GPX4) pathway, detoxifying lipid hydroperoxides and preventing membrane damage. Genetic deletion of GPX4 in T cells results in severe impairment of immune responses, highlighting the importance of ferroptosis control in adaptive immunity⁴. However, how T cells maintain resistance to ferroptosis remains largely unknown.

Wang *et al.* highlight dietary composition as a key factor influencing T cell resistance to ferroptosis. In this study, two commonly used standard rodent diets — AIN93G, a purified formulation, and NIH31, a grain-based formulation — were compared. The PUFA/monounsaturated fatty acid (MUFA) ratio is higher in NIH31 than in AIN93G, although the two diets have similar macronutrient compositions. Splenic T cells from mice fed the two diets for four weeks were analyzed. Upon treatment with the ferroptosis inducer RSL3, T cells from mice fed the AIN93G diet, which has a lower PUFA/MUFA ratio, exhibited greater resistance to ferroptosis, as indicated by reduced lipid peroxidation and decreased ferroptosis-induced cell death compared with those from NIH31-fed mice. Analysis of *Cd4-cre⁺Gpx4^{flox/flox}* (GPX4^{T-KO}) mice further showed that T cells from AIN93G-fed mice exhibit enhanced viability than those from NIH31-fed mice in the absence of the GPX4 protective system, and that CD8⁺ T cells display greater sensitivity to ferroptosis than CD4⁺ T cells. These results indicate that even standard diets with different compositions can exert “dietary effects on ferroptosis” (DEFs) in T cells, thereby modulating T cell survival and peripheral homeostasis.

The functional consequence of these DEFs was profoundly observed in humoral immunity. Follicular helper T (T_{FH}) cells are known to be more susceptible to ferroptosis than non-T_{FH} effector CD4⁺ T cells⁵. To investigate the impact of DEFs on T_{FH}-mediated responses, OT-II GPX4^{T-KO} and GPX4^{WT} T cells were adoptively transferred into CD28-deficient recipient mice, which lack endogenous T_{FH} cells, followed by immuniza-

tion with 4-hydroxy-3-nitrophenylacetyl hapten conjugated to ovalbumin in aluminium salt adjuvant (NP-OVA/Alum). Under these conditions, GPX4-deficient OT-II T cells exhibited enhanced survival in AIN93G-fed mice compared with NIH31-fed mice and showed reduced lipid ROS levels, indicating increased resistance to ferroptosis. Consistent with these findings, the frequencies of germinal center B cells (B_{GC}) and antibody-secreting B cells (B_{ASC}), as well as NP-specific antibody production, were significantly increased in AIN93G-fed mice. Notably, these effects were abrogated by treatment with the ferrostatin-1 (Fer-1), demonstrating that DEFs regulate T cell-dependent humoral immunity, including germinal center responses.

The authors attributed these differences primarily to variations in the dietary PUFA/MUFA ratio. Transcriptomic and proteomic analyses of T cells from mice fed the two diets, together with microbiota depletion experiments, revealed no significant differences, indicating that the observed DEFs arise from dietary composition and metabolism rather than intrinsic transcriptional or microbial factors. Among dietary components potentially influencing ferroptosis — including cysteine, vitamin E, selenium, iron, PUFAs, and MUFAs^{6,7} — only differences in PUFA and MUFA levels accounted for the enhanced ferroptosis resistance observed in T cells from AIN93G-fed mice compared with those from NIH31-fed mice.

To test this hypothesis, the authors generated customized AIN93G diets enriched with either soybean oil (high PUFA/MUFA ratio) or canola oil (low PUFA/MUFA ratio). The soybean oil-enriched AIN93G diet showed greater similarity to NIH31 than the canola oil-enriched diet in both serum lipidomic profiling along principal component 1 (PC1) and T cell ferroptosis susceptibility. Spatial metabolomic analysis further revealed that fatty acids accumulated in the T cell zone of soybean oil-enriched AIN93G-fed mice at approximately twice the PUFA/MUFA ratio observed in canola oil-enriched mice. Consistently, elevated PUFA levels were associated with increased phosphatidylethanolamine PE(20:4_18:0), whereas abundant MUFA oleic acid correlated with higher levels of PE(18:1_18:0). Based on these observations, the authors investigated acyl-coenzyme A synthetase long-chain family member 4 (ACSL4), an enzyme that preferentially esterifies long-chain PUFAs into phospholipids⁸. Genetic deletion of *ACSL4* markedly reduced lipid ROS levels in T cells and increased their resistance to ferroptosis. In addition, *ACSL4* deficiency enhanced T cell survival and promoted the formation of T_{FH}, B_{GC}, and B_{ASC} cells in the NP-OVA/alum immunization model. These results highlight the critical role of *ACSL4* in regulating the generation and function of T_{FH} cells.

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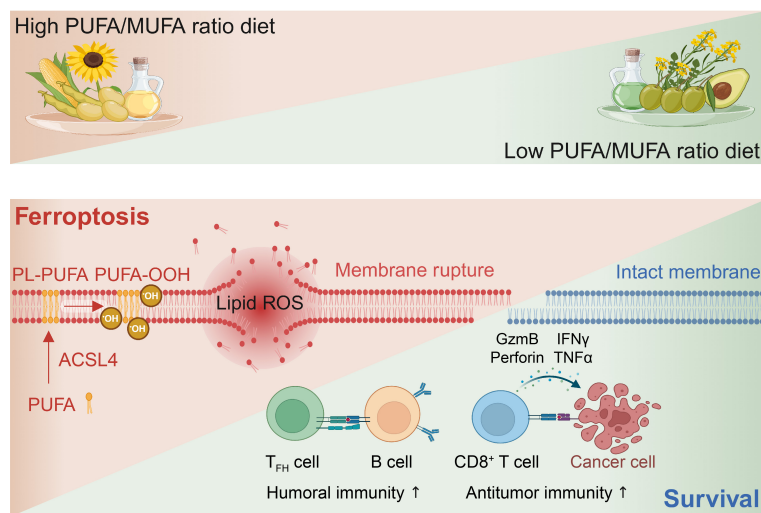


Fig. 1 Dietary lipid composition shapes immune responses by tuning T cell ferroptosis. Dietary lipid composition, reflected by the PUFA/MUFA ratio, influences the susceptibility of T cells to ferroptosis. ACSL4 promotes the incorporation of PUFAs into membrane phospholipids, facilitating the accumulation of oxidized PUFA-containing phospholipids that drive ferroptotic membrane damage. Differences in ferroptosis resistance affect T cell survival and functional capacity, thereby shaping downstream immune responses, including T_{FH} -mediated humoral immunity and $CD8^+$ T cell-dependent antitumor responses. This figure was created with the help of BioRender.com.

Dietary lipid composition also influences antitumor immunity mediated by effector $CD8^+$ T cells. Following subcutaneous injection of B16F10-OVA tumor cells, AIN93G-fed mice exhibited delayed tumor growth compared with NIH31-fed mice. Notably, lipid ROS levels showed negligible differences in tumor cells, whereas tumor-infiltrating $CD8^+$ T cells from AIN93G-fed mice displayed significantly reduced lipid peroxidation. Consistently, $CD8^+$ T cells within tumor-infiltrating lymphocytes (TILs) and tumor-draining lymph nodes (tdLNs) exhibited enhanced effector cytokine profiles in AIN93G-fed mice compared with NIH31-fed mice, abolished by treatment with Fer-1. Furthermore, DEFs significantly influenced the efficacy of chimeric antigen receptor T (CAR-T) cell therapy. In an NALM6 leukemia model, AIN93G-fed mice receiving human CAR-T cells showed markedly improved therapeutic efficacy compared with NIH31-fed counterparts. Together, these findings indicate that dietary intervention modulates T cell susceptibility to ferroptosis and thereby influences the effectiveness of T cell-mediated antitumor immunity and immunotherapy.

Extending beyond murine systems, the authors analyzed human cohorts and found that plasma lipid profiles, rather than body mass index (BMI) itself, correlated with T cell ferroptosis susceptibility. Individuals with higher plasma PUFA/MUFA ratios exhibited greater sensitivity, mirroring the mouse data and revealing that lipid metabolism, rather than body mass, is associated with T cell resistance to ferroptosis.

Diet is an essential for all living organisms. Although increasing attention has been directed toward how dietary lipids influence adaptive immune responses, many aspects of their immunological roles remain unclear. This study provides a novel perspective by linking dietary lipid composition to ferroptosis susceptibility in T cells. The findings demonstrate that differences in dietary lipid composition modulate ACSL4-mediated lipid metabolism and peripheral T cell homeostasis, leading to substantial consequences for both humoral and antitumor immunity.

Notably, diets with a lower PUFA/MUFA ratio appear to confer immunological advantages and raise the possibility that dietary interventions could help mitigate age-associated immune dysfunction and reduced vaccine efficacy. The study

also underscores the importance of standardizing dietary conditions and transparently reporting diet composition in experimental design, as variations in commonly used standard diets can substantially affect immunological outcomes such as T cell survival.

Overall, Wang *et al.* provide important insights into how dietary lipid composition regulates T cell susceptibility to ferroptosis and immune function, offering potential conceptual and clinical implications for dietary modulation of immune responses. Future studies should further elucidate whether other lipid-metabolizing enzymes beyond ACSL4, such as FSP1, or DHODH pathways, synergistically modulate T cell immunity in different tissue microenvironments. Clarifying how these lipid-driven mechanisms contribute to chronic inflammatory diseases or autoimmune disorders in humans will inform lipid-based immunotherapies.

COMPETING INTERESTS

The author declares no competing interests.

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ADDITIONAL INFORMATION

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