Past history of high-fat diet causes persistent susceptibility to ferroptosis in CD8 T cells

Masaki Tajima

CCII, Kyoto University

Abstract

Drastic and rapid changes in lifestyle over recent decades have profoundly impacted our health, with metabolic stress interfering high-order systems and disrupting the sophisticated machinery of homeostasis. Multi-layered adaptations of biological activities to these changes are essential for promoting health and longevity, as failure to do so may lead to pathological conditions including immune disorders such as cancer. Chronic exposure to metabolic stress appears to remain imprinted, resulting in malfunction of the immune system over time. However, the understanding of when, where, and how environmental cues impact the immune system remains limited.

Using a mouse model of different patterns of high fat diet feeding, we found that even transient exposure of metabolic stress induces long-term vulnerability of CD8+ T cells to ferroptosis. Both present and past history of high fat feeding leads to reduction of xanthine in CD8+ T cells along with reduced anti-tumor responses. Through the salvage purine metabolism, xanthine fuels the guanine nucleotide pool and is subsequently metabolized into tetrahydrobiopterin (BH4). Xanthine-derived BH4 serves as a reactive oxygen species-scavenger, rescuing CD8+ T cells from activation-induced ferroptosis. This pathway is critical for supporting the survival, proliferation and effector function of CD8+ T cells involved in anti-tumor responses. Our findings reveal the significance of purine metabolism in anti-tumor responses and highlight that metabolic stress imprinted overtime into immune cells can be potentially targeted by therapeutic strategies.

Biography

2023-present: Senior Lecturer, Graduate School of Medicine, Kyoto University
2021-2023: Assistant Professor, Graduate School of Medicine, Kyoto University
2019-2020: Senior Investigator, Institute for Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation at Kobe
2017-2019: Researcher, Institute of Biomedical Research and Innovation, Foundation for Biomedical Research and Innovation at Kobe
2012-2017: Visiting fellow, National Institute of Allergy and Infectious Diseases, National Institutes for Health
2008–2012: PhD student, Graduate School of Medicine, Hokkaido University