Asparagine deprivation enhances T cell antitumour response in patients via ROS-mediated metabolic and signal adaptations

Huang-Yu Yang
楊皇煜

Kidney Research Center and Department of Nephrology, Chang Gung Memorial Hospital, Taiwan

The immune system is designed to protect the host from foreign pathogens, yet dysregulated immune responses can give rise to autoimmune diseases, impaired tumor immune surveillance, and chronic inflammatory disorders. Nutrient availability is a key determinant of T cell activation, with glucose and amino acid metabolism tightly regulated by multiple signaling pathways. The ability to restore immune balance and improve disease outcomes may therefore depend on specific metabolic cues, including essential nutrients and bioactive molecules.

Beyond serving as building blocks for protein synthesis, amino acids support biomaterial generation and biochemical modifications. However, the impact of amino acid deprivation on T cell activation remains insufficiently understood. In this study, we demonstrate that asparagine deprivation delays $CD8^+$ T cell activation and induces metabolic reprogramming. ATAC-seq analysis revealed enrichment of NFAT and AP-1 transcription factor binding motifs under asparagine-restricted conditions. Mechanistically, asparagine deprivation caused mitochondrial complex I deficiency and elevated ROS production, promoting NFAT nuclear translocation and enhancing T cell activation. ROS scavenging with NAC rescued stress signaling and restored anti-tumor activity, indicating that ROS serves as a key modulator of metabolic adaptation during asparagine restriction. Clinically, immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy, but their efficacy in recurrent–metastatic nasopharyngeal carcinoma (RM-NPC) remains limited. Here, we found that combining asparaginase with pembrolizumab significantly improved progression-free survival and objective response rates in RM-NPC patients compared with pembrolizumab alone. These findings reveal adaptive mechanisms of T cells under nutritional deprivation and provide a strong rationale for exploiting this metabolic vulnerability to augment immunotherapy.