OVERVIEW/ABSTRACT

Metabolism has emerged as a major mechanism central to the regulation of T cell activation and function. T cells dynamically rewire their metabolism during an immune response and can adapt their metabolism to changing nutrient availability and environmental cues. Dysfunctional T cell metabolism can lead to impaired T cell function, contributing to conditions like cancer and chronic infections. T cell metabolic reprogramming is dependent on the availability of nutrients, including amino acids, which are essential building blocks used for protein synthesis and other processes that drive T cell survival, clonal expansion, and epigenetic remodeling. How amino acid metabolism regulates antigen-specific T cell dynamics *in vivo* and how T cells adapt their metabolism to changing nutrient availability remain significant open questions. Published work from the laboratory of the PI indicates that asparagine (ASN) restriction causes suppression of activation-induced T cell metabolic reprogramming, indicating that this amino acid, which is one of the least abundant non-essential amino acids in proliferating cells, is important for T cell activation and function. Recent work from the laboratory of the PI has indicated that the kinase general control nonderepressible-2 (GCN2) regulates the integrated stress response (ISR) of activated CD8 T cells under conditions of ASN restriction. This regulation was correlated with increased expression of activating transcription factor-4 (ATF4), a key effector of the ISR, and asparagine synthase (ASNS), the enzyme responsible for *de novo* ASN synthesis. The application under consideration seeks to evaluate the roles of ASN and GCN2 in regulating antigen-specific CD8 T cell dynamics in response to bacterial infection. Successful completion of the project will provide new, fundamental insights into how CD8 T cells can rewire their metabolism during an immune response and adapt their metabolism to changing nutrient availability. Conceptual advances resulting from the project could open new avenues for targeted modulation of T cell responses as novel approaches to overcome human disease conditions.