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Editorial

T cell activation

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EDITORIAL NOTE

Amino acids are critical nutrients that contribute to metabolic and signalling pathways required to meet energy and biosynthetic demands in T cells. A new study now demonstrates that LCK can sense intracellular asparagine to support T cell receptor-mediated CD8+ T cell activation and effector responses to pathogens and tumours. Prior to antigen encounter, naïve T cells maintain a quiescent state, during which time cells display low levels of proliferation, effector cytokine production, and anabolic metabolism. T cells stimulated by the T cell receptor (TCR) and costimulatory molecule CD28 in the presence of necessary nutrients, such as amino acids and glucose, undergo quiescence exit to become activated. This transitional state is characterised by an upregulation in the expressions of cytokine and nutrient receptors (for example, CD25, CD71, and CD98), anabolic metabolism (for example, glycolysis and glutaminolysis), cell biomass, and mechanistic target of rapamycin complex 1 (mTORC1) signalling. Activated T cells must take up nutrients, including amino acids, and increase rates of aerobic glycolysis to rapidly generate ATP and macromolecules for T cell proliferation. Although the roles of several amino acids have been examined, including arginine, leucine, glutamine, alanine, methionine, and serine, our knowledge of how additional amino acids contribute to T cell activity and how T cells precisely sense amino acids to trigger downstream events is limited. We have expanded upon the known roles of amino acids in T cell biology by identifying the SRC-family tyrosine kinase LCK as an asparagine sensor. Further, demonstrate that asparagine increases the activating phosphorylation of LCK at tyrosine 394 (Y394), thereby enhancing TCR signalling and the effector CD8+ T cell response to bacterial infections and tumours. These findings highlight an unexpected metabolism-independent role for asparagine in regulating T cell activation and function.

Amino acids make up a large portion of the increased cellular mass upon cell activation. As such, activated T cells upregulate the expression of amino acid transporters to accommodate enhanced amino acid uptake. Further, amino acid transporters and intracellular amino acids, including arginine, leucine, and glutamine, cooperate with TCR, CD28, and cytokine signals to induce and maintain mTORC1 signalling and transcription factor MYC expression, which are critical signalling and transcriptional mediators in T cell activation and metabolic reprogramming. Amino acids also regulate mTORC1 signalling through upstream sensors (for example, CASTOR1 and leucyl-tRNA synthetase) and molecular mediators (for example, Rag GTPases and GATOR complexes). Through the regulation of metabolic pathways and mTORC1 and MYC activities, amino acids and their metabolites can promote effector T cell responses, including CD4+ T cell subset differentiation. Thus, in addition to serving as precursors for protein synthesis, amino acids contribute to the regulation of cellular metabolism and intracellular signalling pathways to control T cell activation and differentiation.

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