Abstract

Christopher E Rudd

T-cell activation and function are tightly controlled by a complex array of intracellular signals. The process begins when the T-cell receptor (TCR) complex recognizes an antigen, initiating a signaling cascade through the protein tyrosine kinase $p56^{lck}$ and its associated co-receptors CD4 and CD8. This initial trigger recruits a second kinase, leading to the phosphorylation of various downstream substrates. These substrates include adaptors that integrate signals essential for regulating gene transcription, metabolism, cytokine production, and cell movement. This core signal is further modulated by co-receptors: CD28 provides a necessary positive signal, in part by binding to lipid kinases like PI 3K, while CTLA-4 and PD-1 provide 'brakes' on activation, a mechanism still under active investigation. Following a review of these basic pathways, my lecture will delve into recent findings on T-cell metabolism, specifically examining how new TCR-associated proteins like Rasal1 are coupled to oxidative phosphorylation and adaptors like SLP-76 mediate the necessary metabolic switch to glycolysis upon activation. Finally, I will discuss the critical relevance of these discoveries to human health, including the application of small molecular inhibitors (SMIs), T-cell engagers and chimeric antigen receptor (CAR) T-cell therapies