

Novel mechanism of signalling by CD28

Although most signalling components assemble upon stimulation of the TCR, this alone is not enough to induce full T cell activation *in vivo*. However, simultaneous triggering of the co-receptor CD28 has been demonstrated to prevent anergy and cell death and to promote IL-2 production and clonal expansion. Despite the central function of CD28 in T cell activation *in vivo*, relatively little is known about the molecular basis for the augmented signal transduction upon TCR and CD28 co-stimulation. However, important roles for Lck, Itk, PI3K, SLP-76, Vav-1 and PLC γ have been demonstrated. The talk will focus on a novel aspect of CD28 function by which concomitant TCR and CD28 stimulation leads to recruitment of a phosphodiesterase (PDE)/ β -arrestin complex to lipid rafts that promote degradation of TCR-induced cAMP and rescues the cell from inhibition mediated by cAMP. This contributes to explaining how co-stimulation functions to mediate full T cell activation. The CD28-induced recruitment of β -arrestin in primary T cells was abolished both upon Lck/Fyn- and PI3K-inhibition. Furthermore, PDE4 activity in raft fractions from T cells pretreated with a PI3-kinase inhibitor prior to CD28 stimulation was reduced below basal levels and no increase in PDE4 activity was observed upon CD28 ligation. Taken together, these data indicate a novel mechanism whereby PI3K can regulate cAMP degradation through recruitment of β -arrestin and PDE4 to lipid rafts. Our results suggest opposing functions of PKA and PDE4 isoforms during proximal T cell signalling, thereby titrating the activation-induced response.