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Engagement of distinct epitopes on CD43 induces different co-stimulatory pathways in human T cells

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Co-receptors, being either co-stimulatory or co-inhibitory, play a pivotal role in T cell immunity. Several studies have indicated that CD43, one of the abundant T cell surface glycoproteins, acts not only as a potent co-receptor but also as a negative regulator for T cell activation. Here we demonstrate that co-stimulation of human peripheral blood T cell via two distinct CD43 epitopes recognized by mAbs CD43-6E5 ($T_{6E5\text{-}act}$) and CD43-10G7 ($T_{10G7\text{-}act}$) potently induced T cell proliferation. However, T cell co-stimulation via two CD43 epitopes differentially regulated activation of NFAT and NF-κB transcription factors, T cell cytokine production and effector function. $T_{6E5\text{-}act}$ produced high levels of IL-22 and IFN-γ similar to T cells activated via CD28 ($T_{CD28\text{-}act}$), whereas $T_{10G7\text{-}act}$ produced low levels of inflammatory cytokines but higher levels of regulatory cytokines TGF-β and IL-35. Compared to $T_{6E5\text{-}act}$ or to $T_{CD28\text{-}act}$, $T_{10G7\text{-}act}$ performed poorly in response to re-stimulation and further acquired a T cell suppressive function. $T_{10G7\text{-}act}$ did not directly inhibit proliferation of responder T cells, but formed stable heterotypic clusters with dendritic cells via CD2 to constrain activation of responder T cells. Together, our data demonstrate that CD43 is a unique and polarizing regulator of T cell function.