Novel adaptive signaling pathways that regulate T-cell induce inflammation and cancer therapy

Despite the importance of the co-receptor PD-1 in regulating T cell immunity, the upstream signaling pathway(s) that regulate PD-1 expression has not been defined. Glycogen synthase kinase 3 (GSK-3, isoform α and β) is a serine-threonine kinase implicated in cellular processes. We recently showed that GSK-3 is a key upstream kinase that regulates PD-1 transcription and expression in CD8+ T cells. GSK-3 inactivation increased Tbx21 transcription for enhanced Tbet expression, and its suppression of Pdcd1 transcription in CD8+ cytolytic T-cells (CTLs). We outline a next generation approach using small molecules to inhibit PD-1 expression is as effective as anti-PD-1/PL1 biologics in immunotherapy.

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