DGKα inactivation is an integral component of the costimulatory pathway that amplifies TCR signals

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Abstract

The arsenal of cancer therapies has evolved to target T lymphocytes and restore their capacity to destroy tumor cells. T cells rely on diacylglycerol (DAG) to carry out their functions. DAG availability and signaling are regulated by the enzymes diacylglycerol kinase (DGK) and , whose excess function drives T cells into hyporesponsive states. Targeting DGK is a promising strategy for coping with cancer; its blockade could reinstate T cell attack on tumors while limiting tumor growth, due to positive DGK functions in several oncogenic pathways. Here we made a side-by-side comparison of the effects of commercial pharmacological DGK inhibitors on T cell responses with those promoted by DGK and DGK genetic deletion or silencing. We show the specificity for DGK of DGK inhibitors I and II and the structurally similar compound ritanserin. Inhibitor treatment promoted Ras/ERK (extracellular signal-regulated kinase) signaling and AP-1 (Activator protein-1) transcription, facilitated DGK membrane localization, reduced the requirement for costimulation, and cooperated with enhanced activation following DGK silencing/deletion. DGKiII and ritanserin had similar effects on TCR proximal signaling, but ritanserin counteracted long-term T cell activation, an effect that was potentiated in DGK-/- cells. In contrast with enhanced activation triggered by pharmacological inhibition, DGK silencing/genetic deletion led to impaired Lck (lymphocyte-specific protein tyrosine kinase) activation and limited costimulation responses. Our results demonstrate that pharmacological inhibition of DGK downstream of the TCR provides a gain-of-function effect that amplifies the DAG-dependent signaling cascade, an ability that could be exploited therapeutically to reinvigorate T cells to attack tumors.

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