Effect of Diacylglycerol Kinase Alpha Inhibitors as Immunomodulators for Cancer Treatment

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Abstract

In tumors, the recruitment of immune cells with suppressive capacity and the main characteristics of the tumor microenvironment (increased levels of adenosine, low oxygen and acidic pH) favor that T cells become anergic and the activation of the TCR does not occur or occurs in a deficient manner. Targeting and manipulation of the immune system constitutes thus a major priority in the treatment of cancer. The Diacylglycerol kinases (DGK) are a family of enzymes that phosphorylate diacylglycerol (DAG) transforming this lipid into phosphatidic acid (PA). In T lymphocytes DGK act as negative regulators of the immune response metabolizing the DAG generated upon T cell receptor (TCR) triggering. This lipid second messenger facilitates the activation of the Ras/ERK (extracellular signal-regulated kinase) cascade, providing a direct input for AP-1 (activator protein-1)-mediated transcription and the expression of activation markers such as CD69 or CD25. The over-activation and/or expression of specific DGK isoforms drive T lymphocytes into a hypofunctional or anergic state. Tumor infiltrating lymphocytes (TILs) show elevated expression of certain DGK isoforms. In addition, tumors express high levels of DGK, suggesting the contribution of this enzyme family to the mechanism that regulate tumor immune evasion. Targeting DGK activity could contribute to block tumor growth and enhance T cell immunity. The generation and validation of different tools to monitor the effectiveness of known and potential new DGK inhibitors is needed. Here we design and optimize robust and reproducible cell-based trials for screening processes as well as to develop reliable sensors for DGK activity. We used different strategies to validate the effects of the previously reported DGK inhibitor R59949 and test the effect over DGK activity of a structurally similar molecule previously characterized as an anti-anxiety, antidepressive and antipsychotic agent. In addition, we pursue to better understand the different DGK functions in tumors and immune system, focusing on the possible additional effects of DGK inhibitors and the mechanisms that modulate DGK expression and activity.

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