Role of diacylglycerol kinase alpha (DGKα) in T cells tolerance regulation and tumor evasion

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Abstract

Diacylglycerol kinase α is an enzyme highly expressed in mature T cells, where acts as a negative regulator by consuming Diacylglycerol (DAG). This DGKα role promotes hypofunctional immune response or anergy. DAG is generated in response to lymphocytes activation through their receptor (TCR), G protein-coupled receptors (GPCRs) or different kind of receptors. This molecule facilitates the activation of the Ras/ERK cascade. In tumors, the recruitment of immune cells with suppressive capacity and the characteristics of the tumor microenvironment (increased levels of adenosine, low oxygen and acidic pH) favor that T cells become anergic and that the activation of the TCR does not occur or occurs in a deficient manner. In this situation the transcription of certain genes, including DGKα gene, is promoted. In addition, tumors express high levels of DGKα, suggesting a positive role for this enzyme in these cells. Together these data indicate that DGKα could be relevant as a pharmaceutical target to block tumor growth and enhance T cell immunity. Based on this our main objective is the design and optimization of robust and reproducible trials in order to apply them for screening processes. To reach this objective we have developed and optimized sensors for DGKα activity through the Ras/ERK signaling axis that could be used as a control, both in normal activation and in presence of a positive compound working as an inhibitor of the enzyme. We will describe the optimization of different kind of assays including biochemical analysis, transcription reporters studies, imaging based assays and protein surface analysis by flow cytometry.

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