Diacylglycerol kinase zeta limits IL-2-dependent control of PD-1 expression in tumor-infiltrating T lymphocytes.

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VI Congreso de Señalización Celular, SECUAH 2021.
29 de marzo a 30 de abril, 2021. Universidad de Alcalá. Alcalá de Henares, Madrid. España.

Keywords: Immunotherapy; Programmed Cell Death 1 Receptor; CD8+ T lymphocytes; Drug evaluation; Preclinical; Immune evation

Abstract

Background: The inhibitory functions triggered by the programmed cell death-1 (PD-1) receptor following binding to its ligand (PD-L1) protect healthy organs from cytotoxic T cells, and neutralize anti-tumor T cell attack. Antibody-based therapies to block PD-1/PD-L1 interaction have yielded notable results, but most patients eventually develop resistance. This failure is attributed to CD8+ T cells achieving hypo-responsive states from which recovery is hardly feasible. Dysfunctional T cell phenotypes are favored by a sustained imbalance in the diacylglycerol (DAG)- and Ca2+-regulated transcriptional programs. In mice, DAG kinase zeta (DGKzeta) facilitates DAG consumption, limiting T cell activation and cytotoxic T cell responses. DGKzeta deficiency facilitates tumor rejection in mice without apparent adverse autoimmune effects. Despite its therapeutic potential, little is known about DGKzeta function in human T cells, and no known inhibitors target this isoform.

Methods: We used a human triple parameter reporter (TPR) cell line to examine the consequences of DGKzeta depletion on the transcriptional restriction imposed by PD-1 ligation. We studied the effect of DGKzeta deficiency on PD-1 expression dynamics, as well as the impact of DGKzeta absence on the in vivo growth of MC38 adenocarcinoma cells.

Results: We demonstrate that DGKzeta depletion enhances DAG-regulated transcriptional programs, promoting IL-2 production and partially counteracting PD-1 inhibitory functions. DGKzeta loss results in limited PD-1 expression and enhanced expansion of cytotoxic CD8+ T cell populations. This is observed even in immunosuppressive milieus, and correlates with the reduced ability of MC38 adenocarcinoma cells to form tumors in DGKzeta-deficient mice.

Conclusions: Our results, which define a role for DGKzeta in the control of PD-1 expression, confirm DGKzeta potential as a therapeutic target as well as a biomarker of CD8+ T cell dysfunctional states.

Citation: Arranz-Nicolás, Javier; Martin-Salgado, Miguel; Rodríguez-Rodríguez, Cristina; Liébana, Rosa; Moreno-Ortíz, María del Carmen; Leitner, Judith; Steinberger, Peter; Ávila-Flores, Antonia; Merida, Isabel (2021) Diacylglycerol kinase zeta limits IL-2-dependent control of PD-1 expression in tumor-infiltrating T lymphocytes. Proceedings of the VI Congreso de Señalización Celular, SECUAH 2021. 29 de marzo a 30 de abril, 2021. Universidad de Alcalá. Alcalá de Henares, Madrid. España. dianas 10 (1): e202103a01. ISSN 1886-8746 (electronic) journal.dianas.e202103a01 http://www3.uah.es/dianas?e202103a01.
URI http://hdl.handle.net/10017/15181