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Targeting nucleic acid sensors for cancer immunotherapy

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Abstract

The RNA sensor RIG-I (retinoic-acid inducible gene 1), also known as DDX58, recognizes cytosolic short dsRNA and plays a major role in the antiviral response. RIG-I activation triggers the type I Interferon (IFN) response and the expression of pro-inflammatory cytokines. Activation of cytosolic nucleic acid sensors has been associated with the potentiation of a robust anti-tumor immune response. In the present study, we activated RIG-I using a 5´-triphosphorilated-hpRNA in CT26, a murine colorectal carcinoma cell line. After 24h, we observed 4,474 genes that were differentially expressed between RIG-I activated and control group. According to the functional enrichment analysis, these genes are involved in the antiviral and innate immune responses. Specifically, we found Mx1 as the most differentially expressed gene, among other interferon response genes such as Mx2, Cxcl10, Ifi44l and Oas1. In vivo, injection of RIG-I stimulated CT26 cells markedly decreased tumor growth compared to their non-stimulated counterparts. Consistently, tumor weight was also decreased in RIG-I stimulated group. RNA expression analysis from the RIG-I activated tumors showed significant upregulation of IFN-I response genes which was consistent with our in vitro results. Multicolor flow cytometry analysis showed increased frequencies of Natural Killer Cells (NKs) and Dendritic Cells (DCs). Interestingly, RIG activated tumors also elicited significantly less exhausted CD8+ cells. Overall, our data highlight a critical role of tumor cell RIG-I in shaping the tumor immune microenvironment. Importantly, our work identifies several cellular and molecular immune correlates that can be exploited for combination therapies to enhance immune responses to tumors.