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Combination of an oncolytic virus with PD-L1 blockade keeps cancer in check

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Abstract

An oncolytic vaccinia virus expressing CXCL11 combined with PD-L1 blockade significantly reduces tumor burden and improves survival in murine cancer models.

Cancer immunotherapy has joined surgery, radiation, and chemotherapy as a key pillar of cancer treatment. Checkpoint inhibitors, such as anti–programmed cell death 1 (PD-1) and anti–programmed cell death ligand 1 (PD-L1) antibodies, are now widely used in multiple cancer types. Oncolytic viruses (OV) are immunotherapeutics that can eliminate cancer cells directly through cancer cell death or indirectly through immune activation and alteration of the tumor microenvironment (TME). Efficacy of both checkpoint inhibitors and OV depends on factors such as cancer subtype, PD-1/PD-L1 expression, and the immune milieu. In a new study, Liu *et al*. report that combining an OV promoting PD-L1 expression in both cancer

and TME cells effectively combines with an anti–PD-L1 antibody to overcome these barriers.

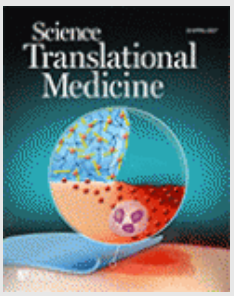
Using the Western Reserve strain oncolytic vaccinia virus (v vDD), Liu *et al*. first demonstrated that infection with v vDD led to up-regulation of PD-L1 expression on several murine and human cancer cell lines. Mice bearing murine colon or ovarian cancer cell lines were then treated with control, anti–PD-L1 antibody, a CXCL11-expressing vvDD strain (VV) that enhances T cell infiltration and PD-L1 expression, and the combination of anti–PD-L1 antibody and VV. Combination therapy produced a dramatic antitumor effect and prolonged survival. Significant decreases in myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T cells were found in the TME of dual-treated tumors. Furthermore, tumor-infiltrating $CD4^+$ and $CD8^+$ effector T cells were increased, with decreased coinhibitory markers and increased activation markers, in the setting of combination therapy. Importantly, long-term surviving mice after dual therapy had significantly impaired tumor growth after tumor reimplantation compared with treatment naïve mice, demonstrating activation of systemic immunity. Depletion experiments showed that $CD4^+$ and $CD8^+$ T cells and IFN-γ were required for combination therapy efficacy.

This study showed that a PD-L1–inducing vaccinia virus strongly combined with PD-L1 blockade to reduce tumor burden and induce long-term survival in murine cancer models. This approach shows the feasibility of using OV to transform anti–PD-L1 resistant tumors into sensitive tumors by enhancing antitumor immunity in the TME and stimulating systemic antitumor immunity. Given the current clinical limitations of OV and checkpoint inhibition approaches, combining OV with PD-L1 blockade represents an exciting new cancer immunotherapy approach with potential broad applicability.

Highlighted Article

Z. Liu, R. Ravindranathan, P. Kalinski, Z. S. Guo, D. L. Bartlett, Rational combination of oncolytic vaccinia virus and PD-L1 blockade works synergistically to enhance therapeutic efficacy. *Nat. Commun.* **8**, 14754 (2017).

View Abstract



Science Translational Medicine
Vol 9, Issue 386
19 April 2017

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