

1098 ONCOLYTIC HSV BLOCKING TUMOR-INTRINSIC PKR SENSITIZES GLIOBLASTOMA TO IMMUNOTHERAPY

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Background Mammalian cells have developed multiple intracellular mechanisms to defend against viral infections. These include RNA-activated protein kinase (PKR), cyclic GMP-AMP synthase and stimulation of interferon genes (cGAS-STING) and toll-like receptor-myeloid differentiation primary response 88 (TLR-MyD88). Among these, we identified that PKR presents the most formidable barrier to oncolytic herpes simplex virus (oHSV) replication in vitro.

Methods To elucidate the impact of PKR on host responses to oncolytic therapy, we generated a novel oncolytic virus (oHSV-shPKR) which disables tumor intrinsic PKR signaling in infected tumor cells.

Results As anticipated, oHSV-shPKR resulted in suppression of innate antiviral immunity and improves virus spread and tumor cell lysis both in vitro and in vivo. Single cell RNA sequencing combined with cell-cell communication analysis uncovered a strong correlation between PKR activation and transforming growth factor beta (TGF- β) immune suppressive signaling in both human and preclinical models. Using a murine PKR targeting oHSV, we found that in immune-competent mice this virus could rewire the tumor immune microenvironment to increase the activation of antigen presentation and enhance tumor antigen-specific CD8 T cell expansion and activity. Further, a single intratumoral injection of oHSV-shPKR significantly improved the survival of mice bearing orthotopic glioblastoma. To our knowledge, this is the first report to identify dual and opposing roles of PKR wherein PKR activates antiviral innate immunity and induces TGF- β signaling to inhibit antitumor adaptive immune responses.

Conclusions Thus, PKR represents the Achilles heel of oHSV therapy, restricting both viral replication and antitumor immunity, and an oncolytic virus that can target this pathway significantly improves response to virotherapy.

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