Molecular Therapy
Oncolytics
Editorial

Oncolytic viruses: Narcissistic or altruistic arsonists?

A central question for oncolytic virotherapy is whether it can take its place as a genuine player at the high table of immuno-oncology. At first glance, its credentials are smoking hot. Viral infection of cold (poorly immune infiltrated) tumors can set a tumor aflame, inducing infiltration of a variety of innate and adaptive immune effectors. And if oncolytic viruses (OVs) can indeed turn cold tumors hot, then they should be able to be used as critical adjuvants in combination with the big players in the game such as immune checkpoint inhibitors and chimeric antigen receptor (CAR) T cells. In the current issue, Mistarz and colleagues[1] provide some compelling data that suggest that OVs can, with a little help, bring the right sort of heat to tumors that will add considerable value to the arsenal of the clinical immuno-oncologist.

Much of the immediate immune heat induced by OV infection of tumors will be innate effectors responding to the viral infection to set up a subsequent adaptive viral antigen-specific response. This raises a key question: can highly inflammatory, viral-induced killing of tumor cells in the presence of non-self, immunodominant viral antigens break immunological tolerance to what are, for the most part, low T cell receptor (TCR)-binding affinity, self, or near-self sub-dominant tumor antigens? If the tumor expresses potently immunogenic antigens—high TCR affinity viral antigens or neoantigens—there may be enough bandwidth in the immune response to generate T cell responses against both OV-derived antigens (OV_As)[2] and tumor antigens (T_As),[3] with the latter being generally, but not exclusively,[4,5] considered the more therapeutically potent of effectors and thus the ideal targets for immune checkpoint inhibitors.[6] So, when we observe immune infiltration into tumors, encouraging as that may be, it is critical to ask if all heat is equal.

Here, Mistarz and colleagues provide compelling data that OVs can be used as vehicles to generate therapeutically valuable endogenous innate and adaptive antitumor responses. The authors compare the ability of vaccinia virus (VV)-mediated oncolytic virotherapy to generate endogenous host T cell responses against tumor cells in mice that are either non-tolerant or fully tolerized to a major tumor-associated antigen. MOVCAR 5009 ovarian carcinoma cells engineered to express the SV40 T antigen (TAg) were grown in either TAg-naive syngeneic wild-type (WT) C57Bl/6 mice or TgMISIIR-TAg-low mice, in which TAg is a self-antigen. Unfortunately, oncolysis induced by virus (VV-GFP) alone was unable to prime or boost a T cell response in either model even against this very immunodominant T_A expressed within the tumor—suggesting that even if tumors express immunogenic neoantigens, oncolysis might not be the antitumor immune adjuvant that we had hoped. However, to turn their virus into a better adjuvant, the authors generated oncolytic VV expressing an antagonist for CXCR4, a chemokine that plays pleiotropic, pro-tumor roles by affecting M2 tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs). And here is where the drum roll should kick in—treatment of TAg^+-MOVCAR 5009 tumors in TgMISIIR-TAg-low mice with the OV construct (VV-CXCR4-A) generated TAg-specific $CD8^+$ T cell responses that corresponded to improved tumor regression despite a high degree of tolerance to TAg. This finding presents exciting immunological evidence for the breaking of tolerance to self-antigens, allowing tumor-specific $CD8^+$ T cells to propagate despite the antiviral response.

Therefore, although the purely oncolytic VV was unable to have much virological or immunological impact on tumor growth, the same OV could, with a little help from its chemokine friends, bring exactly the right sort of both innate (TAM and CAF influencing) and adaptive (anti-T_A $CD8^+$ T cells) heat into tumors by targeting a highly tolerized self-T_A. These are critical data for the field because they show that OV infection can break tolerance to low TCR affinity, low frequency, peripherally tolerized T_A. As always, outcomes are likely to be highly dependent upon the tumor type and location, flavor of the virus used, degree of tolerance to the T_A, patient variability, and so on. Nonetheless, there can be no doubt that OVs are excellent arsonists—setting tumors on fire with a plethora of immune infiltrators. The concern has been that OV-set arson is essentially narcissistic, leading to a swamping of the immune system with exclusively antiviral attention. Mistarz and colleagues now provide concrete evidence that OV-induced inflammation can also be immunologically altruistic by allowing therapeutic antitumor T cells to arise, phoenix-like, from the flames.

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AUTHOR CONTRIBUTIONS

L.K. and R.G.V. shared the opinions expressed and wrote the manuscript.

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