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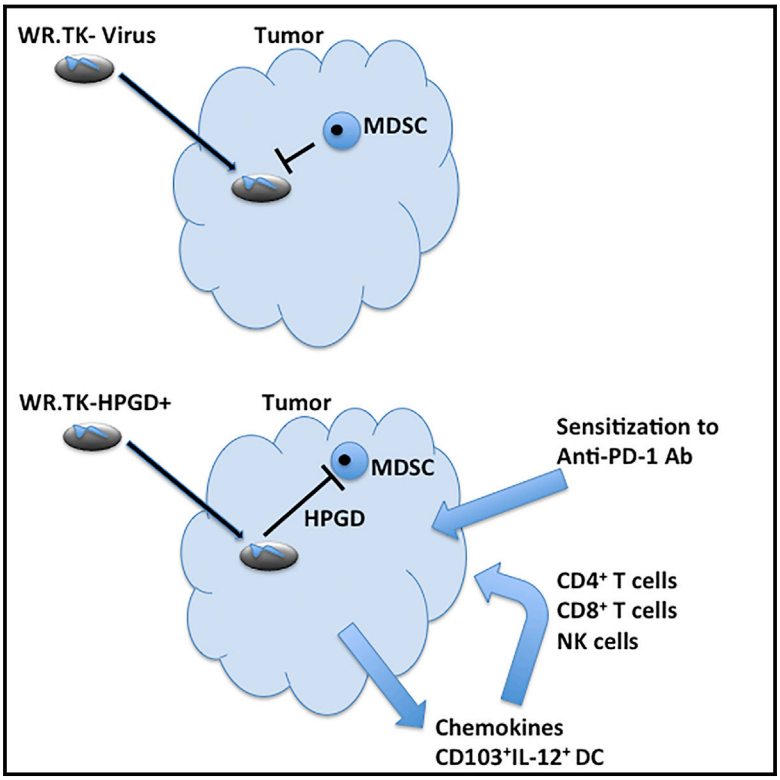
Oncolytic Virus-Mediated Targeting of PGE_2 in the Tumor Alters the Immune Status and Sensitizes Established and Resistant Tumors to Immunotherapy

Graphical Abstract



Highlights

- Identification of granulocytic MDSC as key mediators of resistance to immunotherapy
- Oncolytic virus-expressed HPGD targets PGE_2 and depletes G-MDSC in the tumor
- Reduction in PGE_2 in the tumor alters chemokine profiles and immune cell infiltrate
- Targeting of PGE_2 sensitizes established and resistant tumors to imnmunotherapies

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In Brief

Hou et al. identify the prostaglandin PGE_2 in the tumor as a key mediator of resistance to immunotherapies, including oncolytic virotherapy. Viral vectors engineered to target PGE_2 are capable of overcoming localized immunosuppression to allow for robust anti-tumor adaptive immune responses.

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Oncolytic Virus-Mediated Targeting of PGE_2 in the Tumor Alters the Immune Status and Sensitizes Established and Resistant Tumors to Immunotherapy

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SUMMARY

Immunotherapies are highly promising cancer treatments, but understanding the factors mediating their resistance remains critical. Successes in randomized clinical testing have supported the growing appreciation that oncolytic virotherapies primarily act as immunotherapies. Here we identified prostaglandin E2 (PGE_2) in the tumor as a key mediator of resistance to immunotherapies, including oncolytic vaccinia virotherapy. Elevated levels of PGE_2 coupled to suppressive chemokine profiles and high levels of granulocytic myeloid-derived suppressor cells resulted in loss of immunotherapeutic potential. Viral vectors engineered to target PGE_2 were capable of overcoming localized immunosuppression leading to profound changes in the tumor's immune status. This allowed the viral vectors to raise robust antitumor adaptive immune responses and sensitized established and previously resistant tumors to immunotherapies.

INTRODUCTION

Recent clinical successes have focused interest on the potential of cancer immunotherapies. However, solid tumors often display the capacity to limit immune induction or to mediate early immune shutoff both locally and systemically. Identifying the key mediators of resistance to immunotherapy will allow the development of more robust treatments with more predictable responses.

Oncolytic viruses (OVs) are vectors designed to selectively replicate in and destroy cancer cells, and multiple OVs based on many different viral strains are currently undergoing clinical testing. However, notable among the current clinical generation of oncolytic viral vectors is that those that have succeeded in randomized trials have expressed an immune-activating cytokine (granulocyte-macrophage colony-stimulating factor [GM-CSF]) (Andtbacka et al., 2013; Heo et al., 2013). This reinforces a plethora of pre-clinical data indicating that the immune response can be a key mediator of OV activity (Lichty et al., 2014) and has led to the development of several ingenious strategies to enhance the immune-activating potential of OVs (Kottke et al., 2013; Tysome et al., 2012; Zhang et al., 2014). The situation is complex, however, as enhanced immune activation frequently reduces oncolytic activity and other reports have demonstrated that certain immune-suppression strategies can also enhance OV activity (Alvarez-Breckenridge et al., 2012; Chen et al., 2013; Lun et al., 2009). A better understanding of the importance of OV-mediated immunotherapeutic activity, how this interacts with oncolytic activity, and how OVs can be most beneficially engineered to interact with the host immune response is therefore needed.

Multiple OV strains based on vaccinia have been reported (Kirn et al., 2007; Mastrangelo et al., 1999; Thorne et al., 2007; Zhang et al., 2007), and one of these expressing GM-CSF, Pexa-Vec (JX-594), has produced encouraging responses in randomized clinical testing (Heo et al., 2013; Park et al., 2008).

Significance

Cancer immunotherapies, including oncolytic viruses, offer the potential for curative cancer treatments. However, patients often present with a combination of systemic immune defects and localized immunosuppression within the tumor that limit immune activation or mediate premature immune shutoff, leading to resistance. Through identification of critical pathways and immunosuppressive cell lineages mediating resistance to oncolytic viral therapies, it was possible to develop viral vectors to overcome them. As a result, previously resistant cancer models became sensitive to oncolytic viral therapy and other immunotherapies. These findings have the potential to significantly enhance the effectiveness of oncolytic viral and other immunotherapies in the clinic and to delineate approaches to overcome resistance to other cancer therapies.

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