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How can we trick the immune system to overcome the detrimental effects of oncolytic viral therapy to treat glioblastoma?

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Although China approved the use of the H101 adenovirus for the treatment of various solid cancers in 2005, similar viruses have not obtained clinical approval in the US. [1] While there are several phase III trials testing the therapeutic efficacy of oncolytic viruses (OV) in patients diagnosed with melanoma, bladder, and advanced head and neck cancers (NCT01438112, NCT00769704, NCT01166542), there are currently only phase I/II OV trials for patients with glioblastoma (GB) which highlights the difficulty associated with treating this particular disease. (NCT00157703, NCT01174537, NCT00528684, NCT01301430, NCT01582516). The uniqueness of the brain tumor microenvironment- extracellular matrix, leaky blood vessels, and immune responses- has collectively been shown to limit OV delivery, replication, spread, and efficacy. Of these factors, the impact of the host immune response on OV efficacy is perhaps the most complicated to understand. In the context of OV therapy, the immune response is a double-edged sword. On one hand, the innate immune responses result in rapid viral clearance and decreased OV efficacy, while on the other hand, immune responses elicited after viral infection also have the potential to activate an adaptive anti-tumor immune response to promote tumor eradication. Here we summarize some of the challenges and recent progress made by investigators in manipulating the immune response with respect to OV therapies for GB.

The rapid innate immune response induced by OVs is thought to promote viral clearance, inhibit viral replication, and reduce tumor cell killing. In the brain, the influx of monocytes, neutrophils, and natural killer (NK) cells following OV treatment has been correlated with reduced viral propagation limiting efficacy through the up-regulation of chemokines and cytokines. Several studies testing the efficacy of immunosuppressive agents given in

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conjunction with virotherapy to modulate these early defenses have shown promise. The most well studied of these agents is cyclophosphamide, and it has been shown to improve viral load and efficacy in numerous animal studies when given in conjunction with OV.[2] At high doses, the primary mechanism of action of CPA is thought to be through its cytotoxic effects on immune cells, but the drug has also been shown to reduce the levels of circulating IgM and anti-viral antibodies. Interestingly, treatment of tumor bearing animals with a low dose CPA has also been shown to inhibit T-regulatory cells and enhance NK cell anti-tumor activity activated by viral treatment. In mouse melanoma studies, low dose CPA in conjunction with Reovirus and IL-2 were found to significantly enhance viral efficacy through its immunostiumulatory effects.[3] Irrespective of the underlying mechanism, all of these studies collectively observed increased anti-tumor responses when OV is administered in conjunction with CPA. The ability of CPA to enhance OV therapy is currently being investigated with oncolytic measles virus (MV-NIS) in patients diagnosed with myeloma (NCT00450814).

The role of phagocytic macrophage cells in limiting the efficacy of oncolytic viral therapy has also been studied using agents such as clodronate liposomes (CLs) which can destroy monocytic/macrophage cells in vivo. While treatment with CLs increased tumor viral load it did not enhance the survival of rats bearing intracranial GBs.[4] This result is thought to be due primarily to the inability of CLs to cross the blood brain barrier and neutralize the resident microglia. While the nervous system and brain are considered to be “immune privileged”, immune cells, such as NK cells, infiltrate the CNS upon OV infection. A recent study investigating the negative impact of NK cells on efficacy of OV in treating intracranial GB in mice, found that the deletion of NK cell cytotoxicity receptors improved oHSV therapy, and that the targeting of these receptors may help improve OV efficacy in patients.[5] This study highlights the importance of targeting multiple cell types involved in the initial immune responses to OV infection in the brain.

Tumor cell invasion into the normal brain is one of the hallmarks of glioblastoma, and so treatment with a systemic agent that can reach distant invading cells is considered optimal. The systemic delivery of most OVs has remained a challenge due to their rapid serum neutralization. The use of Cobra Venom Factor (CVF) to inactivate the C3 component of complement has been shown to improve virus stability in serum.[6] Copper present in serum has also been shown to inhibit the ability of oncolytic HSV to destroy and reach intracranial tumors. Interestingly, copper is also vital for tumor angiogenesis, and the anti-neoplastic effects of copper chelation are currently being evaluated in several clinical trials (NCT00383851, NCT00405574, NCT00176800). Treatment of animals bearing GB tumors with the copper chelating agent ATN-224 improved tumor virus loads, increased tumor cell killing, and enhanced animal survival.[7] Copper also plays a key role in immune cell regulation, and it is important for neutrophil, NK cell, and macrophage function.[8] While the impact of copper chelation on reducing innate immune cell function was not directly examined in the ATN-224 study, these experiments provide a foundation for future work examining the combination of copper chelators with OV therapies. It is important to note, however, that copper is also important for T-cell maintenance and function and thus the effects of copper chelation on the development of anti-tumor immune response following OV treatment remain to be elucidated.

The type I interferon (IFN) response is one of the major antiviral responses which limits OV replication. Agents which can transiently suppress this response have been shown to promote virus replication and enhance OV efficacy in various preclinical studies. Histone Deacetylases (HDACs) are important gene regulators and the inhibition of HDAC activity has been shown to inhibit cell growth and induce apoptosis.[9] Importantly, HDAC inhibitors have also been shown to inhibit the IFN-mediated antiviral response.[10] HDAC inhibitors such as Trichostatin A and Valproic Acid have been shown to improve the oncolytic effects of OV against brain tumors in preclinical animal models.[11] The ability of HDAC inhibitors to target cancer cells and modulate immune responses makes combination studies highly significant. We have previously demonstrated that OV treatment induces the expression of the extracellular matrix protein Cysteine Rich 61 (CCN1).[12] CCN1 is known to promote tumor angiogenesis, and we recently reported that this protein also plays a significant role in the induction of a Type-1 IFN antiviral response resulting in the activation of the Jak/Stat Signaling pathway.[13] Future studies will unveil the significance of disrupting CCN1 signaling in oncolytic viral efficacy. Interestingly, strategies to limit tumor angiogenesis in conjunction with viral therapy have been investigated for their immunomodulatory effects.[14] Anti-angiogenic agents not only restrict the flow of oxygen and nutrients into the tumor, but they also destroy the “highways” used by immune cells to infiltrate into the tumor microenvironment. In one study, the treatment of animals with the anti-angiogenic agent Cilengitide decreased the influx of CD45 positive immune cells into the tumor microenvironment following OV therapy and also improved the survival of rats bearing intracranial GBs.[15] Similarly, the combination of Bevacizumab with an oncolytic virus expressing the anti-angiogenic protein angiostatin (G47Δ-mAngio) also significantly reduced tumor vasculature and macrophage accumulation in the tumor microenvironment resulting in increased virus distribution, tumor cell killing, and animal survival.[16] A randomized Phase II study testing safety and efficacy of bevacizumab with Reolysin in patients with metastatic colorectal cancer is ongoing will uncover the clinical efficacy of this strategy (NCT01622543).

While the transient suppression of the innate immune response increases virus replication and tumor cell killing, it is important to note that the generation of a strong anti-tumor immune response is considered to be just as important in creating successful OV therapies. For example, the long term administration of the immune suppressive corticosteroid, dexamethasone, with OV was unable inhibit tumor growth in mice with subcutaneous neuroblastoma tumors. This observation was thought to be the result of dexamethasone mediated suppression of tumor-specific cytotoxic T lymphocytes, and it highlights the importance of generating an anti-tumor immune response.[17] The creation of “armed” viruses to activate and amplify the anti-tumor immune response is currently an intense area of study. oHSVs expressing IL-12 and IL-4 in order to help generate more potent T-cell responses and anti-tumor immunity against treated brain tumors have shown improved anti-tumor efficacy.[18,19] While the generation of an antitumor immune response leading to the eradication of tumors is currently being tested, the activation of an unbridled immune response against central nervous system tumors has to be approached with caution.

Currently, there is an array of pharmacological inhibitors as well as an emerging number of second generation viruses designed to affect different aspects of the immune response to OV

therapy. Future work focusing on the combination of drugs targeting antiviral immune responses with rational, “armed” OVs to generate the optimal anti-tumor immune response will uncover the potential of this very promising therapy.

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