Uncovering a novel mechanism whereby NK cells interfere with glioblastoma virotherapy

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Despite initial promising results, the success of clinical trials testing oncolytic viruses in glioblastoma patients has been limited. Innate immunity appears to be one among several barriers against successful viral oncolysis. Recent findings suggest a mechanism by which natural killer cells limit the efficacy of oncolytic viruses via natural cytotoxicity receptors.

The deleterious impact of innate immunity in virotherapy was first identified in preclinical animal studies demonstrating that the combination of cyclophosphamide (CPA) with an oncolytic herpes simplex virus (oHSV) significantly improves survival. Immunohistochemical studies of tumor-bearing rats treated with CPA and oHSV unveiled a significant reduction in the number of macrophages, microglial cells, and natural killer (NK) cells within the tumor microenvironment, which correlated with increased viral replication. Additionally, the efficacy of CPA combined with oHSV was improved in mice pretreated with clodronate liposomes (which deplete macrophages) as well as in animals genetically deficient for interferon γ.4,5

As they are endowed with both antiviral and antitumor functions, at least hypothetically NK cells may either inhibit the efficacy of virotherapy or promote additional degrees to tumor-cell killing, resulting in improved antineoplastic effects. Using the vesicular stomatitis virus (VSV) for the treatment of hepatocellular carcinoma, Altomonte et al. demonstrated that the depletion of NK cells enhances viral efficacy and increases overall survival. A subsequent study was based on a second generation oncolytic VSV encoding a chemokine-binding protein that limits NK and NKT cell intratumoral infiltration, resulting in improved efficacy.7 While these findings suggest that NK cells constitute an initial barrier to viral oncolysis, several groups have highlighted the necessity of harnessing the antitumor properties of these cells to achieve tumor clearance.8 In this context, by using both xenograft and syngeneic mouse glioma models Alvarez-Breckenridge et al. have recently demonstrated the relevance of NK cells following oHSV infection (Fig. 1).9 Indeed, following the intracranial inoculation of oHSV, NK cells were recruited into the brain and manifested an activated phenotype. In addition, NK cells were found to mediate the inflammatory cytokine and chemokine milieu that stems from viral infection while coordinating the activation of macrophage and microglial cells. Confirming the functional relevance of these findings, the survival of mice bearing either U87dEGFR glioma xenografts or 4C8 murine gliomas increased upon the depletion of NK cells prior to oHSV infection. These findings suggest that—presumably owing to their antiviral functions—NK cells play an important role in limiting the efficacy of oHSV-based therapeutic approaches against GBM.

To further understand the mechanisms underlying these observations, NK cell-mediated cytotoxicity was determined in vitro by co-culturing human NK cells with...
not be overlooked. Indeed, to achieve successful therapeutic responses upon virotherapy, there must be a delicate balance between the antiviral and antitumor immunity. Mathematical modeling has proposed that shortly after infection, the innate immune system should be suppressed to achieve multiple rounds of viral replication. Once a sufficient viral load is attained to achieve tumor killing, antitumor immune effectors including NK cells may constitute a valuable partner for tumor clearance. The challenge for future studies will be to identify both a mechanism and a time point for switching from the suppression of antiviral immunity to the activation of antitumor immune responses.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Figure 1. Deleterious role of natural killer cells in virotherapy. (A) Glioma cells normally express ligands for the natural killer (NK) cell natural cytotoxicity receptors NKp30 and NKp46. (B and C) Upon infection by oncolytic herpes simplex virus (oHSV), these ligands are overexpressed, correlating with a temporal increase in NK cell activation within the tumor microenvironment. NK cells kill oHSV-infected glioma cells via NKp30 and NKp46, in turn resulting in decreased viral titers and limiting the efficacy of viral oncolysis.
References


