Newcastle disease virotherapy induces long-term survival and tumor-specific immune memory in orthotopic glioma through the induction of immunogenic cell death.

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Abstract

The oncolytic features of several naturally oncolytic viruses have been shown on Glioblastoma Multiforme cell lines and in xenotransplant models. However, orthotopic glioma studies in immunocompetent animals are lacking. Here we investigated Newcastle disease virus (NDV) in the orthotopic, syngeneic murine GL261 model. Seven days after tumor induction, mice received NDV intratumorally. Treatment significantly prolonged median survival and 50% of animals showed long-term survival. We demonstrated immunogenic cell death (ICD) induction in GL261 cells after NDV infection, comprising calreticulin surface exposure, release of HMGB1 and increased PMEL17 cancer antigen expression. Uniquely, we found absence of secreted ATP. NDV-induced ICD occurred independently of caspase signaling and was blocked by Necrostatin-1, suggesting the contribution of necroptosis. Autophagy induction following NDV infection of GL261 cells was demonstrated as well. In vivo, elevated infiltration of IFN-γ T cells was observed in NDV-treated tumors, along with reduced accumulation of myeloid derived suppressor cells. The importance of a functional adaptive immune system in this paradigm was demonstrated in immunodeficient Rag2⁻/⁻ mice and in CD8⁺ T cell depleted animals, where NDV slightly prolonged survival, but failed to induce long-term cure. Secondary tumor induction with GL261 cells or LLC cells in mice surviving long-term after NDV treatment, demonstrated the induction of a long-term, tumor-specific immunological memory response by ND virotherapy. For the first time, we describe the therapeutic activity of NDV against GL261 tumors, evidenced in an orthotopic mouse model. The therapeutic effect relies on the induction of ICD in the tumor cells, which primes adaptive antitumor immunity.

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KEYWORDS: Newcastle disease virus; antitumor immunity; glioma; immunogenic cell death; necroptosis

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