**The oncolytic activity of Newcastle disease virus in clear cell renal carcinoma cells in normoxic and hypoxic conditions: the interplay between von Hippel-Lindau and interferon-β signaling**


ABSTRACT

Viral-mediated oncolysis is a promising cancer therapeutic approach offering an increased efficacy with less toxicity than the current therapies. The complexity of solid tumor microenvironments includes regions of hypoxia. In these regions, the transcription factor, hypoxia inducible factor (HIF), is active and regulates expression of many genes that contribute to aggressive malignancy, radio-, and chemo-resistance. To investigate the oncolytic efficacy of a highly virulent (velogenic) Newcastle disease virus (NDV) in the presence or absence of HIF-2Ű, renal cell carcinoma (RCC) cell lines with defective or reconstituted wild-type (wt) von Hippel-Lindau (VHL) activity were used. We show that these RCC cells responded to NDV by producing only interferon (IFN)-ƃ, but not IFN-Ű, and are associated with increased STAT1 phosphorylation. Restoration of wt VHL expression enhanced NDV-induced IFN-ƃ production, leading to prolonged STAT1 phosphorylation and increased cell death. Hypoxia augmented NDV oncolytic activity regardless of the cells' HIF-2Űlevels. These results highlight the potential of oncolytic NDV as a potent therapeutic agent in the killing of hypoxic cancer cells.



**Keyword:** Oncolytic; Newcastle disease virus; Von Hippel-Lindau