

## Human renal carcinoma cells respond to Newcastle disease virus infection through activation of the p38 MAPK/NF- $\kappa$ B/I $\kappa$ B $\alpha$ pathway

### ABSTRACT

**Purpose:** Newcastle disease virus (NDV) is an oncolytic virus that is known to have a higher preference to cancer cells than to normal cells. It has been proposed that this higher preference may be due to defects in the interferon (IFN) responses of cancer cells. The exact mechanism underlying this process, however, remains to be resolved. In the present study, we examined the antiviral response towards NDV infection of clear cell renal cell carcinoma (ccRCC) cells. ccRCC is associated with mutations of the von Hippel-Lindau tumor suppressor gene VHL, whose protein product is important for eliciting cellular responses to changes in oxygen levels. The most common first line treatment strategy of ccRCC includes IFN. Unfortunately, most ccRCC cases are diagnosed at a late stage and often are resistant to IFN-based therapies. Alternative treatment approaches, including virotherapy using oncolytic viruses, are currently being investigated. The present study was designed to investigate the mechanistic pathways underlying the response of ccRCC cells to oncolytic NDV infection.

**Methods and results:** We found that NDV induces activation of NF- $\kappa$ B in ccRCC cells by inducing phosphorylation and subsequent degradation of I $\kappa$ B. I $\kappa$ B was found to be phosphorylated as early as 1 hour post-infection and to result in rapid NF- $\kappa$ B nuclear translocation and activation. Importantly, p38 MAPK phosphorylation was found to occur upstream of the NDV-induced NF- $\kappa$ B activation. Restoration of VHL in ccRCC cells did not result in a reduction of this phosphorylation. A similar phenomenon was also observed in several other cancer-derived cell lines.

**Conclusion:** Our data provide evidence for involvement of the p38 MAPK/NF- $\kappa$ B/I $\kappa$ B pathway in NDV infection and subsequent induction of apoptosis in ccRCC cells.

**Keyword:** Newcastle disease virus; Clear cell renal cell carcinoma; p38 MAPK; NF- $\kappa$ B