



Editorial



Newcastle Disease Virus/HK84: Next Potential Star for Targeted Immunotherapy of Hepatocellular Carcinoma?

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Of all liver cancers, hepatocellular carcinoma (HCC) is reported as the most common globally, with the highest incidence in East Asia.¹ Because of the late diagnosis of disease, HCC is one of the top causes of cancer-related mortality, with the poor overall prognosis, the survival rate largely depends on the stage of diagnosis, the extent of cirrhosis, other associated risk factors and the medical treatment.^{1,2} Therefore, there is urgent need for reliable HCC treatments, which requires further investigation and research. In addition to traditional cancer therapy, such as surgery and chemotherapy, immunotherapy has recently undergone rapid development and now includes checkpoint inhibitors, inhibiting cytokine blockade, adoptive cellular therapies and vaccines, which are under investigation in preclinical and/or in clinical trials. However, the currently available immunotherapy regimens for HCC under investigation have shown limited effectiveness in a relatively small number of patients.

A recent article by Chen *et al.*,³ "Oncolytic Effect of Newcastle Virus HK84 Against Hepatocellular Carcinoma by Activation Interferon Signaling," describes a new strain that is potentially useful for treating HCC. Oncolytic viruses (OVs) are one of the immunotherapies that can be selectively engineered to target certain tumor cells while sparing the normal tissue of the host. In addition, OVs can restore the antitumor immunity of the host.⁴ OVs can be engineered to cause direct lysis of the tumor cells without affecting normal cells and tissues. For example, an OV, JX-594 (Pexa-Vec), has been introduced into the treatment of patients with HCC.⁵ In this present article, the authors identified a wild-type Newcastle disease virus (NDV) HK84 (NDV/HK84) from 10 NDV strains, with proper confirmation of its potential oncolytic ability through both *in vivo* and *in vitro* experiments.

NDV is an OVs under investigation for the treatment of tumors, and although it is contagious among avian species, it is less virulent in humans. Therefore, the biosafety level

is less concerning. There is a general agreement that NDV that it has both lytic and nonlytic strains, which produce infectious progeny that disrupt the plasma membrane of infected cells and stimulate the host immune response upon release.⁴ Reverse genetic engineering of NDV applications for cancer treatment has been studied for years. Preclinical studies of recombinant Newcastle disease virus (rNDV) have activity against various types of cancer, including hepatoma.⁶ Some of rNDV only and rNDV combination treatments have entered clinical trials and shown some clinical benefits, but the results are inconclusive.

In the study by Chen *et al.*,³ NDV/HK84 inhibited growth of SK-Hep-I-Luc HCC cells in tumor-bearing mice and had an oncolytic effect an *in vitro* HCC model, with an inhibitory rate of over 85%. In the *in vivo* experiment, the intratumoral infection with NDV/HK84 inhibited tumor growth in six out of 10 mice. The authors found that NDV/HK84 specifically inhibited HCC compared with the vehicle control without affecting healthy normal tissue. The authors did not observe obvious adverse reactions or weight loss in the NDV/HK84 treated group, which supported the safety of the NDV strain. With the EID50 quantification and viral titer of tumors measurement, the safety of NDV/HK84 was further confirmed in that study.

The JX-594 was found to be well tolerated in a clinical trial,⁷ and was associated with significantly longer overall survival in a high-dose compared with a low-dose regimen.⁸ Sangro *et al.*⁹ reported the result of Phase I trial of a first-generation adenoviral vector encoding herpes simplex virus thymidine kinase (HSV-TK) gene in combination with ganciclovir, in the treatment of advanced HCC. Treatment was well tolerated and no severe side effects were reported, except for fever, flu-like syndrome, pain at the injection site, and pancytopenia. Unlike other viruses under investigation, NDV/HK84 was selected from the widely existing poultry industry without any genetic modification. With a long existence among humans, it may indicate reliable biosafety of NDV/HK87.

Regarding the oncolytic mechanism of NDV/HK84, Chen *et al.*³ reported significant enhancement of RIG-I like receptors, Toll-like receptors (TLRs), and type I interferon (IFN) signaling.³ The IFN-related genes were further analyzed and identified as an important element of the mechanism of NDV/HK84 in inhibiting liver cell lines. Type I IFN has antiviral, pro-apoptotic, and immunomodulatory effects, and the combined effects are responsible for the antitumor response induced by NDV.¹⁰ Dying cells are recognized by pattern recognition receptors, including extracellular TLRs and intracellular RNA helicases such as RIG-1.¹⁰ The recognition of all these patterns leads to the activation of a signaling

Abbreviations: HCC, hepatocellular carcinoma; IFN, interferon; NDV, Newcastle disease virus; OVs, oncolytic viruses; rNDV, recombinant Newcastle disease virus.

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cascade that triggers the transcription and expression of genes encoding proinflammatory cytokines and type I IFN.

Defects in the type I IFN signaling pathway has been identified as a mechanism of the selectivity of NDV for tumor cells in nonpermissive hosts.¹⁰ NDV is a strong inducer of type I IFN and is expected to have effect on both the innate and the adaptive immune system were activated. The authors reported that Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis identified genes consistent with the participation of type I IFN in the inhibition of HCC by NDV/HK84.¹⁰ However, when type I IFN responds to NDV by presenting the innate immune reaction, there is a dilemma about how to achieve a balance between adequate virus replication and tumor lysis in accordance with immunity. That requires further investigation in their future studies.

Various OVs are currently being studied for their potential effect in cancer therapy. Whether or not their antitumor effectiveness is greater than control treatment remains unclear, and the studies are ongoing.⁵ Up to now, only a few OVs are being investigated for the treatment of HCC. Only two, JX-594 vaccinia virus (NCT03071094 and NCT02562755) and VSV-IFN β -NIS vesicular stomatitis virus (NCT03647163), are currently involved in ongoing clinical trials. The reason why NDV/HK84 was selected for further investigation out of ten NDV strains was because of its increased oncolytic effect, which was over 80%. The targeting mechanism of NDV/HK84 was not yet being confirmed in the study by Chen *et al*.³ However, this reported work has presented us a comprehensive experiment *in vivo* and *in vitro* regarding the safety and oncolytic effect of NDV/HK84. The novel potential natural low-toxic oncolytic NDV strain with high efficiency is expected to be the next exciting star in immunotherapy for solid tumors. The further investigation of NDV/HK84 would be worthwhile in the search for a new potential treatment for HCC.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

WH and WC propose the main opinions and write the manuscript cooperatively.

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