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MECHANISMS OF ONCOLYTIC ACTIVITY OF NEWCASTLE DISEASE VIRUS STRAIN AF2240 IN HUMAN RENAL CARCINOMA CELL LINE

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By

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May 2014

Chair: **Assoc. Prof. Norazizah Shafee, PhD**

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Newcastle disease virus (NDV) is an oncolytic virus that is known to selectively replicate in cancer cells compared to normal cells. It has been proposed that this preference is due to a defect in the cancer cells' interferon (IFN) responses. The exact mechanism underlying this process, however, remains unknown. In the present study, the antiviral response towards NDV infection by clear cell renal cell carcinoma (RCC) cells was examined. The most common first line treatment of RCC is using IFN. Unfortunately, most RCC cases are diagnosed at a late stage and often are resistant to IFN therapies. Alternative treatment approaches, including virotherapy, using oncolytic viruses, are currently being investigated. The present study used proteomic, molecular, immunological and biochemical techniques to investigate the mechanistic pathways that are involved in the response of RCC cells with defective or reconstituted wild type (wt) von Hippel-Lindau (VHL) gene activity to an oncolytic NDV infection.

It was observed that NDV induced activation of NF-κB in RCC cells by inducing phosphorylation of IκBα and its subsequent degradation. IκBα was phosphorylated as early as 1 hour post-infection and resulted in rapid NF-κB nuclear translocation and activation. Importantly, p38 MAPK phosphorylation occurred upstream of the NF-κB activation. These data provide evidence for the involvement of the p38 MAPK/NF-κB/IκBα pathway in NDV infection and eventual apoptosis of RCC cells. Since the results indicated that there was a possible correlation between the pathway and IFN-β signaling, additional experiments were performed to further understand the IFN-β signalling, specifically STAT pathway, in NDV-infected RCC cells under various microenvironmental factors.

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-2α, renal cell carcinoma (RCC) cell lines with defective or reconstituted wild type (wt) von Hippel-Lindau (VHL) gene activity were used. The data showed that these RCC cells responded to NDV by producing only IFN-β, but not IFN-α and are associated with increased STAT1 phosphorylation. Restoration of wt VHL expression enhanced NDV-induced IFN-β production, leading to prolonged STAT1 phosphorylation and increased cell death. Hypoxia augmented NDV oncolytic activity regardless of the cells' HIF-2α levels.

In summary, this study demonstrates IFN-β may play important role in NDV oncolysis through activation of p38 MAPK/NF-κB/IκBα and STAT pathways in renal cell carcinoma. Altogether, these findings provide a better mechanistic understanding of NDV-mediated cell death and also highlight the potential of oncolytic local strain of NDV AF2240 as a potent therapeutic agent against normoxic and hypoxic cancer cells, especially renal cell carcinoma.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

MEKANISMA AKTIVITI ONKOLITIK VIRUS PENYAKIT SAMPAR AYAM STRAIN AF2240 DALAM JUJUKAN SEL KARSINOMA GINJAL MANUSIA

Oleh

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Virus penyakit sampar ayam adalah sejenis virus onkolitik di mana ia mempunyai kecenderungan yang lebih tinggi untuk mengganda dalam sel-sel kanser jika berbanding dengan sel-sel normal. Laporan terdahulu mencadangkan bahawa ciri-ciri ini adalah disebabkan sel-sel kanser tidak mempunyai respon interferon (IFN) yang normal. Mekanisme yang terlibat dalam proses ini masih belum diketahui. Dalam kajian ini, respon antivirus dari sel-sel karsinoma ginjal sel jernih (RCC) terhadap infeksi virus telah dikaji. Penggunaan interferon merupakan rawatan barisan hadapan yang paling umum untuk merawat RCC. Malangnya, kebanyakan kes-kes RCC hanya dapat dikesan pada peringkat serius dan biasanya mempunyai daya rintang terhadap terapi interferon. Penggunaan virus onkolitik yang juga dikenali sebagai *virotherapy* merupakan salah satu perawatan alternatif yang sedang dikaji buat masa ini. Kajian ini menggunakan pendekatan proteomik, molekul, imunologi dan biokimia untuk mengkaji laluan mekanisma yang terlibat dalam tindak balas sel-sel RCC terhadap infeksi NDV. Sel-sel tersebut mempunyai aktiviti gen von Hippel-Lindau (VHL) yang berbeza.

Hasil yang diperoleh dalam kajian ini menunjukkan bahawa NDV merangsangkan pengaktifan NF-κB dengan meningkatkan pemfosforilan dan pendegradan IκBα dalam sel-sel RCC. Pemfosforilan IκBα berlaku seawal satu jam selepas infeksi. Ini menyebabkan translokasi NF-κB ke nukleus berlaku dan mengaktifkannya. Di samping itu, pemfosforilan p38 MAPK juga dikesan sebelum pengaktifan NF-κB. Data-data ini telah membuktikan bahawa laluan p38 MAPK/NF-κB/IκBα terlibat dalam aktiviti onkolitik NDV seperti pengaruhan apoptosis. Demikian juga, hasil kajian tersebut menunjukkan bahawa laluan ini mungkin mempunyai korelasi dengan pengisyaratan IFN-β. Kajian selanjutnya telah dijalankan bagi mengkaji penglibatan pengisyaratan IFN-β, terutamanya laluan STAT, dalam sel-sel RCC yang dirawati dengan NDV dan juga di bawah faktor persekitaran yang berlainan.

Kawasan hipoksia selalunya dijumpai dalam tumor pepejal. Faktor induksi hipoksia (HIF) adalah sejenis faktor transkripsi yang aktif di kawasan tersebut. Ia mengawal ekspresi gen-gen yang menyumbang kepada keagresifan maglinan yang rintang terhadap rawatan. Kajian selanjutnya dilakukan untuk mengkaji pula keberkesanan onkolitik virulen NDV di dalam jujukan sel RCC yang mempunyai tahap ekspresi HIF-2α yang berbeza, iaitu jujukan sel RCC yang memiliki jenis liar von Hippel-Lindau (VHL) dan satu lagi tidak memilikinya. Keputusan daripada kajian ini menunjukkan bahawa penghasilan IFN-β dan peningkatan pemfosforilan STAT1 berlaku apabila sel-sel tersebut bertindak balas dengan NDV. Walau bagaimanapun, penghasilan IFN-α tidak dapat dikesan selepas infeksi NDV. Pemulihan jenis liar von Hippel-Lindau (VHL) meningkatkan penghasilan IFN-β, sekali gus menyebabkan pemfosforilan STAT1 yang berpanjangan dan peningkatan kematian sel. Hipoksia juga meningkatkan aktiviti onkolitik tanpa mengira tahap HIF-2α dalam sel-sel tersebut.

Secara keseluruhannya, kajian ini menunjukkan bahawa IFN-β memainkan peranan yang penting dalam onkolisis NDV melalui pengaktifan laluan p38 MAPK/NF-κB/IκBα dan laluan STAT bagi sel karsinoma ginjal. Hasil daripada kajian ini memberi pemahaman yang mendalam tentang mekanisma yang terlibat dalam aktiviti onkolitik dan ia juga menunjukkan bahawa NDV AF2240 onkolitik strain tempatan mempunyai potensi yang tinggi sebagai agen terapeutik untuk membunuh sel-sel kanser terutamanya sel karsinoma ginjal dalam keadaan normoksia dan hipoksia.

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I certify that a Thesis Examination Committee has met on 20 May 2014 to conduct the final examination of Ch'ng Wei Choong on his thesis entitled "Mechanisms of Oncolytic Activity of Newcastle Disease Virus Strain AF2240 in Human Renal Carcinoma Cell Line" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

CPE	Cytopathic effect
DAPI	4',6-Diamidino-2-Phenylindole, Dihydrochloride
FACS	Fluorescence-activated cell sorting
HAU	Hemagglutination unit
HIF	Hypoxia inducible factor
HIF-1α	Hypoxia inducible factor-1 alpha
HIF-2α	Hypoxia inducible factor-2 alpha
hpi	Hour(s) post-infection
IFN	Interferon
IFN-α	Interferon-alpha
IFN-β	Interferon-beta
JAK/STAT	Janus kinase / signal transducer and activator of transcription
MAPK	Mitogen-activated protein kinase
MOI	Multiplicity of infection
MTT	Methylthiazolyldiphenyl-tetrazolium bromide
NDV	Newcastle disease virus
NP	Nucleocapsid protein
PARP1	Poly (ADP-ribose) polymerase 1
PHD	Prolyl hydroxylase domain
PKR	Protein kinase R
RCC	Renal cell carcinoma
RIPA	Radio-immunoprecipitation assay
SOCS	Suppressor of cytokine signaling

STAT1	Signal transducer and activator of transcription 1
TNF-α	Tumor necrosis factor-alpha
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labelling
VHL	Von Hippel-Lindau
VSV	Vesicular stomatitis virus

CHAPTER 1

INTRODUCTION

Newcastle disease virus (NDV) is a type of avian virus belonging to the *Paramyxoviridae* family (Yusoff and Tan, 2001). It is of interest to cancer researchers due to its oncolytic properties. In cancer cells with naturally occurring defective antiviral defense systems, the virus can replicate up to 10,000 times better compared to normal cells (Reichard *et al.*, 1992). In recent years, many scientific reports and phase I/II/III clinical trials revealed that NDV can act as a potent and promising therapeutic agent against cancers (Lam *et al.*, 2011; N.C.I., 2013). Despite various studies, NDV has not been approved by the U.S. Food and Drug Administration for cancer treatment. This is because, in some clinical trials, positive outcomes were not significantly observed (N.C.I., 2013). NDV-modified tumor cells vaccine has been shown to improve both recurrence-free and overall survival of patients with colon carcinoma in a phase II trial (Schlag *et al.*, 1992). Some advanced renal cell carcinoma patients displayed partial responses including partial remission (15%) and stable disease (30%) after the treatment (Pomer *et al.*, 1995). Such vaccine, however, did not show remarkable clinical efficacy in melanoma patients (Voit *et al.*, 2003). The main obstacle in reducing the unfavourable outcome is the lack of sufficient understanding of the mechanisms of NDV infection in cancer cells. The complexity and heterogeneity of the various types of cancers also are major factors.

Renal cancer is a common adult malignancy worldwide (Globocan, 2012). Majority of patients are asymptomatic over a long period of time until the disease become locally advanced. Clear cell renal cell carcinoma (RCC) is the most lethal and dominant subtype of adult renal cancer (Eble *et al.*, 2004; Thomas and Tawfik, 2008; Zhou and He, 2013). This subtype is less susceptible to conventional oncologic treatments including radiotherapy and chemotherapy. To date, several molecular-targeted agents are approved by the U.S. Food and Drug Administration for RCC treatment (Fisher *et al.*, 2013). Unfortunately, complete responses are very rare, with undesirable side effects.

Currently, the first line treatment option available for RCC is using interferon (IFN) therapy. Even though it is the first line option, therapeutic response of patients with metastasis is low, around 15-20% (Unnithan and Rini, 2007). IFN secreted by cells in response to virus infections has been shown to be beneficial, with oncolytic viruses. The specificity of NDV-mediated killing of cancer cells has been proposed to be due to defects in the type I interferon (IFN-α/β) response of the cells (Stojdl *et al.*, 2000; Fiola *et al.*, 2006). Cancer cells responded to NDV infection by producing only IFN-β production (Elankumaran *et al.*, 2010). The efficacy and safety of vesicular stomatitis virus (VSV) as an oncolytic agent has been shown to be enhanced by IFN-β, through immune-mediated mechanisms, in mesothelioma (Willmon *et al.*, 2009). This observation leads to the possibility of manipulating the exclusive IFN-β induction by NDV as a potential strategy to boost the efficacy and

safety of NDV as an oncolytic agent in clinical settings. This option could be closely examined if the detailed mechanism of cellular responses to NDV infection is known.

In the present study, the oncolytic activities of a local isolate of NDV (designated as AF2240) in RCC cell lines was investigated. It is hypothesized that NDV oncolytic properties can be enhanced in renal carcinoma cells through the manipulation of interferon-related pathways. To test this hypothesis, the study was designed with the main objective to investigate the molecular mechanisms underlying NDV oncolysis in human clear cell renal cell carcinoma (RCC) cell lines. The specific aims of the study were:

1. To examine the oncolytic activity of NDV in renal carcinoma cells.
2. To study the response of the p38MAPK/NF-κB/IκBα pathway in NDV-infected renal carcinoma cells.
3. To investigate the involvement of interferons in the oncolytic activity of NDV in renal carcinoma cells.

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