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ONCOLYTIC ACTIVITY OF NEWCASTLE DISEASE VIRUS STRAIN AF2240 IN HYPOXIC CANCER CELLS

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By

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Solid tumors have different microenvironment that can influence the capability of cancer treatments. Cancer cells in low oxygen condition or hypoxia, present an obstacle as they are more resistant towards chemotherapy and radiotherapy. The use of oncolytic viruses as therapeutic agent has demonstrated promising results making it an ideal approach to treat cancer cells. Newcastle disease virus (NDV) is an oncolytic virus that has specificity in targeting tumor cells over normal cells. Despite its potential, the exact mechanism of its oncolysis in hypoxic cancer cells remains unknown. In the present study, the oncolytic activity of NDV in hypoxic cancer cells was investigated. Various cancer cell lines such as osteosarcoma (Saos-2), breast carcinoma (MCF-7) and fibrosarcoma (HT1080) cells were infected with NDV under normoxic or hypoxic conditions. Following NDV infection, molecular, proteomic, immunological and biochemical techniques were performed. Data obtained in this study showed that NDV was capable to infect and replicate in hypoxia tumor microenvironment similar to normoxia. This was confirmed by the equivalent level of NP viral protein expressed in normoxic and hypoxic conditions of Saos-2, MCF-7 and HT1080 cells. The amount of NP viral protein detected in the infected cells was correlated with the production of the viral progeny. It was observed that NDV replicates in hypoxic cancer cells to levels comparable to normoxic cells, leading to induction in cytopathic effects which subsequently caused cell death. MCF-7 cells which displayed better replication upon NDV infection resulted in more cytotoxicity than in Saos-2 and HT1080 cells. These data provide evidence that NDV was able to adapt and exhibit an oncolytic capacity in hypoxic tumor cells in a manner that is equivalent to the normoxic tumor cells and was cell type specific. Hypoxic tumor cells negatively affect therapeutic outcome by overexpressing pro-survival genes under the control of the hypoxia-inducible factor (HIF). HIF-1 is a heterodimer transcriptional factor consisting of a regulated α (HIF-1α) and constitutive β subunit (HIF-1β). Overexpression of HIF contributes to an aggressive malignancy, which is associated with chemoresistance and radioresistance. In the present study, the effects of NDV infection on HIF-1α in cancer cells were examined. Data obtained showed that a velogenic NDV infection diminished hypoxia-induced HIF-1α accumulation, leading to a decreased activation of its downstream target gene, *carbonic anhydrase 9 (CA9)*. This NDV-induced downregulation of HIF-

1α occurred post-translationally and was partially abrogated by proteasomal inhibition. The process appeared to be independent of the tumor suppressor protein, p53. Apart from the ability of NDV in targeting hypoxic cancer cells and HIF-1α, the significance of hypoxia in the antiviral response towards NDV infection was also evaluated in this study. Data obtained showed that IFN-β is the principal antiviral factor produced by cells in response to NDV infection. Hypoxic condition was observed to minimally affect the levels of IFN-β production in MCF-7 cells, but not in Saos-2 and HT1080 cells. NDV infection in hypoxic conditions did not drastically alter the level of IFN-β production including STAT proteins. In addition, NDV induced IFN-β secretion results in increased levels of total STAT1 and STAT1 phosphorylation proteins leading to cell death. In summary, this study demonstrated that NDV infection downregulates HIF-1α and induced cell death in hypoxic tumor cells comparable to normoxic with the involvement of IFN-β signalling. These findings also help in improving the existing data regarding the efficiency of NDV as a promising therapeutic agent to infect and eliminate various types of cells in different tumor microenvironments, particularly in hypoxic cancer cells.

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

AKTIVITI ONKOLITIK VIRUS PENYAKIT SAMPAR AYAM STRAIN AF2240 DALAM JUJUKAN SEL-SEL TUMOR HIPOKSIA

Oleh

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Tumor pepejal mempunyai persekitaran mikro yang berbeza dan boleh mempengaruhi keupayaan rawatan-rawatan kanser. Sel-sel barah dalam keadaan oksigen yang rendah atau hipoksia, menjadi penghalang kerana ia lebih tahan terhadap kemoterapi dan radioterapi. Penggunaan virus onkolitik sebagai agen terapeutik telah menunjukkan hasil yang memberangsangkan dan menjadikannya sebagai salah satu pendekatan yang ideal untuk merawat sel-sel barah. Virus penyakit sampar ayam (NDV) adalah virus onkolitik yang mempunyai pengkhususan dalam mensasarkan sel-sel barah berbanding sel biasa. Walaubagaimanapun, mekanisme sebenar onkolisis dalam sel-sel barah hipoksik tidak diketahui. Dalam kajian ini, aktiviti onkolitik NDV dalam sel-sel barah hipoksik telah diselidiki. Sel-sel sel barah seperti osteosarkoma (Saos-2), karsinoma payudara (MCF-7) dan sel fibrosarkoma (HT1080) telah dijangkiti dengan NDV di dalam keadaan normoksik dan hipoksik. Berikutan jangkitan NDV, teknik-teknik molekul, proteomik, imunologi dan biokimia telah dilakukan. Data yang diperolehi dalam kajian ini menunjukkan bahawa NDV mampu untuk menjangkiti dan mengganda dalam persekitaran mikro tumor pepejal hipoksia sama seperti dalam keadaan normoksia. Ini dapat disahkan dengan penghasilan protein NP yang setara dalam keadaan normoksia dan hipoksia sel Saos-2, MCF-7 dan HT1080. Jumlah protein virus NP yang dikesan dalam sel yang telah dijangkiti mempunyai kaitan dengan pengeluaran progeni virus. Telah diperhatikan bahawa NDV mereplikasi sel-sel barah hipoksik ke paras yang setanding dengan sel-sel normoksik, yang membawa kepada induksi dalam kesan sitopati dan menyebabkan kematian sel. Sel MCF-7 menunjukkan replikasi yang lebih baik apabila dijangkiti NDV dan menyebabkan lebih banyak kesitotoksian berbanding sel Saos-2 dan HT1080. Data-data ini membuktikan bahawa NDV dapat menyesuaikan diri dan mempamerkan keupayaan onkolitik dalam sel-sel barah hipoksik dengan cara yang sama seperti sel-sel barah normoksik, dan merupakan jenis sel khusus. Sel barah hipoksia memberi kesan negatif kepada hasil terapeutik dengan mengungkapkan gen pro-hidup di bawah kawalan faktor induksi hipoksia (HIF). HIF-1 adalah faktor transkrip heterodimer yang terdiri daripada α (HIF-1α) dan subunit β (HIF-1β). Kadar ekspresi HIF yang tinggi menyumbang kepada maglinan agresif, yang dikaitkan dengan rintangan kimia dan radiasi. Dalam kajian ini, kesan jangkitan NDV pada HIF-1α dalam sel-sel barah telah diperiksa. Data yang diperoleh menunjukkan bahawa jangkitan NDV velogenik mengurangkan

pengumpulan HIF-1α dan menyebabkan penurunan pengaktifan gen sasaran khusus, karbonik anhidrase (*CA9)*. Pengurangan regulasi HIF-1α yang disebabkan oleh NDV ini berlaku selepas terjemahan dan sebahagiannya dibatalkan oleh perencatan proteasom. Proses ini kelihatan bebas daripada protein penindas tumor, p53. Selain dari kemampuan NDV dalam mensasarkan sel-sel barah hipoksik dan HIF-1α, kepentingan hipoksia dalam tindak balas antivirus terhadap jangkitan NDV juga dinilai dalam kajian ini. Data yang diperoleh menunjukkan bahawa IFN-β adalah faktor utama antiviral yang dihasilkan oleh sel sebagai tindak balas kepada jangkitan NDV. Diperhatikan, keadaan hipoksik mengurangkan sedikit tahap pengeluaran IFN-β pada sel MCF-7, tetapi tidak pada sel-sel Saos-2 dan HT1080. Infeksi NDV dalam keadaan hipoksia tidak mengubah secara drastik tahap pengeluaran IFN-β termasuk protein STAT. Di samping itu, penghasilan IFN-β oleh NDV mengakibatkan peningkatan protein STAT1 dan fosforilasi STAT1 yang membawa kepada kematian sel. Secara ringkasnya, kajian ini menunjukkan bahawa jangkitan NDV menurunkan kadar HIF-1α, dan menyebabkan kematian sel dalam sel barah hipoksik yang setanding dengan normosik dengan penglibatan isyarat IFN-β. Penemuan ini juga membantu dalam meningkatkan data sedia ada mengenai kecekapan NDV sebagai ejen terapeutik yang menjanjikan untuk menjangkiti dan menghapuskan pelbagai jenis sel dalam persekitaran tumor pepejal yang berbeza, terutamanya dalam sel-sel barah hipoksik.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ARNT	Aryl hydrocarbon receptor nuclear translocater
BCA	Bicinchoninic acid
bHLH	Basic helix-loop-helix
BSA	Bovine serum albumin
CAIX	Carbonic anhydrase IX
CA9	Carbonic anhydrase 9
CO_2	Carbon dioxide
DAPI	4', 6-diamidino-2-phenylindole
DMEM	Dulbecco's modified Eagle's medium
DMSO	Dimethyl sulfoxide
ELISA	Enzyme-linked immunosorbent assay
F	Fusion protein
FBS	Fetal bovine serum
h	Hour
hpi	Hour post-infection
HA	Hemagglutination activity
HAU	Hemagglutination unit
HIF	Hypoxia inducible factor
HIF-1α	Hypoxia inducible factor-1 alpha
HIF-2α	Hypoxia inducible factor-2 alpha
HN	haemagglutinin-neuraminidase protein
HRP	Horseradish peroxidase
HSV	Herpes simplex virus
Hu-IFN-β-1a	Human interferon beta 1a
IFN	Interferon
IFN-α	Interferon-alpha
IFN-β	Interferon-beta
JAK	Januse kinase
JAK/STAT	Januse kinase/signal transducer and activator of transcription
kb	Kilobase
kDa	Kilodalton
L	Large polymerase protein
M	molar/ Matrix protein
min	Minute
mM	Millimolar
MOI	Multiplicity of infection
MTT	3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
ND	Newcastle disease
NDV	Newcastle disease virus
NP	Nucleocapsid protein
P	Phosphoprotein

PBS	Phosphate buffer saline
PHD	Prolyl hydroxylase domain
PI	Proteasome inhibitor
pVHL	von Hippel-Lindau protein
PVDF	Polyvinylidene difluoride membrane
RBC	Red blood cells
RCC	Renal cell carcinoma
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase-polymerase chain reaction
RTCA	Real-time cell analysis
sec	Second
SDS	Sodium dodecyl sulfate
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEM	Standard error of mean
SOCS	Suppressor of cytokine signaling
STAT1	Signal transducer and activator of transcription 1
TAE	Tris-acetate-EDTA
TBS	Tris-buffered saline
TBST	Tris-buffered saline-Tween-20
Tyk2	tyrosine kinase 2
UPP	Ubiquitin proteasome pathway
VHL	von Hippel-Lindau
V	Voltage
VSV	Vesicular stomatitis virus
v/v	volume/volume
w/v	weight/volume
×g	Centrifugal force (multiply gravity)

CHAPTER 1

INTRODUCTION

Hypoxia, a reduced in the normal level of tissue oxygen tension is a common characteristic of solid tumor (Höckel & Vaupel, 2001). Rapid tumor proliferations outstrip the blood supply, leading to the development of hypoxia regions (Rankin, Nam, & Giaccia, 2016; Rofstad, 2000; Subarsky & Hill, 2003). These regions represent the low oxygen tension which is commonly associated with tumor aggression, metastasis and poor survival in various types of cancer cells. The adaptive response of hypoxia confer enhance resistance to chemotherapy and radiotherapy (Brown, 1999; Vaupel, Kelleher, & Höckel, 2001).

Hypoxia inducible factor (HIF) is a crucial player in cellular responses to hypoxia. HIF is a transcription factor that acts as a heterodimer composed of two subunits, α and β. In oxygenated cells, HIF-α subunit is hydroxylated by prolyl hydroxylase (PHD), resulting in binding to von Hippel-Lindau protein (pVHL) which promotes the ubiquitination and degradation of HIF-α by the proteasome (Kamura et al., 2000; Miyata, Takizawa, & van Ypersele de Strihou, 2011; Ratcliffe et al., 1999). While in hypoxia condition, PHD failed to hydroxylate HIF-α, leading to its stabilization and translocation to the nucleus. The stabilized HIF-α subsequently dimerize with constitutively expressed HIF-β and bind to hypoxia response elements of target gene to activate transcription (Bruick & McKnight, 2001; G L Semenza, 2010; Wang, Jiang, Rue, & Semenza, 1995). Over expression of HIF-α activate the expression of various genes that promote angiogenesis, cellular differentiation and apoptosis resistance (Keith, Johnson, & Simon, 2011; Semenza, 2003). Thus, hypoxia or HIF is crucial to be targeted for development of therapeutics.

Oncolytic virotherapy is emerging as an alternative treatment option for cancer patients to overcome the resistance to conventional therapies. There are a number of viruses that exhibit an oncolytic effects in tumor cancer cells. Some of them are capable in infecting and inducing apoptosis in hypoxic cancer cells (Connor, Naczki, Koumenis, & Lyles, 2004; Roos et al., 2010), whereas others showed adverse effect (Hwang, Watson, Der, & Ohh, 2006; Naldini, Carraro, Fleischmann, & Bocci, 1993). Newcastle disease virus (NDV) has become an interest in numerous studies of different tumor cell lines due to its oncolytic properties. NDV is a negative single stranded RNA family of *Paramyxoviridae* member, with known oncolytic properties (Yusoff & Tan, 2001). The oncolytic natures of NDV that replicate selectively in tumor cells over normal cells make it a good candidate for anticancer agent. Due to its rising potential, NDV are currently being tested in a number of phase I/II/III clinical trials (Freeman et al., 2006; Lam et al., 2011; Russell, Peng, & Bell, 2012). Several studies demonstrated that a local isolate of a velogenic strain of NDV designated as AF2240 induced extensive apoptosis in various types of tumor cells (Ahmad, Ahmed, Keong, Abd Manan, & Othman, 2015; Alabsi et al., 2011; Ali et al., 2011; Ch'ng, Stanbridge, Yusoff, & Shafee, 2013; Chia, Tan, Yusoff, & Shafee, 2012; Molouki & Yusoff, 2012).

All the studies however, only reported its oncolytic effects in normoxic cancer cells. Up to now, there has been no study investigate the effects of NDV infection on hypoxic cancer cells specifically HIF-1. Thus far, the oncolytic activity of NDV strain, AF2240 on hypoxic tumor cells still remains unknown. It is hypothesized that NDV oncolytic activity is increased in hypoxic cancer cells leading to cell death. These data are needed in order to determine the effective treatment specifically for hypoxic and most likely, drug-resistant cancer cells. Therefore, the main objective of the study was to investigate the oncolytic activity of NDV in hypoxic cancer cells. The study will be performed with the following specific objectives:

1. To examine the oncolytic activity of NDV in hypoxic cancer cells.

2. To determine the molecular mechanism of NDV infection on HIF activities.

3. To evaluate the types of antiviral responses and the signaling pathways involved in NDV-infected hypoxic cancer cells.

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