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TRANSCRIPTOMIC ANALYSIS OF EJ28 BLADDER CANCER CELLS PERSISTENTLY INFECTED WITH NEWCASTLE DISEASE VIRUS

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By

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Newcastle disease virus (NDV) is a highly contagious avian virus which leads to tremendous economy loss in poultry industry. Nevertheless, NDV shows good oncolytic activities on cancer cells by inducing apoptosis and therefore, it has been assessed in clinical trials for cancer treatment. Despite their promising potential, NDV was found to be able to persistently infect cancer cells *in vitro* without causing any cell death. The morphological characteristics of the cancer cells persistently infected by NDV has been described in the previous studies but the exact mechanism involved has yet to be elucidated. Hence, the objective of this study is to investigate the transcriptomic profiles of cancer cells persistently infected by NDV. By challenging with three rounds of infection with Malaysian velogenic strain AF2240, the NDV persistently infected bladder cancer cells EJ28 was established and was designated as EJ28P. The persistency of EJ28P was confirmed when they have grown to 4-fold of the original seeding number after 5 days post NDV infection; whilst its parental cells was nearly diminished in the same condition. Annexin V apoptosis assay revealed that approximately 60% of parental cells underwent apoptosis at 48 h post infection while the EJ28P was about 30%, which was insignificantly different from mock-infection. EJ28P reinfected with recombinant NDV AF2240 with green fluorescent protein (rAF-GFP) exhibited green fluorescent even after 25 passages. This further confirmed the persistency of NDV in EJ28P. Subsequently, total RNA of EJ28 and EJ28P were extracted and subjected to microarray analyses. A total of 355 genes, which were differentially expressed in EJ28P compared to EJ28, were identified using edgeR program, with their $\log_2$ fold change of 2 or more. Among them, 222 genes were up-regulated while 133 genes were down-regulated. Gene ontology (GO) of these genes were obtained using PANTHER Classification System and Database for annotation, visualisation and Integrated Discovery (DAVID). Genes associated to cytokine and apoptosis such as *IL6*, *IL8*, *GBP2*, *CXCL8*, *HER5* and *TNF* were down-regulated. Pathway analysis revealed that TGF-β signalling was downregulated in EJ28P, which could lead suppression of apoptotic pathway and promotion of cell proliferation. However, the anti-virus responses of EJ28P were not completely suppressed as interferon-induced transmembrane (*IFITM1*), an anti-viral

protein gene was up-regulated. On the other hand, genes associated to solute carrier families that are responsible for glucose and amino acids transportation across the membrane, were significantly up-regulated, suggesting that high demand of energy for virus activities or for the cancer cell's metabolism, or for both. In addition, genes related to keratin group were overexpressed possibly involved in maintaining the cell structural integrity. Since these expressed genes were not only beneficial to cell but also to virus, it may either reflect a competition on both cell and virus for each survival, or an interaction from both sides in order to maintain a co-existing form. Based on these analyses, it is postulated that impairment of apoptosis and defective in pro-inflammatory response, together with overexpression of solute carrier families and keratin groups, contribute to NDV persistent infection in bladder cancer cells. This study expands our understanding on persistent NDV infection in bladder cancer cells.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

ANALISIS TRANSKRIPTOM SEL KANSER PUNDI KENCING EJ28 YANG DIJANGKITI BERTERUSAN DENGAN *NEWCASTLE DISEASE VIRUS*

Oleh

CHAN LEE CHIN

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Newcastle disease virus (NDV) adalah virus burung yang berjangkit dan menyebabkan kerugian yang besar dalam industri penternakan ayam. Walau bagaimanapun, NDV berupaya untuk membunuh sel kanser dengan mencetuskan apoptosis, oleh itu, virus ini dikaji dalam fasa klinikal untuk rawatan kanser. Walaupun NDV berpotensi tinggi dalam rawatan kanser, NDV telah diketahui boleh menjangkiti sel kanser secara berterusan dalam keadaan *in vitro* tanpa menyebabkan kematian sel kanser. Ciri-ciri mofologi jangkitan berterusan NDV telah digambarkan dalam kajian sebelum ini tetapi mekanismenya masih belum diketahui. Oleh itu, objektif keseluruhan kajian ini adalah untuk menyiasat profil transkriptomik jangkitan berterusan NDV. Melalui pencabaran tiga kali dengan jangkitan NDV AF2240, kanser pundi kencing EJ28 yang dijangkiti secara berterusan dengan NDV telah diwujudkan dan dinamakan EJ28P. Selepas 5 hari dijangkiti dengan NDV, jangkitan beterusan EJ28P telah disahkan apabila bilangan sel ini bertambah 4 kali ganda berbanding dengan bilangan sel pada hari pertama. Bilangan sel induk EJ28 pula didapati berkurangan dalam tempoh ujian yang sama. Ujian apoptosis Annexin V menunjukkan bahawa lebih kurang 60% sel induk mengalami apoptosis selepas 48 jam dijangkiti oleh NDV. EJ28P pula, hanya mengalami lebih kurang 30% apoptosis, yang didapati lebih kurang sama dengan peratusan apoptosis sel yang tidak dijangkiti oleh NDV. EJ28P yang dijangkiti NDV berekombinan dengan protein fluorescen hijau masih dapat dikesan selepas dikultur 25 kali dalam flask. Ini membukti bahawa EJ28P yang dijangkiti oleh NDV adalah suatu jangkitan berterusan. Seterusnya, RNA EJ28P telah diekstrak dan diuji dengan analisis microarray. Sejumlah 355 gen telah dikenalpasti dengan program edgeR, dengan log2 perubahan lipat lebih daripada 2. Antara gen-gen ini, 222 gen megalami regulasi meningkat dan 133 gen mengalami regulasi menurun. Pencarian ontologi gen (GO) telah dijalankan melalui Sistem klasifikasi PANTHER dan Database for annotation, visualisation and Integrated Discovery (DAVID). Gen berkaitan dengan sitokin dan apoptosis seperti IL6, IL8, GBP2, CXCL8, HER5 and TNF mengalami regulasi menurun. Analisa lintasan mendedahkan pengisyaratan TGF-beta telah terbantut dalam EJ28P, menyebabkan lintasan apoptosis ditindas dan pada masa yang sama menggalakkan pertumbuhan sel. Namun itu, respon anti-virus EJ28P bukan ditindas sepenuhnya kerana interferon-induced transmembrane

(IFITM1), gen yang mengkod protein anti-virus mengalami regulasi meningkat. Sebaliknya, gen berkaitan dengan solute carrier families yang berfungsi dalam pengangkutan glukos dan asid amino melalui membran sel, mengalami regulasi meningkat, menunjukkan keperluan tenaga dalam aktiviti virus, metabolisma sel, ataupun kedua-duanya. Tambahan pula, gen yang berkaitan dengan kumpulan keratin mengalami ekspresi meningkat. Ini mungkin menunjukkan penglibatan pemeliharaan integriti struktur sel. Kajian ekspresi gen, menunjukkan bahawa gen-gen yang terekspres bukan sahaja membantu sel yang dijangkit untuk terus hidup, malah juga membantu rambatan virus Berdasarkan kepada analisis, faktor-faktor seperti kegagalan sel mencetus apoptosis dan inflamasi serta ekspresi solute carrier family dan keratin yang meningkat menyumbang kepada jangkitan berterusan NDV. Kesimpulannya, kajian ini mengembangkan pemahaman terhadap jangkitan berterusan NDV dan juga menyumbang kepada kajian berikutnya.

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I certify that a Thesis Examination Committee has met on 8 March 2018 to conduct the final examination of Chan Lee Chin on his thesis entitled "Transcriptomic Analysis of EJ28 Bladder Cancer Cells Persistently Infected with Newcastle Disease Virus" 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 Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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BF	Biological Function
BSA	bovine serum albumin
CC	Cellular Component
°C	degree Celsius
cDNA	complementary deoxyribonucleic acid
CO_2	Carbon dioxide
Cy3	green cyanine fluorescent dye
Cy5	red cyanine fluorescent dye
DAPI	4',6-diamidino-2-phenylindole
DAVID	Database of Annotation, Visualisation and Integrated Discovery
DMEM	Dulbecco's Modified Eagle Medium
DNA	deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
FC	Fold change
GE	gene-end sequence
GFP	Green Fluorescent Protein
GM	Growth media
GO	Gene ontology
GS	gene start sequence
h	hour
HA	Haemagglutination
HEK	human embryonic kidney
HIV	human immunodeficiency virus
hpi	hour(s) post-infection
IFN	interferon
IPA	Ingenuity Pathway Analysis
IS	intergenic sequence
KEGG	Kyoto Encyclopedia of Genes and Genomes
L	Litre
µ	micro
M	Molarity
MF	Molecular Function
min	minute(s)
mL	Millilitre
mm	millimetre
MM	Maintenance media
MOI	multiplicity of infection
mRNA	messenger ribonucleic acid
NaCl	sodium chloride
NDV	Newcastle disease virus
nm	nanometer
PBS	Phosphate buffered saline
pH	Puissance of hydrogen
PI	Persistent infection
PPI	protein-protein interaction
rAF-GFP	recombinant NDV AF2240 harbouring GFP Protein gene
RBC	chicken red blood cells
RIN	RNA intergrity number

RNA	ribonucleic acid
Rpm	revolutions per minute
s	second(s)
TBFV	Tickborne Flavivirus
TNF	tumour necrosis factor
U	Unit
(v/v)	(volume/volume)
(w/v)	(weight/volume)

CHAPTER 1

INTRODUCTION

Newcastle disease virus (NDV) is an economically important avian paramyxovirus (Lancaster, 1976; Alexander, 1997). Its non-segmented single-stranded negative sensed RNA genome consists of six genes; which encode for nucleocapsid (NP), phosphoprotein (P), matrix (M), fusion (F), haemagglutinin-neuraminidase (HN) and large polymerase (L) proteins (Yusoff and Tan, 2001). The mesogenic and lentogenic NDV strain causes mild infection while the velogenic strains are highly contagious affecting both wild and domestic avian species alike (Songhua *et al*., 2003).

Despite their pathogenicity in avian species, NDV displays oncolytic properties enabling it to be utilised as a therapeutic agent for cancer treatment (Rusell, 2002). Early observation of its oncolytic potential was reported for leukaemia (Wheelock and Dingle, 1967), cervical cancer (Cassel and Garrett, 1965) and metastatic gastric cancer (Csatary, 1971). Since then, the virus has been studied extensively, both *in vivo* and *in vitro*, followed by clinical trials which showed promising results (Schirrmacher, 2016). Similar to other oncolytic viruses, NDV capitalises on the defective antiviral and apoptotic pathways in cancer cells to allow it to selectively replicate in tumour cells. The suppression of interferon type 1 antiviral pathways by tumour cells in order to evade immunosurveillance, have been reported to potentially permit oncolytic virus replication (Fiola *et al*., 2006; Krishnamuthy *et al*., 2006; Singh *et al*., 2012). Apart from that, overexpression of the anti-apoptotic proteins in tumour cells also promotes virus propagation (Mansour *et al*., 2011; Schirrmacher, 2017).

Interestingly, NDV and other RNA viruses such as measles virus, Sendai virus, and vesicular stomatitis virus were found to be able to cause persistent infections in cancer cell lines (Rima and Martin, 1976). The virus remains in these persistently infected cells without causing cellular apoptosis (Boldogh et al., 1996). This phenomenon could have evolved initially leading to viral tropism (Ahmed et al., 1981; Baric et al., 1999; Pinkert et al., 2011). Initial studies on persistent infection (PI) by NDV during 1960s and 1970s were more focused on the virus and its cellular infection properties (Rodriguez et al., 1967; Thacore and Youngner, 1969; Preble and Youngner, 1973a and 1973b). Since then, studies of NDV PI have been neglected until recently, Chia et al. (2014) reported persistent infection by NDV in the colorectal cancer cell line, SW480, which then produced PI virus with reduced plaques size. Rangaswamy et al. (2017) revealed that PI NDV consists of mutated HN and F genes after it persistently infected ovarian cancer cells. However, the role of the host cell in PI is still obscure.

To have a better understanding of the role of the host cells during persistent infection, microarray analysis will be used to study the transcriptomic profile of the cancer cells in response to persistent NDV infection. Microarray is a tool that can probe thousands of expressed genes and measures their expression level (Quankeenbush, 2006). It has been used to reveal PI mechanism of viruses including Hepatitis C virus (Woodhouse et al.,

2010), Yersinia virus (Avican et al., 2015) and Foot-and-Mouth disease virus (Eschbaumer et al., 2016). By comparing the gene expression profile of PI cells to their parental cells, a list of genes involved in PI can be determined and used for downstream studies.

Most of the previous report on NDV persistent infection focused on characteristics and morphological studies. Genetic information in NDV persistent infection has not been investigated. In view of this, a comprehensive study in genetic level is elementary in better understanding of NDV persistent infection. It is hypothesised that genes associated with cellular apoptosis and virus defence mechanism are supressed in persistent infected cancer cells.

The main objective of this study is to delineate the mechanism of persistent NDV infection in bladder cancer cells using microarray analysis. The specific aims are as follows:

1. To establish persistently NDV-infected bladder cancer cell line;
2. To characterise persistently NDV-infected bladder cancer cell line; and
3. To profile and identify the genes that are related to persistent NDV infection.

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