ESTABLISHMENT AND CHARACTERIZATION OF NEWCASTLE DISEASE VIRUS (NDV) PERSISTENTLY-INFECTED COLORECTAL CANCER CELL LINES

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Newcastle disease virus (NDV) is an avian paramyxovirus that causes Newcastle disease (ND) outbreak worldwide. For the last few decades, NDV has been studied extensively for its oncolytic effect in various cancer cell lines both *in vitro* and *in vivo*. For some strains, they have entered several phases of clinical trials. Recently, studies showed that NDV persistent infection in cancer cell lines emerged which resulted in a development of populations of cancer cells that resisted the oncolytic effect of the virus. Nevertheless, the impact of the persistent infection on the cancer cells, phenotypically and genotypically, is yet to be elucidate. Therefore, the aim of this study was to investigate the phenotypic and genotypic of the NDV persistently-infected colorectal cancer (CRC) cell. To achieve this objective, three CRC cell lines, namely, LoVo, RKO, and HCT116p53$^{+/+}$ were challenged with recombinant NDV expressing green fluorescent protein (rAF-GFP). Following prolonged infection, NDV-resistant subpopulation in each cell line emerged. These cell lines were designated as LoVoPI, RKOPI and HCT116p53$^{+/+}$PI, respectively. Flow cytometry analysis showed that all these PI cells expressed GFP signal, despite diverse in expression level, confirming the presence of actively replicating NDV within the cells. During NDV reinfection, these PI cells resisted NDV-mediated oncolysis, continued to grow, and produce infectious plaques-forming virus progenies.

The phenotypic characteristics of these PI cells such as invasiveness and tumourigenicity were investigated via cell migration assay, colony formation assay, and spheroid formation assay. Results revealed that all PI cells have significantly reduced migration ability and formed lesser colonies compared to that of their parental counterpart. In spheroid formation assay, LoVoPI and HCT116p53$^{+/+}$PI formed smaller size of spheroid compared to their parental cells while RKOPI did not integrate into an intact spheroid, suggesting that persistent infection of NDV negatively affect the tumourigenicity of the PI cells. Despite their

resistant towards NDV infection, a subpopulation in all the mock-infected PI cells were stained positive for Annexin V or 7-AAD, suggesting these PI cells exhibited an elevated basal level of apoptotic cell populations. We further challenged the PI cells with apoptosis-inducer 5-fluororacil (5-FU) and the results showed that all the PI cells were significantly more sensitive to 5-FU treatment compared to their parental cells.

One of the mechanism of NDV mediated oncolysis is via caspase-dependent apoptotic pathway. None of the caspases were upregulated in PI cells suggesting that other apoptotic mechanisms might be involved. Therefore, we examined the expression of Bcl-2 family proteins including pro-survival Bcl-2 proteins (Bcl-2, Mcl-1 & Bcl-xL), pro-apoptotic Bcl-2 proteins (Bax, Bak & Bim) and inhibitor of apoptosis (IAP) protein (Survivin) in these PI cells. Western blot results revealed the elevated expression of the pro-survival Bcl-2 proteins and Survivin proteins in LoVoPI and RKOPI cells, suggesting that these proteins were critical in promoting the survival of PI cells. Knockdown of Survivin by small interfering RNA (siRNA) enhanced the NDV-mediated apoptosis in RKOPI and HCT116p53$^{+/+}$PI but not in LoVoPI; knockdown of Bcl-2 however did not enhance the NDV-mediated apoptosis in all PI cells. Overall, our study revealed that NDV persistent infection may confer clinical benefits as the PI cells were attenuated in their tumourigenicity and became more sensitive to apoptotic inducer.

Keywords: colorectal cancer (CRC), Newcastle disease virus (NDV), persistent infection

SDG: GOAL 3: Good Health and Well Being

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PENUBUHAN DAN PENCIRIAN GARIS SEL KANSER KOLOREKTAL YANG DIJANGKITI SECARA BERTERUSAN OLEH VIRUS PENYAKIT NEWCASTLE (NDV)

Oleh

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Virus penyakit Newcastle (NDV) adalah paramyxovirus yang menyebabkan wabak ND di seluruh dunia. Selama beberapa dekad yang lalu, NDV telah dikaji secara meluas kerana kesan onkolitiknya terhadap pelbagai barisan sel kanser baik in vitro dan in vivo. Beberapa strain telah memasuki dalam beberapa fasa ujian klinikal. Baru-baru ini, kajian menunjukkan bahawa jangkitan berterusan NDV dalam barisan sel kanser menghasilkan populasi sel kanser yang tahan terhadap kesan onkolitik virus tersebut. Walaupun begitu, kesan jangkitan berterusan terhadap sel kanser, dari segi fenotip dan genotip, masih belum dapat dijelaskan. Oleh itu, tujuan kajian ini adalah untuk menyiasat ciri-ciri fenotip dan genotip dari sel kanser kolorektal (CRC) yang dijangkiti NDV secara berterusan. Untuk mencapai objektif ini, tiga garis sel CRC, iaitu, LoVo, RKO, dan HCT116p53$^{+/+}$ dicabar dengan NDV rekombinan yang mengekspresikan protein pendarfluor hijau (rAF-GFP). Setelah jangkitan berpanjangan, subpopulasi tahan NDV di setiap garis sel muncul. Garis sel ini masing-masing dinamakan sebagai LoVoPI, RKOPI dan HCT116p53$^{+/+}$PI. Analisis sitometri aliran menunjukkan bahawa semua sel PI ini mengekspresikan isyarat GFP, walaupun beragam dalam tahap ekspresi, mengesahkan adanya NDV yang mereplikasi secara aktif di dalam sel. Semasa jangkitan semula NDV, sel PI ini menunjukkan ketahanan terhadap onkolisis yang dimediasi NDV, terus tumbuh, dan menghasilkan progeni virus yang membentuk plak berjangkit.

Ciri-ciri fenotip sel PI ini seperti invasif dan tumorgenik diselidiki melalui ujian penghijrahan sel, ujian pembentukan koloni, dan ujian pembentukan sferoid. Hasil kajian menunjukkan bahawa semua sel PI telah mengurangkan keupayaan penghijrahan secara signifikan dan membentuk koloni yang lebih sedikit berbanding dengan sel asal mereka. Dalam ujian pembentukan sferoid, LoVoPI dan HCT116p53$^{+/+}$PI membentuk sferoid yang lebih kecil berbanding dengan sel asal mereka, sementara RKOPI tidak dapat membentuk sferoid yang sempurna,

menunjukkan bahawa jangkitan berterusan NDV memberi kesan negatif terhadap sifat tumorgenik sel PI. Walaupun tahan terhadap jangkitan NDV, subpopulasi dalam semua sel PI yang dijangkiti palsu dicerap positif untuk Annexin V atau 7-AAD, menunjukkan sel PI ini menunjukkan bahawa sel ini mempunyai tahap asas apoptosis yang meningkat. Apabila dicabar dengan agen penginduksi apoptosis 5-fluororacil (5-FU), keputusan menunjukkan bahawa semua sel PI lebih sensitif terhadap rawatan 5-FU berbanding dengan sel asal mereka.

Salah satu mekanisme onkolisis yang dimediasi NDV adalah melalui jalur apoptosis yang bergantung pada kaspase. Tiada peningkatan expresi kaspase dalam sel PI, mencadangkan mekanisme apoptosis lain mungkin terlibat. Oleh itu, kaji seterusnya meneliti ekspresi protein keluarga Bcl-2 termasuk protein pro-kehidupan (Bcl-2, Mcl-1 & Bcl-xL), protein pro-apoptosis (Bax, Bak & Bim) dan protein penghampat apoptosis (Survivin) dalam sel PI ini. Hasil blot Western menunjukkan peningkatan ekspresi protein Bcl-2 pro-kehidupan dan protein Survivin dalam sel LoVoPI dan RKOPI, menunjukkan bahawa protein ini sangat penting dalam meningkatkan kelangsungan sel PI. Penurunan ekspresi Survivin dengan RNA gangguan kecil (siRNA) meningkatkan apoptosis yang dimediasi NDV dalam RKOPI dan HCT116p53$^{+/+}$ tetapi tidak dalam LoVoPI. Secara keseluruhan, kajian ini mendedahkan bahawa jangkitan berterusan NDV dapat memberikan manfaat klinikal kerana sel PI menunjukkan pengurangan sifat tumorgenik dan menjadi lebih sensitif terhadap agen penginduksi apoptosis.

Kata kunci: jangkitan berterusan, kanser kolorektal (CRC), virus penyakit Newcastle (NDV)

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%	percentage
× g	times gravitational acceleration
°C	degree Celsius
µL	microlitre
µm	micromolar
5-FU	5-fluorouracil
AGO	argonaute
ANOVA	analysis of Variance
Apaf-1	apoptotic protease activating factor-1
APMV-1	avian paramyxovirus type I virus
ATCC	American Type Culture Collection
ATV	autologous tumour cell vaccine
BCG	Bacillus Calmette Guerin
BRAF	B-Raf and V-Raf murine sarcoma viral oncogene homolog
CARD	caspase recruitment domain
CASP9	procaspase-9
Caspases	cysteine asparyl-specific proteases
CHS	chalcone synthase
c-IAP1	cellular IAP1
CO_2	carbon dioxide
CRC	colorectal cancer
cyt-c	cytochrome complex
dATP/dADP	deoxyadenosine triphosphate/ deoxyadenosine diphosphate
DGCR8	DiGeorge syndrome critical region 8

DIP	defective interfering particles
DISC	death-inducing signaling complex
DMEM	Dulbecco's Modified Eagle Medium
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
DTH	delayed-type hypersentivity
ECM	extracellular matrix
F	Fusion
FADD	FAS-associated death domain protein
FBS	foetal bovine serum
FDA	Food and Drug Administration
GBM	glioblastoma multiforme
GE	gene end
GFP	green fluorescent protein
GM-CSF	granulocyte macrophage colony-stimulating factor
GS	gene start
h	hour(s)
HAU	hemagglutination unit
HeLa	Henrietta Lacks
HN	haemagglutination-neuraminidase
hpi	hour post infection
HtrA2/Omi	high-temperature requirement protein A2
IAP	inhibitor of apoptosis protein
IFN	interferon
IG	intergenic
IL	interleukin

Inf	infection
KRAF	Kirsten rat sarcoma viral oncogene homolog
L	large polymerase
M	Matrix
Min	minute(s)
mL	Millilitre
MMP-2	Matrix metalloproteinases (MMP)
MOI	multiplicity of infection
MOMP	Mitochondrial Outer Membrane Permeabilization
mRNA	messenger ribonucleic acid
MTT	microculture tetrazolium
NDV	Newcastle disease virus
NIAP	neuronal IAP
nM	nanomolar
NOD	nucleotide-binding oligomerisation domain
NP	nucleocapsid
NS	negative control
Nt	nucleotide(s)
P	Phosphor
PARP	poly(ADP-ribose) polymerase
PBS	phosphate-buffered saline
pfu	plaque forming unit
pH	potential of hydrogen
PI	persistently infected
Pol II	polymerase II
Pol III	Polymerase III

Pre-miRNA	precursor microRNA
Pri-mRNA	primary mRNA
PS	phosphatidylserine
PTS	post-transcriptional silencing
r.u.	relative unit
RanGTP	RAs-related nuclear protein Guanosine 5'-Triphosphate
RIGVIR	Riga virus
RISC	RNA-induced silencing complex
RNA	ribonucleic acid
RNAi	RNA interference
RNP	ribonucleoprotein complex
rpm	revolutions per minute
RPMI	Roswell Park Memorial Institute
SAPK/JNK	Stress-activated protein kinases/ Jun amino-terminal kinases
SD	standard deviation
SFDA	China State Food and Drug Administration
siRNA	small interfering RNA
Smac/DIABLO	Second mitochondria-derived activator of caspase/ Direct Inhibitor of Apoptosis-Binding protein with LOw pI
sRNA	small double-stranded RNA
ssRNA	single-stranded RNA
TRBP	TAR RNA binding protein
TBS	Tris-buffered saline
TBST	Tris-buffered saline with 0.1% Tween® 20 Detergent
TGF-β	Tumour Growth Factor beta
TNFRSF	Tumour Necrosis Factor Receptor

TNFα	Tumour Necrosis Factor Alpha
TRADD	Tumor Necrosis Factor Receptor 1-Associated Death Domain Protein
TRAIL	Tumour Necrosis Factor-Related Apoptosis Inducing Ligand
T-vec	talimogene laherparepvec
UV	ultraviolet
w/v	weight per volume
WHO	World Health Organization
Wnt	wingless-related integration site

CHAPTER 1

INTRODUCTION

1.1 Background

Oncolytic virotherapy has emerged as an alternative treatment in cancer for its advantages over conventional treatment such as chemotherapy and radiotherapy, as it exerts fewer side effects (Wennier *et al*., 2012). This approach utilises the characteristics of oncolytic viruses that selectively replicate in a defective immune response environment and their ability in triggering immunological responses, thus promoting continuous killing effect on cancer cells, without causing collateral harm to normal cells (Motalleb, 2013; Russell & Peng, 2018). Arming of oncolytic viruses with pro-inflammatory genes or immune-stimulant genes have significantly increased the therapeutic effect of oncolytic viruses (Chaurasiya *et al*., 2020). In 2004, RIGVIR, a wild-type human orphan virus has been approved as a first oncolytic agent for melanoma treatment in Latvia (Alberts *et al*., 2018). In 2015, Food and Drug Administration (FDA) approved talimogene laherparepvec, a herpes simplex virus that expresses human granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of advanced melanoma (Conry *et al*., 2018). Chinese Food and Drug Administration approved oncorine (H101) for treatment of advanced head and neck cancer (Liang *et al*., 2018). The approvals of oncolytic viruses in clinical treatment remarkably demonstrate the significance of the virus-mediated therapeutic platform.

Among oncolytic viruses, Newcastle disease virus (NDV) has been proven as a successful oncolytic virus (OV) in preclinical trials for types of cancers. NDV is an avian virus that belongs to the *Paramyxoviridae* family (Yusoff & Tan, 2001). It is a negative sense, non-segmented single stranded RNA virus (Yusoff & Tan, 2001). The NDV genome comprises of approximately 15 kb nucleotides encoded for 6 structural protein genes including nucleocapsid (NP), phospho (P), matrix (M), fusion (F), haemagglutination-neuraminidase (HN) and large polymerase (L) (Krishnamurthy *et al*., 1998). NDV can be classified into 3 pathotypes: velogenic, mesogenic and lentogenic, depending on how severe the disease they cause in avian species (Dortmans *et al*., 2011). Velogenic NDV is highly virulent and can cause 100% mortality in bird (Beard, 1984). Mesogenic NDV is intermediary virulent and cause moderate damage while lentogenic NDV causes only mild or non-symptomatic respiratory infection (Beard, 1984). Although NDV is fatal to avian, it is safe to be used on human. NDV has been reported to selectively infect and replicate in interferon-defective human cancer while sparing normal cells, leaving them unharmed (Zamarine *et al*., 2012).

The main mechanism of NDV-mediated oncolysis has been shown to be associated with the induction of both extrinsic (death receptor) and intrinsic

apoptosis (mitochondrial) pathways (Elankumaran *et al*., 2006). Both pathways crosstalk with each other and require activation of cysteine asparyl-specific proteases (caspases) to cleave the downstream substrates. In the extrinsic pathway, activation of Fas death receptor results in the recruitment of adaptor protein FADD and initiator caspase 8 to form a death-inducing signaling complex (DISC) (Sobrido-Cameán, & Barreiro-Iglesias, 2018). The intrinsic pathway leads to mitochondrial outer membrane permeabilisation (MOMP), resulting with the efflux of cytochrome c into the cytoplasm, leading to activation of caspase 9 (Chen *et al*., 2017). Ultimately, activation of caspase 8 and caspase 9 from the extrinsic and intrinsic pathways respectively converge to the activation of executioner caspase 3 and caspase 7, causing cleavage of actin and degradation of DNA (Kalyanasundram *et al*., 2018). So far, there are a number of NDV strains such as HUJ (Freeman *et al*., 2006), MTH-68 (Csatary *et al*., 2004) and Ulster (Schneider *et al*., 2001) which have already entered into clinical trials. Strategies such as arming of the NDV with pro-inflammatory genes such as interleukin-2 (Wu *et al*., 2016), interleukin-12 (Ren *et al*., 2016), granulocyte macrophage colony-stimulating factor (GM-CSF) (Janke *et al*., 2007), interferon-λ1 (Bu *et al*., 2016) and etc. have been employed to enhance the therapeutic effect of NDV.

Despite our enthusiasm to utilize NDV as a promising treatment option for cancer patients, questions remain as to whether persistent viral infection might occur in cancer cells and become an obstacle to its eradication. Several recent findings showed that NDV is able to persistently infect some cancer cells without triggering cell death. Chia et al. (2014) reported that a subpopulation of SW480 had survived NDV infection and emerged as a NDV-resistant cell line that continually produce virus progenies. These released virus progenies formed small plaques in plaque assay, suggesting formation of incomplete virus or defective interfering particles (DIP) in persistently infected (PI) cells. Rangaswamy et al. (2017) found that in human ovarian cancer cells that are persistently infected with NDV, the released virus progenies exhibited mutation in the F protein cleavage site and HN protein second sialic acid binding site. These mutations made the virus more hyperfusogenic, facilitating cell-cell fusion and spreading of the virus. Nevertheless, the previous studies of NDV persistent infection were focused on the cell morphology and the genetic details are still lacking. In order to improve the efficacy of treatment, identification of determinants that prevents the cancer cells from NDV-mediated cytolysis is important.

Development of resistance to the treatment is one of the major factors of treatment failure in patients. As cancer cells exhibit mutational plasticity, they are able to rapidly cancel out the effect of the virus, causing selection of cancer cells subpopulation which escapes treatment. In many clinical trials of NDV, some patients that initially developed excellent clinical results, suffered with later cancer recurrence. For instance, in a phase II study of NDV strain Ulster, 23 patients with colorectal liver metastasis were vaccinated with the virus and followed up for 18 months (Schlag *et al*., 1992). The results showed 61% cancer recurrence in vaccinated patients despite better performance than patients who solely underwent surgery (87% cancer recurrence). In another example of phase

I/II study, 11 patients with glioblastoma multiforme (GBM) were administered intravenously with NDV strain HUJ. One of the patients initially showed complete tumour remission, but cancer recurrence was observed 3 months later (Freeman *et al*., 2006). The therapeutic outcome of NDV is highly dependent on the battle between the virus and the cancer, hence strategies that eliminate the virus resistance of cancer would be beneficial to enhance the oncolytic effect of NDV. In addition, it also alleviates concerns on NDV effectiveness in cancer treatment.

In this thesis, the establishment of NDV persistent infected (PI) colorectal cancer in three cell lines LoVo, RKO and HCT116p53$^{+/+}$ by using a GFP-bearing NDV, namely rAF-GFP was demonstrated. We describe the characteristic of these NDV persistent infected colorectal cancer cells in terms of their resistance to reinfection, production of virus progenies, cell migration ability, spheroid forming ability and their sensitivity to 5-fluorouracil (5-FU). Furthermore, we demonstrate the elevation of pro-survival proteins Bcl-2 and Survivin in these PI cells. We also took advantage of RNA interference to evaluate whether introduction of siRNA that targets these proteins would enhance the therapeutic effect of NDV.

1.2 Hypothesis

Persistent infection of NDV may attenuate the PI cells' invasiveness and tumourigenicity. Alteration in apoptosis pathways would prevent colorectal cancer cells from NDV-mediated apoptosis and develop into persistent infection. Knockdown of anti-apoptotic genes would enhance the oncolysis effect in these PI cells.

1.3 Research Objectives

The main objective of this study is to evaluate the cellular changes in NDV-infected colorectal cancer PI cells and identify the genetic determinants that contribute to their survival. The specific aims are as follows:

1. To establish NDV-infected colorectal cancer PI cells.

2. To determine the phenotypic characteristics of NDV-infected colorectal cancer PI cells.

3. To determine the expression of pro-survival, pro-apoptotic Bcl-2 proteins and Survivin protein in NDV-infected colorectal cancer PI cells.

4. To study the effect of siRNA targeting pro-survival proteins in colorectal PI cells.

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