UNIVERSITI PUTRA MALAYSIA

ENGINEERING RECOMBINANT NEWCASTLE DISEASE VIRUS WITH PRO-APOPTOTIC GENE TO ENHANCE ONCOLYSIS IN SELECTED COLORECTAL CANCER CELLS

JEEVANATHAN KALYANASUNDRAM

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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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February 2020

Chairman: Prof. Datin Paduka Khatijah Yusoff, PhD, FASc
Faculty: Biotechnology and Biomolecular Sciences

Anticancer therapy manipulating oncolytic Newcastle disease virus (NDV) has been reported to show exciting prospects. Since NDV is an avian virus, it is generally cleared by the human immune system, thus making it safe for humans. However, this also reduces viral replication in cancer cells, therefore compromising its full oncolytic potential. The cloning of pro-apoptotic gene such as apoptin into the NDV genome may produce a recombinant NDV with enhanced oncolytic ability which could result in higher tumour killing before being cleared by the immune system. In this study, development of local NDV strain AF2240 as a vector for pro-apoptotic, apoptin transgene delivery into tumour was explored in order to improve AF2240 oncolytic ability. The main objective of the study is to develop a recombinant AF2240 virus armed with pro-apoptotic transgene, capable of higher oncolysis and increased potency by using a selection of colorectal cancer cells as model. Colorectal cancer cells such as HT29, SW620 and CaCo-2 was selected due to their heterogeneity in supressing pro-apoptotic and anti-viral signalling. A recombinant anti-genomic plasmid, pOLTV5(rAF-ApHGy) was constructed by inserting the apoptin gene into the M and F intergenic region within AF2240 anti-genome. Recombinant AF2240 harbouring apoptin transgene, rAF-ApHGy was successfully recovered from the transfection of the anti-genomic plasmid into BSRT7/5 cells and propagated in embryonated chicken eggs. The recovered rAF-ApHGy virus stably harboured the apoptin transgene through 5 egg passages. The replication kinetics was found to be similar to that of the parental AF2240 strain. The apoptin gene was also detected to be expressed in rAF-ApHGy-infected HT29, SW620 and Caco-2 colorectal cells. The cytotoxicity of rAF-ApHGy was detected to be enhanced compared to wildtype strain AF2240 among infected HT29, SW620 and Caco-2 colorectal cells through MTT assay and flow cytometry analysis. Flow cytometric analysis of infected HT29 showed rAF-ApHGy to result in 26.58%, 34.29% and 31.47% more cell death population compared to AF2240 infection at 24, 48 and 72

h.p.i. Similarly, infection of SW620 cells also revealed rAF-ApHGy resulted in 3.05%, 18.74% and 13.37% more cell death population compared to wildtype AF2240 infection at 24, 48 and 72 h.p.i. Infection of Caco-2 cells with rAF-ApHGy was detected to induce 4.94%, 14.08% and 9.02% more cell death compared to AF2240 infection at 24, 48 and 72 h.p.i. These findings were further corroborated by MTT analysis. Virus infection of HT29 particularly, showed increased population entering into necrotic phase which were determined to be secondary necrosis as appose to necroptosis through RIP-PARP-Caspase 8 cell signalling analysis. The latter also revealed increased cleaved Bax in the rAF-ApHGy infected HT29 cells compared to wildtype strain AF2240, indicating the enhanced oncolytic ability of rAF-ApHGy. Based on these findings, it can be concluded that AF2240 can be genetically modified for pro-apoptotic transgene delivery without compromising virus stability. The enhanced oncolytic ability of rAF-ApHGy highlights the potential of this recombinant strain AF2240 to result in higher oncolysis compared to its wildtype counterpart, before being cleared by patient's immune response during oncovirotherapy.

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

KEJURUTERAAN REKOMBINAN NEWCASTLE DISEASE VIRUS DENGAN GEN PRO-APOPTOTIK BAGI MENINGKATKAN ONKOLISIS SEL KANSER KOLOREKTALTERPILIH

Oleh

JEEVANATHAN KALYANASUNDRAM

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Terapi antikanser menggunakan virus penyakit Newcastle (NDV) dilaporkan mempunyai prospek yang menarik. Oleh kerana NDV adalah virus burung, ia secara umumnya dibasmi oleh sistem keimunan yang menjadikannya selamat bagi manusia. Namun, ini juga mengurangkan replikasi virus dalam sel kanser yang menjejaskan potensi onkolisisnya. Dalam penyelidikan ini, pembangunan strain NDV tempatan AF2240 yang mengandungi transgen apoptin (rAF-ApHGy) dikaji bagi meningkatkan keupayaan onkolisis strain AF2240. Objektif utama kajian ini adalah untuk membangunkan virus AF2240 rekombinan dengan transgen pro-apoptosis, berkeupayaan untuk mencetuskan onkolisis yang lebih tinggi dan lebih mujarab dengan menggunakan pemilihan sel barah kolorektal sebagai model. Sel-sel barah kolorektal seperti HT29, SW620 dan CaCo-2 dipilih kerana heterogenitasnya dalam memberi isyarat pro-apoptosis dan anti-virus. Plasmid anti-genomik rekombinan, pOLTV5(rAF-ApHGy), dikonstruk dengan selitan gen apoptin di antara bahagian gen M-F di dalam anti-genom strain AF2240. Strain AF2240 rekombinan yang mengandungi transgen ApHGy berjaya diperoleh kembali, melalui transfeksi plasmid anti-genomik ke dalam sel BSRT7/5 dan dibiakkan di dalam telur berembryo. Virus rAF-ApHGy yang diperoleh kembali, mengandungi transgen apoptin dengan stabil sepanjang 5 pemindahan dalam telur dan menunjukkan replikasi kinetik selari dengan virus induk strain AF2240. Ekspresi gen apoptin juga dikesan di dalam sel HT29, SW620 dan Caco-2 yang dijangkiti dengan rAF-ApHGy. Kesitotoksian rAF-ApHGy juga didapati lebih baik berbanding virus induk strain AF2240 di kalangan HT29, SW620 dan Caco-2 melalui analisa asai MTT dan aliran sitometri. Kajian aliran sitometri terhadap sel HT29 yang dijangkiti of rAF-ApHGy menunjukkan 26.58%, 34.29% dan 31.47% lebih banyak kematian sel berbanding dengan AF2240 pada 24, 48 dan 72 j.p.i. Begitu juga dengan jangkitan sel SW620 yang menunjukkan 3.05%, 18.74% dan

13.37% lebih tinggi populasi sel mati berbanding dengan AF2240 pada 24, 48 dan 72 j.p.i. Jangkitan sel Caco-2 dengan rAF-ApHGy turut menunjukkan 4.94%, 14.08% dan 9.02% lebih banyak sel mati berbanding dengan AF2240 jangkitan AF2240 pada 24, 48 and 72 j.p.i. Penemuan ini juga disokong oleh asai MTT. Jangkitan sel HT29 dengan virus menunjuk peningkatan populasi sel menjalani fasa nekrosis yang disahkan sebagai nekrosis sekunder dan bukan nekroptosis melalui analisa pengisyaratan sel RIP-PARP-Caspase 8. Analisa pengisyaratan sel juga mendedahkan peningkatan Bax terpotong dalam jangkitan HT29 dengan rAF-ApHGy berbanding virus induk AF2240, yang menunjukkan peningkatan kebolehan onkolisis rAF-ApHGy. Berdasarkan kepada penemuan ini, strain AF2240 boleh diubahsuai secara genetik tanpa menjejaskan kestabilan virus. Peningkatan keupayaan onkolitik rAF-ApHGy, meningkatkan potensi virus rekombinan strain AF2240 ini dalam penghapusan tumur yang lebih tinggi semasa onkoviroterapi sebelum disingkirkan oleh sistem imun.

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I certify that a Thesis Examination Committee has met on (date of viva voce) to conduct the final examination of Jeevanathan Kalyanasundram on his thesis entitled "Engineering Recombinant Newcastle Disease Virus, rNDV (rAF2240) for Targeted Pro-Apoptotic Gene Delivery into Colorectal Cancer Cells" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the University Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the degree of Doctor of Philosophy

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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 Doctor of Philoso phy The members of the Supervisory Committee were as follows:

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Signature: _____
Name of Member of Supervisory Committee: Chia Suet Lin

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~	approximately
°C	degree Celcius
µg	microgram
µL	microlitre
bp	base pairs
cDNA	complementary deoxynucleotide acid
Da	Dalton
dH_20	distilled water
DNA	deoxyribonucleotide acid
dNTP	deoxyribonucleotide triphosphate
EDTA	ethylenediaminetetraacetic acid
g	gravity force
h	hour
h.p.i.	hours post infection/inoculation
HRP	Horse Radish Peroxidase
j.p.i	jam pos infeksi
kb	kilo base pairs
kDa	kilo Dalton
L	litre
LB	Luria-Bertani
M	Molar
µL	microlitre
mA	milliampere
min	minute
mg	milligram
mL	millilitre
mm	millimetre
mM	millimolar
$MgCl_2$	magnesium chloride
NaCl	sodium chloride
NaOH	sodium hydroxide
ng	nanogram
OD	Optical Density
PCR	Polymerase Chain Reaction
RE	Restriction enzymes
rpm	revolutions per minute
sec	seconds
Ta	annealing temperature
Tm	melting temperature
V	volt
v/v	volume per volume
W	Watts
w/v	weight per volume

CHAPTER 1

INTRODUCTION

The Malaysian National Cancer Registry Report 2007-2011 listed colorectal cancer as the most common type of cancer among men and second among women (Azizah *et al.,* 2016). Most colorectal cancer pathogenesis involves the unregulated growth of colonic polyps in the inner lining of colon or rectal which interrupts bowel movement, causing abdominal pain, constipation and bloody stool (Shussman and Wexner, 2014). Surgical resection is the principal form of treatment for the removal of primary colorectal tumours, followed by adjunctive radiotherapy and chemotherapy to prevent localised tumour reoccurrence as well as metastases (Cunningham *et al.,* 2010). However, adverse side effects associated with multi-drug regimens and radiation leads to various medical complications and mortality (Gill *et al.,* 2003; Hafner and Debus, 2016).

In order to circumvent such problems, alternative treatments such as targeted therapy, immunotherapy and hormonal therapy have been developed throughout the years (Palumbo *et al.,* 2013). The intracellular mechanisms as well as immunosuppressive tumour microenvironment developed by colorectal cancer cells in order to resist apoptosis for survival (Watson, 2004), provides targets for alternative anticancer therapy (Kultz, 2005; Lockshin and Zakeri, 2007). Strategies to reinstate the otherwise supressed apoptotic signalling, have been pursued by directing cytotoxic agents towards cancer cells and delivering pro-apoptotic molecules into tumour cells (Gerl and Vaux, 2005).

Whilst numerous alternative anti-tumour therapies showed success in inducing cytotoxicity against tumour cells, naturally occurring oncolytic viruses such the Newcastle disease virus (NDV) exhibit distinct ability to specifically target, replicate and eradicate tumour cells while leaving normal cells unharmed (Mansour *et al.,* 2011; Zamarin and Palese, 2012). Apart from the direct elimination of tumour cells, NDV has an additional immunotherapeutic potential which enables it to indirectly restore tumour immunosurveillance. This highlights the multifaceted feature of NDV oncovirotherapy which includes tumour specific oncolysis and immunogenicity (Zamarin *et al.,* 2014; Schirrmacher, 2016). Besides, oncolytic NDV is also considered to be safe for human application (Zamarin and Palese, 2012). In addition, the advancement in reverse genetics over the past decades, has spurred the explosion of various recombinant viruses armed with specialised characteristics in order to improve oncovirotherapy (Zamarin and Palese, 2012). This includes enhancing the oncolytic ability of viruses such as NDV through genetic modification by incorporating anti-tumour transgenes into its genome (Vigil *et al.,* 2007; Puhler *et al.,* 2008; Zamarin *et al.,* 2009).

The discovery of apoptin which induces tumour specific apoptosis is one of its kind and intensely researched for the past 25 years. The VP3 protein of chicken anemia virus is the protoplast of apoptin which has been shown to selectively induce apoptosis in tumour cells as opposed to normal cells despite being expressed in both type of cells (Danen-Van Oorschot *et al.,* 1997). Since then, apoptin homologs such as human gyrovirus VP3 protein (Bullenkamp *et al.,* 2012), avian reovirus σC protein (Shih *et al.,* 2004), TT virus-derived apoptosis-inducing protein (TAIP) (Kooistra *et al.,* 2004), and porcine circovirus type 2 VP3 protein (Hough *et al.,* 2015) were discovered to display similar specificity in anti-tumour activity. In contrast to native human pro-apoptotic molecules such as granzymes which are directly reactive (Rousalova and Krepela, 2010), apoptin was found to be inducing intrinsic apoptosis by indirectly modulating Bcl-2 associated proteins (Lin *et al.,* 2004; Maddika *et al.,* 2005; Chaabane *et al.,* 2014). This involves increase in cellular pro-apoptotic factors and enhancement of pro-apoptotic signalling through apoptin tumour specific behaviour such as nuclear translocation (Zhuang *et al.,* 1995b), unregulated multimerization (Heckl *et al.,* 2008), co-interacting proteins (Maddika *et al.,* 2007) and DNA binding ability (Leliveld *et al.,* 2003a). Thus, apoptins have been manipulated for anti-cancer applications by delivery through, plasmid DNA (Mitrus *et al.,* 2005), viral (Liu *et al.,* 2012) and bacterial vectors (Cao *et al.,* 2010).

Although NDV is considered safe for human applications, it is worth noting that this oncolytic virus is an avian virus which is subjected to immune-clearance in humans (Zamarin and Palese, 2012).). This could reduce the oncolytic potential of NDV against tumour during clinical oncovirotherapy. Thus, development of a recombinant NDV with enhanced oncolytic ability is essential in order to trigger higher tumour killing ability before being cleared by the human anti-viral response. This study aims to address the need for a more aggressive and potent NDV by cloning in a pro-apoptotic gene such as apoptin into the genome of local Malaysian NDV isolate strain AF2240. The heterogeneity among cultured colorectal cancer cells (Berg *et al.,* 2017), provides a suitable model to test the improved oncolytic recombinant virus tropism in comparison to wild type strain. The hypothesis of this study is the resulting recombinant NDV AF2240 armed with pro-apoptotic gene could result in higher cytotoxicity against cancer cells such as colorectal cancer cells compared to its parental wildtype strain.

The general objectives of this study is to recover two recombinant AFF240 strain harbouring human gyrovirus apoptin, ApHGy transgene (rAF-ApHGy) and green fluorescence protein, gfp reporter gene (rAF-GFP) respectively via reverse genetics. The gene delivery as well as cytotoxicity of both recombinant viruses were investigated by infecting a selection of colorectal cancers, namely, HT29, SW620 and Caco-2. The oncolytic ability rAF-ApHGy against these colorectal cancer cells was also compared to that of rAF-GFP and parental strain AF2240 in order to determine the rAF-ApHGy enhanced oncolytic activity.

The significance of this study is the development of local recombinant NDV AF2240 strain with enhanced oncolysis features which exhibits potential to be utilise as an alternative primary and secondary anti-cancer therapy. Whilst AF2240 has been shown to display oncolytic ability against wide range of tumour cells (Omar *et al.*, 2003), a recombinant virus with potent oncolytic ability would potentially improve AF2240 based treatment by reducing virus dosage, expanding tumour cell tropism as well as treating therapy resistant tumour cells. In addition, the construction of gfp reporter gene harbouring AF2240, rAF-GFP, enabled quick assessment of AF2240 gene delivery ability and verify virus infection which together, substantiated rAF-GFP as reliable infection control for in-vitro infection analysis.

The general objective of this study is to recover two recombinant AF2240 viruses harbouring *ApHGy* gene (rAF-ApHGy) as well as *gfp* reporter gene (rAF-GFP) through reverse genetics. Both recombinant viruses will be tested for gene delivery and cytotoxicity against a selection of colorectal cancer cell lines in comparison to wild-type AF2240.

The specific objectives of this research are as follows:

1. To construct and recover of recombinant NDV strain AF2240 harbouring:
    a. apoptin transgene gene (rAF-ApHGy)
    b. *gfp* reporter gene (rAF-GFP)

2. To compare and analyse cell cytotoxicity induced by recombinant rAF-ApHGy, rAF-GFP and wildtype strain AF2240 through *in-vitro* infection of:
    a. HT29 (epithelial human colon adenocarcinoma cell)
    b. SW620 (metastatic epithelial human colon adenocarcinoma cell)
    c. Caco-2 (epithelial human colon adenocarcinoma cell)
    d. Normal Human Dermal Fibroblasts (NHDF) cells

3. To conduct and compare cell death signalling analysis between rAF-ApHGy and AF2240 by using HT29 infection as a model.
    a. Apoptosis/Necroptosis pathway (RIP-signalling)
    b. Mitochondrial associated-Bcl proteins regulation

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PUBLICATION

Academic:

Kalyanasundram, J., Hamid, A., Yusoff, K. and Chia, S-L. 2018. Newcastle disease virus strain AF2240 as an oncolytic virus: A review. *Acta Tropica* 183:126-133.

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