IDENTIFICATION OF MOLECULAR PATHWAYS ASSOCIATED WITH NEWCASTLE DISEASE VIRUS (AF2240) PERSISTENT INFECTION IN UROTHELIAL CELL CARCINOMA

UMAR AHMAD

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By

UMAR AHMAD

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

June 2020

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DEDICATION

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

This work is specially dedicated:

To the amazing supervisors I have been fortunate enough to learn from, and to the amazing labmates I have been fortunate enough to learn with.

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

IDENTIFICATION OF MOLECULAR PATHWAYS ASSOCIATED WITH NEWCASTLE DISEASE VIRUS (AF2240) PERSISTENT INFECTION IN UROTHELIAL CELL CARCINOMA

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UMAR AHMAD

June 2020

Chairman : Associate Professor Syahril Abdullah, DPhil
Faculty : Medicine and Health Sciences

Urothelial cell carcinoma (UCC) poor prognosis is due to limited treatment options for advance disease and resistance to conventional therapies. Newcastle disease virus (NDV) is a promising novel therapeutic avenue, killing tumour cells while sparing normal cells. However, wild-type NDV AF2240 has been found to persistently infect a subpopulation of cancer cells *in vitro*, making these cells less susceptible to NDV-mediated oncolysis. Moreover, the exact molecular mechanism by which UCC cells acquire NDV persistent infection has not been elucidated. Therefore, the aim of this study was to stratify UCC cell lines based on their sensitivity toward NDV-mediated oncolysis and perform transcriptome profiling to identify potential molecular pathways associated with NDV persistent infection in UCC. NDV-mediated oncolysis on bladder cancer cell lines was assessed by infecting the cells with NDV at MOI of 1 and percentage cell viability was determined using WST-1 assay. Persistent infection was developed in TCCSUP cells by infecting the cells with NDV at low MOI. Confirmation of NDV persistent infection was carried out using ELISA, conventional PCR, flow cytometry, RT-qPCR and transmission electron microscope (TEM). While validation of RNA-Seq data was conducted using RT-qPCR. After quality control analysis, *in silico* quantification of differentially expressed transcripts (DEGs) and functional annotation analysis were carried out using the DESeq2 package in R and metascape respectively. Hallmark pathways enrichment analysis was performed using fast gene enrichment analysis (FGSEA) package in R and Molecular Signature Database (MSigDB). Prediction of related genes was manually curated in MS word excel and the resulting similarity genes were used to mine the GeneCards database for their function. PPI network was performed using NetworkAnalyst via STRING Interactome, while module analysis was carried out by Cytoscape. Then, nodes that are functionally connected in the PPI network were visualized using path explorer function and the top candidate hub genes were further validated using Oncomine database. Amongst the cell lines tested, UMU16, RT112, UMUC10,

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HT1376, EJ28, UMUC3, TCCSUP and SCaBER were less sensitive to NDV infection. Cytopathic effect (CPE) was observed with progressive acute lysis crisis when TCCSUP cells were infected with NDV at low MOI. Cells that survived the viral infection after 5 days were termed as persistently infected TCCSUPPi cells. PCR and qPCR analysis confirmed the presence of viral genes in these cells. Flow cytometric analysis demonstrated that ~85% and ~90% of TCCSUPPi and EJ28Pi cells maintained GFP expression even after fifteen passages when infected with recombinant NDV (rNDV-GFP). NDV particles were observed in some endosomes of the persistent TCCSUPPi cells and striking ultrastructural changes were found in both the persistent TCCSUPPi and EJ28Pi cells. Furthermore, both TCCSUPPi and EJ28Pi cells developed an antiviral state by producing low levels of interferon (IFN) beta. Transcriptomic profiling identified 63 and 134 differentially expressed transcripts in persistently infected TCCSUPPi and EJ28Pi cells, respectively. Of 63 transcripts in TCCSUPPi cells, 25 genes were upregulated (log2 fold-change ≤ 0) and 38 genes were downregulated (log2 fold-change ≥ 0). These genes were significantly enriched in molecular function of calcium binding (GO:0005509) and DNA-binding transcription repressor activity, RNA polymerase II-specific (GO:0001227) and the enriched important upregulated pathways were mainly heme metabolism, TGF-beta signaling and spermatogenesis. Whilst in EJ28Pi, 55 genes were upregulated (log2 fold-change ≤ 0) and 79 genes were downregulated (log2 fold-change ≥ 0). These transcripts resulted in significantly enriched molecular functions such as protein domain specific binding (GO:0019904) and RNA polymerase II regulatory region sequence-specific DNA binding (GO:0000977). The important enriched dysregulated pathways include allograft rejection, KRAS signaling up, interferon gamma response, angiogenesis, apoptosis, and xenobiotic metabolism. Based on PPI network analysis, the bridges were found mainly from pathways of p53 signaling, ECM-receptor interaction, and TGF-beta signaling by the upregulated mRNAs, to the antigen processing and presentation, protein processing in endoplasmic reticulum, complement and coagulation cascades by the downregulated mRNAs in NDV persistent TCCSUPPi cells. Comparatively, in persistently infected EJ28Pi cells, connections were identified mainly from pathways of renal carcinoma, viral carcinogenesis, Ras signalling and cell cycle by the upregulated mRNAs, to the Wnt signalling, HTLV-I infection and pathways in cancer by the downregulated mRNAs. This connection was mainly dependent on of *RPL8*- *HSPA1A*/*HSPA4* in TCCSUPPi cells and *EP300*, *PTPN11*, *RAC1* - *TP53*, *SP1*, *CCND1* and *XPO1* in EJ28Pi cells. Oncomine validation showed that the top hub genes identified in the network that includes *RPL8*, *THBS1*, *F2* from TCCSUPPi and *TP53* and *RAC1* from EJ28Pi are involved in development and progression of bladder cancer. Protein-drug interaction network analysis identified several potential drug targets that could potentially prevent UCC cells from acquiring NDV persistent infection. In summary, this study presents the successful development of NDV persistent infection in bladder cancer cells *in vitro*. The global transcriptomic (RNA-Seq) profiles provide an insight to how UCC cells acquire NDV persistent infection. Resolving the precise mechanism of persistent infection will facilitate the use of NDV for treatment of UCC in the clinic.

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

PENGENALPASTIAN LALUAN MOLEKULAR YANG BERKAITAN DENGAN JANGKITAN BERTERUSAN VIRUS PENYAKIT NEWCASTLE (AF2240) DALAM SEL KARSINOMA UROTELIA

Oleh

UMAR AHMAD

Jun 2020

Pengerusi : Profesor Madya Syahril Abdullah, DPhil
Fakulti : Perubatan dan Sains Kesihatan

Prognosis lemah karsinoma sel urotelia (UCC) adalah disebabkan oleh limitasi pilihan rawatan serta rintangan terhadap terapi konvensional. Virus penyakit Newcastle (NDV) berpotensi dijadikan terapi baru untuk membunuh sel-sel tumor sambil menyelamatkan sel-sel normal. Namun begitu, NDV AF 2240 jenis liar didapati menjangkiti subpopulasi sel kanser *in vitro* secara berterusan yang mengakibatkan sel kurang terdedah kepada onkolisis yang dimediasi dengan NDV. Lebih-lebih lagi, mekanisma molekular yang tepat di mana sel-sel UCC yang dijangkiti oleh NDV secara berterusan belum dikenalpasti. Oleh itu, tujuan kajian ini dijalankan adalah untuk menstratifikasikan sel-sel UCC berdasarkan kepekaan mereka terhadap onkolisis yang dimediasi oleh NDV serta memprofil transkriptom untuk mengenalpasti laluan molekular yang berpotensi berkait jangkitan NDV secara berterusan NDV dalam UCC. Onkolisis yang dimediasi dengan NDV bagi sel-sel kanser pundi kencing dikaji dengan menjangkiti sel-sel tersebut dengan NDV pada 1 MOI dan peratusan sel-sel yang berjaya hidup ditentukan malalui ujian WST-1. Jangkitan secara berterusan dikembangkan dalam sel-sel TCCSUP dengan menjangkiti sel-sel NDV pada MOI yang rendah. Pengesahan jangkitan NDV secara berterusan di tentukan melalui ujian ELISA, PCR konvensional, sitometri aliran, RT-qPCR dan juga mikroskop transmisi electron (TEM). Manakala pengesahan data RNA-Seq dijalankan melalui RT-qPCR. Setelah menganalisa kawalan kualiti, pengukuran transkrip ekspresi berlainan (DEG) serta fungsi anotasi secara *in silico* dijalankan dengan menggunakan DESeq2 dalam pakej R dan juga Metascape. Analisa laluan khas dijalankan dengan menggunakan analisa pengkayaan gen pantas (FGSEA) dalam pakej R dan juga pangkalan data tandatangan molekul (MsigDB). Ramalan berkaitan gene di buat secara manual dalam MS word excel dan hasil gen yang mempunyai ciri yang sama digunakan untuk mencari fungsi terbabit dalam pangkalan data GeneCards. Rangkaian PPI dihasilkan dengan NetworkAnalyst melalui STRING Interactome, manakala analisa modul dilakukan dengan menggunakan Cytoscape.

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Seterusnya, nod yang terangkai dalam rangkaian PPI digambarkan menggunakan fungsi path explorer dan gen calon hab teratas disahkan melalui pagkalan data Oncomine. Diantara sel-sel yang dikaji, sel UMU16, RT112, UMUC10, HT1376, EJ28, UMUC3, TCCSUP dan SCaBER didapati kurang peka terhadap jangkitan NDV. Kesan sitopatik (CPE) yang mempunyai krisis secara mendadak dan progresif dilihat apabila sel TCCSUP dijangkiti dengan NDV pada MOI yang rendah. Sel-sel yang dijangkiti virus tersebut yang didapati masih hidup selepas 5 hari dikenali sebagai sel-sel jangkitan secara berterusan TCCSUPPi. Analisa PCR dan qPCR yang dijalankan mengesahkan kehadiran gen virus dalam sel-sel tersebut. Hasil dari analisa PCR menunjukkan ~85% dan ~90% sel-sel TCCSUPPi dan EJ28Pi berupaya mengekalkan ekspresi GFP walaupun selepas lima belas laluan dijangkiti dengan NDV gabungan NDV (rNDV-GFP). Zarah NDV turut dikesan dalam beberapa endosom sel-sel jangkitan secara berterusan TCCSUPPi serta didapati mempunyai perubahan ultrastruktur yang ketara pada kedua-dua sel-sel berterusan TCCSUPPi dan EJ28Pi. Lebih-lebih lagi, kedua-dua sel-sel TCCSUPPi dan EJ28Pi didapati dalam keadaan anti virus dengan meghasilkan tahap interferon beta (IFN) yang rendah. Melalui pemprofilan transkripsi, 63 dan 134 transkrip yang berlainan dapat dikesan dalam sel-sel jangkitan secara berterusan TCCSUPPi dan EJ28Pi. Dari 63 transkrip yang diperolehi dalam sel-sel TCCSUPPi, 25 gen diatur (log2 fold-change ≤ 0) dan 38 gen didapati tidak teratur (log2 fold-change ≥ 0). Gen-gen ini mempunyai peranan yang signifikasi dalam fungsi molekul yang mengikat kalsium (GO:0005509) dan aktiviti yang menindas pengikatan transkripsi ke DNA, RNA polimerase II-spesifik (GO:0001227) dan laluan yang diperkayakan yang penting dan teratur terutamanya metabolisma heme, pengisyaratan TGF-beta serta spermatogenesis. Manakala dalam EJ28Pi , didapati 55 gene yang teratur (log2 fold-change ≤ 0) dan 79 gene yang tidak teratur (log2 fold-change ≥ 0). Transkrip ini menghasilkan fungsi-fungsi molekul yang diperkayakan yang amat signifikasi seperti pengikat domain protein spesifik (GO:0019904) dan polimerasi II pengawalseliaan kawasan urutan spesifik yang mengikat DNA (GO:0000977). Laluan tak teratur yang diperkayakan termasuk penolakan allograft, pengisyaratan KRAS, respon interferon gamma, angiogenesis, apotosis dan juga metabolisma xenobiotik. Berdasarkan analisa rangkaian PPI, rangkaian dijumpai terutamanya dari laluan isyarat p53, interaksi reseptor ECM dan isyarat TGF-beta dari mRNA teratur sehingga ke pemprosesan dan persembahan antigen, pemprosesan protein dalam retikulum endoplasma, pelengkap dan pembekuan cascade yang terhasil dari nRNA tak teratur di dalam sel-sel jangkitan secara bertesrusan TCCSUPPi NDV. Manakala didalam sel-sel EJ28Pi yang dijangkiti secara berterusan pula, rangkaian yang dikenalpasti adalah terutamanya dari laluan karsinoma buah pinggang, karsinogenesis viral, pengisyaratan Ras, dan kitaran sel hasil dari nRNA teratur sehingga ke pengisyaratan Wnt, infeksi HTLV-1 dan laluan dalam kanser hasil dari nMRA tak teratur. Rangkaian ini terutamanya bergantung pada *RPL8- HSPA1A*/*HSPA4* dalam sel-sel TCCSUPPi dan juga *EP300*, *PTPN11*, *RAC1* - *TP53*, *SP1*, *CCND1* dan *XPO1* dalam sel-sel EJ28Pi. Pengesahan Oncomine menunjukkan bahawa gen hab teratas yang dikenalpasti dalam rangkaian tersebut termasuk *RPL8*, *THBS1*, *F2* dari sel-sel TCCSUPPi serta *TP53* dan *RAC1* dari sel-sel EJ28Pi terlibat dalam pembentukkan dan perkembangan kanser pundi kencing. Analisa dari rangkain protein-ubat mendapati beberapa ubat berpotensi yang berupaya menghindari sel-sel UCC dari dijangkiti NDV secara berterusan. Secara kesimpulannya, kajian ini menunjukkan pengembangan jangkitan NDV secara berterusan dalam sel-sel kanser pundi kencing secara *in vitro*. Profil transkriptomik

global (RNA-Seq) memberi pencerahan bagaimana sel-sel UCC yang dijangkiti oleh jangkitan NDV secara berterusan. Penyelesaian mekanisma jangkitan ini secara tepat dapat membantu penggunaan NDV untuk rawatan UCC di klinik.TCCSUPPi dan EJ28Pi mengekalkan pengekspresan GFP walaupun selepas lima belas passage apabila dijangkiti dengan NDV rekombinan (rNDV-GFP). Zarah NDV turut dikesan dalam beberapa sel endosoma TCCSUPPi dan perubahan ultrastruktur yang ketara boleh dilihat dalam sel TCCSUPPi dan EJ28Pi melalui analisa TEM. Tambahan pula, kedua-dua sel TCCSUPPi dan EJ28Pi telah menghasilkan respon anti-virus dengan menghasilkan tahap ekspresi interferon beta (IFN) yang rendah. Melalui analisa transkriptomik, 63 dan 134 transkrip yang mempunyai ekspresi yang berbeza telah dikesan dalam sel TCCSUPPi dan EJ28Pi. Laluan penting yang dikenalpasti ditermasuk penolakan allograf, isyarat KRAS, respon gamma interferon, angiogenesis, apoptosis, dan metabolisme xenobiotik. Berdasarkan analisa rangkaian PPI, hubungan utama yang dikenalpasti adalah berkaitan dengan laluan isyarat p53, tindak balas reseptor ECM, isyarat TGF-beta, pemprosesan dan persembahan antigen, pemprosesan protein dalam retikulum endoplasma serta pemprosesan dan pembekuan protein. Seterusnya, analisa rangkaian interaksi antara ubat dan protein telah mengenal pasti beberapa sasaran ubat yang boleh digunakan untuk mencegah jangkitan NDV secara berterusan dalam sel UCC. Kesimpulannya, kajian ini berjaya menghasilkan model jangkitan NDV secara berterusan dalam sel UCC secara in vitro. Analisa transkriptomik global (RNA-Seq) telah meningkatkan ilmu berkatian mekanisma bagaimana sel UCC memperolehi jangkitan NDV secara berterusan. Penghuraian mekanisma ini secara terperinci adalah penting supaya NDV boleh berjaya dijadikan sebagai agen terapeutik UCC pada masa depan.

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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 Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

°C	Degree Celsius
ABU	Ahmadu Bello University
AJCC	American joint committee on cancer
ANOVA	Analysis of variance
APMV1	Avian paramyxovirus type 1
ATCC	American Type Culture Collection
BCG	Bacillus Calmette-Guerin
BCL	Binary base call
BH	Biohazard
BP	Biological process
BRCA	Breast cancer gene
CC	Cellular component
cDNA	Complimentary deoxyribonucleotide acid
CIS	Carcinoma *in situ*
cm	Centimetre
CM	Convoluted membrane
CMV	Cytomegalovirus
CO2	Carbon dioxide
CPE	Cytopathic effect
CPE	Cytopathic effect
CT	Computer tomography
DAPI	Diamidino-2-phenylindole
DDH_{20}	Deionized distilled water
DEGs	Differentially expressed genes

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DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleotide acid
E	Endosomes
Ebr	Ethidium bromide
EBV	Epstein Barr virus
EC	Epidermoid carcinoma
EDTA	Ethylenediamine tetra-acetic acid
ELISA	Enzyme-linked immunosorbent assay
ER	Endoplasmic reticulum
F	Fusion protein
FACS	Fluorescence-activated cell sorting
FBS	Fetal bovine serum
FDR	False discovery rate
FGFR3	Fibroblast growth factor receptor 3
FGSEA	Fast preranked gene set enrichment analysis
FPKM	Fragments per kilobase of gene model per million mapped
GFP	Fluorescence protein
GM-CSF	Granulocyte macrophage colony-stimulating factor
GO	Gene ontology
GRMCR	Genetics and regenerative medicine research centre
GSEA	Gene set enrichment analysis
HA	Haemagglutination
HAU	Haemagglutination unit
HBV	Hepatitis B virus
HN	Haemagglutination neuraminidase

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hpi	Hours post infection
HPV	Papillomavirus
Hrs	Hours
HSV-1	Herpes simplex virus type 1
IBS	Institute of Bioscience
IDs	Identifications
IFN	Interferon
IFN-β	Interferon beta
IL	Interleukin
IPA	Ingenuity pathway analysis
IVP	Intravenous pyelogram
Kb	Kilobases
kDa	Kilo Dalton
L	Large protein
M	Matrix protein
M	Matrix protein
MF	Molecular function
MGI	Malaysia Genome Institute
MGL	Medical genetic laboratory
MHC	Major histocompatibility complex
Mi	Mitochondria
MIBC	Muscle invasive bladder cancer
mL	Millilitre
mm	Millimetre
MM	Maintenance medium
MOI	Multiplicity of infection

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MRI	Magnetic resonance imaging
MS	Microsoft
MSigDB	Molecular signatures database
MTT	Microculture tetrazolium
NaOH	Sodium hydroxide
NCCN	National comprehensive cancer network
NCR	National Cancer Registry
ND	Newcastle disease
NDV	Newcastle disease virus
NFW	Nuclease free water
NGS	Next-generation sequencing
NM	Nuclear membrane
NMIBC	Non-muscle invasive bladder cancers
NP	Nucleocapsid protein
NTE	NaCl, Tris-HCl and EDTA
NYSC	National youth service corps
OD	Optical density
OH	Hydroxyl
OVs	Oncolytic viruses
P	Phosphoprotein
PBS	Phosphate buffer saline
PCR	Polymerase chain reaction
PFU	Plaque forming unit
pH	Hydrogen ion concentration
PhD	Doctor of philosophy
PI	Persistently infected

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PPI	Protein-protein interaction
qPCR	Quantitative polymerase chain reaction
RBC	Red blood cells
RIN	RNA integrity number
RNA	Ribonucleic acid
RNA-Seq	RNA-Sequencing
RNase	Ribonuclease
rNDV-GFP	Recombinant Newcastle disease virus- green fluorescence protein
rpm	Rotation per minute
rRNA	Ribosomal RNA
RT	Radiotherapy or radiation therapy
RT	Room temperature
RT-qPCR	Real time quantitative polymerase chain reaction
SAW	Sallallahu alaihi wasallam
SCC	Squamous cell carcinoma
SD	Standard deviation
SEM	Scanning electron microscope
SPF	Specific pathogen free
SWT	Subhanahu wata'alah
TAE	Tris-acetate EDTA
TBFV	Tick-Borne Flavivirus
TCC	Transitional cell
TdT	Terminal deoxynucleotidyl Transferase
TEM	Transmission electron microscope
TK	Thymidine kinase

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TNF	Tumour necrosis factor
TNM	Tumour, node and metastasis
TSHIP	Targeted states high impact project
TUR	Transurethral resection
TURBT	Transurethral resection of the tumour
UCC	Urothelial cell carcinoma
UCC-LN	Urothelial cell carcinoma of lymph nodes
UICC	International union against cancer
UK	United Kingdom
UPM	Universiti Putra Malaysia
USA	United States of America
USAID	United States agency for international development
UV	Ultraviolet
Vi	Viral particles
VSV	Vesicular stomatitis virus
w/v	Weight per volume
WHO	World Health Organization
wNDV	Wild type NDV
WSTs	Water soluble tetrazolium salts
µL	Microlitre

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CHAPTER 1

INTRODUCTION

1.1 Background

Cancer is a very complex human genetic disease and is due to uncontrolled abnormal cellular growth (malignant cancer) that is driven because of the mutation in the cell's DNA. The lost years of life and productivity caused by cancer represents the single largest drain on the global economy as compared to other causes of death such as infectious and heart diseases. Bladder cancer also known as urothelial cell carcinoma (UCC) is the ninth most common cancer in the world (Antoni *et al.*, 2017), accounting for 4.7% of all the new cancer cases that translated to an incidence of 79,030 new cases/year with an estimated deaths of 16,870 in 2017 (Siegel *et al.*, 2017). In men, it is the fourth most commonly diagnosed cancer while it's the eight most common cancer in women (Metts *et al*.,2000). Transitional or urothelial cell carcinoma is the most common type of bladder cancer and accounts for 90% of all bladder cases globally (Kaufman *et al.*, 2009). Squamous cell carcinoma and adenocarcinoma are the less common types of this cancer (Kantor *et al*., 1988; Rausch *et al*., 2014) while sarcomas that accounts for 1% of bladder cancer is rarely found.

The risk for developing bladder cancer are mostly non-environmental factors that include age, sex, ethnicity, body weight, lifestyle, and familial history (Jankovic & Radosavljevic, 2007). Study has shown that mutations of pRb may contribute to the risk of developing bladder cancer (Marees *et al*., 2008). Pathways related to p53/pRp are also reported to sometimes be altered in bladder cancer. Moreover, smokers with genetically overactive CYP1A2 may be at high risk of developing bladder cancer (Pavanello *et al*., 2010). Carcinogens found in cigarette smoke have been reported to activate specific mutations in the CYP1A2 gene and that affect other genes as well (Pavanello *et al*., 2010). High incidence rates and financial burdens are associated with care of patients with bladder cancer (Park & Hahn, 2014) and the progress in managing patients has been modest. In addition, no new therapeutic agents for treatment of bladder cancer have been discovered and approved over the past decades.

Recent multimodal treatment concepts including chemotherapy (Ali *et al*.,1997; SOLSONA *et al*., 1999), immunotherapy (BCG) (Khalifa *et al*., 1991), surgery (cystectomy) (Stein & Skinner, 2006; Gamé *et al*., 2001), radiation therapy (Goffinet *et al*., 1975), combination therapy(Hashine *et al*., 2009; Kaufman *et al*., 1993) have only led to a modest improvement of the disease. Despite the use of advanced techniques over the past three decades, urothelial cell carcinoma has remained a mysterious challenge to both the clinical and basic scientists. Therefore, novel intervention and therapeutic strategies will not only save lives of patients with this deadly disease but could also contribute economically. Hence, a new, cheaper, cost-effective and safe anti-cancer agents such oncolytic viruses could be the best

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candidates for virotherapy application and as a novel promising treatment modality for urothelial cell carcinoma (UCC).

Oncolytic viruses are a promising novel class of cancer-specific agents, killing tumour cells of various species including cells of human origin while sparing normal cells unharmed (Ahmad *et al.*, 2015; Lacroix *et al.*, 2010). In addition to the oncolytic effect observed both *in vitro* and *in vivo*, these viruses also provide immunostimulatory signals, inducing the elimination of virus-infected tumour cells (Lam *et al.*, 2014; Washburn *et al.*, 2003). The group of candidate oncolytic viruses used in cancer therapeutic approach includes genetically modified viruses, such as herpes virus (Parikh *et al.*, 2005), poliovirus (Toyoda *et al.*, 2009), or adenoviruses (El-Andaloussi & Bonifati, 2012), and wild-type viruses, such as reovirus (Heinemann *et al.*, 2011), myxoma virus (Vähä-Koskela *et al.*, 2007), vaccinia virus (Guo *et al*.,2008),vesicular stomatitis virus (VSV) (Yamaki *et al.*, 2013) and Newcastle disease virus (NDV) (Hl *et al.*, 2012). It could be shown *in vitro* and in animal models that urothelial cell carcinoma may be a promising target for the clinical application of oncolytic Newcastle disease virus.

Newcastle Disease Virus (NDV) is a member of the new genus *Avulavirus* within the family *Paramyxoviridae*. The virus causes a highly contagious disease in poultry (Yusoff & Tan, 2001). Exposure to humans however, results in mild conjunctivitis, laryngitis and influenza-like symptom (Fenner & White, 1987). A very virulent strain of the virus known as AF2240 has been shown to be responsible for a very high mortality and morbidity among poultry flocks in Malaysia (Lam *et al.*, 2011). The NDV viral genome is RNA rather than DNA (Fábián *et al.*, 2007; Bruce S. Seal *et al.*, 2000), consisting of a non-segmented negative stranded RNA genome of about 15.9 kb long (Chellappa *et al.*, 2012; de Leeuw & Peeters, 1999) and contains six genes (Phillips *et al.*, 1998), encoding at least eight proteins (Steward *et al.*, 1995; Steward *et al.*, 1993). The six essential structural proteins: nucleoprotein (NP), phosphoprotein (P), and the large polymerase protein (L) form the nucleocapsid (Kumar *et al.*, 2012; Ravindra *et al.*, 2009) and haemagglutinin-neuraminidase (HN) and fusion protein (F) attached in the lipid bilayer of membrane in the external envelope (Scheid & Choppin, 1973; Bruce S. Seal *et al.*, 2000), while the inner layer of the virion envelope is formed by the matrix protein (M). The HN protein mediates the binding of virus to cell surface receptors through its haemagglutinating activity and it also displays neuraminidase activity (Scheid & Choppin, 1973; Bruce S. Seal *et al.*, 2000).The F protein is responsible for the fusion between the viral envelope and the target membrane. NDV can also be grown in cell culture which causes cell fusion, resulting from the co-expression of the F and HN proteins which are responsible for viral infectivity and virulence (Murawski *et al.*, 2010; Zamarin & Palese, 2012). The two additional non-structural proteins, V and W are formed by the RNA editing process during P gene transcription (Park *et al.*, 2003). Studies have also explored that; V protein plays an important role in preventing interferon responses and apoptosis in chicken cells, but not in human cells. These species specific effects of V make it a determinant of host range restriction (Park, García-Sastre*, et al.*, 2003; Steward *et al.*, 1995). The W protein is also certainly to play a role in viral replication and pathogenesis (Park *et al.*, 2003).

Interest in the use of Newcastle disease virus (NDV) has been identified because of its great potential as an effective cancer vaccine that was proven to specifically target and selectively kill human cancer cells without causing damage to healthy and normal cells (Fournier & Schirrmacher, 2013; Reichard *et al.*, 1992). NDV has been shown to have higher oncolytic specificity against most cancer cell types as compared to normal cells (Lam *et al*., 2014). Once it is inside the cancer cell, the virus replicates and has the propensity to infect the surrounding cancer cells. The virus also stimulates the host anti-cancer immunological system (Schirrmacher *et al.*, 1998; Schirrmacher *et al.*, 2001). NDV is currently being evaluated as a cancer vaccine in Phase I/II clinical trials in patients with recurrent glioblastoma multiforme (GBM). It was reported that this therapy is well tolerated, and no serious side effects have been observed in any of the trials (Arnold *et al.*, 2006). The results have been encouraging and thus provide a strong foundation for further research to improve its efficacy and clinical application. Thus, NDV is used as an antineoplastic and immunostimulatory agent in clinical tumour therapy.

Different strains of NDV such as 73-T, MTH68, Italian, Ulster, and HUJ have been shown to exhibit an oncolytic activity (Csatary *et al.*, 2003; Schirrmacher *et al.*, 2001; Walter *et al.*, 2012; Yaacov *et al.*, 2008). In addition, the oncolytic effects of two Malaysian strains of NDV, AF2240 and V4-UPM, have also been studied *in vitro* and *in vivo* on several human tumour such as breast cancer (Ahmad *et al.*, 2015), astrocytoma cell lines (Ali *et al.*, 2011), and leukemia (Alabsi *et al.*, 2011). However, the oncolytic effect of wild type AF2240 on urothelial cell carcinoma (UCC) has not been evaluated so far. Furthermore, wild type NDV AF2240 has been found to persistently infect subpopulation of colorectal cancer cells due to its resistance to NDV-mediated oncolysis (Chia *et al.*, 2014). Thus, persisten infection poses a potential problem for maximising the efficacy potential of the use of this virus for treatment of cancer. Although, wild type NDV has been used even in clinical trials (Batliwalla *et al.*, 1998; Cassel *et al*., 1992; Csatary *et al.*, 1993; Freeman *et al.*, 2006; Kirchner *et al.*, 1995) but the risk of persistent infection will still remain unchanged (Rangaswamy *et al.*, 2017). Hence, no report that seems to characterize the development of persistent infection of wild type NDV AF2240 in UCC and explore the dysregulated genes in UCC persistently infected cells or even to determine the signalling pathways associated with persistence infection. Chia *et al.* (2014) reported that NDV AF2240 exhibits a smaller plaque morphology and reduced oncolysis but the genetics determinants of these nature are unclear and are not studied. Thus, understanding the mechanisms by which cancer cells acquire persistent infection and repealing these mechanisms will be crucial in ensuring the efficacy of NDV AF2240 in treatment of cancer.

Thus, this thesis describes the successful screening of bladder cancer cell lines that were susceptible to NDV-mediated oncolysis and those that were less sensitive to oncolytic effect of NDV which led to identification of small number of cells that evade the lytic crisis and drive the establishment of *in vitro* model of persistence infection in human bladder cancer cell lines (TCCSUP and EJ28) that has to date been grown and maintained for over 250 passages. In this thesis, we also demonstrated that the persistently infected cell lines carries NDV RNA as it does expresses the major genes

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such as *F*, *HN* and *NP* that plays a significant role in NDV oncolysis and viral particles were observed in some endosomes of the persistently infected cells as well as a striking ultrastructural changes were noticed. Furthermore, we observed that the persistently infected cell lines developed an antiviral state by producing low levels of interferon (IFN) beta. To examine the mechanism that support the establishment of NDV persistent infection in these bladder cancer cell lines, we employed whole transcriptome sequencing (RNA-Seq) on the persistently infected cell lines by next-generation sequencing (NGS) technology to compare gene expression patterns in these cells and that of the untreated control cells to enable identification of dysregulated genes, signaling pathways and networks associated with persistent infection. The findings from this thesis suggested that evasion of apoptosis may be crucial for establishment of NDV persistent infection in bladder cancer cells.

1.2 Hypothesis

Newcastle disease virus (NDV) AF2240 displays differential oncolytic potential across different UCC cell lines. Some UCC resist NDV-mediated oncolysis and develop NDV persistency of infection. There is cohesive transcriptomic dysregulation of specific molecular pathways that are associated with NDV persistency of infection.

1.3 Research Objectives

1.3.1 General objective

The main objective of this research was to identify the molecular pathways associated with Newcastle disease virus (NDV) AF2240 persistency of infection in UCC.

1.3.2 Specific objectives

1) To stratify UCC cells based on their sensitivity towards Newcastle disease virus (NDV) AF2240 infection.
2) To develop and characterise persistently infected UCC cells post-Newcastle disease virus (NDV) AF2240 infection.
3) To identify dysregulated genes in Newcastle disease virus (NDV) AF2240-persistently infected UCC cells.
4) To determine signaling pathways associated with Newcastle disease virus AF2240 persistence infection in UCC cells.

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1.4 Significance of study

This research work presented in this thesis contributes directly to the field of research in bladder cancer virotherapy. The significance of the study includes the establishment of a model of persistent infection in bladder cancer cells that enables the future development of strategies to overcome persistency of infection. By elucidating the genes that are involved in the signaling pathways associated with persistent infection, new insights have been generated that will potentially lead to the development of safer NDV viral vaccines that could be used in management of bladder cancer patients in clinic.

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