UNIVERSITI PUTRA MALAYSIA

EFFECTS OF NEWCASTLE DISEASE VIRUS INFECTION ON CISPLATIN-RESISTANT BREAST CANCER CELL LINE

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By

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EFFECTS OF NEWCASTLE DISEASE VIRUS INFECTION ON CISPLATIN-RESISTANT BREAST CANCER CELL LINE

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Chair : Assoc. Prof. Norazizah Shafee, PhD
Faculty : Biotechnology and Biomolecular Science

Cancer recurrence has been a major problem due to failure of primary treatment such as chemotherapy. Over time, decrease of efficacy in killing tumors by drugs such as cisplatin signals, the need for a new alternative cancer treatment. Oncolytic effects of Newcastle disease virus (NDV) has been demonstrated on a wide spectrum of cancers; thus making it an ideal option to fight chemoresistant cancers. As the whole mechanisms of resistant are still being studied, survivin has been identified as one of the proteins that involve in prolonging the survival of cancer cells during chemotherapy treatment. This study will provide an insight into NDV infection on cisplatin-resistant MCF7 and its correlation with survivin expression. To investigate the oncolytic efficacy of a local strain of NDV strain AF2240 in cisplatin-resistant cancer cells, cisplatin-resistant cell line (MCF7-CR) was established from the MCF7 human breast adenocarcinoma cell line. Both cells were infected with NDV and cell viability was determined by using flow cytometry. Viral proteins and survivin expression throughout infection period was probed and production of virus progeny was assessed by using plaque assay technique. Infection of a mass population of the MCF7-CR with NDV resulted in 50% killing in the first 12 hours post-infection (hpi), comparable to the parental MCF7. From 12 hpi onwards, the remaining MCF7-CR became less susceptible to NDV killing. This reduced susceptibility led to increased viral protein synthesis and virus progeny production. The reduction was also associated with a prolonged cell survival via stabilization of the survivin protein. The findings showed for the first time, the involvement of survivin in the reduction of NDV-induced oncolysis in a subpopulation of cisplatin-resistant cells. The outcome of this research will give a new insight in relationship between NDV, chemoresistant cancer and survivin; allowing researcher to exploit the information to establish a new alternative treatment with better efficacy.

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

KESAN JANGKITAN VIRUS PENYAKIT SAMPAR AYAM (NDV) TERHADAP KANSER PAYU DARA YANG BERKETAHANAN MELAWAN CISPLATIN

Oleh

MOHD HAFIFI BIN JAMAL

Julai 2015

Pengerusi : Profesor Madya Norazizah Shafee, PhD
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Kejadian penyakit kanser yang berulang telah menjadi masalah yang besar kerana kegagalan rawatan utama terhadap kanser seperti kemoterapi. Sejak kebelakangan ini, penurunan keberkesanan terhadap ubat-ubatan seperti cisplatin telah memberi isyarat bahawa perlunya rawatan alternatif yang baru. Keupayaan virus penyakit sampar ayam (NDV) untuk membunuh sel kanser telah berjaya ditunjukkan pada pelbagai jenis kanser; oleh itu, ianya sesuai dijadikan sebagai pilihan yang ideal untuk melawan kanser yang telah meningkat daya ketahanannya terhadap ubat-ubatan kemoterapi. Dalam mengkaji mekanisma bagaimana sesuatu sel kanser boleh menahan keberkesanan kemoterapi, didapati bahawa survivin merupakan salah satu daripada protein yang mampu memanjangkan jangka hayat sel kanser ketika rawatan berlangsung. Kajian ini bakal memberikan kefahaman tentang jangkitan NDV dan kaitannya dengan kadar penghasilan survivin. Untuk mengkaji keberkesanan virus NDV AF2240 iaitu strain tempatan, sejenis sel kanser yang mampu melawan cisplatin telah dihasilkan daripada sel kanser MCF7. Kedua-dua sel (MCF7 dan sel baru MCF7-CR) telah dijangkitkan dengan NDV dan kadar kematian sel telah ditentukan dengan menggunakan kaedah sel sitometri. Protein daripada virus dan juga protein survivin telah dikaji serta bilangan virus baru yang telah dihasilkan turut dikira dengan menggunakan teknik assay plak. Hasil daripada jangkitan NDV, hampir 50% bilangan sel kanser MCF7-CR telah mati berbanding dengan MCF7 dalam tempoh 12 jam yang pertama. Bagaimana pun, selepas 12 jam, bilangan sel MCF7-CR yang mati telah menurun. Penurunan ini telah menyebabkan peningkatan penghasilan protein virus dan juga virus yang baru. Penurunan ini dikaitkan dengan kemandirian sel yang lebih panjang disebabkan oleh kestabilan protein survivin itu. Penemuan ini telah berjaya menunjukkan penglibatan survivin dalam mengurangkan bilangan kematian sel yang telah dijangkiti NDV. Hasil maklumat ini adalah penting bagi meningkatkan keberkesanan NDV sebagai ejen pembunuh kanser yang baru.

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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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LIST OF ABBREVIATIONS

BCA	Bicinchoninic acid
BCIP	5-Bromo-4-chloro-3-indolyl phosphate
CDDP	cis-diaminedichloroplatinum(II)
DAPI	4',6-diamidino-2-phenylindole
DMEM	Dulbecco's Modified Eagle's Medium
DNA	Deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
F	fusion protein
HA	Haemagglutination assay
HN	haemagglutination-neuramidase protein
IAPs	Inhibitor of apoptosis proteins
IFN	Interferons
MOI	multiplicity of infection
mRNA	Messenger ribonucleic acid
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NBT	Nitro blue tetrazolium
NDV	Newcastle disease virus
NTE	Nacl-Tris EDTA
PBS	phosphate-buffered saline
pfu	plaque forming unit
PVDF	Polyvinylidene fluoride
RNA	Ribonucleic acidaaZ
rpm	revolutions per minute
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis

TBS	tris-buffered saline
TEMED	Tetramethylethylenediamine
v/v	volume / volume
w/v	weight / volume

CHAPTER 1

INTRODUCTION

Commercially available drugs are often being used as a treatment to battle cancers. Cisplatin [*cis*-diaminedichloroplatinum(II), CDDP], is one of the widely used drug to treat cancer patients. Its efficacy in eliminating cancers was first discovered in 1969 and since then, it has been a major tool to treat a variety of malignant tumors such as ovarian, head and neck, lung, bladder and testicular cancers (Siddik, 2003). Several studies have shown that cisplatin works by binding its platinum molecule onto DNA of target cell. This will result in formation of interstrand and intrastrand crosslinks adducts. The DNA-platinum adducts will prevent cells from undergoing efficient DNA replication, suppressing RNA transcription and cell cycle which eventually lead them to apoptosis (Siddik, 2003).

Even though cisplatin has been an excellent treatment to eradicate cancer, its efficacy can be decreased over time due to acquired resistancy. Several cell lines and tumors has shown to develop resistancy towards this drug and studies have shown that its mechanism towards resistancy is multifactorial (Stewart, 2007). One of the proposed mechanisms involved apoptosis inhibitor proteins (IAPs) such as survivin. Survivin is usually found at low level in normal cells but it is highly expressed in most tumors (Ambrosini, 1997). High survivin expressions in cancer cells correlated to poor prognosis, decreased apoptosis and increased angiogenesis (Steward, 2007; Nomura, 2005). As a bifunctional protein, survivin, like other member of IAPs, suppress apoptosis by binding to caspase-3, 7 and 9 (Nachmias, 2004). Besides that, previous reports suggested that survivin played major roles in cell division where it was dominantly induced during G2/M phase to assist mitosis and cytokinesis (Vong, 2005).

The inability of cisplatin to completely eradicate cancer has led to several research in finding an alternative treatment. The idea of using oncolytic virus as virotherapy has been surfaces several times as early as in 1960s but its safety issues proved to be a stumbling block. Numerous amount of DNA and RNA virus has been tested and identified to possess oncolytic properties and Newcastle Disease Virus (NDV) is one of the promising candidates. NDV was first discovered in 1927 in Newcastle upon Tyne and it was identified as a highly contagious disease-causing virus affecting poultry and birds (Nelson, 1999). NDV oncolytic activity was first reported by Cassel and Garret in 1965, and since then, the number of research involving NDV as anti-cancer agent has increased (Cassel, 1965). NDV possess a number of anti-cancer characteristics. Firstly, exposure of NDV to human only causes mild influenza-like symptom but otherwise it does not possess any hazard on normal cells. This selective killing characteristic by NDV is believed to be resulted from defective interferon (IFN) signalling pathways in tumor cells (Krishnamurthy, 2006). Secondly, NDV is a single stranded RNA virus and its replication takes place in the cytoplasm, thus preventing any integration into host genome which may result in unwanted recombinant or deleterious complication. Thirdly, NDV can be used on different tumors as it is known to enter the cell by binding to sialic acid membrane protein, which ubiquitously present on a wide variety of human cancer cells (Reichard, 1992).

A local NDV strain, AF2240, was first isolated in the 1960s from a field outbreak and it was reported to cause a high mortality and morbility in poultry. Previous studies showed that this NDV has the ability to infect MCF7 cell line resulting in apoptosis.

However, the activity of NDV AF2240 on cisplatin-resistant MCF7 cell line has not been reported. Thus, the main objective of this study is to investigate the oncolytic effect of NDV AF2240 strain on cisplatin-resistant MCF7 cancer cells and its relationship with survivin expression. It is hypothesized that the NDV would induce oncolysis in the cisplatin-resistant cells via the survivin protein regulation. To test this hypothesis, the study is designed with these specific aims:

1) To establish cisplatin-resistant breast cancer cell line.
2) To investigate the effects of NDV infection on cisplatin-resistant cells.
3) To study the effects of survivin expression following NDV infection.

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