UNIVERSITI PUTRA MALAYSIA

ANTI-TUMOUR EFFICACY OF HUMAN MESENCHYMAL STEM CELL EXPRESSING TRAIL ON LUNG CANCER CELL LINES-DERIVED CANCER STEM CELL

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By

SHAIK AHMAD KAMAL BIN SHAIK M FAKIRUDDIN

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Disturbing increase in the global lung cancer cases and cancer-related mortality justifies the needs for therapies that are effective and tumour selective. TNF-related apoptosis inducing ligand (TRAIL) has been shown to be a promising therapeutic agent against several tumours, including cancer stem cells (CSCs). However, due to its short half-life and poor bioavailability, TRAIL needs a delivery system to be effective. Mesenchymal stem cells (MSCs) have recently emerged as an effective anti-tumour cytotherapy, able to deliver TRAIL in pre-clinical tumour models. However, investigations on its efficacy to target CSC in non-small cell lung cancer (NSCLC), is lacking. Thus, this study is designed to investigate the efficacy of MSCs expressing TRAIL (MSC-TRAIL) either as a single agent or in combination with first line chemotherapies to destroy CSC isolated from NSCLC cell lines (A549, H2170 and H460). The human MSCs were successfully transduced with TRAIL-encoding lentivirus which resulted in MSC-TRAIL. The generated MSC-TRAIL expressed elevated levels of TRAIL protein and maintained mesodermal lineages differentiation and MSCs surface markers. The CD133+ CSC was isolated from the NSCLC cell lines and verification assays were subsequently performed. It was observed that the sorted CD133+ population strongly exhibited the characteristics of CSCs based on their bigger sphere size detected in an anchorage independent culture, significantly higher number of colonies, and expression of aldehyde dehydrogenase (ALDH), when compared to the non-CSC's control (CD133-). Furthermore, flow cytometry analyses have also revealed that the expression of DR5 TRAIL receptor was high in the CD133+ CSC population in both H2170 and H460 compared to A549. It was observed that the co-culture of MSC-TRAIL and the CD133+ population from both H460 and H2170

induced a significant inhibition to the CSCs. Furthermore, inhibitions to both the unsorted and CD133- cells were also found, indicating that the MSC-TRAIL was effective in destroying the tumour. The MSC-TRAIL was noticed to induce apoptosis and cell death to both H460 and H2170-derived CD133+ CSCs, indicated by the positive annexin V and sytox-green stained cells. Through investigation of the mitochondrial membrane potential, it was also found that MSC-TRAIL was able to induce intrinsic apoptosis to the CSCs. Sensitisation of the NSCLC cell lines using first line chemotherapies prior to exposure to MSC-TRAIL was able to induce a chemo-sensitising effect to the CSCs. Further analyses using gene expression profiling have uncovered candidate genes including NFKB1, BAG3, MCL1, GADD45A, and HRK in CD133+ CSCs, which, if targeted, might increase the sensitivity of NSCLC to MSC-TRAIL-mediated inhibition. As such, these findings add credibility to the use of MSC-TRAIL as anti-tumour cytotherapy and help to uncover a unique therapeutic potential of MSC-TRAIL in the treatment of NSCLC by targeting the CD133+ CSCs.

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

POTENSI KECEKAPAN ANTI-KANSER SEL PUNCA MESENKIMA MANUSIA YANG MENGHASILKAN TRAIL TERHADAP SEL PUNCA TERBITAN KANSER PARU-PARU

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Peningkatan kes kanser paru-paru dan kematian yang berkaitan menunjukkan terdapatnya keperluan terhadap terapi yang lebih efektif dan selektif kepada tumor. Ligan pengaruh apoptosis yang berkaitan dengan TNF (TRAIL) telah menunjukkan potensi sebagai agen terapeutik untuk beberapa jenis tumor, termasuk sel-sel punca kanser (CSCs). Namun, disebabkan jangka hayatnya yang pendek dan bioketerdapatan yang lemah, TRAIL memerlukan sistem penghantaran yang efektif. Sel-sel punca mesenkima (MSCs) kini telah muncul sebagai agen anti-tumor sitoterapi yang berkesan dan mampu menghantar TRAIL seperti mana yang telah ditunjukkan di dalam model tumor pra-klinikal. Walau bagaimanapun, kajian mengenai keberkesanannya untuk menyasar CSC, yang mana merupakan penyebab utama kepada pertumbuhan tumor kanser paru-paru sel bukan kecil (NSCLC), masih kurang. Oleh itu, kajian ini bertujuan untuk mengkaji potensi kecekapan MSC yang menghasilkan TRAIL (MSC-TRAIL) sama ada sebagai agen tunggal atau bersama kemoterapi baris hadapan untuk memusnahkan CSC daripada sel terbitan NSCLC (A549, H2170 dan H460). MSC manusia berjaya ditransduksi dengan lentivirus yang mengekodkan TRAIL untuk menghasilkan MSC-TRAIL. MSC-TRAIL yang dihasilkan dalam kajian ini telah menunjukkan kebolehan dalam menghasilkan protein TRAIL serta pembezaan pewarisan mesoderma dan penanda permukaan MSC. CD133+ telah diasingkan daripada sel terbitan NSCLC dan ujian pengesahan kemudiannya dilakukan. Hasil pemerhatian mendapati populasi CD133+ yang diasingkan mempamerkan ciri-ciri CSC yang kuat berdasarkan saiz sfera yang lebih besar yang dikesan dalam kultur bebas labuhan serta jumlah koloni yang lebih tinggi dan pengekspresan aldehid dehidrogenase (ALDH) yang bererti, berbanding sel-sel bukan CSC (CD133-). Selain itu, analisis sitometri aliran juga telah menunjukkan bahawa DR5, iaitu reseptor TRAIL adalah tinggi dalam populasi CD133+ CSC pada kedua-dua H2170 dan H460 berbanding A549. Hasil pemerhatian juga mendapati kultur

bersama antara MSC-TRAIL dan populasi CD133+ dari kedua-dua H460 dan H2170 telah mengaruh perencatan bererti terhadap CSC. Selain itu, perencatan terhadap kedua-dua sel H460 dan H2170, dan sel CD133- juga menunjukkan bahawa MSC-TRAIL sangat berkesan untuk memusnahkan tumor. MSC-TRAIL diketahui mengaruh apoptosis dan kematian sel terhadap CD133+ CSC daripada kedua-dua H460 dan H2170, yang ditunjukkan melalui ujian sel sitotoksik dan anneksin V yang positif. Penyelidikan mengenai potensi membran mitokondria juga mendapati bahawa MSC-TRAIL mampu mengaruh apoptosis intrinsik kepada CSC. Pemekaan titisan sel NSCLC melalui pra-rawatan penggunaan kemoterapi baris hadapan (sisplatin dan 5-FU) diikuti oleh MSC-TRAIL mampu mengaruh kesitotoksikan untuk membunuh CSC. Walau bagaimanapun, kesan sitotoksik antara vinorelbina dan MSC-TRAIL hanya dapat dilihat pada H2170 dan H460 terbitan CSC dan bukan pada sel tumor A549. Analisis lebih lanjut menggunakan profil ekspresi gen dalam kajian ini telah menemui gen NFKB1, BAG3, MCL1, GADD45A, dan HRK dalam CD133+ CSC, yang mana jika disasarkan, ianya dapat meningkatkan kepekaan NSCLC terhadap MSC-TRAIL. Oleh yang demikian, penemuan ini menambahkan kredibiliti penggunaan MSC-TRAIL sebagai sitoterapi anti-tumor dan membantu merungkai potensi terapeutik unik MSC-TRAIL dalam rawatan NSCLC, terutamanya dengan menyasarkan CD133+ CSC.

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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

ABCG2	ATP-Binding Cassette Sub-Family G Member 2
ATP	Adenosine Triphosphate
APAF1	Apoptotic Protease Activating Factor 1
ALK	Anaplastic Lymphoma Receptor Tyrosine Kinase
ALDH	Aldehyde Dehydrogenase
A549	Adenocarcinoma Cell Line
ATRA	All-trans Retinoic Acid
BAG3	BCL2-Associated Athanogene 3
BAK	BCL-2 Antagonist Killer 1
BCL2	B-Cell Lymphoma 2
BMP	Bone Morphogenic Protein
BIRC3	Baculoviral-Encoded Inhibitor of Apoptosis
BID	BH3 Interacting-Domain Death Agonist
BNIP2	BCL2-Interacting Protein 2
CAS	Caspases
CT	Computed Tomography
CD	Cluster of Differentiation
CSC	Cancer Stem Cell
CXCL12	Chemokine-C-X-C Motif Ligand 12
CXCR4	C-X-C chemokine Receptor Type 4
cDNA	Complementary Deoxyribonucleic Acid
CPD	Cumulative Population Doublings
CD40	Cluster of Differentiation 40
CIDEB	DFFA-like effector B

DR4/5	Death Receptor 4/5
DcR1/2	Decoy Receptor ½
DISC	Death Inducing Signalling Complex
DMEM	Dulbecco's Modified Eagle's medium
EMT	Epithelial Mesenchymal Transition
EPO	Erythropoietin
EML	Echinoderm Microtubule-Associated Protein-Like 4
EPCAM	Epithelial Cell Adhesion Molecule
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
FADD	FAS-Associated Protein with Death Domain
FBS	Foetal Bovine Serum
FGF	Fibroblast Growth Factor
FACS	Fluorescence Activated Cell Sorting
FITC	Fluorescein Isothiocyanate
FAS	Fas Cell Surface Death Receptor
GADD45A	Growth Arrest and DNA Damage Inducible Alpha
H460	Large Cell Lung Carcinoma
H2170	Squamous Cell Lung Cancer
HDAC	Histone Deacetylases
HNF4α	Hepatocyte Nuclear Factor 4 Alpha
HRK	Harakiri BCL2-Interacting Protein

CHAPTER 1

INTRODUCTION

1.1 Background

Lung cancer is an uncontrolled growth of malignant cells that can occur in any part of the lungs. These malignant cells do not have the function of normal lung cells and are able to metastasize into different parts of the body and organs (Zappa & Mousa, 2016). Majority of lung cancer is detected as non-small cells which accounts for 85% of all cases, while the other 15% are detected as small cells (Bray et al., 2018). Lung cancer is the major cause of mortality and morbidity worldwide, killing more than 1.7 million people annually (Bray et al., 2018). In Malaysia, 11, 256 lung cancer cases were detected between 2012 to 2016, where 7, 686 cases were in males and 3, 570 cases in females, accordingly (National Cancer Registry 2012-2016). Lung cancer is also the 3rd leading cancer in Malaysia, after colorectal cancer, and the major cause of cancer related death, accounting for 19.8% of all certified cancer related mortality (National Strategic Plan for Cancer Control, 2016-2020). It is anticipated for the next decades, cases of lung cancer in the developing countries will rise significantly due to the adaptation of the smoking habits into the modern lifestyle (Latimer, 2018). More than half of lung cancer patients are diagnosed at an advanced stage with only 19% chances of survival for the following 5 years (R. L. Siegel et al., 2019). Despite considerable advancements in the treatment of lung cancer, our capacity to effectively treat the disease is limited. This is due to the current treatments that can only manage to reduce the burden of the primary lesion but are rarely effective to eradicate the tumour cells completely, which may subsequently lead to relapse and death (Mascaux et al., 2017).

Lung cancer is a heterogeneous population of tumour cells with each of this population varying in its differentiation, proliferation and tumorigenic capacity (O'Flaherty et al., 2012). Pre-clinical studies have demonstrated that only a few percentages of cells within these populations are able to initiate tumour growth in vivo (Sterlacci et al., 2014). These cells are known as cancer stem cells (CSCs) or tumour initiating cells, capable of producing differentiated or non-differentiated progenies inside a rapidly dividing tumour (M. Zhao et al., 2020). The CSCs are also highly chemoresistant and able to stay dormant to avoid the effects of chemotherapies (De Angelis et al., 2019). It is also the main reason for tumour metastasis and relapse (W. Li et al., 2017). These cells may undergo reversible phenotypic changes or trans differentiation into a non-CSC or vice versa during therapy, a characteristic known as plasticity, making the tumour highly adaptive and resistant to the effect of chemotherapies (Marjanovic et al., 2013).

1.2 Problem Statement

First line chemotherapies may initially destroy the bulk tumour. However, the surviving chemoresistant CSCs will eventually repopulate, leading to the formation of highly resistant tumours and subsequent metastasis (Phi et al., 2018). Therefore, to avoid tumour relapse and metastasis, it is crucial to develop therapies that are effective in killing the CSCs without leaving any residual or surviving CSC which are able to repopulate (Annett & Robson, 2018).

The tumour necrosis factor-related apoptosis inducing ligand or TRAIL is an apoptotic inducing protein that has been proven effective in pre-clinical models in targeting and destroying a variety of tumours including ovarian cancer (Fabi et al., 2018), colorectal cancer (Yesi Shi et al., 2020), prostate tumour (Shishodia et al., 2018) and lung cancer (E. O. Kim et al., 2016). Furthermore, TRAIL either alone or in combination with other agents, has also been proven effective in targeting CSCs of NSCLC (Baojie Zhang et al., 2020), colorectal cancer (R. Zhang et al., 2017), breast cancer (Z.-J. Li et al., 2020), lung cancer (Y. Yang et al., 2015), glioblastoma (Junfeng Liu et al., 2018) and liver cancer (S.-H. Lee et al., 2016). TRAIL seems to have a high specificity against various tumours and CSCs with minimal toxicity due to the high expression of its cognate receptors (DR4 and DR5) in tumours, including CSCs (Eng et al., 2016b; S.-H. Lee et al., 2016), but not in normal cells (Sadarangani et al., 2007; X. D. Zhang et al., 2000). Furthermore, unlike conventional chemotherapies that are dependent on TP53 (tumour protein-53) activation to induce intrinsic apoptosis, TRAIL is capable of inducing both the intrinsic and extrinsic apoptotic pathways without the need for TP53 activation (Abdulghani & El-Deiry, 2010; Prasad et al., 2011). Since TRAIL is able to bypass TP53 activation to induce apoptosis, tumours and CSCs that are chemoresistant due to the mutation of TP53, are sensitive to the effect of TRAIL (Willms et al., 2019). However, the use of TRAIL as a treatment for cancer is limited due to its short half-life and poor systemic bioavailability (Kelley et al., 2001). Thus, a delivery system is needed to enhance the efficacy of TRAIL (Wajant et al., 2013).

Mesenchymal stem cells or MSCs are adult multipotent stem cells derived from several sources including adipose tissue (Gimble et al., 2007), umbilical cord (Kern et al., 2006), and bone marrow (Kemp et al., 2005). The ability of MSCs to migrate and home to the tumour environment has promoted MSCs as an anti-tumour cytotherapy capable of delivering TRAIL to the target site (D'Souza et al., 2012; Kalimuthu et al., 2018). This novel tumour homing characteristic of MSCs engineered to express TRAIL (MSC-TRAIL) has been proven effective to kill several tumours, such as breast cancer (Kamalabadi-Farahani et al., 2018), metastatic breast cancer (M. Liu et al., 2020), gliomas (Kamalabadi-Farahani et al., 2018), melanoma (Salmasi et al., 2020), pancreatic cancer (Spano et al., 2019), colon cancer (Eom et al., 2020) and lung cancer (H. Ding et al., 2017). Ability of MSC-TRAIL to destroy tumours was noticed not only as a single agent but also in combination with several other chemotherapies, such as cisplatin (B Zhang et al., 2012) doxorubicin (Yoon et al., 2015), 5-fluorouracil (R. Yu et al., 2013), panobinostat (Choi et al. 2019) and paclitaxel (Rossignoli et al. 2019).

Although several have reported the efficacy of MSC-TRAIL against NSCLC, the ability of MSC-TRAIL to kill CSC, that is the culprit that drives tumorigenesis in NSCLC, is insufficiently reported. Filling this knowledge gap may support the therapeutic applications of MSC-TRAIL for the treatment of NSCLC, through targeting the CSCs and using MSC-TRAIL with other antitumor agents as a combination therapy. Thus, this study is designed to investigate the efficacy of MSCs expressing TRAIL (MSC-TRAIL) to target and kill CD133+ CSCs isolated from NSCLC cells lines using several assays related to cell proliferation and apoptosis of both intrinsic and extrinsic pathways. The effective cytotoxic combinations between MSC-TRAIL and first line chemotherapies such as cisplatin, 5-fluorouracil and vinorelbine to destroy the CD133+ CSCs in NSCLC was investigated. Lastly, genes involved in TRAIL resistance in CSCs were identified using pathway-specific gene expression profiling.

1.3 Hypothesis

The MSC-TRAIL is able to induce cell inhibition and apoptosis to NSCLC-derived CD133+ CSCs alone and in combination with first line chemotherapies.

1.4 Objectives

1.4.1 General Objective

To evaluate the cytotoxic efficacy of MSC-TRAIL either alone or in combination with first line chemotherapies against NSCLC derived- CD133+ CSCs.

1.4.2 Specific Objectives

1. To generate MSC-TRAIL and verify the TRAIL expression from the MSC-TRAIL.
2. To analyse the sensitivity of NSCLC cell lines (A549, H460 and H2170) to MSC-TRAIL.
3. To characterise CD133+ CSCs isolated from NSCLC cell lines (A549, H460 and H2170).
4. To evaluate efficacy of MSC-TRAIL against CD133+ CSCs derived from NSCLC cell lines either alone or in combination with chemotherapy.
5. To identify apoptotic molecules that contribute to TRAIL and MSC-TRAIL resistance in the CD133+ CSCs.

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BIODATA OF STUDENT

Shaik Ahmad Kamal Bin Shaik M Fakiruddin was born on 1st of November 1985, in Kuala Lumpur. He obtained his primary education at Sekolah Rendah Kebangsaan Taman Permata, Kuala Lumpur before continued his lower secondary education at Sekolah Menengah Kebangsaan Taman Melawati, Kuala Lumpur. He was offered a place at MARA Junior Science College (MRSM) Muar, Johor for his upper secondary education where he successfully completed the Sijil Pelajaran Malaysia (SPM) in 2002. He continued his education at the Perak Matriculation Centre and obtained the matriculation certificate in 2003. Later he joined the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (UPM) and obtained a second-class upper degree in Biomedical Science in 2007. Subsequently, he was offered a higher education scholarship by Majlis Amanah Rakyat (MARA) in 2008 and successfully obtained a Master's Degree in Cancer Therapeutics from Queen Mary, University of London, UK in 2009. He joined Cancer Research Malaysia (CRM) formerly known as CARIF in 2010 as research associate under the supervision of the oral cancer group leader, working on the molecular characterisation of inhibin beta A (INHBA) in oral cancer pathogenesis. In 2011, he joined the Ministry of Health (MOH), Malaysia where currently he serves as a research officer at the Haematology Unit, Cancer Research Centre, Institute for Medical Research (IMR), Kuala Lumpur, as well as in Setia Alam. He was offered a scholarship and a 4-year study leave from 2017 to 2021 by the government of Malaysia, where currently he is in the process of completing his PhD in Cancer Biology and Oncology at the Institute of Bioscience, UPM.

Mr. Kamal was also actively involved in various societies and activities where he served as an honorary treasure for the Malaysian Society for Stem Cell Research and Therapy (MSCRT) from 2014 until 2017. He is also a member of the Malaysian Society of Human Genetics, Tissue Engineering & Regenerative Medicine Society of Malaysia (TESMA) and Malaysian Association of Research Scientist (MARS). He was awarded the excellence service award (APC) in 2015 for his achievement during his service.

LIST OF PUBLICATIONS

Kamal Shaik Fakiruddin, Lim Moon Nian, Norshariza Nordin, Rozita Rosli, Syahril Abdullah. Chemo-Sensitization of CD133+ Cancer Stem Cell Enhances the Effect of Mesenchymal Stem Cell Expressing TRAIL in Non-Small Cell Lung Cancer Cell Lines. *Biology*, (2021): (Accepted for Publication).

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