PROTEOMIC ANALYSIS OF POTENTIAL MEMBRANE PROTEINS IN BLADDER CANCER

By

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Chairman : Armania Nurdin, PhD
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Bladder cancer (BC) recurrence is one of the primary clinical problems encountered by patients following chemotherapy. However, the mechanisms underlying their resistance to chemotherapy remain unclear. Alteration in the pattern of membrane proteins (MPs) is thought to be associated with this recurrence outcome, often leading to cell dysfunction. Therefore, to identify the highly expressed potential MPs in the BC, MPs were extracted from four different stages of BC cell lines (RT 112 - non-invasive, 5637- grade-2 invasive, J82- grade-3 invasive, and UM-UC-13- metastasis bladder cancer cells) using Mem-PER™ Plus Membrane Protein Extraction Kit. The isolated MPs weredigested into peptides and identified by a global proteomics approach using LC-MS/MS, followed by peptide selection. Protein localisation of the identified protein was further analysed using the transmembrane domain prediction algorithms (TMpred and TMHMM v. 2.0) and the UniProt database. Based on these analyses, over 20 MPs were found in each BC cell line, with a total of more than 1000 peptides initially identified. Two potential MP biomarkers were selected: CD147 and caveolin-1, which have previously been reported to be highly expressed in BC tissues clinical specimens. CD147 was detected on the cell membrane by immunocytochemistry, while caveolin-1 showed a positive signal without clear staining on the membrane, suggesting that MP exists in multilocation. Validation by Western blot analysis revealed that CD147 was significantly reduced in invasive grade-2 (5637) and invasive grade-3 (J82) compared to non-invasive (RT 112). In contrast, CD147 expression increased significantly in metastasis (UM-UC- 13) compared to invasive grade-2 (5637) and invasive grade-3 (J82) bladder cancer cells. No significant difference was observed in the expression of caveolin-1 in the different bladder cancer cells. However, the expression of caveolin-1 was slightly higher in grade- 2 invasive (5637) and non-invasive (RT 112) bladder cancer cells, but lowest in metastasis (UM-UC-13) bladder cancer cells. In conclusion, CD147 was identified predominantly expressed in non-invasive (RT 112) and metastasis (UM-UC-13) bladder cancer cells. Thus, it is considered a potential MP biomarker of non-invasive and metastatis bladder cancer cells. Contrarily, the higher expression of caveolin-1 in non- invasive (RT 112) and

invasive grade-2 (5637) bladder cancer cells compared to metastasis (UM-UC-13) bladder cancer cells, suggests that caveolin-1 is a potential MPbiomarker for low-grade bladder cancer. These identified MPs could be used as targeteddrug therapy to improve drug sensitivity in the treatment of bladder cancer.

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

ANALISIS PROTEOMI POTENSI PROTEIN MEMBRAN DALAM KANSER PUNDI KENCING

Oleh

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Disember 2022

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Keberulangan laku kanser pundi kencing adalah salah satu masalah klinikal utama yangdihadapi oleh pesakit selepas kemoterapi. Walau bagaimanapun, mekanisma yang mendasari resistans mereka terhadap kemoterapi adalah masih tidak jelas. Perubahan dalam corak protein membran (MP) dianggap dikaitkan dengan keberulangan laku ini, yang sering membawa kepada disfungsi sel. Oleh itu, bagi mengenal pasti MP yang berpotensi tinggi dalam kanser pundi kencing, MP telah diekstrak daripada empat titisan sel kanser pundi kencing yang berbeza peringkat (RT 112 – tidak invasif, 5637- invasif gred-2, J82 – invasif gred-3, dan UM-UC-13- metastasis sel kanser pundi kencing) menggunakan *Mem-PER™ Plus Membrane Protein Extraction Kit.* MP telah dicernakan kepada peptida dan dikenal pasti melalui pendekatan proteomik global menggunakan LC-MS / MS, diikuti dengan pemilihan peptida. Pensetempatan protein bagi protein yang telah dikenal pasti dianalisis selanjutnya menggunakan algoritma ramalan domain transmembran (TMpred dan TMHMM v. 2.0) dan pangkalan data UniProt. Berdasarkan analisis ini, lebih 20 MP telah ditemui dalam setiap titisan sel kanser pundi kecing, dengan lebih daripada 1000 peptida yang dikenal pasti dalam pemeriksaan awal. Dua biomarker MP yang berpotensi telah dipilih: CD147 dan caveolin-1, seperti yang dilaporkan dijumpai dalam tisu spesimen kanser pundi kencing. CD147 dikesan pada membran sel oleh imunositokimia, manakala caveolin-1 menunjukkan isyarat positif tanpa kesan yang jelas pada membran dan menunjukkan bahawa MP wujud dalam pelbagai lokasi. Pengesahan oleh analisis Western blot mendedahkan bahawa ekspresi CD147 telah berkurangan dengan ketara dalam sel-sel kanser pundi kencing invasif gred-2 (5637) dan invasif gred-3 (J82), dibandingkan dengan sel-sel kanser pundi kencing tidak invasif (RT 112). Sebaliknya, ekspresi CD147 meningkat dengan ketara dalam sel kanser pundi kencing metastasis (UM-UC-13), dibandingkan dengan sel kanser pundi kencing invasif gred-2 (5637) dan invasif gred-3 (J82). Tiada perbezaan yang ketara diperhatikan dalam ekspresi caveolin-1 dalam sel kanser pundi kencing yang berbeza. Walau bagaimanapun, ekspresi caveolin-1 diperhatikan sedikit lebih tinggi dalam sel kanser pundi kencing invasif gred-2 (5637) dan tidak invasif (RT 112), tetapi paling rendah dalam sel kanser pundi kencing metastasis (UM-UC-13). Kesimpulannya,

CD147 dikenal pasti terutamanya dalam sel kanser pundi kencing tidak invasif (RT 112) dan metastasis (UM-UC-13). Oleh itu, ianya dianggap sebagai biomarker MP yang berpotensi bagi sel kanser pundi kencing tidak invasif dan metastasis. Sebaliknya, ekspresi caveolin-1 yang lebih tinggi dalam sel kanser pundi kencing tidak invasif (RT 112) dan invasif gred-2 (5637) berbanding sel kanser pundi kencing metastasis (UM-UC-13), menunjukkan bahawa caveolin-1 ialah MP yang berpotensi sebagai biomarker kanser pundi kencing gred rendah. MP yang dikenal pasti ini boleh digunakan sebagai terapi sasaran drug untuk meningkatkan sensitiviti drug dalam rawatan kanser pundi kencing.

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ABC	ATP-binding cassette
ANOVA	Analysis of variance
ATCC	American type culture collection
BCA	Bicinchoninic acid assay
BCG	Bacillus Calmatte-Guerin
Cat.no	Catalogue number
CIS	Carcinoma-in-situ
CLS	Cell Lines Service
DAB	Diaminobenzidine
DNA	Deoxyribonucleic acid
DMSO	Dimethyl sulfoxide
ECACC	European collection of animal cell culture
EDTA	Ethylenediamine tetraacetic acid
EMEM	Minimum Essential Medium Eagle (EMEM) with Earle's Salt
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FGFR3	Fibroblast growth factor receptor 3
G	Gravitational force
ICAT	Isotope-coded affinity tags
ICC	Immunocytochemistry
IHC	Immunohistochemistry
iTRAQ	isobaric tags for relative and absolute quantification
LC-MS	Liquid chromatography mass spectrometry
LC-MS/MS	Liquid chromatography tandem mass spectrometry
Mg	Milligram

mL	Millilitres
mM	Millimolar
MIBC	Muscle-invasive bladder cancer
MMC	Mitomycin C
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
m/z	Mass to charge ratio
Nm	Nanometer
NMIBC	Non-muscle-invasive bladder cancer
P	Significance difference
PBS	Phosphate buffer saline
Rpm	Revolutions per minute
RT-PCR	Reverse transcriptase-PCR
SEM	Standard error mean
SPSS	Statistical package for the social sciences
Tis	Tumour *in-situ*
TURBT	Transurethral resection of bladder tumour
T1	Tumours invading the subepithelial connective tissue or laminar Propria
T2	Tumour invades muscle
T3	Tumour invades perivesical fat
T4	Tumour invades the prostate gland, uterus, vagina, pelvic wall or abdominal wall
UTI	Urinary tract infection
v/v	Volume per volume
WB	Western blot
WHO	World Health Organisation
µg	Microgram
µL	Microliter

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Bladder cancer is the most common malignancy of the genitourinary system, and the majority of patients are diagnosed between the ages of 50 and 70 years old (Konety & Isharwal, 2015; Bray et al., 2018). It accounts for 3% of all current cancer cases being treated globally, with 573 278 new cases and 212 536 deaths reported in 2020. The prevalence is three-fold higher in men than in women (Sung et al., 2021); however, women have a higher risk of developing an advanced stage. In Malaysia, a totalof 2122 bladder cancer cases were reported from 2012 to 2016, with a 4-fold higher incidence reported in men compared with women (Azizah et al., 2019). The differences in incidence and outcomes between men and women are yet to be understood. Nevertheless, the disparities are thought to be due to exposure to environmental factors and the differences in anatomical and physiological characteristics, including genetics and hormones (Marks et al., 2016).

Bladder cancer is classified based on the depth of invasion of the lamina propria:

(1) non-muscle invasive (NMIBC) and (2) muscle-invasive bladder cancer (MIBC).

NMIBC is confined to the inner layer of the bladder wall (lamina propria) without invading the muscle layer, unlike MIBC, which can be found in the muscular wall of the bladder (Bhindi et al., 2021). It is estimated that NIMBC is the most commonly diagnosed bladder cancer among cancer patients, representing about 75% of the population, while the rest of the patients suffer from MIBC and metastases. However, several studies have shown that patients diagnosed with NIMBC have a high recurrence rate of up to 70% within 5 years (Akagashi et al., 2006; Breau et al., 2014) and up to 30% of patients die from the disease (Quek et al., 2003). Even more alarming, approximately 5 to 20% of the patients will progress to invasive carcinoma (Donat, 2003).

Depending on the severity of the malignant cell, various alternatives have been practically implemented to inhibit the growth of the bladder cancer cell. The administration of chemotherapy before or after surgical resection is widely implemented and has shown a promising result in inhibiting cancer cell progression (Galsky et al., 2016). In patients with bladder cancer who received three years of intravesical chemotherapy with mitomycin-C (MMC), the study found that the three-year recurrence- free interval increased by up to 18 % with NMIBC (Friedrich et al., 2007). Nevertheless, disease recurrence has always been the main problem despite the treatment given. Terrifyingly, the inability to eliminate this cancer from the body system can lead to the enlargement of the existing tumour, which is likely the cause of the increase in mortality rate (Chamie et al., 2013; Sung et al., 2021). Studies have

shown that bladder cancer recurrence could be due to chemotherapy resistance (Drayton & Catto, 2012; Housman et al., 2014). Concurrently, this condition strengthens the formidable features of the cancer cells, which eventually raised the interest in understanding the mechanism of drug resistance.

The transport protein regulates the movement of the chemotherapeutic drug; consequently, alteration of the membrane proteins may interfere with the substantial effect of the treatment (Tada et al., 2002; Kilari et al., 2016). Drug resistance can occur due to the modification of membrane protein composition, reduction of drug transporters, increase in efflux pumps and alteration or loss of drug targets (Agarwal & Kaye, 2003; Holohan et al., 2013; Avril et al., 2017). For example, multidrug resistance protein 1 (MRP1) acts as an efflux pump that rapidly extrudes anticancer drugs from cancer cells (Longley & Johnston, 2005; Roy et al., 2007). Overexpression of MRP1 can reduce the intracellular concentration and cellular cytotoxicity of anticancer drugs, leading to resistance to these treatments (Tada et al., 2002). Similarly, several membrane proteins, such as vascular endothelial growth factor receptor-1 (VEGFR-1) and vascular endothelial growth factor receptor-2 (VEGFR-2), which are significantly increased in bladder cancer, have been proposed as potential biomarkers for bladder cancer (Manickam et al., 2011; Lee et al., 2015). Significantly increased expression of VEGFR- 1 can promotes cell proliferation, and its co-expression with VEGFR-2 can further enhance cancer cell proliferation, survival, and invasion via activation of VEGF/VEGFRpathways. Thus, abundant expression of these membrane proteins may aid in defining the stage or prognosis of bladder cancer (Kopparapu et al., 2013). Moreover, several studies reported that the membrane proteins of bladder cancer have a different composition than those of normal cells (Dobrzyńska et al., 2015). Due to this fact and their cross-membrane localisation, membrane proteins represent as potential biomarkersand therapeutic targets that serve as diagnostic or prognostic tools for bladder cancer.

At the present moment, the assessment of protein biomarkers in patient samples is performed by antibody-based proteomic analysis. Immunohistochemistry (IHC) staining and enzyme-linked immunosorbent assay (ELISA) are among the classical method for quantification of tissue- and biofluid-based protein biomarkers, respectively(Liu et al., 2013). For biomarker discovery, the development of multiplex and high- throughput array-based proteomics techniques such as reverse-phase protein array (RPRA) and bead-based multiplex arrays have provided valuable benefits in tissue-based and biofluid-based protein quantification, respectively (Solier & Langen, 2014; Wilson et al., 2015). RPRA quantifies protein expressions by assessing protein-specific antibody binding of microscale dot-blot protein lysates embedded on a slide (Solier & Langen, 2014; Nishizuka & Mills, 2016). With a minimal starting amount of protein lysate and aprobe consisting of a highly specific antibody, this technique allows the measurement ofa biomarker in a large number of samples. In bead-based multiplex arrays, however, theuse of distinct fluorescent beads covered with different antibodies allows the measurement of different protein indicators in a single protein suspension (Lash et al., 2006; Dejager & Rijkers, 2006). This multiplex antibody array-based proteomic analysis has been employed in several studies as a platform for cancer proteomics and biomarkerdevelopment.

Previous studies have used this multiplex antibody array-based proteomicanalysis as a platform for cancer proteomics and biomarker discovery (Ostendorff et al., 2013; Ummanni et al., 2014), but this technique comes with a limitation. Since the antibody-based array relies mainly on a highly specific antibody, biomarker discovery is highly dependent on the availability of these antibodies and is limited to the targeted quantification of proteins. To overcome this limitation, label-free mass spectrometry (MS)-based proteomic analysis has become the most attractive method for the discovery of novel protein biomarkers and therapeutic targets for bladder cancer. Without requiring antibodies for screening proteins, liquid chromatography-tandem mass spectrometry (LC-MS/MS) also offers improvement in the specificity accuracy, and selectivity by upto 96% in a single analysis (Tsai et al., 2008).

To date, the determination of biomarkers, including membrane proteins of the bladder cancer cells, has been widely performed to better interpret the effectiveness of current treatment in preventing cancer cell progression. Although several membrane proteins have been proposed as biomarkers, their correlation with cancer grade and effects before or after intravesical therapy requires further investigation. Specific and sensitive biomarkers have yet to be ascertained, thus, continuous effort should be made to obtain definite outcomes.

1.2 Problem Statement

Bladder cancer recurrence is not the only concern, but there is a lack of targeted biomarkers that possibly increase the sensitivity of anticancer drugs. Membrane proteinsbecome the main interest as a potential biomarker and therapeutic target for the diagnosis and prognosis of bladder cancer. They are critically important for normal physiological function, whereby alteration in protein patterns often leads to cellular dysfunctions (Carter et al., 2004). Since membrane proteins represent 70-80% of all drug targets which underlines their clinical relevance (Bünger et al., 2009), the identification of potential membrane proteins as a biomarker for bladder cancer is therefore vital and crucial.

1.3 Significance of Study

There are very few potential bladder cancer biomarkers that have been proposed and established to allow the selection of effective drugs for bladder cancer chemotherapy. The research will identify the potential membrane protein biomarkers from different grades of bladder cancer cell lines. It is also hoped that the research findings would help in the development of targeted therapies for bladder cancer in the advancement of personalised medicine. Given that drug reactions vary significantly amongst patients, hence specific treatments can be prescribed based on the biomarkers expressed by individual patients.

ObjectivesGeneral objective:

To discover potential membrane protein biomarkers in bladder cancer cells.

1.4 Specific objectives:

1. To identify a panel of potential membrane protein biomarker candidates inbladder cancer cells by global proteomic LC-MS/MS analysis.
2. To determine the localisation of the selected potential membrane protein biomarkers in the bladder cancer cells.
3. To quantify the level of protein expression of the selected potential membraneprotein biomarkers in the bladder cancer cells.

1.5 Hypothesis

1 Highly expressed potential membrane protein biomarker candidates in bladdercancer cells will be identified through global proteomic LC-MS/MS analysis.

2 The selected potential biomarkers in the bladder cancer cells will be detected as membrane proteins by performing bioinformatic analysis and immunocytochemistry (ICC).

3 The changes in protein expression of the potential biomarkers will be analysedin bladder cancer cells and quantified by Western blot.

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