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DISSECTING THE POTENTIAL ROLE OF CALRETICULIN AS A PROGNOSTIC BIOMARKER FOR INVASIVE BREAST CANCER

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By

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Chairman : Professor Rozita binti Rosli, PhD
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Breast cancer is the most common cancer occurring in women and the second leading cause of death in women after lung cancer worldwide. In cancer studies, invasion is an essential hallmark that allows cells to metastasize and spread to other parts of the body. Therefore, the focus of cancer studies is increasingly on invasion and metastasis-related biomarkers to detect the progression of breast cancer. Calreticulin (CRT) is a multipurpose endoplasmic reticulum (ER) protein which has been proposed as a potential biomarker for breast cancer. The high level of CRT expression has been reported to correlate with the range of invasiveness in breast cancer patients. In addition, presence of the extracellular matrix and stroma in the tumorigenic environment significantly increase the invasive phenotype and malignancy of breast cancer. Hence, a three-dimensional (3D) co-culture system using Matrigel as extracellular matrix offers a significant advantage in developing an *in vivo*-like model. In the first part of this study, MCF-7, MDA-MB-231 and MCF-10A breast cell lines were co-cultured with MRC-5 fibroblast cell line in the ratio of 3:1 in a 3D culture system to recapitulate *in vivo*-like expression of Calreticulin, the protein of interest. Subsequently, in the second part of this study, gene expression profiling of CRT and CRT-related candidate metastasis genes were carried out in 3D co-cultured cells developed in the first step. Finally, the correlation between CRT and CRT-related candidate metastasis genes were identified through statistical analysis. The results on the characterization of the developed 3D co-cultured micro-tissues showed occasional foci of lumen-like morphology and standard neoplastic features in the 3D structure. Moreover, the expression level of calreticulin and its localization in the micro-tissue samples were detected through immunohistochemistry revealed a patchy pattern of micro-tissues with wide positive signals of cytoplasmic CRT as well as irregular positive-stained nuclei. It was found that the expression of CRT and CRT-related candidate metastasis genes were down-regulated in all 3D co-cultured samples, in which PCMT1 and ER-Alpha genes were found to be significantly downregulated (P <

0.01) in invasive breast cancer cells. While this study was unable to completely recapitulate *in vivo*-like expression of the CRT protein in the 3D co-cultured model due to technical constraints, it can serve as a baseline from which future work can be built upon. Nevertheless, based on the gene expression study, CRT and CRT-related candidate metastasis genes are shown to be involved in the progression of invasive breast cancer cells. This study also found that the CRT gene expression is highly correlated with all CRT-related candidate metastasis genes obtained from the developed micro-tissues. To conclude, this study suggests that CRT and CRT-related candidate metastasis genes may potentially serve as prognostic biomarkers for invasive breast cancer.

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Kanser payudara adalah kanser kedua yang sering menjadi penyebab utama kematian di kalangan wanita di dunia selepas kanser paru-paru. Dalam kajian kanser, pencerobohan merupakan satu ciri penting yang membenarkan sel untuk melakukan metastasis dan tersebar ke bahagian lain pada badan. Oleh yang demikian, semakin banyak kajian kanser yang tertumpu kepada pencerobohan dan penanda biologi berkaitan metastasis untuk mengawal perjanjangan kanser payudara. Kalretikulin (CRT) ialah protein retikulum endoplasma pelbagai fungsi yang telah dikenalpasti sebagai penanda biologi di dalam kanser payudara. Kadar ekspresi CRT telah dilaporkan sejajar dengan kadar keserbuan di dalam pesakit kanser payudara. Selain itu, kehadiran matriks luar sel dan stroma di dalam persekitaran tumorigenik meningkatkan pencerobohan dan fenotip kemalignan secara signifikan di dalam kanser payudara. Disebabkan itu, satu sistem ko-kultur 3D menggunakan Matrigel sebagai matriks luar sel memberikan nilai signifikan dalam pembentukan eksperimen seakan in-vivo. Oleh itu, bahagian pertama kajian ini, titisan sel payudara MCF-7, MDA-MB-231 dan MCF-10A dikultur bersama dengan titisan sel fibroblast MRC-5 dengan nisbah 3 kepada 1 dalam sistem kultur 3D bagi merekapitulasi ekspresi in-vivo Kalretikulin, protin tumpuan dalam kajian ini. Kemudian, pada bahagian kedua kajian ini, pemprofilan ekspresi gen CRT dan gen calon metastasis yang berkaitan dengan CRT telah dikaji di dalam sampel ko-kultur 3D daripada bahagian pertama. Akhir sekali, korelasi diantara CRT dan gen calon metastasis yang berkaitan dengan CRT telah dikenalpasti menerusi analisis secara statistik. Keputusan terhadap pencirian tisu mikro ko-kultur 3D yang telah dibina menunjukkan morfologi fokus tidak tetap seperti lumen dan ciri neoplastik standard dalam struktur 3D. Selain itu, kadar ekspresi Kalretikulin dan pensetempatannya dalam sampel tisu mikro telah dikesan melalui kaedah imunohistokimia menunjukkan corak tisu mikro yang bertompok dengan isyarat positif tinggi bagi sitoplasma CRT dan juga nukleus berwarna (positif) yang tidak tetap. Keputusan ekspresi gen juga menunjukkan pengawalaturan rendah bagi

ekspresi gen CRT dan gen calon metastasis yang berkaitan dengan CRT di dalam semua sampel ko-kultur 3D selain gen PCMT1 dan ER-Alpha menunjukkan pengawalaturan rendah secara signifikan ($P < 0.01$) di dalam sel kanser payudara invasif. Walaupun kajian ini tidak dapat merekapitulasi ekspresi protin CRT dalam sample ko-kultur 3D secara in-vivo dengan sempurna berikutan masalah teknikal namun ianya akan menjadi garis panduan bagi kajian yang boleh dibina pada masa hadapan. Selain itu, berdasarkan kajian ekspresi gen ekspresi gen CRT dan gen calon metastasis yang berkaitan dengan CRT menunjukkan keterlibatan gen-gen tersebut didalam perjanjangan sel kanser payudara yang invasif. Kajian ini juga menemukan gen CRT ialah sangat berkolerasi dengan gen calon metastasis berkaitan dengan CRT yang didapati daripada tisu mikro yang telah dibina. Sebagai kesimpulan, kajian ini menunjukkan gen CRT dan gen calon metastasis yang berkaitan dengan CRT berpotensi bertindak sebagai penanda biologi prognosis bagi kanser payu dara invasif.

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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2D	Two dimensional
3D	Three dimensional
AJCC	American Joint Committee on Cancer
ATM	Ataxia-telangiectasia mutation
bp	Base pairs
BRCA1	Breast Cancer 1
BRCA2	Breast Cancer 2
BSA	Bovine Serum Albumin
Ca^{2+}	Calcium ion
cDNA	Complementary DNA
CHEK2	Checkpoint homolog 2
cm	Centimetre
CRT	Calreticulin
CTTN	Cortactin
DAB	Diaminobenzene
DCIS	Ductal carcinoma *In Situ*
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
E-cadherin	Epithelial cadherin
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
ER	Endoplasmic reticulum

ER-Alpha	Estrogen receptor alfa
ERE	Estrogen receptor element
ESRK	Extracellular signal related kinase
FC	Fold Change
FFPE	Formalin fixed paraffin embedded
FGF	Fibroblast growth factor
FGFR2	Fibroblast growth factor receptor 2
GH	Growth hormone
H & E	Hematoxylin and eosin
IDC	Invasive ductal carcinoma
IGF1	Insulin-like growth factor-1
IHC	Immunohistochemistry
kDa	Kilo Dalton
LRP1	Low density lipoprotein receptor-related protein 1
LSP1	Lymphocyte-specific protein 1
MAPK1	Mitogen-activated protein kinase 1
MCF-7	Michigan Cancer Foundation - 7
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
p53	Tumor protein p53
PCR	Polymerase chain reaction
PI3K	Phosphoinositide 3-kinase
PTEN	Phosphatase and tensin homolog
Rb	Retinoblastoma

RNA	Ribonucleic acid
RNase	Ribonuclease
rpm	Revolutions per minute
SR	Sarcoplasmic reticulum
Slug	Snail homolog
STAT3	Signal transducer and activator of transcription 3
TBS	Tris Buffered Saline
TDLU	Terminal duct lobular unit
TNM	Tumor node metastasis
Tris	Tris(hydroxymethyl)aminomethane
TSP	Thrombospondin
UICC	International Union Against Cancer

CHAPTER 1

INTRODUCTION

Breast cancer remains a significant problem for women as it is diagnosed more than one million times every year worldwide (Dimitriou et al. 2019). According to the breast cancer statistics provided by the World Cancer Research Fund, it is the most commonly occurring cancer in women and the second most common cancer overall (after lung cancer). In developing countries such as Iran and Malaysia, breast cancer is also an increasing issue in women's health (Montazeri et al. 2008; Azizah et al. 2016).

Strategies for treatment in breast cancer depend on the extent of disease progression in the body that is usually estimated through various criteria such as tumor size, lymph node involvement, and the presence of distant metastasis. The development of distant metastasis is a direct consequence of the invasion of cancer cells into their surrounding tissues, followed by entering into the blood circulation and, finally, seeding in distant organs (Fidler 2003). For successful management of breast cancer, including early diagnosis, individualized therapy, and determining a patient survival, it is necessary to clarify the molecular basis of mechanisms involved in cancer cell invasion and metastasis (Dowsett and Dunbier 2008).

CRT is an essential endoplasmic reticulum (ER) protein that has important functions inside and outside of the ER (Michalak et al. 1999). Two critical functions of CRT, including protein chaperoning and calcium homeostasis, are carried out inside the lumen of ER (Helenius et al. 1997; Nakamura et al. 2001). Based on a previous study conducted in-house, the CRT protein was found to be overexpressed in tumor tissues compared to their adjacent healthy tissues. Subsequently, the results on whole-genome sequencing, and CRT-knockdown samples indicated several candidate genes as possible contributors to functional pathways involved in CRT pro-invasive effects on breast cancer (Zamanian 2011).

Moreover, CRT has been shown to be involved in cellular proliferation and even metaplasia (Opas et al. 1991). CRT has also been described to be related to cancerous and malignant states (Yoon et al. 2000), while as a major calcium homeostasis contributor, it also plays a role in cancer invasion and metastasis (Chen et al. 2005). A number of studies have tried to reveal the relationships between evolution and progression of various cancers and the presence of CRT. In brief, the progressive effects of CRT or its overexpression have been reported in ductal carcinoma of the breast (Bini et al. 1997; Chahed et al. 2005), bladder cancer (Kageyama et al. 2004), prostatic adenocarcinoma (Alaiya et al. 2000) hepatocellular carcinoma (Kim et al. 2004), pancreatic malignancies (Hong et al.

2004), esophageal cancer (Du et al. 2007; Nishimori et al. 2006), gastric cancer (Chen et al. 2009a), colon cancer (Vougas et al. 2008), melanoma (Dissemond et al. 2004; White, Zhu, and Tanzer 1995); and leukemia (Helbling et al. 2005).

A number of studies have shown the correlations between the presence of CRT in the evolution and progression of cancer and also higher expression of CRT in the protein profile of breast ductal adenocarcinoma (Bini et al. 1997; Franzén et al. 1997; Zamanian 2011). CRT overexpression has also been reported to coincide with a higher chance of invasion and metastasis in breast cancer patients (Erić et al. 2009). Due to the significant influence of CRT expression in breast cancer progression, it has been proposed as a potential prognostic biomarker of breast cancer (Lwin et al. 2010; Xu et al. 2018; Zamanian et al. 2016).

1.1 Problem Statement

Current prognostication in breast cancer relies on the clinicopathological parameters and individual molecular markers, For example, estrogen receptor (ER), progesterone receptor (PR), hormone receptors and human epidermal growth factor status (HER2) and ki67 (Abubakar et al. 2019). Although these traditional prognostic markers are able to confidently identify approximately 30% of patients who are most likely to have either a very favourable or a very poor outcome, of the remaining 70% of patients, approximately 30% will still develop metastases. Hence, new prognostic markers are urgently required for identification of low-risk and high-risk patients for developing metastasis in order to expedite the adapting of treatment strategies by oncologists. According to the literature, the expression level of CRT (as a potential prognostic biomarker) has been correlated with advanced disease and a higher chance for the development of distant metastasis of breast cancer. In addition, stability of the tissue structure provided by extracellular matrix and stroma also significantly increase the invasion and aggressive phenotype of breast cancer (Fischbach et al. 2007; Zamanian et al. 2016) and hence, their influences are essential to be considered in the present study. Annually, billions of animals are killed in laboratories for biology lessons, medical training, curiosity-driven experimentation, and chemical, drug, food, and cosmetics testing (U.S. Department of Agriculture 2018). Hence, developing a 3D co-culture system instead of following through animal study may be an alternative way to provide the required multilayer micro-environment for cancer study. Based on this, the research questions are:

1. Is the 3D co-culture able to recapitulate the *in vivo*-like expression of Calreticulin protein?
2. Is there any correlation between the expression of CRT and the candidate genes with the invasive potential of breast cancer cells?
3. What are the correlation level of the expression of CRT-related candidate metastasis genes with the expression of CRT gene obtained from developed breast cancer micro-tissues?

1.2 Research objectives

1.2.1 General objective

To functionally characterize the possible role(s) of Calreticulin as a prognostic biomarker in conferring an invasive phenotype to breast cancer cells.

1.2.2 Specific objectives

The specific objectives of the study were:

1. To develop a 3D culture system to recapitulate *in vivo*-like expression of Calreticulin protein.
2. To analyse gene expression profiles of previously identified candidate Calreticulin-related metastasis genes in breast cancer progression.
3. To analyse the correlation of CRT and CRT-related candidate metastasis genes obtained from developed breast cancer micro-tissues.

1.3 Research hypothesis

In this study, it is hypothesized that the 3D co-culture system be able to recapitulate the *in vivo*-like expression of Calreticulin protein, moreover, the gene expression of *CRT* and the candidate metastasis genes have correlation with the invasive potential of breast cancer cells. Additionally, to identify the correlation level of the expressed *CRT*-related candidate metastasis genes with the expression of *CRT* gene obtained from developed breast cancer micro-tissues.

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