UNIVERSITI PUTRA MALAYSIA

IDENTIFICATION OF LONG NON-CODING RNAS IN SERUM EXOSOMES FROM COLORECTAL CANCER PATIENTS AND EFFECTS OF EXOSOMES ON TUBE FORMATION BY ENDOTHELIAL CELLS

NG CHIN TAT

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By

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

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September 2019

Chairman : Prof.essor Seow Heng Fong, PhD
Faculty : Medicine and Health Sciences

Extracellular vesicles (exosome-like vesicles) are small membrane vesicles ranging from 20-150nm in size that are released by various cells into the extracellular space. This extracellular vesicles play a major role in cell-to-cell communication and contain materials, such as proteins, mRNAs, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Recent studies have reported that the components in exosomes vary based on the type of cell. Long non-coding RNAs (lncRNAs) are non-protein-coding RNAs consisting of more than 200 nucleotides in length. It has been shown that lncRNAs play an important role in various cellular processes including angiogenesis by interacting with RNA, DNA or proteins through diverse mechanisms to regulate gene expression. However, the effect of exosomes derived from an invasive colorectal cancer cell line on angiogenesis is unclear and the potential of lncRNAs in circulating exosomes as biomarkers have not been completely studied. Hence, the aims of this study is to investigate the effect of exosomes derived from an invasive colorectal cancer cell line on angiogenesis of endothelial cells and to identify the potential of lncRNAs in circulating exosomes as biomarkers for detection of colorectal cancer. In the present study, the exosomes from the cell culture supernatants of an invasive colorectal cancer cell line SW480-7 were characterized and lncRNAs in these exosomes were profiled. The effect on tube formation and expression of angiogenic genes in a microvascular endothelial cell, telomerase-immortalized microvascular endothelial cell (TIME) cocultured with exosomes were also determined. In addition, RT^2 lncRNA PCR array was used for exosomal lncRNA profiling to determine the relative expression level of lncRNAs in the exosomes of sera from 18 CRC (colorectal carcinoma) and 21 non-cancer patients. The expression level of lncRNAs was compared between 8 early-stage (stages I and II) and 10 advanced-stage (stages III and IV) of CRC patients. Results showed that exosomes derived from SW480-7 increased tube formation and up-regulated expression FGFR3 mRNA in TIME. Zetasizer result showed average diameter of exosomes derived from SW480-7 was

274.6 nm and morphology analysis showed the majority of exosomes size less than 200 nm. Western blot analysis demonstrated that exosomes from SW480-7 contained exosomal protein, Alix. A total number of 32 lncRNAs were detected in SW480-7-derived exosomes and some have been reported to be associated with angiogenesis. In clinical studies, six lncRNAs, namely GAS5, H19, LINC00152, SNHG16, RMRP, and ZFAS1 were detected in the sera of 18 CRC patients. These lnRNAs may serve as potential biomarkers for detection of CRC. Among these six lncRNAs, expression level of LINC00152 was found to be significantly lower in CRC patients as compared to non-cancer patients ($p=0.04$). The expression level of lncRNAs was compared for early versus advanced-stage of CRC patients. Expression level of exosomal lncRNA H19 was significantly up-regulated in advanced-stage of CRC (p value= 0.04).In conclusion, exosomal lncRNAs derived from SW480-7 increased tube formation and up-regulated expression of FGFR3 mRNA in TIME. Among the six exosomal lncRNAs detected in the sera, LINC00152 and H19 may be useful as biomarkers in liquid biopsies for diagnosis and treatment monitoring in colorectal cancer.

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

IDENTIFIKASI LONG NON-CODING RNA DI DALAM SERUM EKSOSOM DARIPADA PESAKIT KANSER KOLOREKTAL DAN KESAN EKSOSOM TERHADAP FORMASI TIUB SEL ENDOTELIAL

Oleh

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Vesikel ekstraselular (vesikel menyerupai eksosom) adalah vesikel membran kecil, saiz di antara 20-150 nm dan dirembeskan oleh pelbagai jenis sel ke dalam ruang ekstraselular. Vesikel ekstraselular ini memainkan peranan penting dalam komunikasi di antara sel-sel dan mengandungi komponen seperti protein, mRNAs, microRNAs (miRNAs) dan long non-coding RNAs (lncRNAs). Kebelakangan ini, banyak kajian melaporkan bahawa komponen dalam eksosom adalah berbeza dan bergantung kepada jenis sel yang merembesnya. LncRNAs adalah non-protein-coding RNAs (RNA yang tidak terlibat dalam pengekodan protein) yang melebihi 200 nukleotida. Kajian telah membuktikan lncRNAs memainkan peranan penting dalam pelbagai proses sel termasuk angiogenesis (pembentukan pembuluh darah baru) yang melibatkan interaksi di antara RNA, DNA atau protein melalui pelbagai mekanisma yang mengawal ekspresi gen. Walau bagaimanapun, kesan eksosom dari sel kanser kolorektal yang invasif terhadap angiogenesis dan potensi lncRNAs di dalam eksosom sebagai biopenanda kanser kolorektal (CRC) masih belum ditentukan. Oleh itu, tujuan penyelidikan ini adalah untuk mengkaji kesan eksosom dari sel kanser kolorektal yang invasif terhadap angiogenesis sel endotelial dan potensi lncRNAs sebagai biopenanda kanser kolorektal. Dalam kajian ini, ciri-ciri eksosom ditentukan dan lncRNAs daripada eksosom sel kanser kolorektum SW480-7 diprofilkan. Kesan eksosom terhadap formasi tiub dan ekspresi angiogenik gen dalam sel endotelial mikrovaskular, *telomerase-immortalized microvascular endothelial cell* (TIME) juga dikaji. Selain itu, RT^2 lncRNA PCR array digunakan untuk pemprofilan lncRNA di dalam eksosom untuk menentukan tahap expresi lncRNAs dari 18 pesakit kanser kolorektal dan 21 pesakit bukan kanser kolorektal. Tahap ekspresi lncRNA dibandingkan antara 8 pesakit CRC yang berperingkat awal (peringkat I dan II) dengan 10 pesakit CRC yang berperingkat lanjut (peringkat III dan IV). Hasil kajian menunjukkan bahawa eksosom yang berasal dari SW480-7 meningkatkan formasi tiub dan meningkatkan ekspresi *FGFR3* mRNA di dalam sel TIME. Keputusan *Zetasizer* menunjukkan purata

diameter eksosom yang berasal dari SW480-7 ialah 274.6 nm dan analisis morfologi menunjukkan majoriti saiz eksosom kurang daripada 200 nm. Analisis *Western Blot* menunjukkan bahawa eksosom yang berasal dari SW480-7 mengandungi protein eksosom, *Alix*. Sebanyak 32 lncRNAs dikesan di dalam eksosom yang berasal dari SW480-7 termasuk yang telah dilaporkan yang terlibat dengan angiogenesis. Dalam kajian klinikal, enam *lncRNAs* iaitu GAS5, H19, LINC00152, SNHG16, RMRP dan ZFAS1 dikesan di dalam serum eksosom daripada 18 pesakit CRC. LnRNA ini berpotensi sebagai biopenanda dalam pengesanan CRC. Di antara enam lncRNAs ini, tahap ekspresi LINC00152 adalah lebih rendah di dalam pesakit CRC berbanding dengan pesakit bukan CRC ($p = 0.04$). Tahap ekspresi lncRNA dibandingkan antara pesakit CRC peringkat awal dengan pesakit CRC peringkat lanjut. Tahap ekspresi lncRNA H19 di dalam eksosom meningkat dengan ketara bagi pesakit CRC peringkat lanjut (nilai $p = 0.04$). Kesimpulannya, lncRNA di dalam eksosom yang berasal dari SW480-7 meningkatkan formasi tiub dan meningkatkan ekspresi mRNA FGFR3 dalam TIME. Antara 6 lncRNAs di dalam serum eksosom yang dikesan, LINC00152 dan H19 mungkin berguna sebagai biopenanda dalam biopsi cecair untuk diagnosa dan rawatan pemantauan bagi kanser kolorektal.

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This thesis was submitted to the Senate of the 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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This is to confirm that:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

%	Percent
µ	Micro
AEG-1	Astrocyte elevated gene-1
AKAP-9	A-kinase anchor protein 9
ANGPT2	Angiopoietin 2
BCAR4	Breast cancer anti-estrogen resistance 4
bFGF	Basic fibroblast growth factor
bFGFR	Basic fibroblast growth factor receptor
BLACAT1	Bladder cancer associated transcript 1
BSA	Bovine serum albumin
CA19-9	Carbohydrate antigen 19-9
CA242	Carbohydrate antigen 242
CBR3-AS1	Cbr3 antisense RNA 1
CCAT1	Colon cancer associated transcript 1
CCAT1-L	Colorectal cancer-associated transcript 1-long
CCAT2	Colon cancer-associated transcript-2
CEA	Carcinoembryonic antigen
ceRNAs	Competing endogenous RNAs
CLMAT3	Colorectal liver metastasis-associated transcript 3
CRNDE	Colorectal neoplasia differentially expressed
CRNDE-h	Colorectal neoplasia differentially expressed – h
DANCR	Differentiation antagonizing non-protein coding RNA
DLEU2	Human leukemia-associated protein 2
DNMT1	Dna methyltransferase 1

DNMT3A	Dna methyltransferase 3a
DNMT3B	Dna methyltransferase 3b
ECM	Extracellular matrix
EMT	Epithelial–mesenchymal transition
ESCRT	Endosomal sorting complexes required for transport
EZH2	Enhancer of zeste homolog 2
FGF2	Fibroblast growth factor 2
FGFR3	Fibroblast growth factor receptor 3
FTX	Five prime to xist
GAS5	Growth arrest-specific 5
GDF15	Growth differentiation factor 15
HCC	Hepatocellular carcinoma
hEGF	Human recombinant epidermal growth factor
HEIH	Hepatocellular carcinoma up-regulated ezh2-associated long non-coding RNA
hFGF-B	Human fibroblast growth factor basic with heparin
HOTAIR	Hox transcript antisense RNA
HOTAIRM1	Hoxa transcript antisense RNA, myeloid-specific 1
HOTTIP	Hoxa transcript at the distal tip
HULC	Highly upregulated in liver cancer
JAK-STAT	Janus kinase/signal transducer and activator of transcription
LINC00152	Long intergenic non-coding RNA 00152
LINC00261	Long intergenic non-protein coding RNA 261
LINC00312	Long intergenic non-protein coding RNA 321
LINC00963	Long intergenic non-protein coding RNA 963
LINC01234	Long intergenic non-protein coding RNA 1234

LINC01296	Long intergenic non-coding RNA 1296
lincRNAs	Large intervening non-coding RNAs
lncRNA-ATB	LncRNA activated by tgf-β
lncRNAs	Long non-coding RNAs
LSD1	Lysine-specific demethylase 1
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
MDM2	Murine double minute 2
MEG3	Maternally expressed gene 3
miR	MicroRNA
MIR17HG	Mir-17-92 cluster host gene
MIR31HG	Mir31 host gene
miRNAs	MicroRNAs
MMP	Matrix metallopeptidase
mRNAs	Messenger RNAs
MTX	Methotrexate
MVB	Multivescular body
MYC	Myelocytoma
NaHCO3	Sodium bicarbonate
NBR2	Neighbor of brca1 gene 2
ncRNA	Non-protein ribonucleic RNA
NEAT1	Nuclear paraspeckle assembly transcript 1
OXA	Oxaliplatin
OS	Overall survival
PAR-1	Protease-activated receptor-1
PBS	Phosphate buffered saline
PCA3	Prostate cancer antigen 3

PCAT1	Prostate cancer-associated transcript 1
piRNAs	Piwi-interacting RNAs
POU3F3	Pou class 3 homeobox 3
PRNCR1	Prostate cancer associated non-coding RNA 1
PTBP2	Polypyrimidine tract binding protein 2
PTENP1	Phosphatase and tensin homolog pseudogene 1
PVDF	Polyvinylidene fluoride
PVT1	Plasmacytoma variant translocation 1
R3-IGF-1	Human recombinant insulin-like growth factor
REST	Re1 silencing transcription factor
RIPA	Radioimmune precipitation assays
RMRP	RNA component of mitochondrial RNA-processing
RMRP	RNA component of mitochondrial RNA processing endoribonuclease
RN7SK	RNA, 7sk small nuclear
RPLP0	Ribosomal proteins ribosomal protein, large, p0
SBDSP1	Shwachman-bodian-diamond syndrome pseudogene 1
SCID	Severe combined immunodeficiency disease
SFPQ	Splicing factor proline and glutamine rich
shRNA	Small hairpin RNA
siRNAs	Small interfering RNAs
SNHG 16	Small nucleolar RNA host genes 16
SNORA73A	Small nucleolar RNA, h/aca box 73a
SNP	Single nucleotide polymorphism
SPIA	Single primer isothermal amplification
SRPK1	Serine-arginine protein kinase 1

TCF7L2	Transcription factor 7-like 2
TEM	Transmission electron microscopy
TERC	Telomerase RNA component
TGF-β	Transforming growth factor beta
TNM	Tumour node metastasis
TUG1	Taurine up-regulated gene 1
TUSC7	Tumor suppressor candidate 7
UCA1	Urothelial carcinoma-associated 1
VDR	Vitamin d receptor
VEGF	Vascular endothelial growth factor
VEGFA	Vascular endothelial growth factor a
VEGFR	Vascular endothelial growth factor receptor
ZEB	Zinc finger e-box-binding protein
ZFAS1	Zinc finger antisense 1

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Colorectal cancer (CRC) is the third most common type of cancer (Moriarity et al., 2016) that causes high mortality worldwide (Arnold et al., 2017). Despite decades of research, the mortality rate of CRC patients is still high. In 2018, CRC was estimated to cause 551,269 deaths (5.8% of total cancer death) and about 1.09 million (6.1% of total new cases) new cases were reported at the same year from 185 countries (Bray et al., 2018). Most previous genomic studies in the pathogenesis of CRC are mainly about protein-coding genes (Xie et al., 2016). Surprisingly, current genomic studies via latest next generation sequencing methods and transcriptome analysis have discovered that larger part of genome is transcribe into RNA including non-protein ribonucleic RNA (ncRNA)(Saus et al., 2016). These ncRNAs encompass a variety of subclasses. One of the subclasses known as regulatory ncRNA consists of two main groups namely short RNAs (miRNAs siRNAs and piRNAs) and long non-coding RNA (lncRNAs).

LncRNAs are transcripts more than 200 nucleotides (Han et al., 2015) in length with no or limited protein-coding potential and are found in significant amounts in exosomes. In the past, lncRNAs were described as transcriptional 'noise' (Raut and Khullar, 2018; Ward et al., 2015) but recent studies have demonstrated that lncRNAs play an important role in central cellular process such as epigenetic modulation, transcription and translation. When compared with protein-coding genes, lncRNAs are tissue-specific although expressed at low levels (Balas and Johnson, 2018; Ward et al., 2015). In CRC, lncRNAs have been shown to play significant roles in carcinogenesis via various mechanisms such as cell proliferation (Smolle et al., 2014; Ye et al., 2016; Yin et al., 2015), apoptosis (Takahashi et al., 2014), migration (Qi et al., 2015; Smolle et al., 2014), invasion and metastasis (Smolle et al., 2014). Exosomes are extracellular vesicles ranging between 20 nm – 120 nm in size and contain significant amount of nucleic acids including lncRNAs. These vesicles are secreted into the extracellular space by various cells including cancer cells. Cancer derived exosomes are able to trigger the angiogenic process and enhance metastasis of tumour. Exosomes can be used as liquid biomarker for various cancer diagnosis as exosomal contents are originated from parental cells (Li et al., 2017d; Roma-Rodrigues et al., 2014). Currently, the screening tests are inadequate and factors such as false positive or negative results, cumbersome preparatory procedures and expensive molecular testing are major obstacles to early detection of CRC. Hence, there is a dire need for development of a diagnostic test for cancer detection. Exosomes carried biomarkers specific to the origin of cancer cells (Roma-Rodrigues et al., 2014) that are present in serum and their profiles may potentially be useful as a novel biomarkers for CRC patients and are emerging as a new diagnostic approach.

To date, no circulating exosomal marker in serum has been developed for use in CRC as of yet. Recently circulating miRNAs or exosomal miRNAs have been recognized as promising biomarkers for ovarian cancer (Yokoi et al., 2017), lung cancer (Farran et al., 2018; Yu et al., 2018), colon cancer (Fang et al., 2015; Zhang et al., 2018; Zheng et al., 2014a), prostate cancer (Sapre and Selth, 2013)and breast cancer (Hamam et al., 2017). It is likely that circulating exosomes in body fluids containing lncRNAs may present new, relatively non-invasive cancer biomarkers. The results will enable the development of diagnostic and prognostic tests (Saus et al., 2016) for non-invasive and early detection of CRC. Hence, the aims of this study was to isolate the exosomal lncRNAs in sera from apparently non-cancer patients and patients with colorectal adenoma and carcinoma, examine the lncRNA expression profile and identify the differentially expressed serum lncRNAs related to the colorectal carcinogenesis. Recently, many studies revealed the effect of exosomes derived from various cancer cells on angiogenesis. However, the effect of exosomes from invasive colorectal cancer cell line on angiogenesis is unknown. Hence, this study also determine the effects of invasive colorectal cancer cell line (SW480-7) derived exosomes on angiogenesis and determine angiogenic gene expression in telomerase- immortalized microvascular endothelial cells (TIME). SW480-7 is an invasive subpopulation of SW480 that was established *via* 7 sequential passages through matrigel-coated transwells. The hypothesis of the present study is that, there are differences in lncRNA expression between non-cancer patientsand patients with colorectal adenoma and carcinoma. For the *in vitro* study, it is hypothesized that exosomes derived from SW480-7 will increase tube formation of TIME, and up-regulate angiogenic gene expression.

1.2 Objectives

a. To purify and characterize the exosomes secreted by SW480-7 colon cancer cell line.
b. To identify lncRNAs in exosomes secreted by SW480-7.
c. To determine the effects of SW480-7 derived-exosomes on angiogenesis.
d. To isolate and identify the exosomal lncRNAs in sera from non-cancer patients and patients with colorectal adenoma and carcinoma.
e. To examine the profile of lncRNA expression and identify the differentially expressed serum exosomal lncRNAs related to stages of colorectal carcinoma.

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