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PHENOTYPIC EFFECTS OF IN VITRO MIR-141 EXPRESSION MODULATION IN BLADDER CANCER

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in the Fulfillment of the Requirement for the Degree of Master of Science

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Abstract of the thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

THE PHENOTYPIC EFFECTS OF *IN VITRO* MIR-141 EXPRESSION MODULATION IN BLADDER CANCER

By

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June 2013

Chair: **AbhimanyuVeerakumarasivam, PhD**

Faculty: **Medicine and Health Sciences**

Cancer initiation and progression is a multi-step process that involves the accumulation of somatic mutationsthat lead to the dysregulation of specific genes. Epigenetic modifications play a key role in the regulation of gene expression during cellular differentiation. Amongst the emerging epigenetic players in cancer biology are miRNAs. MiRNAs areshort non-coding endogenous RNAsthatregulate gene expression by inhibiting translation efficiency or enhancing mRNA decay.Depending on the mRNA target it regulates, in cancer, miRNAs can act either as tumoursuppressors or promoters. Hence, the orchestration of miRNA regulation and functionishighly biological significant in cancer initiation and progression. In this study, we aimed to investigatethe association of miR-141 expression and bladder cancer cell phenotypes. Using *in silico* prediction tools, several genes that were found to be dysregulated in bladder cancer were predicted to be potentially regulated by miR-141. ZEB family members, *MAP2K4* and *DLC1* genes were found to be

potentially targeted by miR-141 and were associated with a malignant invasive potential. EJ28 invasive bladder cancer cell line was selected in this study due to its invasive phenotype. To characterise the phenotypic effects of miR-141expression modulation, several phenotypic assays (cell cycle, migration and matrigel invasion) were conducted after theectopic upregulation of miR-141 expression*in vitro* by miR-141 mimics in EJ28 cells. All the experiments were completed in three independent replicates (n=3).The overexpression of miR-141 was confirmed in miR-141 upregulated EJ28 cells by RT-qPCR quantification. MiR-141-overexpressingcells demonstratedno apparent differences in cell-cycle distribution as compared tountransfected and mock controls. Therefore upregulation of miR-141doesnotaffectthe cell cycle.Using the cell migration assay, miR-141-overexpressing cells exhibited adecrease in the relative gap closure rate as compared to untransfected and mock controls.Specifically, aminor shift in relative gap closure rate was observed between9 and24 hours after wounding.The number of invaded cells using the matrigel invasion assay was significantlylower inmiR-141-overexpressing cells as compared to both untransfected and mock control groups of cells(T-test, $p<0.05$, n=3). Thus, miR-141 expression impacts the invasive potential of EJ28 cells. In conclusion, the overexpression of miR-141decreasedthe migratory and invasivepotential of EJ28 cells but did not affect the cell cycle. Althoughfurther validation is required, this study demonstratedmiR-141 asapotential key regulator of bladder tumourigenesis and its utility as apotential prognostic and/ortherapeutic biomarker in bladder cancer management.

Abstraktesis yang dikemukakankepadaSenatUniversiti Putra Malaysia
sebagaimemenuhikeperluanuntukijazah Master Sains

KESANFENOTIPMODULASIEKSPRESIMIR-141 *IN VITRO*DALAM BARAH PUNDI KENCING

Oleh

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Permulaandan perkembangan barah adalah proses pelbagai langkah yang melibatkan pengumpalan mutasi somatik serta penyahkawalseliaan gen-gen khusus. Perubahanepigenetik memainkan peranan yang penting dalam regulasi ekspresi gen ketika pembezaan selular. MiRNA merupakan salah satu faktor epigenetik baru dalam biologi barah.MiRNA adalah molekul RNA endogenus bukan pengekod pendek yang meregulasi ekspresi genmelaluiperencatan kecekapan translasi atau peningkatan susutan RNA pengutus (mRNA). Bergantung kepada sasaran mRNA yang diregulasi, dalam barah, miRNA boleh memainkan peranan sebagai penahan atau pengalakbarah. Oleh itu, pengorkestraan regulasi dan fungsimiRNAadalah sangat penting dalam permulaan dan perkembangan barah. Dalam kajian ini, kami bertujuan untuk menyiasatkan perkaitan antara ekspresi miR-141 dengan fenotip sel barah pundi kencing. Dengan menggunakan perisian ramalan *in silico*, beberapa gen berkaitan dengan barah pundi kencing telah diramalkan berkemungkinan diregulasi

oleh miR-141. Ahli kumpulan gen ZEB, gen MAP2K4 dan gen DLC1 telah diramal sebagai gen sasaran yang berkemungkinan dikawal atur oleh miR-141 serta berkaitan dalam potensi barah pundi kencing invasif. Kultur sel barah pundi kencing invasif EJ28 telah dipilih dalam kajian ini kerana sifat invasifnya.Untuk mencirikan kesan fenotip selepas peningkatan ekspresi miR-141, beberapa ujian fenotip (kitaran sel, migrasi dan pencerobohan matrigel) telah dijalankan selepas peningkatan ektopik regulasi ekspresi miR-141 secara*in vitro* dengan menggunakan pemimik miR-141 dalam sel-sel EJ28. Ekspresi berlebihan miR-141 dipastikan dengan kuantifikasiRT-qPCR. Sel-sel yang ditingkatkan ekspresi miR-141 menunjukkan tiada perbezaan yang ketara dalam analisi kitaran sel dibandingkan dengan kawalan tidak transfeksi dan olok. Oleh itu, peningkatan ekspresi miR-141 tidak mengubah kitaran sel. Dengan menjalankan ujian migrasi sel, sel-sel yang ditingkatkan ekspresi miR-141 mempamerkan perkurangan dalam kadar penutupan celahrelatifberbanding dengan kawalan tidak transfeksi dan olok. Peralihan yang kecil dalam kadar penutupan celahrelatifdiperhatikan dalam jam 9 hingga 24 selepas percelahan. Pengurangan nombor sel-sel yang mencerobohi dalam ujian pencerobohan matrigel adalah signifikan untuk sel-sel yang ditingkatkan ekspresi miR-141 dibandingkan dengan sel kawalan tidak transfeksi dan olok (T-test, $p<0.05$, $n=3$). Dengan ini, ekspresi miR-141 memberi kesan kepada potensi invasif sel-sel EJ28. Kesimpulannya, ekpresi berlebihan miR-141 mengurangkan potensi migrasi dan invasif dalam sel-sel EJ28 tetapi tidak mempengaruhi kitaran sel. Walaupun pengesahan yang lanjutan diperlukan, kajian ini telah menunjukan potensi untuk miR-141 dalam peranan meregulasi perkembangan barah pundi kencing dan keperluan sebagai potensi ramalan dan/atau terapi bio-penanda dalam pengurusan barah pundi kencing.

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I certify that a Thesis Examination Committee has met on June2013 to conduct the final examination of Lai Jiun Yee on his thesis entitled "The Phenotypic Effects of *in vitro* MiR-141 Expression Modulation in Bladder Cancer" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U. (A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

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LAI JIUN YEE

Date: 20 June 2013

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LIST OF ABBREVIATIONS

Ago2	Argonaute 2
ATF1	Activating Transcription Factor 1
ATF2	Activating Transcription Factor 2
BCL2	B-cell CLL/Lymphoma 2
Bp	Base pair
CDC25a	Cell Division Cycle 25 Homolog A
CDKN2	CyclinDependent Kinase 2
CDKN6	Cyclin Dependent Kinase 6
C. elegans	Caenorhabditiselegans
CEA	CarcinoembryonicAntigen
CIS	Carcinoma *In Situ*
CLL	Chronic Lymphatic Leukimia
CO_2	Carbon Dioxide
CREB1	cAMPResponsive Element Binding Protein 1
DGCR8	DiGeorgeSyndrome Critical Region Gene 8
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-Mesenchymal Transition
ERCC1	Excision-repair Cross-complementary group 1
ETS1	ErythroblastosisVirus E26 Oncogene Homolog 1
Exp5	Exportin-5
E2F3	E2F Transcription Factor 3

FBS	Fetal Bovine Serum
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FSCN 1	FascinHomolog 1, actin-bundling protein
GALNT1	Polypeptide N-acetylgalactosaminyltransferase 1
HIF-1A	Hypoxia Inducible Factor 1, alpha subunit
HIF-3A	Hypoxia Inducible Factor 3, alpha subunit
HMGA2	High-Mobility Group AT-hook 2
HRAS	Harvey Rat Sarcoma Virus Oncogene
H_2O_2	Hydrogen Peroxide
IL-1	Interleukine1
KRAS	KirstenRat Sarcoma Virus Oncogene
Let-7	Lethal-7
Lin-4	Lineage-4
MAPK	Mitogen-Activated Protein Kinase
MIBC	Muscle Invasive Bladder Cancer
miRNA	Micro Ribonucleic Acid
miRISC	miRNAInduced Silencing Complex
MRE	miRNARegulatory Element
mRNA	messengerRibonucleic Acid
MTS1	Multiple Tumour Suppressor 1
MTS2	Multiple Tumour Suppressor 2
MUC1	Mucin 1
NMIBC	Non Muscle Invasive Bladder Cancer
NPM1	Nucleophosmin

OncomiR	Oncogenic miRNA
PAH	Polycyclic Aromatic Hydrocarbons
PBS	Phosphate Buffered Saline
PDCD4	Programmed Cell Death Protein 4
PI3K	Phosphatidylinositol 3-Kinase
PPARγ2	PeroxisomalProliferator-Activated Receptorγ2
pre-miRNA	Precursors Micro Ribonucleic Acid
pri-miRNA	Primary Micro Ribonucleic Acid
PTEN	Phosphatase and TensinHomolog
P-450	Cytochrome P-450 enzymes
Ran-GTP	RAs-related Nuclear protein - Guanosine 5’ Triphosphate
RAS	Rat Sarcoma Virus Oncogene
RB	Retinoblastoma
RECK	Reversion-Inducing-Cysteine-Rich
SOX4	SRY-related HMG-box 4
STAT1	Signal Transducer and Activator of Transcription 1
TAGLN2	Transgelin 2
TAE	Tris base, Acetic acid and Ethylenediaminetetraacetic
TGF-β	Transforming Growth Factor beta
TP53INP1	Tumour Protein 53-Induced Nuclear Protein 1
TRAIL	TNF-related Apoptosis-Inducing Ligand
TRBP	TransactivatingRegion Binding Protein
Trypsin-EDTA	Trypsin-EthylenediaminetetraaceticAcid
TURBT	Transurethral Resection of Bladder Tumour
UCC	Urothelial Cell Carcinoma

VEGF	Vascular Endothelial Growth Factor
ZEB1	Zinc Finger E-box-Binding Homeobox 1
ZEB2	Zinc Finger E-box-Binding Homeobox 2

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CHAPTER 1

INTRODUCTION

Cancer is a multistepprogressive disease that has emerged as one of the leading causesof death globally. Generally, cancer is caused by complex genetic alterations and modifications,ranging from inherited traits to acquired somatic changes that lead to systemic dysregulation. Bladder cancer is ranked the 7th most common cancer among males worldwide (Jemal*et al.*, 2011). The socio-economic burden of bladder cancer recurrence and invasion has prompted greater public awareness and scientific efforts from researchers globally (Bottema*et al.*, 2003). After decades of effort in understanding bladder carcinogenesis, we have begun to understand the divergent pathways in thedevelopment and progression of bladder tumors,which correspond to the dysregulation of different genes or sets of genes (Wu, 2005). The alteration of specific genes leads to two types of bladder cancers, muscle invasive and non-muscle invasive bladder cancer. However distinguishing non-invasive bladder cancer from an invasive bladder cancer early in tumorigenesis is not clear-cut.

The cost ofbladder cancer clinical management severely burdens the government and patients fromthe time of diagnosis to death (Noyes *et al.*, 2008). Since decades ago, periodic cystoscopic examination for bladder cancer recurrence especially for non-invasive bladder cancers has been a necessitysince no single effective diagnostic and/or prognostic biomarkers have been clinical validated with high specificity and sensitivity(Aldousari and Kassouf, 2010). Although several biomarkers have been introduced to complement cytoscopyfor more accurate prognosis (Shariat*et al*., 2008),

the cost of bladder cancer managementremains exorbitant. This is because none of these biomarkers can replace cystoscopy as the gold-standard method. Thus, the searchfor non-invasive diagnostic markers remains. It is hoped that the discovery of biomarkers with high specificity and sensitivity will be fundamental in theenhancement of the prospect of developing cost-effective diagnostics and therapeutically efficacious modalities.

Recently, miRNAs have been identified as key regulators of gene expression through translational repression and mRNA decay. These small non-coding RNAs play a role at the post-transcriptional level and have tissue specific-expression profiles (Song *et al.,* 2010). Alterations of miRNAs expression profiles could lead to specific pathogenesis. Normal and cancer cells appear to have distinct miRNA expression profiles(Catto *et al.,* 2011). Thesedifferences in miRNA expression profiles can potentially beapplied for the purpose of cancer diagnosis and prognosis.Recent studies support the postulate that carcinogenesis is closely associated with gross dysregulation of miRNA expression profiles (Lu *et al*., 2005). Hence, the identification and development of specific tumour-associatedmiRNAsfor distinguishing between invasive and non-invasive phenotypes of bladder cancer is an exciting prospect. In addition, the biological significance of the dysregulatedmiRNAs expression in the various processes involved in bladder tumourigenesis should be investigated.

The miR-200 family has been implicated in various cancers including breast, prostate, colon, ovarian and bladder cancers(Wszolek *et al.,* 2011; Baffa*et al.,* 2009). Burk and colleagues (2008) found that miR-200 family members were commonly

suppressed in metastatic and invasive epithelial tumors. This finding is thought to be associated with the epithelial-mesenchymal transition (EMT) process (Burk *et al.,* 2008).MiR-141,a member of the miR-200 family has been shown to play a role in invasive cancers such as colon and ovarian cancers(Cheng *et al.,* 2011; Mateescu*et al.,* 2011). The expression of miR-141 was found to be significantly repressed in urine sediments from patients with bladder cancer as compared to healthy controls (Wang *et al*., 2012). Incidentally, miR-141 expression is found to be elevated after radical cystectomy (Cheng *et al*., 2011).In addition, high levels of the circulating miR-141 in plasma havealso been suggested to serve as a novel biomarker for metastatic colon cancer (Cheng *et al*., 2011). Since the discovery of miRNAsis relatively new, more studies are needed to gain a better understanding of the role of miRNAsin tumourigenesis to fast-track their utility as clinical biomarkers. This study revealed miR-141 as a potential target of dysregulation in invasive bladder cancers.

The hypotheses of this study were:

1. MiR-141 targets genes that are involved or implicated in invasion and metastasis.
2. Overexpression of miR-141 affects the cell cycle progression of bladder cancer cells *in vitro*.
3. Overexpression of miR-141 downregulates the migratory and invasivepotential of bladder cancer cells *in vitro*.

Thus, this study was aimed at investigating the phenotypic effects of miR-141 expression modulation in bladder cancer cells as well as predicting potential mRNA targets of miR-141.

The specific objectives of this study were:

1. topredict the miR-141 targeted mRNA by using*in silico*prediction tools.
2. to overexpress miR-141 in invasive bladder cancer cells *in vitro*.
3. to determine the effect of miR-141 modulation on cell cycle, migration and invasion in bladder cancer cells *in vitro*.

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