بسم الله الرحمن الرحيم

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Biochemistry Department

MicroRNAs Profiling in Egyptian Breast Cancer Patients

Thesis Submitted by

Mohamed Anwar Mohamed

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Supervised by

Late Prof. Dr. Hala M. EL-Desouki

Professor of Biochemistry
Faculty of Science
Ain Shams University

Prof. Dr. Ibrahim M. Abd Elsalam

Professor of Medical Biochemistry
National Cancer Institute
Cairo University

Prof. Dr. Mahmoud M. Said

Professor of Biochemistry
Faculty of Science
Ain Shams University

Prof. Dr. Hanan R. Nassar

Professor of Oncology Medicine
National Cancer Institute
Cairo University

Prof. Dr. Amany M. Hilal

Professor of Oncology Medicine
National Cancer Institute
Cairo University

2022

Faculty of Science
Biochemistry Department

Biography

Name: **Mohamed Anwar Mohamed**

Date of graduation: May 1995, Faculty of Science

Biochemistry department

Ain Shams University

Degree awarded: B.Sc. in Biochemistry (1995)

(Good)

M.Sc in Biochemistry (2010)

Occupation: Laboratory Specialist

Ministry of Interior Hospitals

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MicroRNA Profiling in Egyptian Breast Cancer Patients

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ABSTRACT

Our study aimed at evaluating the clinical utility of specific types of plasma microRNAs (miRs) as diagnostic biomarkers in early-stage breast cancer (BC) patients and to study their relation with BRCA1 and BRCA2 mutations in BC patients and high-risk females. The study included 45 early-stage BC patients (30 non-familial and 15 familial), 15 high-risk subjects and 20 clinically healthy females as control. Using quantitative RT-PCR, the relative expression levels of some plasma miRs (10b, 21, 155, 145 and let-7c) were determined in breast cancer patients and high-risk, compared to controls. Also, multiplex PCR was applied for the detection of 185delAG and 5382insC mutations in BRCA1 gene, and 6174delT mutation in BRCA2 gene using multiplex PCR and mutations were confirmed using High Resolution Melting (HRM) technique. Plasma miR-10b and miR-21 levels were significantly up-regulated, while miR-155 and miR-let-7c levels were significantly down-regulated in BC patients and high-risk subjects, compared to controls. MiR-21 was significantly up-regulated, whereas miR-155 level was significantly down-regulated in patients with lymphatic invasion. MiR-21 showed a significant association with mutation in exon 2 of BRCA 1 in high-risk individuals. Deregulated expression

of miR-10b, miR-21, miR-155, and let-7c serves as a potential non-invasive diagnostic marker in early-stage II BC, and surveillance biomarkers for individuals at a higher-expected risk of developing BC. Also, high-risk individuals harbor classical mutations in BRCA1 gene, considering it a high priority for these individuals to have had a strict follow-up.

Keywords: MiRs, mutations, BRCA1, BRCA2, early-stage II breast cancer

List of Abbreviations

Abb.	Full term
ADH	Atypical ductal hyperplasia
AFAP1-AS1	Actin fiber-associated protein 1-antisense RNA1
Ago	Argonaute
Akt	Protein kinase B
ALH	Atypical lobular hyperplasia
AntagomiRs	Antagonistic miRNAs
ARS	Age-standardized rate
ATM gene	Ataxia Telangiectasia Mutant gene
ATM	Ataxia telangiectasia mutated
BAP1	BRCA1-Associated −Protein 1
BARD1	BRCA1-Associated RING Domain1
BASC	BRCA1-Associated genome Surveillance complex
BC	Breast cancer
Bcl2	Anti-apoptotic protein
BCSC	Breast cancer stem cell
BER	Base Excision Repair
BIC	Breast cancer Information Core
BMPs	Bone morphogenetic proteins
BRCA1,2	Breast cancer gene1,2
BRCT	BRCA1Carboxy- Terminal
BRIP	BRCA1Interacting Protein -1
CA	Capside protein
CCL-18	Chemokine (C-C motif) ligand 18
CCND2	Cyclin D2
CDK	Cyclin-dependent kinase
CHEK2	Checkpoint kinase 2
C-myc	C-Myelocytomatosis oncogene product
DBD	DNA-Binding Domain
DCIS	Ductal Carcinoma In Situ
DGGE	Denaturing Gradient Gel Electrophoresis
DNA	Deoxyribonucleic acid
EGF	Epidermal growth factor

List of Abbreviations

Abb.	Full term
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
ER	Estrogen receptor
ERK	Extracellular- signal regulated kinase
FADD	Fas-associated death domain
FOXO3	Forkhead box O3
G	Grade
GC	Genetic counseling
Grb2	Growth factor receptor-bound protein 2
GSK3	Glycogen synthase kinase 3
HER	Human epidermal growth factor receptor
HIF1a	Hypoxi-ainducible factor 1a
HIF2a	Hypoxia-inducible factor 2a
HMGA2	High mobility group athook 2
HOXD	Homeobox D
H-ras	Harvey rat sarcoma
HRM	High Resolution Melting
HRR	Homologous recombination repair
IDC	Infiltrating Ductal Carcinoma
IHC	Immunohistochemistry
ILC:	Infiltrating Lobular Carcinoma
IQGAP1	IQ-motif containing GTPase activating protein 1
IQR	Inter quartile range
IRB	Institution Review Board
JAK/STAT	Janus kinase/signal transducer and activator of transcription
Ki 67	Kiel clone-67
KLF4	Krüppel-like factor 4
K-ras	Kirsten rat sarcoma
LA	Luminal A
LABC	Locally advanced breast cancer
LB	Luminal B
Let7-c	Lethal-7c

List of Abbreviations

Abb.	Full term
LN	Lymph nodes
LNA	Locked nucleic acid
LncRNAs	Long noncoding RNAs
LOH	loss of heterozygosity
LR	Likelihood ratio
MAPK	Mitogen activated protein kinase
MEK	Mitogen/extracellular signal-regulated kinase
miRs	MicroRNAs
MMP	Matrix metalloprotease
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MT1-MMP	α3-integrin, and membrane type-1 matrix metalloproteinase
MTH1	MutT homolog-1
mTOR	Mammalian target of rapamycin MUCIN 1 Transmembrane glycoprotein mucin1
NACT	Neoadjuvant chemotherapy
NCAD	Neural cadherin
ncRNA	Non-coding RNAs
NF1	Neurofibromatosis type 1
NS	Non significant
4-Oct	Octamer-binding transcription factor 4
OncomiRs	Oncogenic miRNAs
p53	Tumor protein
PAK4	P21-activated kinase 4
PALB2	Partner and localizer of BRCA2
PBX3	Pre-B-cell leukemia homeobox 3
PCR	Polymerase Chain Reaction
PR	Progesterone receptor
PTEN	Phosphatase and tensin homolog
q PCR	Quantitative Polymerase Chain Reaction
Raf	Rapidly accel-erated fibrosarcoma
RAS	Rat sarcoma
Rho and Rac	Ras-like proteins

List of Abbreviations

Abb.	Full term
RHOA	RAS homolog family member A
RISC	RNA-induced silencing complex
ROC	Receiver operating characteristic
ROCK1	Rho-associated coiled-coil kinase 1
RTKN	Rhotekin
SMAD	small mothers against decapentaplegic
SOX1	SRY-box transcription factor 1
SOX2	Sex-determining region Y-box2
SPSS	Statistical Package for Social Sciences
STK11	Serine/threonine kinase 11
SU	Surface protein
Tag	Thermus aquaticus
TAMs	Tumorassociated macrophages
TGF-b	Transforming growth factor beta
TIMP3	Tissue inhibitor of metalloproteinases-3
TM1	Tropomyosin-1
TMEM49	Transmembrane protein 49
TN	Triple negative
TNBC	Triple negative breast cancer
TP53	Tumor Protein 53
TRBP	TAR-RNA binding protein
TsmiRs	Tumor suppressor miRNAs
uPAR	urokinase plasminogen activator receptor
USA	United Stated of America
UTR	Untranslated region
VEGF	Vascular endothelial growth factor
WHO	World health organization
χ^2	Chi-square
ZEB1	Zinc-finger e-box binding homeobox 1

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