بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / هناء محمد علي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: ....

Ain Shams University
Faculty of Science
Biochemistry Department

Molecular study on Micro RNAs 122 and 221 as biomarkers for hepatocellular carcinoma and hepatitis C virus

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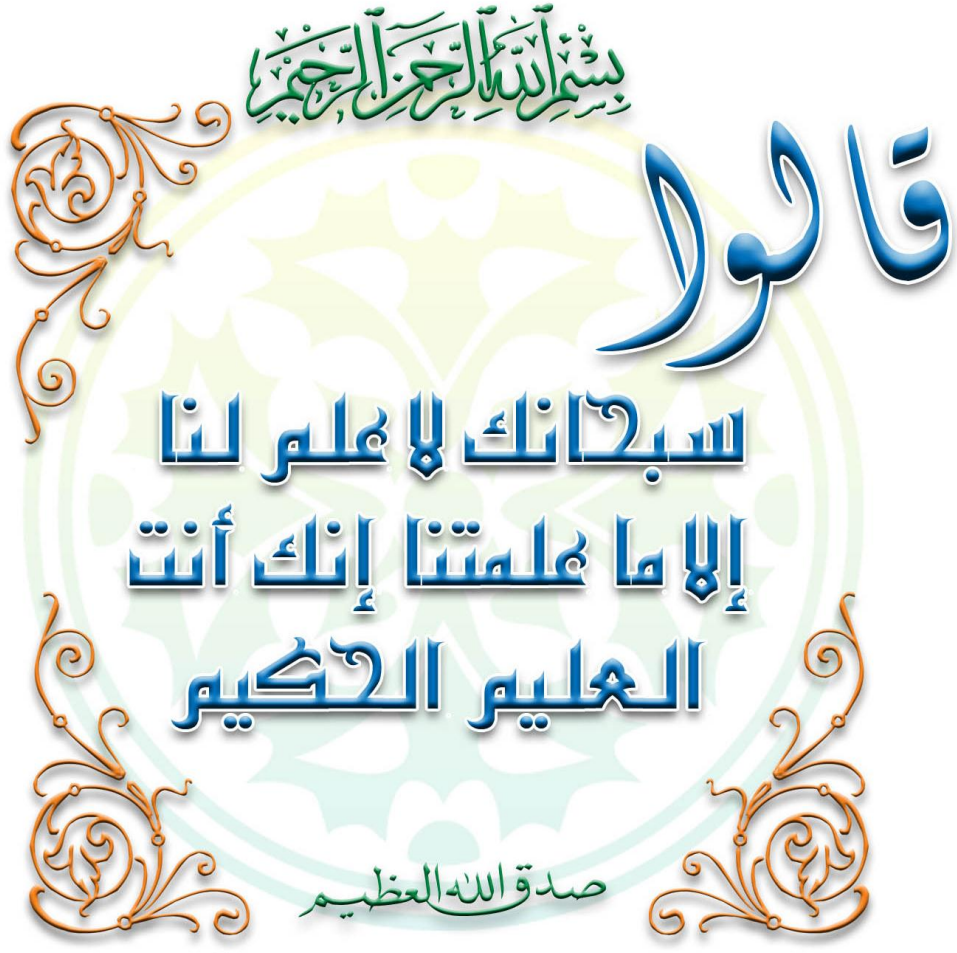

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Hanan Hanafy AbdElhamed Zedan

Declaration

I declare that this thesis has not been submitted for a degree at this or any other university.

Hanan Hanafy AbdElhamed Zedan

Dedication

TO…

My lovely family

For their support in every step in my life giving everything and never waiting for anything.

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Abstract

Hepatocellular carcinoma (HCC) is a common solid organ malignancy worldwide, with about 600,000 new cases diagnosed each year, and it is the fifth most frequent human cancer and a fatal disease. MicroRNAs (miRs) are small non-coding RNA segments of nearly 22 nucleotides, regulating gene expression after transcription. MiRs have an essential role in cellular proliferation, differentiation, apoptosis, as well as carcinogenesis process. The present study aimed at evaluating the expression level of miR-122, miR-221 and cyclin G1 in hepatitis C virus (HCV) and HCC patients in order to evaluate whether they could be used as sensitive biomarkers for HCC development and its different stages as surrogate biomarkers for α-fetoprotein (AFP). The study included 28 HCV patients and 36 HCC patients, further subdivided into stage I HCC patients (n=10), stage II HCC patients (n=14) and stage III HCC patients (n=12). In addition, normal healthy individuals (n=13) were recruited into this study. MiR-122, miR-221 and cyclin G1 gene expression levels were determined by quantitative real time polymerase chain reaction (qRT-PCR). The HCV patients demonstrated a significant increase in serum AFP level expression, compared to the healthy subjects. On the other hand, HCC patients manifested a sharp significant elevation in serum AFP expression level, compared to healthy subjects as well as HCV patients. In addition, HCV patients demonstrated a significant increase in serum miR-221 and cyclin G1 expression levels, compared to healthy subjects, while HCC patients manifested a significant elevation in serum miR-122, miR-221 and cyclin G1 expression levels, compared to healthy subjects. Moreover, ROC curve analysis demonstrated that serum miR-122 and cyclin G1 were able to discriminate between HCV and HCC patients. In conclusion, serum miR-122 and miR-221 may serve as non-invasive diagnostic biomarkers for HCC. MiR-122 and miR-221 were better than AFP, the gold standard biomarker for HCC, in the diagnosis of the early HCC stage with high sensitivity and specificity. Moreover, the combination between the serum biomarkers miR-122, miR-221 and cyclin G1 could be a more useful diagnostic tool for HCC better than each of them individually, and also as a substitute for AFP.

Keywords: Micro RNA 122; Micro RNA 221; Cyclin G1; Hepatocellular Carcinoma; Hepatitis C virus, α-fetoprotein.

List of Abbreviations

Abbreviation	Full term
AASLD	American associated for the study of liver diseases
ADAM10	A disintegrin and metallopeptidase domain 10
AFP	α-fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive AFP
AGO2	Argonaute 2
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMVRT	Avian myeloblastosis virus reverse transcriptase
ASSF1	Ras association domian-contaninig protein family member 1
AST	Aspartate aminotransferase
AUC	Area under curve
BCLC	Barcelona Clinic Liver Cancer
BMF	Bcl-2 modifying factor
cDNA	Covalently closed circular DNA
CCND1	Cyclin D1
E-CDH 1	Epithelial cadherin
CDKN1C	Cyclin-dependent kinase inhibitor 1 C
CDKs	Cyclin-dependent kinases
cDNA	Complementary DNA
CIP	CDK interacting protein
CKI	CDK inhibitor
CLIP	Cancer of the Liver Italian Program
CT	Computer tomography
Ct	Cycle threshold
CTNNB1	Catenin beta 1
CUPI	Chinese University Prognostic Index
CUTL1	Cut-like homeobox 1
Cyc	Cyclins
DAA	Direct acting antiviral
DCP	Des-Gamma-carboxy prothrombin
DEAE	Diethylaminoethyl
DGCR8	DiGeorge syndrome critical region gene 8
DM	Diabetes mellitus

List of Abbreviations

Abbreviation	Full term
E2F	E 2 factor
EDTA	Ethylene diamine tetraacetic acid
EGFR	Epithelial growth factor receptor
EL	Erythrocytes lysis
ELISA	Enzyme linked immunosorbent assay
G1	Gap1
G2	Gap2
GAPDH	Glyceraldehyde 3-phosphate glyceraldehyde
GGT	Gamma-glutamyl transferase
GHSS	Global health system solution
GPC	Glypican-3
GRETCH	Group d' Etude et de Traitement du Carcinoma Hepatocellulaire.
HBV Ab	Hepatitis B virus anyibody
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV-RNA	HCV viremia
HDAC	Histone deacetylase
HEK-293 T	Human embryonic kidney 293
HEPG2	Human hepatoma G2
HMOX1	Heme oxygenase 1
HNF	Hepatocyte nuclear factor
IFN	Interferon
IGFR1	Insulin growth factor receptor 1
IRES	Internal ribosome entry site
JIS	Japanese Integrated System
KIP	Kinase inhibitor protein
LC	Liver cirrhosis
LETFs	Liver-enriched transcription factors
LNA	Locked nucleic acid
LR	Likelihood ratio
M	Mitosis
MGB	Minor groove binder
MiRs	MicroRNAs

List of Abbreviations

Abbreviation	Full term
MOPS	Morpholino propanesulfonic acid
mRNAs	Messenger RNAs
mTOR	Mammalian target of rapamycin
MWA	Microwave ablation
NAFLD	Non-alcoholic fatty liver disease
NCRP	National cancer registry program
NFQ	Non-fluorescent quencher
NPV	Negative predictive value
NTR	Non- translated RNA
NS	Nonstructural
PCR	Polymerase chain reaction
PEI	Precutaneous ethanol injection
PIVKA-II	Protein induced by vitamin K absence or antagonist II
PKB	Protein kinase B
POL II	RNA polymerase II
PPV	Positive predictive value
pRb	Retinoblastoma family of protien
pre-miRs	Precursor miRs
pri-miRs	Pri-microRNAs
PTEN	Phosphatase and tensin homolog
qRT-PCR	Quantitative real time polymerase chain reaction
RASSF1	Ras association domain-containing protein family member 1
RanGTP	RAS-related nuclear protein GTP-dependent transporter
RFA	Radio frequency ablation
RISC	RNA-induced silencing complex
RNU6B	U6B small nuclear RNA
ROC	Receiver operating characteristics
RQ	Relative quantitation
RT	Revers transcription
S	Synthesis of DNA
SIRT	Selective internal radiation therapy

List of Abbreviations

Abbreviation	Full term
SNPs	Single nucleotide polymorphisms
SOCS1	Suppressor of cytokine signaling 1
SVR	Sustained virological response
TACE	Transarterial chemoembolization
TAE	Transarterial embolization
TGF-13	Transforming growth factor-13
TGF-β1	Transforming growth factor beta-1
TIMP3	Tissue inhibitor of metalloproteinase 3
TMB	Tetramethlbenzidine
TNM	Tumor-node metastasis
tRNA	Transfer RNA
UTR	Untranslated region
VEGFA	Vascular endothelial growth factor A
WHO	World health organization
$\chi 2$	Pearson's chi square
β-ME	β-Mercaptoethanol

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