



The Role of Aberrant Promoter Methylation in Chronic Liver Patients and Hepatocellular Carcinoma Patients

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Master of Science
by
Fatma El-Zahraa Aly Sayed

Supervised by

Prof. Dr./ Fahmy T.Ali

Professor of Biochemistry
Faculty of Science
Ain Shams University

Dr./ Gilane M.Sabry

Professor of Biochemistry
Faculty of Science
Ain Shams University

Prof. Dr./Abdel Rahman N. Zekri

Professor and Head of Molecular
Virology & Immunology Department
National Cancer Institute
Cairo University

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دور مثيلة البادئ الضال في مرضي الالتهاب الكبدي المزمن وسرطان الكبد

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(2002)

تحت إشراف

أ.د./ جيلان محمد صبري
أستاذ الكيمياء الحيوية
قسم الكيمياء الحيوية
كلية العلوم
جامعة عين شمس

أ.د./ فهمي توفيق علي
أستاذ الكيمياء الحيوية المتفرغ
قسم الكيمياء الحيوية
كلية العلوم
جامعة عين شمس

أ.د./ عبد الرحمن نبوي ذكري
أستاذ ورئيس وحدة الفيروسات والمناعة
المعهد القومي للأورام
جامعة القاهرة

(2013)

ABSTRACT

Hepatocellular carcinoma (HCC) is one of the few tumors in which the incidence is on the rise worldwide. The increasing incidence of HCC is associated with the rise in hepatitis C virus (HCV) infection. Egypt has the highest prevalence of HCV/genotype 4 infection in the world, with 14% of the population infected. Little is known about the role(s) of epigenetic changes that may participate in HCV-induced HCC. Epigenetic studies directed at mapping the etiology of HCV disease progression to HCC and how they correlate with patients clinicopathological parameters are expected to provide new insights that will aid in the design of effective strategies for earlier detection and management of the disease. The aim of the current study was to investigate the aberrant methylation of 11 genes in liver tissue samples obtained from Egyptian patients infected with HCV/genotype 4, and to explore possible relationships between aberrant methylation and clinicopathological features in HCC. Thirty-one HCC and matching non-tumor tissues, thirty-four chronic hepatitis liver tissues, and thirteen normal liver tissues were analyzed for the methylation status of APC, FHIT, p15, p73, p14, p16, DAPK1, CDH1, RAR β , RASSF1A and O⁶MGMT genes by qualitative methylation-specific PCR. Based on methylation profiles, a methylation of only 7 genes was found to be highly significant, which is dependent on disease state. Our data indicate that DNA methylation may serve as a marker for HCV-associated HCC, and demonstrate the importance of considering the clinicopathological variables as predictors of disease state.

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ABBREVIATIONS

AAIR	Age-adjusted Incidence Rate
5- aza-cdR	5- aza- deoxycytidine
AASLD	American Association for the Study of Liver Disease
AFP	Alpha-fetoprotein
AFP-L3	Lectin-bound Alpha fetoprotein
AML	Acute Myelogenous Leukaemia
APC	Adenomatosis Polyposis Coli
ARF	Alternative Reading Frame
CAH	Chronic Active Hepatitis
CDH	E-Cadherin
CDKN2a	Cyclin- Dependent Kinase INhibitor 2a
CH	Chronic Hepatitis
CLL	Chronic Lymphocytic Leukaemia
CML	Chronic Myelogenous Leukaemia
CpG	Cytosine phosphate Guanine
CRP	Chromatin Remodeling Protein
CT	Computed Tomography Scan
DAPK	Death-Associated Protein Kinase
DHF	Dihydrofolate
DN	Dysplastic Nodules
DNMT	DNA methyltransferase
ECM	Extra Cellular Matrix Components
ER	Endoplasmic Reticulum
FAP	Family Adenomatous Polyposis
FHIT	Fragile Histidine Triad
HATs	Histone Acetyltransferases
HDACs	Histone Deacetylases
HMTs	Histone Methyltransferases
HP	Heterochromatin Protein
HVR	Hypervariable region
IDU	Injection Drug use
IFN α	Interferon- α
INK4a	INhibitor of Cyclin dependent kinase 4a

MBD	Methyl CpG binding Domain
MDM2	Murine Double Minute 2
MeCP	Methyl CpG binding Protein
MGMT	Methyl guanine DNA- Methyltransferase
miRNAs	Micro ribonucleic Acids
MRI	Magnetic Resonance Imaging
MS	Methionine Synthase
MS-PCR	Methylation specific Polymerase Chain Reaction
MTHFR	Methylene Tetrahydrofolate reductase
MTs-1	Major Tumor suppressor-1
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NS	Non-Structural
NSCLC	Non-Small Cell Lung Cancer
NTR	Non-Translated Region
ORF	Open Reading Frame
RARβ	Retinoic Acid Receptor beta
RASSF1A	RAS association domain Family1 isoform A
RT-PCR	Real Time Polymerase Chain Reaction
SAH	S- adenosylhomocysteine
SAM	S- adenosylmethionine
TAE	<i>Tris</i> Acetate EDTA
TDG	Thymine DNA Glycosylase
THF	Tetrahydrofolate
TMB	Tetramethyl benzidine
TSGs	Tumor Suppressor Genes
UDG	Uracil DNA Glycosylase
UMP	Uridine monophosphate

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