Impact of Human Leukocyte antigen (HLA) typing on the outcome of Hepatitis C Virus (HCV) infection in Egyptian patients

Thesis submitted for M.Sc. Degree
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(Microbiology)

By

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا ۖ إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

{ البقرة آيه: 32}

Declaration

I certify that the thesis titled "Impact of Human leukocyte antigen (HLA) Typing on the Outcome of Hepatitis C Virus (HCV) Infection in Egyptian patients" is my own work. The work has not been presented elsewhere for assessment. Where material has been used from other sources it has been properly acknowledged / referred.

Signed

Mai Mohamed El-Sayed Lotfy

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Acknowledgment

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Abstract

Abstract:

Hepatitis C (HCV) is the most pressing public health challenge in Egypt; 10% of Egyptians between 15 – 59 years of age had been infected with HCV infection, while 7% are chronic active hepatitis C patients. Although, progresses were made in antiviral therapies; this cannot ensure controlling the virus infection due to many reasons one of which is the lack of HCV vaccine. Achievement of this goal will be fulfilled from a clear understanding of virus–host interactions and protective immunity in HCV infection taking in consideration the ethnic and geographical variations. This preliminary study was designed aiming to find out the frequencies of HLA Class I and II alleles in HCV infected Egyptian patients for assessing the correlations between HLA phenotypes and the consequences of HCV infection.

Two hundreds and eighty two HCV subjects were enrolled in the present study and they were categorized into 7 groups; Group1: Spontaneous clearance (**SC**: n=37), Group 2: Asymptomatic HCV infection (**AS**: n=40), Group 3: Chronically infected HCV patients (**CHCm**: n= 86 with no, mild or moderate fibrosis); Group 4: Chronically infected HCV patients (**CHCa: n=**12 with advanced fibrosis); Group 5: Cirrhotic liver disease either compensated or decompensated (**LC**: n=42), Group 6:

Hepatocellular Carcinoma patients (**HCC**: n=40), Group 7: Healthy Controls (**N**: n=25). HLA alleles were typed by DNA based Typing method "LABType® sequence-specific oligonucleotide (SSO) probes" for HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQ (A and B) alleles from peripheral blood of all participants.

The results of this work implicate that special HLA patterns were found; *HLA-DRB1*03, -DRB1*14* antigen may play a role in viral persistence. While, *HLA-C*05, -DRB1*11, -DQA1*05* and *-DQB1*03* is associated with viral clearance. In conclusion, HLA system is an ideal system in which to explore predictions on the outcome of HCV infections in Egyptians' gene pool. These data support the critical role of the critical role of some HLA alleles of class I and II that consequently confirm that successful clearance of HCV infection requires strong CD4+ and CD8+ T cell responses. Also, the data generated from our study may help clinicians to predict the treatment outcome for HCV- seropositive individuals in Egypt. Further investigations in this regard with larger number of HCV patients are recommended.

Keywords: HLA, MHC, Hepatitis C virus, Egyptian patients

LIST OF ABBREVIATIONS

AFP:	Alpha Feto Protein
ALT:	Alanine aminotransferase
APC:	Antigen Presenting Cells
AST:	Aspartate aminotransferase
bDNA:	branched DNA Assay
C:	Core protein
CDC:	Centers for Disease Control and Prevention
Cen:	Centromeric
CHC:	Chronic hepatitis C
CLIP:	Class II-associated Invariant Chain Peptide
CTL:	Cytotoxic T Lymphocytes
DAAs:	Directly Acting Antivirals
DCs:	Dendritic Cells
DNA:	Deoxyribonucleic Acid
dsRNA:	double strand RiboNucliec Acid
E:	Envelope Glycoproteins
EIA:	Enzyme Immunoassay
ELISA:	Enzyme linked immunosorbent assay
EM:	Electron Microscopy
EOT:	End of Treatment
ER:	Endoplasmic Reticulum
eRVR:	Extended Rapid Virological Response
ETR:	End of Treatment Response
EVR:	Early Virological Response
FDA:	Food and Drug Administration
GAG:	Glycosaminoglycans
GWAS:	Genome Wide Association Studies

LIST OF ABBREVIATIONS

HAV:	Hepatitis A virus
HCC:	Hepatocellular Carcinoma
HCV:	Hepatitis C virus
HIV:	Human Immunodeficiency Virus
HLA:	Human Leukocyte Antigen
HSPs:	Heat-Shock Proteins
HVR:	Hypervariable Region
IDU:	Injecting Drug Use
IFN:	Interferon
Ii:	Invariant Chain
IL:	Interleukin
INR:	International Normalized Ratio of prothrombin time of blood coagulation
IRES:	Internal Ribosome Entry Site
IRF:	IFN Regulatory Factors
ISGs:	Interferon Stimulated Genes
IU:	International Unit
KB:	Kilobase
KDa:	Kilodalton
KIR:	Killer cell Immunoglobulin like Receptors
LDL:	Low-Density Lipoproteins
LDL-R:	Low-Density Lipoproteins Receptor
LMP:	Low-Molecular-weight Proteins
MAVS:	Mitochondrial Antiviral Signaling
MHC:	Major Histocompatibility Complex
mRNA:	Messenger RNA
NAT:	Nucleic acid Testing

LIST OF ABBREVIATIONS

NHANES:	Health and Nutrition Examination Study
NK:	Natural Killer Cells
NR:	IFN Non Responders
NS:	Non Structural Proteins
NTRs:	Non-translated Regions
OD:	Optical Density
ORF:	Open Reading Frame
PAMPs:	Pathogen Associated Molecular Patterns
PCR:	Polymerase Chain Reaction
PCT:	Porphyria Cutanea Tarda
PEG-IFN α:	Pegylated interferone-α
PKR:	Protein-Kinase R
pMHC:	peptide-MHC Complex
PRRs:	Pattern Recognition Receptors
RBV:	Ribavirin
RdRp:	RNA-dependent RNA polymerase
RGT:	Response Guided Therapy
RIBA:	Recombinant Immunoblot Antibody Assay
RIG-I:	Retinoic-acid-Inducible Gene I
RNA:	Ribonucleic Acid
RT-PCR:	Reverse transcription polymerase chain reaction
RVR:	Rapid Virological Response
SR-BI:	Scavenger Receptor class B type I
SVR:	Sustained Virological Response
TAP:	Transporter Associated with Antigen- Processing
TCR:	T Cell Receptor
Tel:	Telomeric
Th:	T Helper cells

LIST OF ABBREVIATIONS

TLR:	Toll Like Receptors
TMA:	Transcription-Mediated Amplification
TNF:	Tumor Necrosis Factor
Tregs:	Regulatory T cells
UTR:	Untranslated Region
WHO:	World Health Organization