Role of Chronic Hepatitis C Virus (cHCV) Infection in Liver Fibrogenesis: Relationship to Transforming Growth Factor- Beta 1 (TGF-β1) and Collagen I (Col I) Expression

A thesis Submitted to Zoology Department
Faculty of Science, Ain Shams University
For the Master Degree of Science
By

Maiada Hussien Ahmed Hussien
B.Sc. (Zoology/Chemistry)
Faculty of Science, Ain Shims University
2003

Supervisors

Prof. Dr. Nahed Hussein Ahmed Riad
Professor of Histology and Histochemistry
Faculty of Science
Ain Shams University

Prof. Dr. Mahmoud I. Hassan
Professor of Medical Biochemistry and Molecular Biology
Faculty of Medicine
Ain Shams University

Prof. Dr. Fathy M. Tash
Professor of Medical Biochemistry
Faculty of Medicine, Ain Shams University

Zoology Department
Faculty of Science
Ain Shams University
2010

دور الأصابة المزمنه بفيروس الألتهاب الكبدى سى فى تليف الكبد : علاقتها بتعبيرعامل النمو المحول بيتا-١ والكولاجين-١

رسالة مقدمة تمهيدا للحصول علي درجة الماجستير في قسم الحيوان

مقدمة من

ميادة حسين أحمد حسين

بكالوريوس علوم جامعة عين شمس

قسم حيوان- كيمياء ٢٠٠٣

تحت إشراف

ا.د/ ناهد حسين احمد رياض

أستاذ الأنسجة وكيمياء الأنسجة

كلية العلوم – جامعة عين شمس

ا.د/ محمود اسماعيل حسن

أستاذ الكيمياء االحيوية والبيولوجيا الجزيئية

كلية الطب – جامعة عين شمس

ا.د / فتحى محمد طا ش

أستاذ الكيمياء االحيوية

كلية الطب – جامعة عين شمس

قسم علم الحيوان

كلية العلوم – جامعة عين شمس

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List of Abbreviation

αCP2 : Alpha globins transcription factor.

`3H : Thymidine.

AAIR : Age-adjusted incidence rate.

ADAM : A disintegrin and metalloprotease domain.

ADAMTS2 : ADAM metallopeptidase with thrombospondin type 1 motif, 2.

ADAMTS 3 : A disintegrin and metalloprotease with thrombospondin motifs 3.

ADAMTS14 : A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 14.

ADH2 : Alcohol Dehydrogenase 2.

ALDH2 : Aldhyde Dehydrogenase 2.

AFP : Alpha Feto Protein.

AFU : Alpha-L-Fucosidase.

ALB : Albumin.

ALP : Alkaline phosphotase.

ALT : Alanine Amino Transferase.

ARFP : Alternate Reading Frame Protein.

AST : Aspartate Amino Transferase.

Bcl-2 : B cell lymphoma leukemia 2.

Bcl-xs : Small protein of Bclx Gene.

b-DNA : Branched DNA Technology.

BMI : Body mass index.

BMPs : Bone morphogenic proteins.

BMPs : Bone morphogenic proteins.

CD : Cluster of differentiation.

c-DNA : Complementary Deoxy Ribo Nucleic Acid .

CHC : Chronic Hepatitis C.

CLD : Chronic Liver Disease.

ClCP : C-terminal of type 1 collagen.

COL 1 : Collagen type 1.

CT : Computed tomography.

DCP : Des-Gamma-Carboxy-Prothrombin.

DPC : Deleted in Pancreatic Cancer.

E1 : Envelope region 1.

E2 : Envelope region 2.

ECM : Extra Cellular Matrix.

ELISA-3 : Third generation Enzyme Linked Immuno Sorbent Assay.

FACITs : Fibril-Associated Collagens with interrupted Triple Helices.

FACS : Flow cytometric analysis

G1 : Gap 1.

G2 : Gap 2.

GbE : Ginkgo biloba extract.

GPC : Glypican.

GPC3 : Glypican 3.

HBsAg : Hepatitis B Surface Antigen.

HBV : Hepatitis B Virus.

HCC : Hepatocellular Carcinoma.
HCCSMC : Human corpus cavernosum smooth muscle cells.
HCOL1A1 : Human collagen type I α1 gene.
HCV : Hepatitis C Virus.
HCV-Ab : Hepatitis C Virus Antibody.
HDV : Hepatitis D Virus.
HRP : Horseradish peroxidase
HSC : Hepatic Stellate Cells.
HSCs : Hepatic stellate cells.
HSPGs : Heparan sulfate proteoglycans.
IBD : Inflammatory Bowel Diseases.
IgG : Immunoglobulin G.
IMx : Full automated immuno analyzer system.
KDA : Killodalton.
LAP : Latency associated Peptide.
LC : Liver cirrhosis.
LD : Lactate dehydrogenase.
LFT : Liver function test.
MEIA : Microparticle enzyme Immunoassay.
MMP-2 : Matrix metalloproteinase 2.
MMP-9 : Matrix metalloproteinase 9.
MMPs : Matrix MetalloProteinases.
MRI : Magnetic Resonance Imaging.
MRNA : Messenger RNA.
mRNA : Messenger Ribonucleic Acid.
MU : Methyl umbelliferone.

MUP : Methyl umbelliferyl phosphate.

NAD^+ : oxidizing agent of Nicotinamide adenine dinucleotide

NASH : Non-alcoholic steatohepatitis.

NC : Non Collagenous.

NK : Natural Killer cells.

NS2 : Non structural protein 2.

NS-3 : Non structural protein 3.

NS-5 : Non structural protein 5.

NS3-4A : Serine protease.

OD : Optical Density.

P53 : Protein 53.

PCR : Polymerase Chain Reaction.

PDGF : Platelet-derived growth factor.

PEPCK : Phospho-Enolpyrovate Carboxykinase.

PGCP : Plasma Glutamate Carboxypeptidase.

PIVA-II : protein Induced by Vitamin K Absence II.

PLA2G13 : Phospholipase A2 Gene 13.

PLA2G7 : Phospholipase A2 Gene 7.

PNPP : para-Nitro phenyl phosphate.

PTEN : Phosphatase and tensin homolog.

Ras : Reactive oxygen species.

RGD : Arg-Gly-Asp sequence.

RIBA : Recombinant immunoblot Assay.

RIBA-3 : Third generation Recombinant-Immuno Blot Assay.

RNA : Ribonucleic Acid.

ROC : Receiver Operating Characteristic.

RT-PCR : Reverse Transcription Polymerase Chain Reaction.

SA : Sialic Acid.

S Alb : Serum Albumin.

SGOT : Serum glutamic oxaloacetic transaminase.

SGPT : Serum glutamic pyruvic transaminase.

Smad : proteins involved in cell signaling.

SR-B1 : Scavenger Receptor Class B 1.

SR-B1 : Scavenger receptor class.

STK 15 : Serine/Therionine kinase 15.

TGF-b1 : Transforming growth factor beta 1.

TGF-β : Transforming Growth Factor β.

TMA : Transcription Mediated Amplification.

TMB : Tetra methyl Benzidine.

Tp53 : Tumor suppressor gene.

UL : Ultrasound.

U/L : Unit per liter.

WHO : World Health Organization.

Abstract

The prognosis of chronic liver disease is closely related to the development of hepatic fibrosis. Fibrosis is characterized by excessive deposition of collagen and other components of the extracellular matrix, which leads to a disturbed function of the organs involved, while TGF-β was involved in the development of fibrosis by modulating myofibroblast proliferation and collagen secretion. This study aimed to investigate the contributing effects of Transforming Growth Factor beta1 (TGF- β1) and Collagen type 1 (COL -1) as the inducers of liver fibrosis and/or cirrhotic changes among HCV infected patients with HCC development. In this study, 89 patients were selected and subjected to symptom questionnaire, clinical evaluation, abdominal ultrasonography and laboratory investigations including liver profile, hepatitis markers, assay of TGF-β1 (by ELISA), COL -1 (by ELISA) and AFP assay.

The mean of AFP was significantly higher in HCC group (mean; 360.0±253.4) than cirrhotic group (mean; 137.2±82.9), CHC group (mean; 23.9±15.3) and control group (mean; 2.2±1.2), (p; 0.001). The mean of TGF-β1and collagen 1 were significantly higher in cirrhotic group (mean 246.48±51.5) than HCC group (mean 87.66±11.07), CHC group (mean 62±14.9) and control group (mean 43.05±12.00), (p;0.001). By using ROC curve the best cutoff of TGF-β1 was specially selected at 58.0 which give sensitivity 83% and specificity 100% and the best cutoff of COL -1 was 126.5 which give sensitivity 88% and specificity 100%.

Conclusion: The circulating TGF-β1 and COL -1 could be used as sensitive biomarkers for diagnosis of any abnormal disorder in liver at an early stage.

Acknowledgement

No words could express my sincere appreciation and deepest gratitude to ***Prof. Dr. Nahed Hussein Ahmed Riad***, Professor of Histology and Histochemistry, Faculty of Science, Ain Shams University for her guidance, valuable criticism and continuous encouragement. The words will never be enough to express my thanks to her continual support during the whole work.

I wish to express my deepest gratitude and sincere appreciation to ***Prof. Dr. Mahmoud I. Hassan***, Professor of Medical Biochemistry and Molecular Biology Faculty of Medicine, Ain Shams University, for supporting me throughout the course of this study. I would like to thank him for step by step guidance and assistance to complete this work. The words cannot express my thanks to his kind supervision.

I would like to express my deepest thanks to ***Prof. Dr. Fathy M. Tash,*** Professor of Medical Biochemistry, Faculty of Medicine, Ain Shams University, for his expertise supervision, generous guidance and encouragement to fulfill this work. The words cannot express my thanks to his kind supervision.

I have the greatest pleasure in acknowledging ***Dr. Naglaa Samir Ahmed,*** Assistant Professor of Pathology, Faculty of Medicine, Ain Shams University, for her willing assistance, guidance and encouragement during this work.

Finally, I would like to express my deepest gratitude to all friends of the ***Oncology Diagnostic Unit,*** Faculty of Medicine, Ain Shams University for kind help and support, which facilitated the performance of this work.

Aim of the work

The aim of the present study is to investigate the contributing effects of Transforming Growth Factor beta1 (TGF-β1) and Collagen type 1 (COL -1) as the inducers of liver fibrosis and/or cirrhotic changes among HCV infected patients. Furthermore, the impact of clinicopathological factors on liver fibrogenesis and HCC will be addressed.

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