Laminin and Syndecan-1 levels as Biomarkers in Patients with Hepatitis C

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Abstract

The hepatitis C virus (HCV) epidemic in Egypt is unique in the world as there are many publications suggest that over 15% of the people in Egypt are infected ,this is ten times greater than in any other country in the world.**Aim:** To test whether Syndecan-1 and laminin could serve as non-invasive markers for detection of liver fibrosis in patients with chronic hepatitis C and thereby reduce the need for liver biopsy. **Methods:** Estimation of Syndecan-1 and laminin in plasma by ELISA were done on 50 subjects (20 normal healthy persons and 30 chronic hepatitis C patients). **Results:** The mean levels of plasma syndecan-1 and laminin were significantly higher in group II (chronic HCV patients) when compared to group I (control subjects).
Conclusion: Plasma Syndican-1 and laminin could serve as non-invasive markers for detection of liver fibrosis in patients with chronic hepatitis C .

Keywords: Syndecan-1, laminin, chronic hepatitis C, non-invasive marker, liver biopsy.

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List of Abbreviations

- HCV: Hepatitis C virus.
- SDC1: Syndecan 1.
- RNA: Ribonucleic acid.
- NANBH: Non-A, Non-B Hepatitis.
- UTR: Untranslated regions.
- IRES: Internal Ribosomal Entry Site.
- Th1 lymphocyte: T helper1 lymphocyte
- CD81: Cluster of Differentiation 81.
- ORF: Open reading frame.
- NS: Non-structural.
- PCR: Polymerase chain reaction.
- LFTs: Liver function tests.
- Rh : Rhesus factor.
- HIV: Human Immunodificiency Virus.
- MPGN: Membranoproliferative glomerulonephritis.
- HBV: Hepatitis B virus.
- TMA : Transcription mediated amplification.
- HCC: Hepatocellular carcinoma .
- PEG-Intron: Pegylated interferon.
- AST: Aspartate aminotranseferase.
- ALT: Alanine aminotranseferase.
- IG: Immunoglobulin.
- AChR: Acetylcholine receptors.
- EHS : Engelbreth Holm-Swan.
- LG : Laminin globular motifs.

- DG : Dystroglycans.
- NMJ : Neuromuscular junction.
- MuSK: Muscle- specific kinase.
- PDGF : Platelet-derived growth factor.
- GBM : Glomerular basement membrane.
- CMD : Congenital muscular dystrophies .
- ECM : Extra cellular matrix.
- HSC : Hepatic stellate cells .
- NASH: Nonalcoholic steatohepatitis .
- NAFLD: Nonalcoholic fatty liver disease.
- ASH : Alcoholic steatohepatitis.
- HA : Hyaluronic acid.
- LA : Laminin.
- CD138: Cluster of Differentiation138
- V : Variable.
- TNF-α : Tumor necrosis factor-α .
- TGF-β2: Transforming growth factor-beta 2.
- FGF2 : Fibroblast growth factor-2.
- HGF : Hepatocyte growth factor.
- βFGF : Fibroblast growth factor Beta.
- MMP-9: Matrix metalloproteinase .
- IL-8 : Interleukin-8.
- CCL7 : Chemokine (C-C motif) ligand 7 .
- CCL11: Chemokine (C-C motif) ligand 11.
- CCL17: Chemokine (C-C motif) ligand 17.
- PMNs: Polymorph nuclear leukocytes .
- EphB4: Ephrin-B4.
- HPSE-1: Heparanase .

- HS : Heparan sulfate.
- APRI : Aspartate aminotransferase to platelet ratio index.
- FT : Fibrotest .
- FM : FibroMeter.
- EGF : Epidermal growth factor .
- GGT : Gamma glutamyl transeferase.
- ELISA: Enzyme Linked Immuno Sorbent Assay.
- AFP : Alpha fetoprotein.
- ROC : Reactive Operating Curve.
- AUC : Area Under Curve .
- F : Fibrosis.
- GPT : Glutamate Pyruvate Transaminase.
- GOT : Glutamate Oxaloacetate Transaminase.
- mRNA: Messenger ribonucleic acid.
- IFN : Interferon.
- EDTA : Ethylene Diamine Tetraacetic Acid.
- EIA : Enzyme immunoassay.
- POD : Peroxidase.
- SPSS : Self-Propelled Semi-Submersible.

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Introduction and Aim of Work

Introduction

The hepatitis C virus (HCV) epidemic in Egypt is unique in the world as there are many publications suggesting that over 15% of the people in Egypt are infected ,this is ten times greater than in any other country in the world.(***The Global Burden of Hepatitis C Working Group,2004).***

Laminin is one of the main glycoproteins of the basement membrane and participates in a series of such biological phenomena as adhesion, migration, cellular differentiation and growth.In normal liver, laminin is found around the vessels and biliary ducts, where basement membranes are identified ***(Kershenobich and Weissbrod, 2003).*** Serum levels of laminin have been used by several authors as a non-invasive parameter to assess liver fibrosis in chronic hepatitis C patients ***(Lebensztejn et al., 2007).***

Syndecan- 1 (SDC1), a cell surface heparan sulfate proteoglycan is expressed predominantly on epithelial cells but is also found on distinct stages of differentiation of normal lymphoid cells, mesenchymal cells during development and in mature plasma cells ***(Saunders and Bernfield, 1988).***

The syndecan-1 proteoglycan regulates cell proliferation, cell migration, cell signaling, cytoskeletal organization and mediates both cell-cell and cell-extracellular matrix interactions ***(Tumova et al., 2000).*** Additionally, via its heparan sulfate chains, it binds a wide range of bioactive molecules (e.g., growth factors, chemokines) that regulate cell behaviors important in normal and pathological processes ***(Bernfield et al.,1999).***The process of liver fibrosis is similar to wound healing and it

may result in shedding of syndecans, which may then be detected in the serum ***(Friedman ,1993).***

Aim of work

The aim of this study is to test whether syndecan-1 and laminin could serve as non-invasive markers, for detection of liver fibrosis in patients with chronic hepatitis C and thereby reduce the need for liver biopsy.

Review

Hepatitis C Virus

Hepatitis C virus (HCV) is a small (55-65 nm in size), enveloped, positive sense single strand RNA virus in the family Flaviviridae **(*Laures and Walker, 2001).***

History

In the mid 1970s, Harvey J. Alter, demonstrated that most post-transfusion hepatitis cases were not due to hepatitis A or B viruses. Despite this discovery, international research efforts to identify the virus, initially called non-A, non-B hepatitis (NANBH), failed for the next decade. In 1988, the virus was confirmed by Alter by verifying its presence in a panel of NANBH specimens. In April of 1989, the discovery of the virus, re-named hepatitis C virus (HCV), was published in two articles in the journal Science (***Kuo et al., 1989***).

Sructure

The structure of the hepatitis C virus consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope (***Op De Beeck and Dubuisson, 2003***).

Genome

Hepatitis C virus has a positive sense RNA genome that consists of a single open reading frame of 9600 nucleoside bases ***(Kato, 2000).*** At the 5̀ and 3̀ ends of the RNA are the UTR regions, which are not translated into proteins but are important to translation and replication of the viral RNA. The 5̀ UTR has a ribosome binding site ***(Jubin, 2001).*** Internal Ribosomal Entry Site (IRES) starts the translation of a 3000 amino acid

containing protein that is later cut by cellular and viral proteases into 10 active structural and non-structural smaller proteins ***(Dubuisson, 2007).***

Replication

The exact mechanism by which HCV enters host cells to initiate infection is not well understood (***Forns and Bukh, 1999***). However, it is known that the E1 and E2 envelope proteins of different HCV isolates exhibit significant genetic heterogeneity. It is possible that these proteins play a role in cellular receptor binding, and subsequent fusion of the virus to a host cell (***Forns and Bukh, 1999***).

CD81 cell surface molecule is a potential receptor for HCV (***Pileri et al., 1998***). Further support comes from the fact that this molecule is expressed on the membranes of hepatocytes and lymphocytes, both of which are cells that support HCV replication (***Pileri et al., 1998***). Once inside the hepatocyte, HCV initiates the lytic cycle. It utilizes the intracellular machinery necessary to accomplish its own replication (***Lindenbach and Rice, 2005***).

HCV is a linear RNA virus, with a positive-sense single stranded genome (***Kato, 2000***). This single, large open reading frame (ORF) encodes a polyprotein of approximately 3000 amino acids (***Dubuisson, 2007***). The open reading frame is flanked at each terminus by untranslated regions (UTRs), which are highly conserved among the HCV isolates. The 5` UTR is considered important in initiating translation of the viral genome, while conserved elements within the 3` UTR are essential for RNA synthesis and genome packaging (***Forns and Bukh, 1999***).

Hypervariable regions of the ORF encode envelope proteins. The 3` end of the viral genome codes for non-structural (NS) proteins. The