The Role of Signal Transducer and Activator of Transcription 5 and Transforming Growth Factor- β_1 in Hepatic Fibrosis Induced by Chronic Hepatitis C Virus Infection in Egyptian Patients

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Significance of the Study

- This study evaluated the role of signal transduction and activator of transcription 5 (STAT5) in the pathogenesis of liver fibrosis in Egyptian patients with chronic hepatitis C and its possible relationship with transforming growth factor- β_1 (TGF- β_1) and α -smooth muscle actin. STAT5 may play a role in liver fibrosis through the induction of TGF- β_1 .

Keywords

Liver fibrosis · Signal transducer and activator of transcription 5 · Transforming growth factor- β · α -smooth muscle actin · Insulin resistance

Abstract

Objective: To investigate the possible role of signal transducer and activator of transcription 5 (STAT5) in the pathogenesis of liver fibrosis in Egyptian patients with chronic hepatitis C (CHC) virus infection and its relation to hepatic stellate cells (HSC). **Subjects and Methods:** Sixty-five patients (46 males and 19 females) were divided into 4 groups based on the severity of fibrosis as detected by Fibroscan as follows: F1, $n = 15$; F2, $n = 21$; F3, $n = 13$; and F4, $n = 16$. Twenty age- and gender-matched healthy persons volunteered as controls. The serum levels of STAT5, TGF- β_1 , α -smooth muscle actin (α -SMA), fasting blood sugar, and fasting insulin, as well as homeostasis model assessment of insulin resistance

(HOMA-IR), were determined and compared for all groups. The usefulness of the studied serum biomarkers for predicting liver fibrosis was evaluated using a receiver operating characteristic curve. **Results:** Serum levels of STAT5 were significantly lower in patients compared to controls (9.69 ± 5.62 vs. 14.73 ± 6.52 , $p \leq 0.001$); on the contrary, TGF- β_1 , α -SMA, and HOMA-IR were significantly higher in patients compared to controls (mean: 1,796.04 vs. 1,636.94; 14.94 vs. 8.1; and 7.91 vs. 4.18; $p \leq 0.01$ and 0.001, respectively). TGF- β_1 and α -SMA showed a progressive increase with advancing severity of hepatic fibrosis (mean TGF- β_1 : 2,058.4 in F1-F2 and 1,583.8 in F3-F4, $p \leq 0.04$; mean α -SMA: 13.59 in F1-F2 and 16.62 in F3-F4, $p \leq 0.05$). STAT5 had a significant negative correlation with TGF- β_1 ($p \leq 0.001$), while no correlation was detected with α -SMA ($p \leq 0.8$). **Conclusions:** STAT5 may play a significant role in hepatic fibrogenesis through the induction of TGF- β_1 but not through the activation of hepatic stellate cells.

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Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver diseases including steatosis, cirrhosis, fibrosis, and hepatocellular carcinoma [1]. Hepatic fibrosis develops primarily as a consequence of chronic viral hepatitis [2]. The mechanism of hepatic fibrosis is not fully understood. In response to liver injury, many inflammatory cytokines such as interleukin (IL)-6, interferon (IFN)- γ , IFN- α/β , and IL-22 are produced by different liver cells and play roles in regulating liver fibrogenesis [3]. Many of these cytokines can activate the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway through binding to its corresponding transmembrane receptor complex [4]. STAT5 is activated mainly in hepatocytes by growth hormone (GH) [5]. Several physiological processes are regulated by GH-STAT5 signaling through expression of target genes. Alteration of STAT5 signaling is associated with liver conditions such as fatty liver, fibrosis, and hepatocellular carcinoma [6]. Hepatocyte and cholangiocyte deletion of STAT5 in animal studies has revealed early and severe liver fibrosis through a reduced expression of important hepato-protective genes as well as increased numbers of apoptotic hepatocytes [7]. Loss of hepatic GH-STAT5 signaling causes defects in lipid and glucose metabolism leading to steatosis, hyperglycemia, and insulin resistance. TGF- β_1 is secreted from HSC and Kupffer cells, but with inflammation hepatocytes gradually become the major source of TGF- β_1 [8–11]; it is the most important cytokine that stimulates the production of extracellular matrix (ECM) by HSC [12] and can induce apoptosis in hepatocytes, leading to cirrhosis [13].

Hepatic stellate cells (HSC) are the primary producers of connective tissue in response to liver injury. Chronic liver injury, however, leads to the persistent activation of HSC, accumulation of ECM and the eventual development of hepatic fibrosis [14]. Activation of HSC is induced by paracrine stimulation of the surrounding cells in the liver, such as hepatocytes, Kupffer cells, endothelial cells, leukocytes, and platelets, and the stimuli include cytokines, lipid peroxides, growth factors, and reactive oxygen species [15]. Activated HSC lose lipid droplets stored in the cytoplasm, proliferate, and gain an abundance of microfilaments that consist mainly of α -smooth muscle actin (α -SMA). Hence, α -SMA is established as a reliable marker of activated HSC, although these cells express other markers as well [16].

Although the functions of hepatocyte STAT5 have been extensively investigated in animal models, little is

known about STAT5 in human studies. Therefore, the objective of this study was to test whether STAT5 has a role in the pathogenesis of liver fibrogenesis in patients with chronic hepatitis C (CHC) and if it has any relationship to TGF- β_1 and α -SMA as well as to metabolic factors such as lipid and insulin resistance.

Subjects and Methods

Due to the rarity of similar previous studies, it was difficult to calculate the sample size via the usual methods. Therefore, during the study period all eligible cases were included. Sixty-five naive patients with compensated CHC who attended the Liver Unit at Minia University Hospital, El Minia, Egypt, were included in this study.

The Institutional Review Board approved this study. Written informed consent was obtained from each participant. This study was conducted from February 2015 to January 2016 in accordance with the ethical guidelines of the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. The target population included patients with CHC suffering different grades of fibrosis. Grades of hepatic fibrosis were estimated using Fibroscan (transient elastography). Accordingly, the patients were classified into 4 groups based on the breakpoints in relation to the METAVIR score [17] (F0-F1: 2.5–7, F2: 7–9.5, F3: 9.5–12.5, and F4: >12.5) according to transient elastography. The inclusion criteria were: age ≥ 18 years, CHC infection based on the presence of anti-HCV antibodies, and detectable serum HCV-RNA for >6 months. The exclusion criteria were: diabetes mellitus diagnosed according to American Diabetes Association classification criteria and other causes of liver disease including concomitant hepatitis B virus infection, human immunodeficiency virus, *Schistosoma* infection, autoimmune hepatitis, and an alcohol intake >40 g/day in the last 6 months prior to the start of antiviral treatment. Twenty healthy persons (10 males and 10 females, age 20–60 years) from among the medical and paramedical staff working in the same hospital volunteered to participate in this study as control subjects.

Clinical Assessment

All of the participants underwent a full history taking and a thorough clinical examination with a special emphasis on age, gender, and route of HCV transmission. Weight (kg) and the height (m) were measured and the BMI calculated as weight divided by the square of the height (kg/m^2). Waist circumference was measured 1 inch above the navel or midpoint between the lower margin of the last palpable rib and the top of the iliac crest parallel to the floor, while the hip circumference was measured at the widest part of the buttocks or hip parallel to the floor and the waist/hip ratio was calculated.

Laboratory Assessment

Venous blood was drawn after a 12-h overnight fast to determine the serum levels of hemoglobin, white blood cells, platelet count, bilirubin, alanine aminotransferase, aspartate aminotransferase, albumin, prothrombin time, international normalized ratio, total cholesterol, HDL, LDL cholesterol, triglycerides, glucose,

Table 1. Demographic and baseline characteristics of chronic hepatitis C patients

Variable	Value
Age, years	46.8±12.4 (20–67)
Male/female ratio	46/19 (70.8%/29.2%)
BMI	22.28±1.9 (16–25)
Hypertension (yes/no)	6/59 (9.2%/90.8%)
Smoking (yes/no)	7/58 (10.8%/89.2%)
Waist/hip ratio	0.93±0.019 (0.9–0.97)
Platelets, $n \times 10^9/L$	190.4±48 (1–322)
Albumin, g/L	4.15±0.6 (2.1–5.4)
Total bilirubin, mg/L	0.88±0.51 (0.1–3)
ALT, IU/L	50.1±20.0 (21–103)
AST, IU/L	50.8±25.8 (17–163)
Fasting glucose, mg/dL	4.9±0.94 (2.8–8.6)
Fasting insulin, $\mu IU/mL$	18.87±9.9 (3.9–277)
HOMA-IR	6.8±7.03 (2.8–8.7)
Triglycerides, mg/dL	98±40.8 (35–225)
HDL cholesterol, mg/dL	42.1±5.8 (31–58)
LDL cholesterol, mg/dL	76.9±31.9 (24–148)
Cholesterol, mg/dL	141±33.37 (70–200)
Viral load	5.2±1.3 (2.04–7.9)
Cirrhosis (1/2)	47/17 (73.8%/26.2%)
Fibrosis stage (Fibroscan), <i>n</i>	
F1	15
F2	21
F3	13
F4	16
F1, F2-F3, F4	36–29 (55.4–44.6%)
STAT5, ng/mL	9.8±5.5 (4–22.6)
TGF- β_1 , ng/mL	1,796.04±932.79 (140–3,871)
α -SMA, ng/mL	14.9±6.34 (1.2–40)

Values are presented as means $\pm$ SD (range) unless otherwise stated. The total number of patients was 65. ALT, alanine transaminase; AST, aspartate transaminase; HOMA-IR, homeostasis model assessment of insulin resistance; STAT5, signal transducer and activator of transcription; TGF, transforming growth factor; α -SMA, α -smooth muscle actin.

insulin, STAT5, α -SMA, TGF- β_1 and serum glucose, alanine aminotransferase, aspartate aminotransferase, total and HDL cholesterol, and triglycerides were determined by automated procedures. Electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA) was used to determine serum insulin levels. Insulin resistance was then calculated in all patients by homeostasis model assessment of insulin resistance (HOMA-IR) using the standard formula (HOMA-IR = fasting insulin [$\mu IU/mL$] $\times$ fasting glucose [mmol/L]/22.5). Serum STAT5, α -SMA, and TGF- β_1 were measured using an enzyme-linked immunosorbent assay (Quantikine ELISA; R&D Systems, Minneapolis, MN, USA).

Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS) software

Table 2. Metabolic factors, lipid profile, STAT5, TGF- β_1 , and α -SMA in patients and controls

Variable	Patients (<i>n</i> = 65)	Controls (<i>n</i> = 20)	<i>p</i> value
Cholesterol, mg/dL	141.00±33.37	154±40.5	0.148
TG, mg/dL	98.84±40.74	89±22.40	0.347
LDL cholesterol	76.9±31.85	92.42±41.77	0.08
HDL cholesterol	42.1±5.8	40.8±5.86	0.231
Fasting glucose, mg/dL	88.95±17.05	82.05±12.84	0.107
Fasting insulin, $\mu IU/mL$	29.41±25.44	19.57±11.79	0.08
HOMA-IR	7.91±7.77	4.18±3.1	0.008
STAT5, ng/mL	9.69±5.62	14.73±6.52	0.001
TGF- β_1 , ng/mL	1,796.04±932.79	1,636.94±278.57	0.001
α -SMA, ng/mL	14.94±6.34	8.1±2.4	0.001

Values are presented as means $\pm$ SD. HOMA-IR, homeostasis model assessment of insulin resistance; STAT5, signal transducer and activator of transcription; TGF, transforming growth factor; α -SMA, α -smooth muscle actin; TG, triglycerides.

version 20 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were done and the results are reported as means, SD, and ranges for parametric quantitative data and as numbers and percentages for categorical data. Analyses were done for parametric quantitative data between 2 groups using an independent-samples *t* test, and for nonparametric quantitative data the Mann-Whitney test was used. Analyses were done for qualitative data using the χ^2 test (if the number per cell was more than 5) and the Fisher exact test (if the number per cell was <5). Correlations between 2 quantitative variables were determined using the Pearson correlation coefficient and for qualitative ordinal variables they were evaluated using the nonparametric Spearman ρ correlation coefficient. The receiver operating characteristic curve was done to determine the cutoff point, the area under the curve (AUC), and the sensitivity and specificity of the studied serum biomarkers for predicting severe fibrosis. The level of significance was taken as $p \leq 0.05$.

Results

Table 1 presents the demographic and base line characteristics of CHC patients. The mean age was 46.4 ± 12.4 years (range 20–67 years); the male/female ratio was 46/19. The mean BMI was 22.28 ± 1.9 (range 22–34). Based on the Fibroscan examination, 36 patients had mild fibrosis (F1, *n* = 15; F2, *n* = 21), while 29 patients had moderate to severe fibrosis (F3, *n* = 13; F4, *n* = 16).

Table 2 presents the levels of the metabolic factors, lipid profile, STAT5, TGF- β_1 , and α -SMA in CHC patients compared to controls. The levels of HOMA-IR, TGF- β_1 , and α -SMA were significantly higher in patients compared to

Table 3. Metabolic factors, lipid profile, STAT5, TGF- β_1 , and α -SMA according to stage of fibrosis

Variable	F1-F2 (<i>n</i> = 36)	F3-F4 (<i>n</i> = 29)	<i>p</i> value
Cholesterol, mg/dL	142.83±33.71 (80–200)	138.72±33.38 (70–196)	0.8
TG, mg/dL	102.58±39.03 (35–195)	93.38±42.93 (35–225)	0.370
LDL cholesterol	78.03±35.2 (24–148)	75.55±22.69 (31–143)	0.152
HDL cholesterol	41.1±5.8 (31–53)	43.8±5.86 (31–58)	0.235
Fasting glucose, mmol/dL	4.87±0.78	5.02±1.12	0.5
Fasting insulin, μ U/mL	31.72±27.52 (6.4–155)	26.53±22.73 (3.9–100)	0.259
HOMA-IR	7.32±6.73 (1.32–38.75)	8.63±8.97 (0.82–33.48)	0.900
STAT5, ng/mL	9.43±5.39 (4.8–22.6)	10.02±5.98 (1–22.6)	0.716
TGF- β_1 , ng/mL	1,583.8±853.88 (140–3,871)	2,058.48±973.5 (893–3,871)	0.04
α -SMA, ng/mL	13.59±5.1 (1.2–22.2)	16.62±7.32 (2.3–40)	0.05

Values are presented as means $\pm$ SD (range). STAT5, signal transducer and activator of transcription; TGF, transforming growth factor; α -SMA, α -smooth muscle actin; TG, triglycerides; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 4. Correlation of biomarkers with the stages of hepatic fibrosis

Biomarker (ng/mL)	Stage of fibrosis (F1 to F4)	
	<i>r</i>	<i>p</i> value
α -SMA	0.195	0.120
TGF- β_1	0.285	0.038
STAT5	0.102	0.419

STAT5, signal transducer and activator of transcription; TGF, transforming growth factor; α -SMA, α -smooth muscle actin.

controls ($1,796.04 \pm 932.79$ vs. $1,636.94 \pm 278.57$, 14.94 ± 6.34 vs. 8.1 ± 2.4 , and 7.91 ± 7.77 vs. 4.18 ± 3.1 , respectively). *p* values were ≤ 0.01 and 0.001 respectively. However, the levels of STAT5 were significantly lower in patients versus controls (9.69 ± 5.62 vs. 14.73 ± 6.52 , $p \leq 0.001$), and no significant difference was found in the lipid profile.

The levels of TGF- β_1 and α -SMA increased progressively with advancing stages of hepatic fibrosis (Table 3). The TGF- β_1 values were $2,058.4 \pm 973$ in F1-F2 and $1,583.8 \pm 853.88$ in F3-F4 ($p \leq 0.04$). The α -SMA values were 13.59 ± 5 in F1-F2 and 16.62 ± 7.3 in F3-F4 ($p \leq 0.05$). However, fasting insulin, HOMA-IR, the lipid profile, and STAT5 were not significantly different.

TGF- β_1 levels showed a significant positive correlation with the stage of hepatic fibrosis ($p \leq 0.038$); however STAT 5 and α -SMA were not significantly correlated (Table 4).

Table 5 presents the association of the serum STAT 5 level and TGF- β_1 with some demographic, biochemical, metabolic factors in CHC patients. STAT5 levels showed a significant negative correlation with TGF- β_1 ($r = -0.746$ and $p \leq 0.001$) and a weak positive correlation with HDL cholesterol ($r = 0.236$ and $p \leq 0.05$). TGF- β_1 levels were positively correlated with serum triglyceride levels and negatively correlated with HDL cholesterol ($r = 0.240$ and -0.250 , respectively, and $p \leq 0.04$ and ≤ 0.05 , respectively). α -SMA levels had a nonsignificant correlation.

Figure 1 shows the receiver operating characteristic analysis for demonstration of the accuracy of indices and cut-off values for the studied serum biomarkers for predicting liver fibrosis according to the Fibroscan scoring system. The AUC for TGF- β_1 was 0.641 ($p < 0.05$), with a sensitivity of 58.6% and a specificity of 52.8% at a cut-off of 1,397. For α -SMA, the AUC was 0.629 ($p < 0.07$), with a sensitivity of 62.1% and a specificity of 52.8% at a cut-off of 14.1. The AUC for STAT5 was 0.526 ($p < 0.7$), with a sensitivity of 55% and a specificity of 52.8% at a cut-off 7.4.

Discussion

This study showed that STAT-5 levels were significantly lower while TGF- β_1 levels were significantly higher in CHC patients than in control subjects, with a negative correlation between them. TGF- β_1 levels showed a highly significant positive correlation with the stage of hepatic fibrosis. α -SMA levels were significantly higher

Table 5. Association of serum STAT5 level and TGF- β_1 with some demographic, biochemical, metabolic factors in chronic hepatitis C patients

Variable	STAT5		TGF- β_1	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age (years)	-0.034	0.787		
Gender	0.132	0.293	0.114	0.365
BMI	-0.038	0.763	0.058	0.644
Waist/hip ratio	-0.195	0.119	-0.131	0.300
ALT (IU/L)	-0.154	0.220	-0.451	0.420
AST (IU/L)	-0.094	0.455	-0.091	0.742
Hb (g/dL)	0.119	0.34	-0.22	0.078
WBC	0.019	0.879	0.019	0.879
Platelets ($n \times 10^9/L$)	0.043	0.732	0.42	0.127
Cholesterol (mg/dL)	-0.180	0.152	-0.104	0.411
TG (mg/dL)	-0.113	0.269	0.240	0.05
LDL cholesterol (mg/dL)	-0.186	0.137	0.08	0.524
HDL cholesterol (mg/dL)	0.236	0.05	-0.250	0.04
Fasting glucose (mg/dL)	0.188	0.134	0.021	0.870
Fasting insulin ($\mu IU/mL$)	-0.109	0.389	-0.104	0.409
HOMA-IR	-0.122	0.333	-0.113	0.37
TGF- β_1 (ng/mL)	-0.746	0.001		
α -SMA (ng/mL)	-0.023	0.856	0.023	0.856

Hb, hemoglobin; WBC, white blood cells; ALT, alanine transaminase; AST, aspartate transaminase; HOMA-IR, homeostasis model assessment of insulin resistance; STAT5, signal transducer and activator of transcription; TGF, transforming growth factor; α -SMA, α -smooth muscle actin; TG, triglycerides.

in patients than in controls and showed a significant progressive increase with advancing stages of hepatic fibrosis.

The mechanism of serum STAT5 reduction in patients with CHC is not clearly understood [18]. Animal studies showed that cytokine-induced activation of the JAK-STAT pathway plays a variety of important functions in liver pathophysiology. Experiments on knockout mice showed that the loss of STAT5 in hepatocytes resulted in elevated TGF- β_1 levels and enhanced the GH-induced STAT3 activity in the liver after chronic carbon tetrachloride treatment, suggesting that STAT5 inhibits liver fibrogenesis via the downregulation of TGF- β_1 and STAT3 [6, 19]. However, an acquired GH resistance in liver fibrosis, because of low GH receptor levels, has been previously reported [20, 21]. The reduction of STAT5 might also occur irrespectively of GH, because hepatocytes lose their hormonal response during early stages of fibrosis. The absence of STAT5 could lead to engagement of its receptors by other STAT members, especially STAT3 and

Fig. 1. Receiver operating characteristic curves of serum biomarkers for the prediction of significant fibrosis (F3 and F4 based). Data were analyzed considering patients with Fibroscan results in the chronic hepatitis group. α -SMA, α -smooth muscle actin; TGF, transforming growth factor; STAT5, signal transducer and activator of transcription 5.

STAT1, which in turn would result in their aberrant activation [5, 22]. STAT5 might reduce hepatic fibrosis through its counteractive effect on the TGF- β_1 as described in experimental studies [8, 19]. These possible mechanisms suggest how STAT5 might be an antagonist of fibrosis.

In this study, TGF- β_1 levels showed a significant increase in patients compared to controls, with a highly significant positive correlation with the stage of liver fibrosis. As activation of latent TGF- β_1 was reported to be the starting point of fibrogenesis, its levels might reflect the histologic stage [23, 24], and some of the antifibrotic effects may be mediated by inhibition of profibrogenic TGF- β_1 [25–27]. Other studies have reported a significant elevation of TGF- β_1 in liver cirrhosis, with a moderate correlation of its levels with the grade of activity [28, 29]. TGF- β_1 plays a role in liver fibrosis through stimulation of the activation of HSC and the production of ECM as it may lead to cirrhosis through induction of hepatocyte apoptosis [13].

In this study, the serum levels of α -SMA were significantly higher in CHC patients in compared to controls and their levels significantly increased with worsening of

fibrosis, as with TGF- β 1, but no significant correlation could be detected with serum STAT 5.

Despite extensive experimental investigations on the effects STAT5 on hepatocytes, little is known about its possible effects on HSC. Moreover, the production of abnormal ECM and activated HSC may trigger the expression of α -SMA [30].

Serum STAT5 levels in this study showed a weak positive correlation with HDL cholesterol; thus, a possible protective role of STAT5 against hepatic steatosis could be suggested. GH-STAT5 signaling may be involved in controlling the lipid metabolism in the liver, and thus the loss of STAT5 may induce hepatosteatosis [6]. Liver-specific STAT5 ablation in mice was shown to lead to the development of hepatosteatosis, glucose intolerance, and insulin resistance [6].

The absence of any significant relation between STAT5 levels and glucose levels or IR in this study might be explained by the exclusion criteria of obese and diabetic subjects. Despite the exclusion of diabetic and obese patients, an interesting positive correlation was found between TGF- β 1 and serum triglyceride levels; there was also a negative correlation with HDL-c. Actually, hypertriglyceridemia and low HDL levels represent 2 important criteria of the metabolic syndrome. The hepatic fibrogenic response induced by TGF- β 1 could be directly inhibited in vitro by using an antihypertriglyceridemic agent, i.e., bezafibrate [31]. Herder et al. [32] reported an association between elevated serum concentrations of TGF- β 1 and the incidence of type 2 diabetes mellitus. In addition, TGF- β 1 has the potential to increase insulin resistance.

As liver fibrosis represents a complex process that triggers many cellular events and inflammatory cytokines, its

exact mechanism is still a matter of debate [3, 4]. This may explain the low sensitivity and specificity of STAT5 in the prediction of liver fibrosis. However, this study suggests that STAT5 may play a significant role in hepatic fibrogenesis mostly through induction of TGF- β 1 and not through the activation of HSC. This study also suggests the therapeutic potential of the reduction of TGF- β 1 and the induction of STAT5 in hepatic fibrosis.

Despite being limited by the small number of patients, this study is suggestive of a novel role for STAT5 in developing liver fibrosis in CHC patients. Another limitation of this study is the difficulty of performing liver biopsies, as our national program for new antiviral therapy has stopped the use of liver biopsy as a diagnostic tool for eligibility for enrollment in the treatment program. Instead, we used Fibroscan for detection of the stage of hepatic fibrosis.

Conclusions

In Egyptian patients with HCV infection, STAT5, TGF- β 1, and α -SMA are important contributing factors to fibrogenic activity. Reduced STAT5 in CHC patients may play a significant role in hepatic fibrogenesis through the induction of TGF- β 1 and not through the activation of HSC. Further research and more clarification through tissue expression of STAT5, TGF- β 1, and α -SMA in CHC patients are indicated.

Disclosure Statement

None.

References

- 1 Forner A, Llovet JM, Bruix J: Hepatocellular carcinoma. *Lancet* 2012;379:1245–1255.
- 2 Kocakoc E, Bakan A, Poyrazoglu O, et al: Assessment of liver fibrosis with diffusion-weighted magnetic resonance imaging using different b-values in chronic viral hepatitis. *Med Princ Pract* 2015;24:522–526.
- 3 Friedman SL: Mechanisms of hepatic fibrogenesis. *Gastroenterology* 2008;134:1655–1669.
- 4 Abroun S, Saki N, Ahmadvand M, et al: STATs: an old story, yet mesmerizing. *Cell J* 2015;17:395–411.
- 5 Cui Y, Hosui A, Sun R, et al: Loss of signal transducer and activator of transcription 5 leads to hepatosteatosis and impaired liver regeneration. *Hepatology* 2007;46:504–513.
- 6 Baik M, Yu JH, Hennighausen L: Growth hormone-STAT5 regulation of growth, hepatocellular carcinoma, and liver metabolism. *Ann NY Acad Sci* 2011;1229:29–37.
- 7 Blaas L, Kornfeld JW, Schramek D, et al: Disruption of the growth hormone-signal transducer and activator of transcription 5-insulinlike growth factor 1 axis severely aggravates liver fibrosis in a mouse model of cholestasis. *Hepatology* 2010;51:1319–1326.
- 8 Takehara T, Tatsumi T, Suzuki T, et al: Hepatocyte specific disruption of Bcl-xL leads to continuous hepatocyte apoptosis and liver fibrotic responses. *Gastroenterology* 2004;127:1189–1197.
- 9 Canbay A, Friedman S, Gores GJ: Apoptosis: the nexus of liver injury and fibrosis. *Hepatology* 2004;39:273–278.
- 10 Gao C, Gressner G, Zoremba M, et al: Transforming growth factor β (TGF- β) expression in isolated and cultured rat hepatocytes. *J Cell Physiol* 1996;167:394–405.
- 11 Jeong WI, Do SH, Yun HS, et al: Hypoxia potentiates transforming growth factor- β expression of hepatocyte during the cirrhotic condition in rat liver. *Liver Int* 2004;24:658–668.
- 12 Nassef YE, Shady MM, Galal EM: Performance of diagnostic biomarkers in predicting liver fibrosis among hepatitis C virus-infected Egyptian children. *Mem Inst Oswaldo Cruz* 2013;108:887–893.

- 13 Divella R, Daniele A, Gadaleta C, et al: Circulating transforming growth factor- β and epidermal growth factor receptor as related to virus infection in liver carcinogenesis. *Anticancer Res* 2012;32:141–145.
- 14 Tomanovic NR, Boricic IV, Brasanac DC, et al: Activated liver stellate cells in chronic viral C hepatitis: histopathological and immunohistochemical study. *J Gastrointest Liver Dis* 2009;18:163–167.
- 15 Li JT, Liao ZX, Ping J, et al: Molecular mechanism of hepatic stellate cell activation and antifibrotic therapeutic strategies. *J Gastroenterol* 2008;43:419–428.
- 16 Guyot C, Lepreux S, Combe C, et al: Hepatic fibrosis and cirrhosis: the (myo)fibroblastic cell subpopulations involved. *Int J Biochem Cell Biol* 2006;38:135–151.
- 17 Ziol M, Handra-Luca A, Kettaneh A, et al: Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005;41:48–54.
- 18 Gressner AM, Gao CF, Gressner OA: Non-invasive biomarkers for monitoring the fibrogenic process in liver: a short survey. *World J Gastroenterol* 2009;15:2433–2440.
- 19 Hosui A, Kimura A, Yamaji D, et al: Loss of STAT5 causes liver fibrosis and cancer development through increased TGF- β and STAT3 activation. *J Exp Med* 2009;206:819–831.
- 20 Moller S, Becker U, Gronbaek M, et al: Short-term effect of recombinant human growth hormone in patients with alcoholic cirrhosis. *J Hepatol* 1994;21:710–717.
- 21 Shen XY, Holt RI, Miell JP, et al: Cirrhotic liver expresses low levels of the full length and truncated growth hormone receptors. *J Clin Endocrinol Metab* 1998;83:2532–2538.
- 22 Hosui A, Hennighausen L: Genomic dissection of the cytokine controlled STAT5 signaling network in liver. *Physiol Genomics* 2008;34:135–143.
- 23 Neuman MG, Benhamou JP, Bourliere M, et al: Serum tumor necrosis factor-alpha and transforming growth factor-beta levels in chronic hepatitis C patients are immunomodulated by therapy. *Cytokine* 2002;17:108–117.
- 24 Iagoda AB, Koroi PV, Geivandova NI, et al: Growth factors and the histologic picture of the liver in chronic viral hepatitis and hepatic cirrhosis (in Russian). *Klin Med (Mosk)* 2006;84:44–47.
- 25 Weiskirchen R, Meurer SK, Gressner OA, et al: BMP-7 as antagonist of organ fibrosis. *Front Biosci (Landmark Ed)* 2009;14:4992–5012.
- 26 Zeisberg M, Hanai J, Sugimoto H, et al: BMP-7 counteracts TGF- β_1 -induced epithelial-to-mesenchymal transition and reverses chronic renal injury. *Nat Med* 2003;9:964–948.
- 27 Kinoshita K, Iimuro Y, Otagawa K, et al: Adenovirus-mediated expression of BMP-7 suppresses the development of liver fibrosis in rats. *Gut* 2007;56:706–714.
- 28 Luo R, Yang S, Xie J, et al: Diagnostic value of five serum markers for liver fibrosis (in Chinese). *Zhonghua Gan Zang Bing Za Zhi* 2001;9:148–150.
- 29 Nawar EA, Abul-Fadl AM, Hassanin BE, et al: Clinical value of transforming growth factor beta as a marker of fibrosis in adolescents with chronic liver diseases. *J Am Sci* 2011;7:464–471.
- 30 Hernandez-Gea V, Friedman SL: Pathogenesis of liver fibrosis. *Annu Rev Pathol* 2011;6:425–456.
- 31 Nakano S, Nagasawa T, Ijio T, et al: Bezafibrate prevents hepatic stellate cell activation and fibrogenesis in a murine steatohepatitis model, and suppresses fibrogenic response induced by transforming growth factor- β_1 in a cultured stellate cell line. *Hepatol Res* 2008;38:1026–1039.
- 32 Herder C, Zierer A, Koenig W, et al: Transforming growth factor- β_1 and incident type 2 diabetes: results from the MONICA/KORA case-cohort study. *Diabetes Care* 2009;32:1921–1923.