

Association of STAT-1, IFNAR-2 & IRS-2 Gene Expression in Subjects with Hepatitis C (HCV) Resistant and Responding to Interferon Therapy

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Abstract

Background: HCV prevention as well as control is based on comprehensive circulation of the virus, valuation of the increasing causes liable for advancement of the HCV and determination of the risk factors involved.

Aim of Study: The Study was designed to reveal the gene expression of Signal transducer and activator of transcription 1 (STAT-1), the interferon- α/β receptor 2 (IFNAR-2) and insulin receptor substrate 2 (IRS-2) in subjects with Hepatitis C, resistant and responding to Interferon Therapy and in healthy control.

Material and Methods: This Cross-sectional analytical study included 45 subjects. The subjects were categorized into three groups. Group 1: 15 HCV subjects resistant to interferon therapy Group 2: 15 subjects responding to interferon. Group 3: 15 healthy control. Biochemical enzyme activity was measured. Gene expressions were carried out using RT-PCR technique.

Results: HCV subjects resistant to interferon therapy showed low expression of STAT1, while subjects responding to interferon therapy showed high level of expression of STAT1 when compared to control and low expression of IFNAR was also seen in subjects resistant to interferon therapy and high expression of IFNAR2 was seen in subjects responding to interferon therapy as compared to control. No expression of IRS-2 was seen in both subjects resistant and responding to interferon therapy. Furthermore, the study revealing no association between STAT1, IFNAR2 and IRS-2 expression and biochemical enzyme levels.

Conclusion: Subjects with HCV resistant to interferon therapy illustrated low expression of STAT-1, and also low expression of IFNAR-2 which can be used as a potential indicator of significant liver damage, fibrosis and thus, might prove to be valuable prognostic or diagnostic marker for HCV.

Key Words: Gene expression – HCV – STAT1 – IRS2 – Interferon therapy – IFNAR-2.

Introduction

WORLDWIDE almost 180 million people was affected by Hepatitis C Virus (HCV) [1]. HCV is

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an enveloped virus of Flaviridae family having size of 9.4kb with numerous subtypes and having six genotypes. The virus limits the interferon signaling pathways for its survival [2]. HCV prevention as well as control is based on comprehensive circulation of the virus, valuation of the increasing causes liable for advancement of the HCV and determination of the risk factors involved [3]. After intracellular localization HCV assembles itself [4].

STAT proteins employ vital part in antiviral battle against hepatitis in addition to limiting injury, inflammation, tumorigenesis and healing. Advancement of liver disease can be regulated by several cellular mediators. JAK-STAT pathway has a crucial part and acquires stimulation through growth factors and nearly 40 cytokines [5,6]. Usually, on binding with the receptor cytokines induce receptor and JAK dimerization which in turn leads to the phosphorylation. JAK-receptor complex phosphorylates several STAT proteins and engaging them with other numerous pathways. These phosphorylated STATs after forming heterodimers or homodimers are shifted into nucleus [7] and function as transcription factors and encourage transcription of genes to control several cellular functions. STAT1 boosts host resistance and interferon administration encouraged rejuvenation of liver [8]. Subsequently binding of interferon1 leads to start of signaling cascade and encourage transcription of interferon stimulated genes [5]. SOCs 1 constrain STAT1 with privileged reticence of IFN- γ signaling [8].

Human cells contain one isoform of IFNAR-1, whereas IFNAR-2 has three isoforms [9]. The genes of IFNAR-2 are bunched on chromosome 21 [10]. IFNAR-2, showed efficient affinity to IFN because of an extracellular domain which further comprehends 2 domains of fibronectin type III [11]. The

cytoplasmic portion of IFNAR-2 comprises 250 amino acids, and has potent binding affinity with Janus kinase 1 (Jak1), as the part consists 3 motifs aimed at the recruitment of STAT [12,13]. The binding sites of IFNAR complementing the IFN have been recognized by several investigations [14]. Many studies revealed that hepatitis C virus results interference in the insulin signaling pathway [15]. Insulin employs its effects after binding to the extracellular portion of the insulin receptor having tyrosine kinase activity. This binding results in receptor activation which leads to the IRS2 phosphorylation and inturn encourages cascade of numerous proteins like Akt and PI3K [16,17]. HCV by its core protein, NS-3 and NS-5 disturbs the insulin signaling pathway which leads to insulin resistance [17]. Impaired IRS-2 signaling because of HCV infection is allied with insulin resistance and subsequently the type 2 diabetes mellitus. Insulin resistance is connected to fibrosis [18] and non-response to the standard therapy [19].

The current research data on whether expression of, IFNAR-2, IRS-2 and STAT-1 are significant elements in producing response of the host to interferon therapy are not conclusive. In addition, there is also scarcity of data on the prospect that causes other than expression of IRS-2, STAT-1, and IFNAR-2 may similarly be engaged in non-responsive cases that showed expression of IRS-2 STAT-1, and IFNAR-2. We, therefore, designed this study to detect the expression of IRS-2 STAT-1, and IFNAR-2 in subject with Hepatitis C resistant and responding to interferon therapy.

Material and Methods

Study design and sampling:

This Cross-sectional analytical study included 45 HCV subjects with resistant and responding to Interferon Therapy and health control. The subjects were categorized into three groups:

- Group 1: 15 HCV subjects resistant to interferon therapy.
- Group 2: 15 HCV subjects responding to interferon.
- Group 3: 15 Healthy control.

Samples were collected after approval from ethical committee of King Faisal university, Hofuf, Saudi Arabia. This Cross-sectional analytical study was conducted from January 2018 to August 2019. Informed written consents were obtained from all participants. Blood samples of from healthy control and HCV subjects resistant and responding to interferon, therapy were collected were included in the study. Being responsive or nonresponsive

to interferon therapy was discriminated by virological tests. Samples from male and female patients (age range 22-69 yrs) were collected. Demographic as well as clinical features were taken, including gender, age, sex, family history, marital status, and BMI (Body mass Index).

RNA extraction:

mRNA was quarantined from blood sample using Promega Cat. # Z3101. The first strand cDNA synthesis was prepared by using High-Capacity cDNA Reverse Transcription Kit (ABI Catalog number: 4368814).

Gene expression analysis by RT-PCR:

The reaction mixture was prepared to contain 10µl fastStart Universal SYBR Green Master (Roche, Germany), 6µM reverse primers, and 10µg cDNA, with RNAase free water added to a total volume of 20µl. The amplification and real-time analysis were done for 40 cycles with the following factors; 95°C (10min) to activate of Fast Start Taq DNA polymerase; 60°C (1 min) for amplification and real-time analysis [20]. The gene expression levels were determined using ^{2-CT}. The primer sequence for STAT-1, IFNAR-2 and IRS-2 are shown in Table (1).

Table (1): Primer Sequence.

Candidate gene	Primer
STAT-1	F: 5'-GTCGGGGAATATTCAGAGCA-3' R: 5'-GGTACCCCCAGAGACCTCAT-3'
IFNAR-2	F: 5'-TGAGTCTGTCCGGAATGTGA-3' R: 5'-GAGTCAACCTCATACCATGAA-3'
IRS-2	F: 5'-CTACCTGCGCAAGCAGAAG-3' R: 5'-TGATGTTTCAGGCAGCAGTC-3'

Biochemical analysis of serum:

The serum was used for the estimation of Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), aspartate aminotransferase (AST), Alkaline phosphatase (ALP), and Urea by AMP diagnostic kits according to the instruction of the manufactures.

Statistical analysis:

All data is accessible as the mean \pm standard error of mean. Data examined by one-way ANOVA performed through software SPSS version 16.0. $p < 0.01$ was considered significantly significant.

Results

Forty-five patients participated in the current study. Twenty of them were HCV resistant to interferon therapy, twenty were responding to interferon therapy which was administered twice

weekly for six months and twenty were of healthy subjects, Majority of subjects were male (M/F: 86/14) with the age range from 22 to 69 years. The mean age of both healthy control and responsive was lower as compared to nonresponsive groups. Liver enzymes, and BMI, reports before and after interferon therapy were normal in interferon resistant and responding group when compared with control (Tables 2,3).

Data are mean ± SEM, (n=7). *p*=0.000 versus Control respectively. Data analyzed was by One-way ANOVA test followed by Tukeys multiple comparison test.

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Table (2): Features of the subjects included in the study.

Characteristics of subjects	HCV subjects resistant to interferon therapy (n=15)	HCV subjects responsive to interferon therapy (n=15)	Normal Healthy control (n=15)	<i>p</i> -value
Age	49.2±6.2	43.7±6.1	46.2±6.4	0.01
Sex:				
Male	28 (93.3%)	17 (85%)	16 (80%)	1
Female	2 (6.6%)	3 (15%)	4 (20%)	
Marital status:				
Single	None	None	3 (15%)	0.115
Married	20 (100%)	20 (100%)	17 (85%)	
BMI (Body mass index)	23.2±0.3	22.4± 1.5	23.4±1.2	0.165

Table (3): Estimation of ALT, ALP, and Bilirubin.

Enzymes	Control subjects	HCV subjects resistant to interferon therapy	HCV subjects responding to interferon therapy	<i>p</i> -value
ALT U/L	28.3865±6.736929	39.4000±8.31233	29.8353±8.05540	<i>p</i> =0.000
ALP U/L	225.4±58.3	256.4±54.4	218.4±72.6	<i>p</i> =0.000
Bilirubin U/L	0.84±0.16	1.08±0.28	1.06±0.26	<i>p</i> =0.000

Our results illustrated that subjects with HCV resistant to interferon therapy showed low expression of STAT3 while subjects responding to interferon therapy showed high expression of STAT3. Furthermore, subjects with HCV resistant to interferon

therapy showed low expression of IFNAR-2 while subjects responding to interferon therapy showed high expression of IFNAR-2 (Fig. 1). No expression of IRS-2 was seen subjects with HCV resistant and subjects responding to interferon therapy.

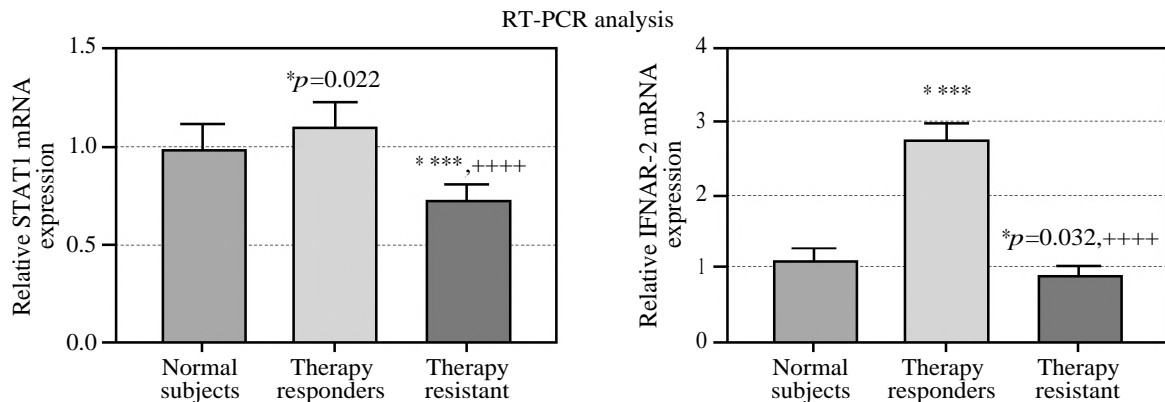


Fig. (1): RT-PCR analysis of STAT 1 and IFNAR-2 mRNA expression.

- Data analyzed by one way ANOVA followed by Tukeys multiple comparison test.
- *,**** Indicated significant difference compared to healthy normal subjects.
- *p*-values of * is indicated inside each graph while. **** Indicated *p*<0.0001. +++++ Indicated significant difference at *p*<0.0001 from therapy responder group.

Discussion

Interferons has a substantial part in constraining viral replication nonetheless as infected cell generate deficient interferon consequently it has to be specified exogenously. Reaction of interferon greatly differs from individual to individual, a fact that warrants the need of extensive investigation of interferon response. Main determination of our investigation was to investigate cellular factors i.e., IFNAR-2, STAT1, and IRS-2 and their overall role in interferon response. The genotyping examination was carried out on laboratory-stored liver biopsies of genotype 3 infected HCV patients. IFNAR-2, STAT-1, and IRS-2 was examined HCV subjects nonresponsive to IFN therapy (administered once or twice), HCV subjects responsive to IFN therapy and healthy controls. Their blood samples were then used to gene expression of IFNAR-2, STAT-1, and IRS-2. The consequence of this work lies in the fact that IFN has a potent affinity to IFNAR-2, STAT-1, and IRS-2, signifying them crucial elements. The former investigations showed that sex raised LFTs and BMI in overweight group could be the reason accountable for interferon treatment response separately from STAT1 and current investigation supported the study carried earlier [21,22].

Our results illustrated that subjects with HCV resistant to interferon therapy showed low expression of STAT3 while subjects responding to interferon therapy showed high expression of STAT3 when compared to control. Our results are inconsistent with the previous studies revealing that STAT1 expression was identified in 27 samples out of 30 HCV patients nonresponsive to interferon therapy. The STAT1 expression was noticed in as much as 40% of the responsive subjects and normal controls. Furthermore, the study revealing no association between STAT1 expression and biochemical enzyme levels. There may be possibly other reasons for this manifestation, e.g., STAT1 phosphorylation interruption by HCV core protein, HCV NS5A16, or STAT1 ubiquitin-mediated proteasome-dependent deprivation by the HCV core protein [21].

Furthermore, our data illustrated that subjects with HCV resistant to interferon therapy showed also low expression of IFNAR-2 while subjects responding to interferon therapy showed high expression of IFNAR-2 when compared to control. Our data showed inconsistency with previous data revealing that 90% of the subjects showed expression of IFNAR-1 whereas overall the subjects examined were positive for IFNAR-2. Furthermore, our data was reinforced by a previous study per-

formed on human Huh-7 cell lines, resistant and sensitive to interferon therapy. The expression of IFNAR-1 and IFNAR-2 was seen in all Huh-7 cell lines that were non-responsive to interferon therapy [23].

Our data revealed that HCV infection has no association with IRS-2. No expression was seen in both HCV subject resistant and responsive to interferon therapy. Current investigation are in consistence with the observation conducted by Aytug et al., revealing that no IRS-1 expression was seen, while phosphorylation of PI3k, Akt and IRS-1 was irregular [24]. Our data are also supported by Bernsmeier et al., showing that insulin signaling is normal in all chronic hepatitis C patients [15]. Furthermore, our results are in consistency with observation done by Hsieh et al., revealing that there was no changes in expression of mRNA levels by HCV E2 protein though IRS-1 expression of protein level was reduced [25].

Conclusion:

The findings of our study are suggestive of the fact that interferon is the gold standard conduct of HCV infection, non-responsiveness of the host to the therapy is challenging, particularly in clinical setting. Clinicians, recommending interferon therapy for the HCV subjects, need to analyze the response possibility for the patients by expression of IFNAR-2, IRS-2 and STAT-1, which if identified are likely to have progressive effect on the consequence of interferon therapy. Future research studies may be carried out on a larger scale including an assortment of ethnic and geographical distributions. It is suggested that additional host and viral aspects should be examined to form the mechanism. We remained of the opinion that a rodent model or cell line approximately approaching natural HCV infection should be designed and considered. Furthermore, additional molecular and genetic and markers which are potent and feasible ought to recognize to progress the treatment strategy of HCV patients. However, in cases IFNAR-2 and STAT-1 expression is missing, another combination therapy ought to reconnoiter and set as trial to avoid the high cost, longer duration and side effects of standard interferon therapy.

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علاقة تعبير الجينات (STAT-1 و IFNAR-2 و IRS-2) في مرضى الإلتهاب الكبدى الوبائى سى المقاومين والمستجيبين للعلاج بالانترفيرون

خلفية البحث: تستند الوقاية من إلتهاب الكبد الفيروسي، وكذلك السيطرة عليه، إلى الدوران الشامل للفيروس، وتقييم الأسباب المتزايدة المسؤولة عن تقدم إلتهاب الكبد الفيروسي، وتحديد عوامل الخطر التى تنطوى عليها.

الهدف من العمل: صممت الدراسة للكشف عن التعبير الجينى لمحول الإشارة ومنشط النسخ ١ (STAT-1)، مستقبلات الإنترفيرون (2)-IFNAR /2، وركيزة مستقبل الأنسولين ٢ (IRS-2) فى الأشخاص المصابين بالتهاب الكبد الوبائى سى، والمقاومة والاستجابة للعلاج بالإنترفيرون والتحكم الصحى.

المواد والأساليب: شملت هذه الدراسة التحليلية المقطعية ٤٥ موضوعاً. تم تصنيف الموضوعات إلى ثلاث مجموعات. المجموعة الأولى احتوت على ١٥ شخصاً من فئة الإلتهاب الكبدى الوبائى سى والمقاومة للعلاج بالإنترفيرون. المجموعة الثانية احتوت على ١٥ شخصاً يستجيبون للإنترفيرون. المجموعة الثالثة (المجموعى الضابطة) اشتملت على ١٥ من أشخاص الأصحاء. تم قياس نشاط الانزيم البيو كيميائى. تم إجراء التعبير الجينية باستخدام تقنية RT-PCR.

النتائج: أظهر الأشخاص المصابون بفيروس التهاب الكبد سى والمقاوم للعلاج بالإنترفيرون تعبيراً منخفضاً عن جين STAT1، بينما أظهر الأشخاص الذين يستجيبون للعلاج بالإنترفيرون مستوى عالياً من التعبير عن نفس الجين عند مقارنتهم بالمجموعة الضابطة والتعبير المنخفض لجين IFNAR أيضاً فى الأشخاص المقاومين للعلاج بالإنترفيرون والتعبير العالى لجين IFNAR2 قد شوهد فى الأشخاص الذين يستجيبون للعلاج بالإنترفيرون مقارنة بالمجموعة الضابطة. لم يظهر أى تعبير عن IRS-2 فى كلا الموضوعين المقاومين والاستجابة للعلاج بالإنترفيرون. علاوة على ذلك، لم تكشف الدراسة عن أى ارتباط بين تعبيرات STAT1 و IFNAR2 و IRS-2 ومستويات الإنزيمات البيوكيميائية.

الخلاصة: الأشخاص الذين يعانون من مقاومة التهاب الكبد الفيروسي (سى) للعلاج بالإنترفيرون أوضحت تعبيراً منخفضاً عن STAT1، وكذلك تعبيراً منخفضاً عن IFNAR-2 والذي يمكن استخدامه كمؤشر محتمل لتدمير كبدى كبير، والتليف الكبدى، وبالتالي، قد يثبت أنه عامل تنبؤى وتشخيصى لالتهاب الكبدى الوبائى سى ذات قيمة عالية.