Journal of
Clinical & Cellular Immunology

Akhtar et al., J Clin Cell Immunol 2013, 4:1
DOI: 10.4172/2155-9899.1000136

Review Article Open Access

Interferons as Immune Regulators: A Rivalry between HCV and Interferons

Hashaam Akhtar[1], Samar Akhtar[2], Ummar Raheel[1], Muhammad Faheem[1,4]*, Muhammad Arshad[3], Muhammad Yameen[1] and Najam us Sahar Sadaf Zaidi[1]

[1]*Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, H-12 Sector, 44000, Islamabad, Pakistan*
[2]*Riphah Institute of Pharmaceutical Sciences, Riphah International University, 7th Avenue, Sector G-7/4, Islamabad, Pakistan*
[3]*Department of Biological Sciences, University of Sargodha, Sargodha, Pakistan*
[4]*Ciencias Genomicas e Biotecnologia, Universidade Catolica de Brasilia, Asa Norte, SGAN 916 Avenida W5, Brasilia, DF 70790-160, Brasil*

Abstract

Interferons (IFNs) are an integral part of the immune system, which upon stimulation results in recruitment of cytokines for viral clearance. IFNs have been characterized as potent antiviral agents that which can reduce viral titer and have been found to act as critical mediators for tumor regression in few cases. During the course of time Hepatitis C virus (HCV) has evolved and influence IFN efficiency through various pathways. Rapidly occurring amino acid substitutions in HCV's core protein, sequence homology with protein kinase (PKR), increased numbers of quasi-species and wild-type Interferon sensitivity determining region (ISDR) strains are linked with an inefficient response to IFN therapy. This article describes the pharmacodynamics of IFNs with an aim to decipher the possible involvement of HCV proteins in subverting these responses. We hereby discuss IFN-based therapies targeting the host and viral genetic factors, since they have a strong impact in determining the efficacy of an IFN in HCV infected host.

Keywords: Interferon; HCV proteins; Interferon resistance; Interferon therapy; Hepatitis C virus

Introduction

Hepatitis C virus (HCV) is an RNA virus which was first discovered in year 1989 [1,2]. Since its discovery, interferons (IFNs) have been used against HCV as a cornerstone of the anti-HCV therapy. Isaacs and Lindenmann in 1957 discovered this family of cytokines and named them inter-ferons because of their ability to "interfere" with the viral replication, conferring resistance to viral infection transferred from infected chick cells into uninfected cells [3]. IFNs are one of the key components of the innate immune system, considered as the first cytokines to be cloned, sequenced, purified to recombinant forms and have therefore been utilized in a wide range of applications [4]. Some of the much emphasized functions performed by this class of cytokines includes; inhibition of cell proliferation [5,6], up-regulation of Major histocompatibility complex (MHC) class I [7,8], induction of maturity in Dendritic cells (DC), promotion of B-cell differentiation to plasmablasts [9], promotion of T-cell responses and induction of expression of pro-inflammatory cytokines [10-14]. With the discovery of its isoforms, IFNs have been categorized into three distinct groups (Type 1-3) based on their amino acid sequences and specific receptor recognition [15]. The therapeutic potential of Type-1 IFNs in viral infection was first discovered through its inhibitory action against respiratory viral infections. Since then IFNs have been acknowledged clinically as effective antiviral and anti-neoplastic therapeutic agents. Various functions performed by this group of cytokines have been highlighted in figure 1.

On the other hand, viruses have evolved many mechanisms to block IFN synthesis and alter their actions by interfering at various stages of IFN signaling pathway to evade the IFN mediated host responses. Viruses such as Influenza virus, Ebola virus, Papilloma viruses and the Human Herpes Kaposi's Sarcoma-associated virus (KSHV) encode proteins that interfere with interferon regulatory factors (IRF) activation or induction [16]. Chemical modulators which may either selectively activate IFN synthesis or block the synthesis of inflammatory cytokines can have a broad therapeutic potential in autoimmunity and are yet to be developed [17]. It can therefore reasonably be argued that complex organisms like mammals can only survive as long as their immune defenses are able to adjust with the strategies of invading pathogens. Hence, an adaptable IFN system is essential for mammals to make them capable of evading viral infections [18].

Some of the other related subjects widely discussed over the years include, the identification of viral mechanisms that resist the actions of IFN proteins and IFN-stimulated genes (ISGs). Amino acid substitutions in HCV's core protein, sequence homology, higher numbers of quasi-species and wild-type Interferon sensitivity determining region (ISDR) strains are also linked to an inefficient response with IFN therapy. This article elucidates the pharmacodynamics of IFNs with an emphasis on the possible involvement of HCV proteins in subverting these responses [19]. The effects of mutations and suppressions of gene products which are initiated by the IFN system and leads to the progression of cancers have also been explained in this article [20,21].

IFN Family of Proteins

IFNs are categorized into three distinct groups, named as type 1, type II and type III IFNs [10]. In humans 17 non-allelic functional genes have been identified that encode type I IFNs [22,23]. All of them are clustered on chromosome 9 and lack introns [23].

The complex evolutionary history demonstrated by type I IFNs predict the fact that it may be the consequence of various viral combats resulting in its divergence to at least eight distinct subfamilies: IFN-

***Corresponding author:** Muhammad Faheem, Ciencias Genomicas e Biotecnologia, Universidade Catolica de Brasilia, Asa Norte, SGAN 916 Avenida W5, Brasilia, DF 70790-160, Brasil, Tel: +55-61-83111719; E-mail: mohammad_faheem2003@yahoo.com

Received November 26, 2012; **Accepted** February 19, 2013; **Published** February 26, 2013

Citation: Akhtar H, Akhtar S, Raheel U, Faheem M, Arshad M, et al. (2013) Interferons as Immune Regulators: A Rivalry between HCV and Interferons. J Clin Cell Immunol 4: 136. doi:10.4172/2155-9899.1000136

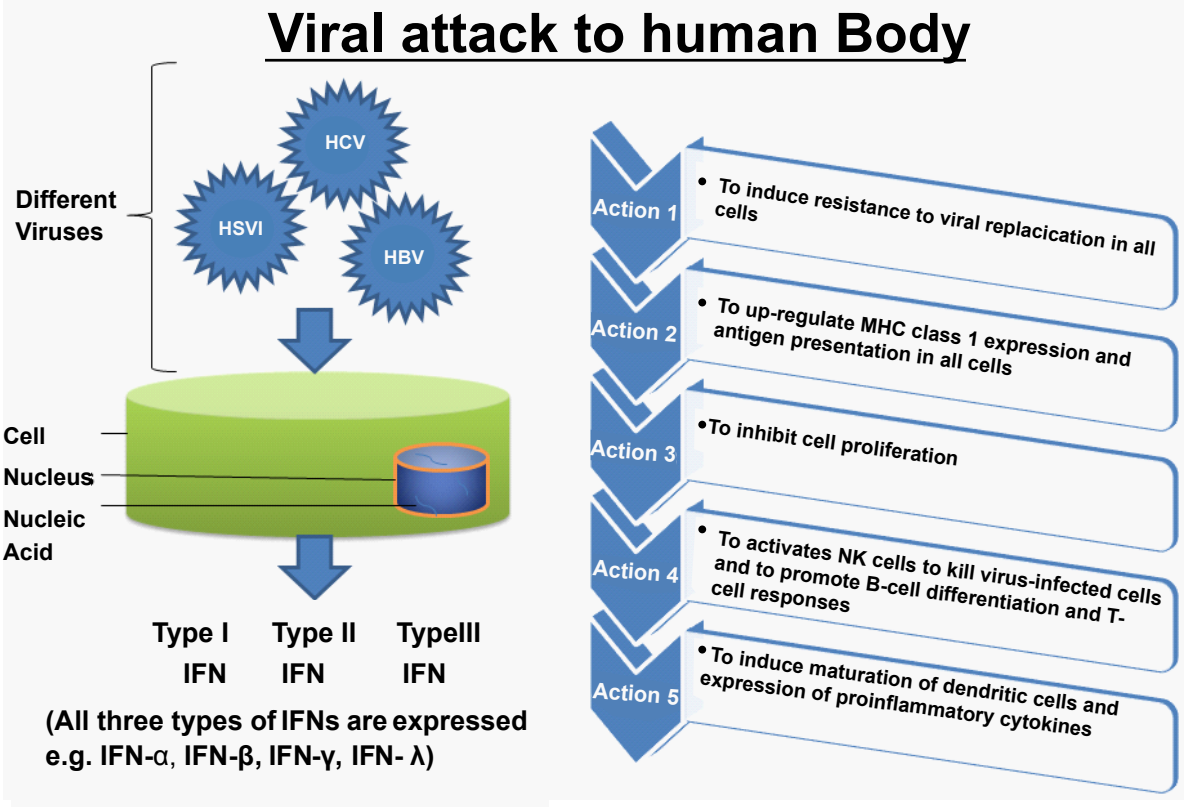

Figure 1: Significance of interferons in immune response against different viruses.

alpha (IFN-α), IFN-beta (IFN-β), IFN-epsilon (IFN-ε), IFN-kappa (IFN-κ), IFN-omega (IFN-ω), IFN-delta (IFN-δ), IFN-zeta (IFN-ζ) (limitin) and IFN-tau (IFN-τ) [22]. The first five are found in humans, of which there is only one IFN β but 13 IFN α subtypes [22]. All of them have a relatively higher specific potencies whereas most of them are non-glycosylated proteins of 165–200-plus amino acids as well, sharing homologies that range between 30–85% within a specie [24]. IFN τ is produced in trophectoderm of ruminants and appears to be important in early period of pregnancy [25]. IFN σ is expressed by trophoblasts of pigs [26]. IFN ζ (limitin) is expressed only in mice having a significantly greater homology to human IFNs [27,28]. Type II IFNs are believed to be the primary IFNs expressed after any viral attack and comprise of IFN-Gamma (IFN-γ) only, whereas type III IFNs consist of four recently identified members: IFN-λ1, IFN-λ2, IFN-λ3 and IFN-λ4 [10,29-31]. The distinct feature of type III IFNs is the selective expression behavior of their heterodimer receptors [10].

Role of IFNs and Immune Responses

Interaction of IFN with its receptors activates intracellular signaling cascades rapidly induce the expression of a variety of overlapping and unique genes involved in inflammatory immune responses. The advent of novel cytokines is changing our approach towards pathogenesis and hence treatment of infectious diseases, allergies and autoimmunity [32]. Production of IFNs requires stimulation by viruses, microbial products or chemical inducers [20]. Various DNA and RNA viruses, bacteria and protozoa have also been reported to induce IFNs through activation of toll like receptors (TLRs) [31,33].

Retinoic acid–inducible gene (RIG)-I–like receptors (RLRs) are cytosolic RNA helicases that sense viral RNA and trigger signaling pathways which induce the production of IFNs and proinflammatory cytokines [34]. Immunohistochemical analysis has shown that RLRs are present in virus induced stress granules, accompanied by viral RNA and other antiviral proteins; altogether which is now termed as antiviral stress granules (avSGs) [34].Whereas for type III IFNs; a heterodimer of IFNLR1 and IL10R2 is necessary to form a functional receptor, to initiate the defensive cascade of activated factors [31]. IFN genes are induced by the binding of TLR-activated transcription factors to their promoters. The most important transcription factors for induction are IFN regulatory factors (IRF), specifically IRF3, IRF7, ATF-2/c-Jun, and NFκB families [35-37]. Mammalian NFκB/Rel family comprises of five members; NFκB-1 (p50), NFκB-2(p52), RelA (p65), RelB, and c-Rel. All of them play critical roles in the regulation of innate immune system by activating various immune responsive genes, such as cell adhesion molecules, proinflammatory cytokines and chemokines [38-40]. NFκB RelA is required during early phase of viral infections, whereas NFκB RelB with CCL19 plays a role in forming heterodimers with p50 and p52 in various genes transactivation [37,41-43]. IFNs also induce some GTPases in the activation of its pathway and Mx proteins are one of those GTPases, which belongs to the dynamin superfamily of Large GTPases. The antiviral activity showed by MxGTPases against a wide range of RNA viruses is a unique property belonging to this group member [44]. Direct and indirect mechanisms exploited by IFNs to counter viral attacks are outlined in table 1.

After recognizing the antiviral efficacy of IFNs against RNA and DNA viruses, they were included in the regimen against HCV and HBV. IFN-α and IFN-β have also shown reduced viral titers and

Direct	Indirect
PKR (Protein Kinase-R)	Up-regulation of human leukocyte antigen (HLA) class 1 expression. Which leads to Enhancing terminal differentiation of DCs
2'-5' oligoadenylatesynthetase (2'-5' OAS/ Rnase system)	T-Cell antiproliferative effects
Mx Protein	Stimulation of IFN-γ by CD-4 T cells
	Up regulation of the expression of HCV antigens (modification of immunoproteosomes) required for presentation of antigens

Table 1: The direct and indirect mechanisms followed by interferons to counter viral attack and enhance host immunity.

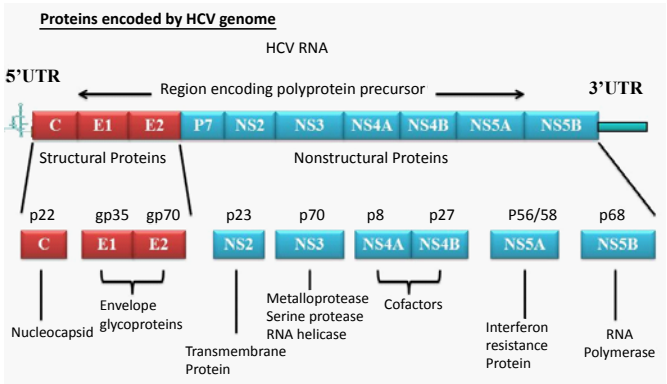

Figure 2: Genomic and proteomic organization of Hepatitis C Virus (HCV).

decreased clinical manifestations in cases of herpes zoster, Herpes Simplex virus (HSV) and cytomegalovirus infections (CMV) [45].

IFNs provide fundamental cellular defense mechanisms against viral infections and cancers thus they hold significant importance in the health of humans and other animals [19]. Despite the fact that IFN therapy has not attained patient compliance, they are nevertheless the drug of choice because of their clinical effectiveness in limiting viral replication, reduction of tumor cell mass, regulation of disease symptoms and prolonging survivals [45]. As all biological effects of IFNs are manifested through the action of ISGs, understanding the functions of these genes may present antiviral therapeutics with higher efficacies [3,6,10].

Different viral and host factors may also determine the impact on the outcomes of the antiviral therapy, which includes age [46], gender [46], ethnicity [47,48], fibrosis score [49], immune response [50], IL-28 genetic polymorphism [51], alcohol intake [52], insulin resistance [53], hormonal imbalances [54], obesity [55] and anemia [56] as host factors and viral load [57], genotypes [58-60], mutations [61-64] and co-infections [65,66] as important host factors [19,57] (Table 2).

Biology of HCV and Its Role in Immune Subversion

HCV is a single stranded RNA virus, whose genome comprises of a single open reading frame that undergoes alternative splicing to yield structural (core and envelope proteins) and non-structural (NS 2,3,4, and 5) protein components (Figure 2).

Efficacy of IFN therapy also depends on the genotype of HCV to a large extent as there are six genotypes of HCV (1-6); classified on the sequence homology, the sustained virologic response (SVR) rates, including many other factors depend indeed on the genotype of the virus infecting the host [67]. SVR is an efficacy measure for HCV

Host Factors	Viral Factors
Age Less than 40 years	Genotypes 2 and 3
Gender; female	Viral Load <2 million IU
Ethnicity; nonblack	Lack of mutations in Interferon-sensitive determining region (ISDR)
Lack of liver fibrosis	Decrease in E2 sequence homology with Protein Kinase R (PKR)
Anemic conditions	Viral Kinetics; Rapid Decline with therapy
Immune response	Increased duration of therapy
Interleukin-28 genetic polymorphism	Co-infections
Sex hormones and menopause	
Non-alcoholic	
Organ transplant	
Insulin resistance	
Obesity	

Table 2: Various host and viral factors determining the effectiveness of interferon therapy in clearing the viral infection.

therapy which is quantified through detection of HCV's RNA in patient's blood serum, at least six months after completion of antiviral therapy against chronic HCV infection [68]. After attaining a viremia during this period, the incidence of late relapses are minimal (<1%) [69].

Different proteins of HCV have been reported to regulate or inhibit the production or working of IFNs, which has been discussed as follows:

Core protein of HCV

Role of HCV proteins in reversing the actions of IFNs in host defense mechanisms are being identified with the passage of time through various experiments. Both viral and human polymorphisms have been correlated with the outcomes of IFN therapies. IL-28B polymorphism is under thorough studies now days, as it is believed to predict the efficacy of IFN therapy in different groups. Moreover, in a study conducted in Japan, it was concluded that host polymorphism (IL-28B) and viral polymorphism (HCV Core protein) contribute independently to a successful IFN therapy [51]. It was concluded that HCV core protein with mutations at position 70 and 91 is known to be very critical in non-responders of IFN therapy with genotype 1b in Japan [70]. The overall role for these positions is not much clear but they are believed to have an inhibiting activity in Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway however no correlation has yet been made in any other genotype of HCV [57,71]. The core protein also plays a role in generation of the suppressor of cytokine signaling 3 (SOCS3), which inhibits the function of interferon-stimulated gene factor 3 (ISGF3) [72]. SOCS-3 is a member of STAT-induced STAT inhibitor (SSI), which is cytokine-inducible negative regulators of cytokine signaling and their expression can also be induced by various cytokines, including IL-6, IL-10, and interferon-gamma [73-76]. SOCS proteins can bind to JAK2 kinase and inhibits its activity [77]. HCV core protein is also known to perform some other tasks; it help in inhibition of SOCS1, it accelerates the degradation of STAT1 and lastly it blocks DNA binding by ISGF3 (Figure 3) [19,78].

Envelope protein (E2) of HCV (Genotypes and IFN resistance)

HCV reportedly undermines the effectiveness of IFNs through sequence homology between a small region of an endoplasmic reticulum (ER) – bound E2 protein with the phosphorylation sites of double-stranded RNA-activated protein kinase PKR and its substrate, the eukaryotic translation initiation factor 2α (eIF2α) (Figure 4)[79].

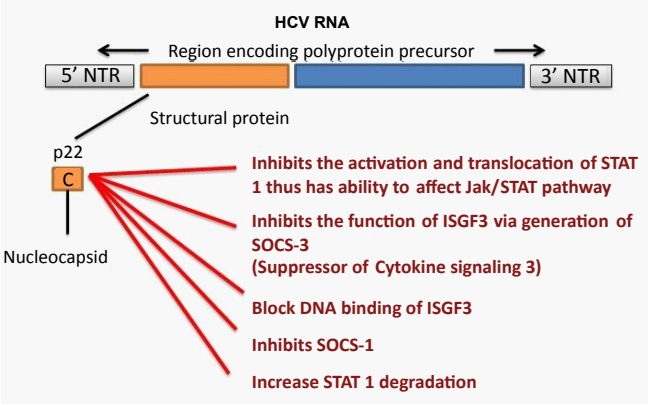

Figure 3: Interaction of HCV Core protein in evading IFN mediated immune response; the core protein of HCV plays different roles in disrupting the signaling of interferon through inhibiting STAT-1, ISGF-3 and SOCS-1.

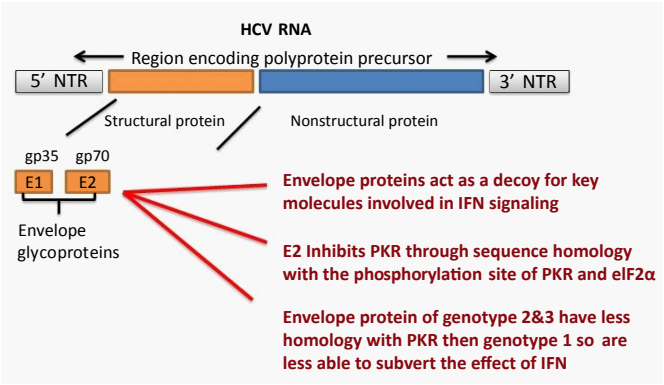

Figure 4: Interaction of HCV Envelope protein in down regulation of Interferon mediated immune response; E1 and E2 disturbs the interferon signaling at different steps, as they have sequence homology with phosphorylation sites of PKR and eIF2α.

E2 plays two important roles by modulating global translation through inhibition of the interferon-induced antiviral protein PKR via its PKR-eIF2α phosphorylation site homology domain (PePHD) and binding with the PKR-like ER-resident kinase (PERK), to inhibit its function [79]. This inhibition and binding can be related with the inherent resistance of chronic HCV genotype 1 patients to IFN therapy, but weaker links may be found in account of those with genotypes 2 or 3, in accordance with the clinical data [80]. PKR is basically an antiviral protein, which can blocks protein synthesis by phosphorylation of eIF2a [81]. Although the inhibition of PKR is correlated with the similarity in sequences of PePHD sequence of E2, elF2a and PKR, but it still stays controversial because it can only explain the resistances shown by genotype 1 of HCV, whereas research have proved that the PePHD sequences are highly conserved within any genotype of HCV, which fails to explain the altered outcomes of IFN against same genotype. Thus, considering only this fact, cannot explain the variations in SVR of different isolates within same genotype and other HCV proteins do have a role in resistance of IFN therapy, which will be discussed under their related topics [82].

Nevertheless, the interaction between E2 and PKR is one of the mechanism by which HCV may act as a "decoy" for key molecules involved in IFN signaling. Moreover owing to greater sequence homology between PKR and E2 protein of HCV genotype 1, it shows more resistance to INF therapy [82]. Different viral and host factors, which play a vital role in the outcomes of IFN therapies are been shown in table 2.

PEGylation is a process whereby one or more molecules of polyethylene glycol (PEG) covalently attaches to a biological molecule or drug and therefore transforms it into a improved drug with better pharmacokinetic and pharmacodynamic parameters [83]. The process of PEGylation involves incubation of a reactive derivative of PEG with the targeted protein and this attachment can mask the therapeutic protein from the host's immune system, reducing antigenicity and immunogenicity. Furthermore it also increases the hydrodynamic size of the protein, which prolongs its half-life inside the body and decreases its renal clearance [83,84]. PEG is therefore added with therapeutic IFN to make it long lasting and to reduce dose frequencies, hence improves patient compliance with the treatment. SVR rates of combined pegylated interferon (PEG-IFN) therapy for genotypes 1, 2, 3 and 4 are approximately 50%, 80%, 70%, and 50% respectively (Figure 5).

Combined and mono therapies have strong effect on the SVR rates as 20% of HCV genome is not conserved at amino acid level in different genotypes, moreover HCV genotypes can be further subdivided into subtypes denoted by lower case alphabets (1a,1b,1c,etc) [19,61,84]. In common circumstances an individual is reported to be infected with a single subtype, however infection with multiple genotypes and subtypes have also been documented. Within each host, HCV is capable of multiplying number of directly related but discrete viral strains called quasi-species [84].

Hepatologists and scientists are facing many problems in the treatment of HCV all over the world because the genome of HCV is 10 times more diverse than human immunodeficiency virus (HIV) since the RNA-dependent RNA polymerase in HCV lacks the proof reading capacity [85]. Poor responses to IFN therapy have been reported with an increase in number of quasi species visible before therapy [84].

The varieties of genotypes differ with the differences in geographic locations and five genotypes have been mainly identified. Genotype 1 is predominant in United States of America (USA) and Western Europe accounting for 60-65% infected HCV individuals, genotype 3 is mostly prevalent in Pakistan [86], genotype 4 is widespread in Middle East,

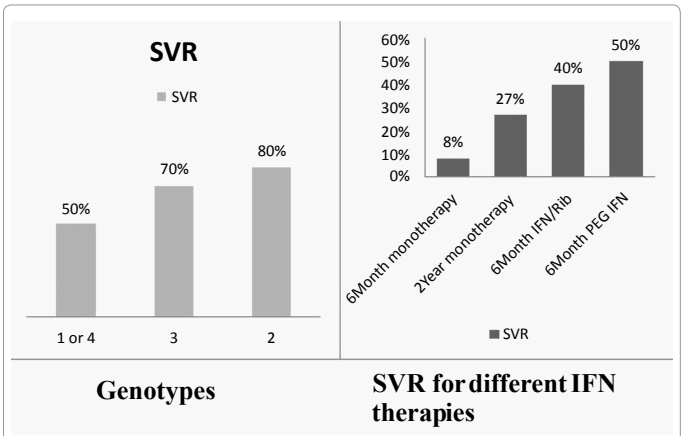

Figure 5: Sustained virological response (SVR) of different IFN therapies with reference to different genotypes: **(a)** SVR attained through IFN-α and ribavirin for genotype 1, 2, 3 and 4. **(b)** SVR attained through either monotherapy of interferons or through different combinations of antiviral drugs with IFN or PEG-IFN.

Egypt and Central Asia whereas genotypes 5 and 6 are commonly found in South America and South East Asia respectively [87].

During the last century, there have been sudden outbreaks in the USA and Western Europe. A small number of subtypes including subtypes 1a, 1b, and 3a have been found prevalent, but genotype distribution has changed and diversified, which can be associated with intravenous drug use, blood transfusions and immigration to Europe and USA from endemic areas [88,89]. However efficacy of IFN therapy in different genotypes of HCV is found to be irregular. The reason behind this irregularity is a broad discussion but one of them is believed to be the outcome of sequence homology of envelope proteins of HCV genotype 1 with PKR (as discussed earlier) and this makes HCV capable of undermining the antiviral effects of IFN [90].

NS3/4A protein of HCV

The nonstructural proteins of HCV also possess a capacity of subverting the IFN activity. HCV NS3/4A serine protease prevents the phosphorylation of IRF3 and thus inhibits IFN induction [91], it also performs another duty with similar result by cleavage of the "Toll-IL-1 receptor domain- containing adaptor inducing IFN-β (TRIF)" protein that plays a key role in linkage of TLR3 to kinases responsible for the activation of IRF3 which has also been proved within an *in vivo* study that IRF3 is activated in the livers of patients infected with HCV (Figure 6) [92,93]. IFN induction is also interfered and down regulated through the disruption of RIG1 signaling by NS3/4A [94].

NS5A protein of HCV

The exact function of HCV NS5A is still unknown but it is possibly involved in the induction of proinflammatory chemokine interleukin-8 (IL-8), which leads to the fractional inhibition of the IFN antiviral response [61,95]. Studies have shown that the increase in levels of IL-8 in HCV patients under IFN treatment is directly related to the failure of IFN therapy [61,95]. Recently, a study has reported from Taiwan on HCV 1b patients concluded that SVR is inversely proportional to the hepatic IL-8 mRNA expression and ISDR mutations [49]. These types of studies suggest that HCV-induced changes in levels of proinflammatory cytokines and chemokines expression may play a role in anti-HCV therapy (IFN-therapy), endurance or pathogenesis [95]. Prediction of IL-8 mRNA expression is also possible through fibrosis scores and alanine aminotransferase levels (ALT), as both of these diagnostic tests informs us towards the progression of disease [49]. Most of the chronic liver diseases are accompanied with liver fibrosis, which is the excessive accumulation of extracellular matrix proteins and

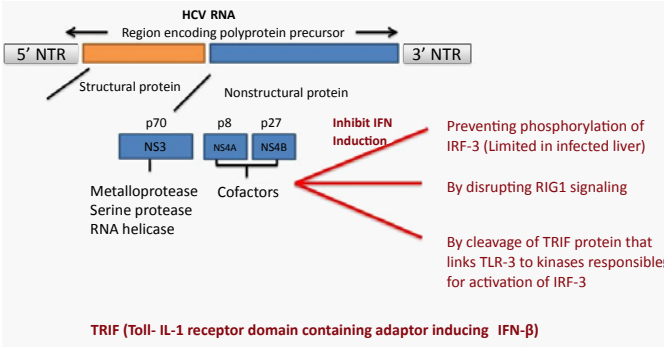

Figure 6: Inhibition of Interferon mediated immune response by HCV non-structural protein. The non-structural proteins of HCV play an active role in demoting the actions on interferon by performing different actions.

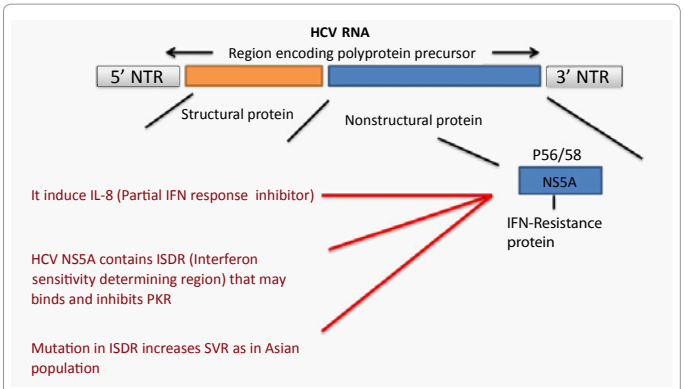

Figure 7: IFN resistance associated with HCV-NS5A protein: NS5A induces IL-8, which leads to the fractional inhibition of IFN antiviral response. NS5A also contains ISDR (interferon sensitivity determining region), which is believed to inhibit PKR through its dimerization domain. Sustained virological response (SVR) is an efficacy measure of HCV therapy and mutations in ISDR increases SVR in various genotypes of HCV.

it may lead to liver cirrhosis, in which blood flow and liver functions get disrupted and fibrosis scoring is done to predict the advancement in the disease [96]. Whereas ALT is mainly found in liver and its measure helps us inspecting the liver damage. Amount of enzymes in the blood can be measured in this test, which helps in identifying liver diseases and their causes [49].

Interferon sensitivity-determining region (ISDR) is present in NS5A that may bind and inhibit protein kinase R (PKR) [97,98], but this inhibition of PKR is different from that of HCV E2, which is through sequence homology [90]. The ISDR (amino acid 2209-2248) is located within NS5A portion of the genome of HCV and has been reported to play an important role in determining the efficacy of exogenous IFN therapy on replication of virus through inhibition of PKR (Figure 7) [64,97,98]. Studies have shown that when NS5A binds and inactivates PKR, dsRNA (produced during RNA virus genome replication) activates an IFN induced gene product [81]. Protein translation shuts down as PKR phosphorylates the translation initiation factor elf-2α [99]. In addition to ISDR, another 26 residues of C- terminal to ISDR are required by NS5A to interact with PKR and their binding results in inhibition of PKR autophosphorylation and phosphorylation of an exogenous substrate [81,99]. The binding site of PKR was identified as the dimerization domain [63]. Different studies have proven that mutation of more than one amino acid in the ISDR elevates the SVR percentages in patients; however conflicting data has also been reported in this association [62,100].

Conclusion

Interferon therapy is a major treatment option in HCV infections but with the passage of time HCV has evolved mechanisms to cope with IFN therapy. Since HCV is an RNA virus having higher rates of mutations, these mutations play a pivotal role in virus survival [48,49]. Over the years, these mutations have helped HCV to evade host immune responses leading towards the failures of antiviral therapies. As a result HCV continues to be a challenging target being the foremost cause of demise and cancers related with livers. This article emphasizes the possible role of HCV proteins contributing towards reduced efficacy of IFN therapy. HCV core protein can hamper IFN mediated therapy by substitution of its amino acids resulting in development of IFN resistance and failure of treatment [51,57]. PEG-IFN and ribavirin therapies have varying effects on various genotypes of HCV; many

quasi-species are also responsible for resistance to IFN therapy.

HCV also evades antiviral effects of IFN on account of homology between different host factors and viral proteins; NS5A protein has an important role in inhibition of IFN [62-64]. The ISDR region in HCV genome also contributes towards resistance against IFN therapy. These factors contribute to virus survival, and as a result, the host immune system fails to curb viral infection which may later damage the liver in case of HCV infection. HCV is a global threat effecting millions of people each year. Although IFN, PEG-IFN and other antiviral approaches have reduced the mortality rate, the HCV still remains a serious pathogen through its ability to persist by manipulating various host factors. Therefore, the need for modification of existing anti-HCV therapeutics as well as production of novel anti-HCV therapeutic agents is necessary to reduce the rate of HCV associated annual deaths.

Acknowledgements

We are thankful to Mr. Sanjay Rao [Senior lecturer, National University of Science and Technology (NUST), Islamabad, Pakistan] and Dr. Muhammad Ashraf [Principal, Atta-ur-Rahman School of Applied Biosciences (ASAB), National University of Science and Technology (NUST), Islamabad, Pakistan] for their assistance in writing the article.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, et al. (1989) Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 244: 359-362.
2. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, et al. (1989) An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 244: 362-364.
3. ISAACS A, LINDENMANN J (1957) Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 147: 258-267.
4. Billiau A (2006) Interferon: the pathways of discovery I. Molecular and cellular aspects. Cytokine Growth Factor Rev 17: 381-409.
5. Friesel R, Komoriya A, Maciag T (1987) Inhibition of endothelial cell proliferation by gamma-interferon. J Cell Biol 104: 689-696.
6. Asao H, Fu XY (2000) Interferon-gamma has dual potentials in inhibiting or promoting cell proliferation. J Biol Chem 275: 867-874.
7. Zanon RG, Cartarozzi LP, Victorio SC, Moraes JC, Morari J, et al. (2010) Interferon (IFN) beta treatment induces major histocompatibility complex (MHC) class I expression in the spinal cord and enhances axonal growth and motor function recovery following sciatic nerve crush in mice. Neuropathol Appl Neurobiol 36: 515-534.
8. Yang Y, Xiang Z, Ertl HC, Wilson JM (1995) Upregulation of class I major histocompatibility complex antigens by interferon gamma is necessary for T-cell-mediated elimination of recombinant adenovirus-infected hepatocytes in vivo. Proc Natl Acad Sci U S A 92: 7257-7261.
9. Marshak-Rothstein A (2006) Toll-like receptors in systemic autoimmune disease. Nat Rev Immunol 6: 823-835.
10. Li M, Liu X, Zhou Y, Su SB (2009) Interferon-lambdas: the modulators of antivirus, antitumor, and immune responses. J Leukoc Biol 86: 23-32.
11. Korthals M, Safaian N, Kronenwett R, Maihöfer D, Schott M, et al. (2007) Monocyte derived dendritic cells generated by IFN-alpha acquire mature dendritic and natural killer cell properties as shown by gene expression analysis. J Transl Med 5: 46.
12. Hall AO, Beiting DP, Tato C, John B, Oldenhove G, et al. (2012) The cytokines interleukin 27 and interferon-γ promote distinct Treg cell populations required to limit infection-induced pathology. Immunity 37: 511-523.
13. Goodbourn S, Didcock L, Randall RE (2000) Interferons: cell signalling, immune modulation, antiviral response and virus countermeasures. J Gen Virol 81: 2341-2364.
14. Cowan J, Pandey S, Filion LG, Angel JB, Kumar A, et al. (2012) Comparison of interferon-γ-, interleukin (IL)-17- and IL-22-expressing CD4 T cells, IL-22-expressing granulocytes and proinflammatory cytokines during latent and active tuberculosis infection. Clin Exp Immunol 167: 317-329.
15. Ank N, Iversen MB, Bartholdy C, Staeheli P, Hartmann R, et al. (2008) An important role for type III interferon (IFN-lambda/IL-28) in TLR-induced antiviral activity. J Immunol 180: 2474-2485.
16. Spann KM, Tran KC, Chi B, Rabin RL, Collins PL (2004) Suppression of the induction of alpha, beta, and lambda interferons by the NS1 and NS2 proteins of human respiratory syncytial virus in human epithelial cells and macrophages [corrected]. J Virol 78: 4363-4369.
17. Fabricius D, Neubauer M, Mandel B, Schütz C, Viardot A, et al. (2010) Prostaglandin E2 inhibits IFN-alpha secretion and Th1 costimulation by human plasmacytoid dendritic cells via E-prostanoid 2 and E-prostanoid 4 receptor engagement. J Immunol 184: 677-684.
18. Qi Z, Nie P, Secombes CJ, Zou J (2010) Intron-containing type I and type III IFN coexist in amphibians: refuting the concept that a retroposition event gave rise to type I IFNs. J Immunol 184: 5038-5046.
19. Rajoriya NEB (2010) Factors determining effectiveness of interferons in managing hepatitis C: new targets and new approaches. Int J Infereron Cytokine Mediator Res 2: 85-95.
20. Dumoutier L, Tounsi A, Michiels T, Sommereyns C, Kotenko SV, et al. (2004) Role of the interleukin (IL)-28 receptor tyrosine residues for antiviral and antiproliferative activity of IL-29/interferon-lambda 1: similarities with type I interferon signaling. J Biol Chem 279: 32269-32274.
21. Zitzmann K, Brand S, Baehs S, Göke B, Meinecke J, et al. (2006) Novel interferon-lambdas induce antiproliferative effects in neuroendocrine tumor cells. Biochem Biophys Res Commun 344: 1334-1341.
22. Pestka S, Krause CD, Walter MR (2004) Interferons, interferon-like cytokines, and their receptors. Immunol Rev 202: 8-32.
23. Hardy MP, Owczarek CM, Jermiin LS, Ejdebäck M, Hertzog PJ (2004) Characterization of the type I interferon locus and identification of novel genes. Genomics 84: 331-345.
24. Borden EC, Sen GC, Uze G, Silverman RH, Ransohoff RM, et al. (2007) Interferons at age 50: past, current and future impact on biomedicine. Nat Rev Drug Discov 6: 975-990.
25. Leaman DW, Roberts RM (1992) Genes for the trophoblast interferons in sheep, goat, and musk ox and distribution of related genes among mammals. J Interferon Res 12: 1-11.
26. Lefèvre F, Boulay V (1993) A novel and atypical type one interferon gene expressed by trophoblast during early pregnancy. J Biol Chem 268: 19760-19768.
27. Oritani K, Tomiyama Y (2004) Interferon-zeta/limitin: novel type I interferon that displays a narrow range of biological activity. Int J Hematol 80: 325-331.
28. Oritani K, Kanakura Y (2005) IFN-zeta/ limitin: a member of type I IFN with mild lympho-myelosuppression. J Cell Mol Med 9: 244-254.
29. Schoenborn JR, Wilson CB (2007) Regulation of interferon-gamma during innate and adaptive immune responses. Adv Immunol 96: 41-101.
30. Kotenko SV, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, et al. (2003) IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat Immunol 4: 69-77.
31. Uzé G, Monneron D (2007) IL-28 and IL-29: newcomers to the interferon family. Biochimie 89: 729-734.
32. Akira S, Uematsu S, Takeuchi O (2006) Pathogen recognition and innate immunity. Cell 124: 783-801.
33. Saito T, Gale M Jr (2008) Differential recognition of double-stranded RNA by RIG-I-like receptors in antiviral immunity. J Exp Med 205: 1523-1527.
34. Onomoto K, Jogi M, Yoo JS, Narita R, Morimoto S, et al. (2012) Critical role of an antiviral stress granule containing RIG-I and PKR in viral detection and innate immunity. PLoS One 7: e43031.
35. Levy DE, Marié I, Prakash A (2003) Ringing the interferon alarm: differential regulation of gene expression at the interface between innate and adaptive immunity. Curr Opin Immunol 15: 52-58.
36. Falvo JV, Parekh BS, Lin CH, Fraenkel E, Maniatis T (2000) Assembly of a functional beta interferon enhanceosome is dependent on ATF-2-c-jun heterodimer orientation. Mol Cell Biol 20: 4814-4825.
37. Wang J, Basagoudanavar SH, Wang X, Hopewell E, Albrecht R, et al. (2010)

NF-kappa B RelA subunit is crucial for early IFN-beta expression and resistance to RNA virus replication. J Immunol 185: 1720-1729.

38. Chen LF, Greene WC (2004) Shaping the nuclear action of NF-kappaB. Nat Rev Mol Cell Biol 5: 392-401.

39. Beinke S, Ley SC (2004) Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. Biochem J 382: 393-409.

40. Natoli G, Saccani S, Bosisio D, Marazzi I (2005) Interactions of NF-kappaB with chromatin: the art of being at the right place at the right time. Nat Immunol 6: 439-445.

41. Pietilä TE, Veckman V, Lehtonen A, Lin R, Hiscott J, et al. (2007) Multiple NF-kappaB and IFN regulatory factor family transcription factors regulate CCL19 gene expression in human monocyte-derived dendritic cells. J Immunol 178: 253-261.

42. Franzoso G, Bours V, Park S, Tomita-Yamaguchi M, Kelly K, et al. (1992) The candidate oncoprotein Bcl-3 is an antagonist of p50/NF-kappa B-mediated inhibition. Nature 359: 339-342.

43. Bours V, Franzoso G, Azarenko V, Park S, Kanno T, et al. (1993) The oncoprotein Bcl-3 directly transactivates through kappa B motifs via association with DNA-binding p50B homodimers. Cell 72: 729-739.

44. Haller O, Kochs G (2002) Interferon-induced mx proteins: dynamin-like GTPases with antiviral activity. Traffic 3: 710-717.

45. Keller MA, Stiehm ER (2000) Passive immunity in prevention and treatment of infectious diseases. Clin Microbiol Rev 13: 602-614.

46. Hayashi J, Kishihara Y, Ueno K, Yamaji K, Kawakami Y, et al. (1998) Age-related response to interferon alfa treatment in women vs men with chronic hepatitis C virus infection. Arch Intern Med 158: 177-181.

47. Kimball P, Elswick RK, Shiffman M (2001) Ethnicity and cytokine production gauge response of patients with hepatitis C to interferon-alpha therapy. J Med Virol 65: 510-516.

48. Slavenburg S, Heijdra YF, Drenth JP (2010) Pneumonitis as a consequence of (peg) interferon-ribavirin combination therapy for hepatitis C: a review of the literature. Dig Dis Sci 55: 579-585.

49. Lee CM, Yen YH, Hung CH, Lu SN, Wang JH, et al. (2011) Liver interleukin-8 messenger RNA expression and interferon sensitivity-determining region mutations relate to treatment response in hepatitis C 1b. Antivir Ther 16: 825-832.

50. Fabrizi F, Dixit V, Martin P (2006) Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis. Aliment Pharmacol Ther 24: 781-788.

51. Mangia A, Thompson AJ, Santoro R, Piazzolla V, Tillmann HL, et al. (2010) An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. Gastroenterology 139: 821-827, 827 e821.

52. Mochida S, Ohnishi K, Matsuo S, Kakihara K, Fujiwara K (1996) Effect of alcohol intake on the efficacy of interferon therapy in patients with chronic hepatitis C as evaluated by multivariate logistic regression analysis. Alcohol Clin Exp Res 20: 371A-377A.

53. Ryan P, Resino S, Miralles P, Cosín J, López JC, et al. (2010) Insulin resistance impairs response to interferon plus ribavirin in patients coinfected with HIV and hepatitis C virus. J Acquir Immune Defic Syndr 55: 176-181.

54. Villa E, Karampatou A, Cammà C, Di Leo A, Luongo M, et al. (2011) Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. Gastroenterology 140: 818-829.

55. Lam NP, Pitrak D, Speralakis R, Lau AH, Wiley TE, et al. (1997) Effect of obesity on pharmacokinetics and biologic effect of interferon-alpha in hepatitis C. Dig Dis Sci 42: 178-185.

56. Takaki S, Tsubota A, Hosaka T, Akuta N, Someya T, et al. (2004) Factors contributing to ribavirin dose reduction due to anemia during interferon alfa2b and ribavirin combination therapy for chronic hepatitis C. J Gastroenterol 39: 668-673.

57. Akuta N, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, et al. (2006) Predictive factors of virological non-response to interferon-ribavirin combination therapy for patients infected with hepatitis C virus of genotype 1b and high viral load. J Med Virol 78: 83-90.

58. Zein NN, Rakela J, Krawitt EL, Reddy KR, Tominaga T, et al. (1996) Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity, and response to interferon therapy. Collaborative Study Group. Ann Intern Med 125: 634-639.

59. Lau JY, Davis GL, Prescott LE, Maertens G, Lindsay KL, et al. (1996) Distribution of hepatitis C virus genotypes determined by line probe assay in patients with chronic hepatitis C seen at tertiary referral centers in the United States. Hepatitis Interventional Therapy Group. Ann Intern Med 124: 868-876.

60. Martinot-Peignoux M, Marcellin P, Pouteau M, Castelnau C, Boyer N, et al. (1995) Pretreatment serum hepatitis C virus RNA levels and hepatitis C virus genotype are the main and independent prognostic factors of sustained response to interferon alfa therapy in chronic hepatitis C. Hepatology 22: 1050-1056.

61. Polyak SJ, Khabar KS, Paschal DM, Ezelle HJ, Duverlie G, et al. (2001) Hepatitis C virus nonstructural 5A protein induces interleukin-8, leading to partial inhibition of the interferon-induced antiviral response. J Virol 75: 6095-6106.

62. Paterson M, Laxton CD, Thomas HC, Ackrill AM, Foster GR (1999) Hepatitis C virus NS5A protein inhibits interferon antiviral activity, but the effects do not correlate with clinical response. Gastroenterology 117: 1187-1197.

63. Macdonald A, Harris M (2004) Hepatitis C virus NS5A: tales of a promiscuous protein. J Gen Virol 85: 2485-2502.

64. Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, et al. (1996) Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 334: 77-81.

65. Zheng YH, He Y, Yang X, Gong GZ, Zhou HY, et al. (2005) [Interferon-alpha and ribavirin combination therapy for co-infection of hepatitis C virus and human immunodeficiency virus]. Zhonghua Gan Zang Bing Za Zhi 13: 741-744.

66. Tossing G (2002) Interferon-alpha in treatment of chronic hepatitis C in co-infected HIV-patients in combination with ribavirin and as a pre-load therapy in treatment-naive HIV-positive patients. 8th European Conference on Clinical Aspects and Treatment of HIV Infection (8th ECCATH), 29-31 October, Athens Greece. Eur J Med Res 7: 44-46.

67. Simmonds P, Alberti A, Alter HJ, Bonino F, Bradley DW, et al. (1994) A proposed system for the nomenclature of hepatitis C viral genotypes. Hepatology 19: 1321-1324.

68. Richard A, Helms DJQ (2006) Textbook of Therapeutics: Drug and Disease Management. (8edn) Lippincott Williams & Wilkins, Philadelphia, USA.

69. Pearlman BL, Traub N (2011) Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis 52: 889-900.

70. Hayes CN, Kobayashi M, Akuta N, Suzuki F, Kumada H, et al. (2011) HCV substitutions and IL28B polymorphisms on outcome of peg-interferon plus ribavirin combination therapy. Gut 60: 261-267.

71. Akuta N, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, et al. (2010) Amino acid substitutions in the hepatitis C virus core region of genotype 1b affect very early viral dynamics during treatment with telaprevir, peginterferon, and ribavirin. J Med Virol 82: 575-582.

72. Bode JG, Ludwig S, Ehrhardt C, Albrecht U, Erhardt A, et al. (2003) IFN-alpha antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3. FASEB J 17: 488-490.

73. Kovarik A, Fojtova M, Boudny V, Adamkova L, Lauerova L, et al. (2005) Interferon-gamma, but not interferon-alpha, induces SOCS 3 expression in human melanoma cell lines. Melanoma Res 15: 481-488.

74. Yamamoto K, Yamaguchi M, Miyasaka N, Miura O (2003) SOCS-3 inhibits IL-12-induced STAT4 activation by binding through its SH2 domain to the STAT4 docking site in the IL-12 receptor beta2 subunit. Biochem Biophys Res Commun 310: 1188-1193.

75. Croker BA, Krebs DL, Zhang JG, Wormald S, Willson TA, et al. (2003) SOCS3 negatively regulates IL-6 signaling in vivo. Nat Immunol 4: 540-545.

76. Dong Q, Fan R, Zhao S, Wang Y (2009) Over-expression of SOCS-3 gene promotes IL-10 production by JEG-3 trophoblast cells. Placenta 30: 11-14.

77. Haan S, Wüller S, Kaczor J, Rolvering C, Nöcker T, et al. (2009) SOCS-mediated downregulation of mutant Jak2 (V617F, T875N and K539L) counteracts cytokine-independent signaling. Oncogene 28: 3069-3080.

78. de Lucas S, Bartolome J, Carreno V (2005) Hepatitis C virus core protein down-

regulates transcription of interferon-induced antiviral genes. J Infect Dis 191: 93-99.

79. Pavio N, Romano PR, Graczyk TM, Feinstone SM, Taylor DR (2003) Protein synthesis and endoplasmic reticulum stress can be modulated by the hepatitis C virus envelope protein E2 through the eukaryotic initiation factor 2alpha kinase PERK. J Virol 77:3578-3585.

80. Heim MH, Moradpour D, Blum HE (1999) Expression of hepatitis C virus proteins inhibits signal transduction through the Jak-STAT pathway. J Virol 73: 8469-8475.

81. Gale MJ Jr, Korth MJ, Tang NM, Tan SL, Hopkins DA, et al. (1997) Evidence that hepatitis C virus resistance to interferon is mediated through repression of the PKR protein kinase by the nonstructural 5A protein. Virology 230: 217-227.

82. Abid K, Quadri R, Negro F (2000) Hepatitis C virus, the E2 envelope protein, and alpha-interferon resistance. Science 287: 1555.

83. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, et al. (2000) Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 343: 1666-1672.

84. Farci P, Strazzera R, Alter HJ, Farci S, Degioannis D, et al. (2002) Early changes in hepatitis C viral quasispecies during interferon therapy predict the therapeutic outcome. Proc Natl Acad Sci U S A 99: 3081-3086.

85. Nyanguile O, Devogelaere B, Vijgen L, Van den Broeck W, Pauwels F, et al. (2010) 1a/1b subtype profiling of nonnucleoside polymerase inhibitors of hepatitis C virus. J Virol 84: 2923-2934.

86. Ali A, Ahmed H, Idrees M (2010) Molecular epidemiology of Hepatitis C virus genotypes in Khyber Pakhtoonkhaw of Pakistan. Virol J 7: 203.

87. Pybus OG, Barnes E, Taggart R, Lemey P, Markov PV, et al. (2009) Genetic history of hepatitis C virus in East Asia. J Virol 83: 1071-1082.

88. Esteban JI, Sauleda S, Quer J (2008) The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol 48: 148-162.

89. Demetriou VL, van de Vijver DA, Hezka J, Kostrikis LG; Cyprus IVDU Network, Kostrikis LG (2010) Hepatitis C infection among intravenous drug users attending therapy programs in Cyprus. J Med Virol 82: 263-270.

90. Taylor DR, Shi ST, Romano PR, Barber GN, Lai MM (1999) Inhibition of the interferon-inducible protein kinase PKR by HCV E2 protein. Science 285: 107-110.

91. Foy E, Li K, Wang C, Sumpter R Jr, Ikeda M, et al. (2003) Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science 300: 1145-1148.

92. Li K, Foy E, Ferreon JC, Nakamura M, Ferreon AC, et al. (2005) Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. Proc Natl Acad Sci U S A 102: 2992-2997.

93. Lau DT, Fish PM, Sinha M, Owen DM, Lemon SM, et al. (2008) Interferon regulatory factor-3 activation, hepatic interferon-stimulated gene expression, and immune cell infiltration in hepatitis C virus patients. Hepatology 47: 799-809.

94. Meylan E, Curran J, Hofmann K, Moradpour D, Binder M, et al. (2005) Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature 437: 1167-1172.

95. Polyak SJ, Khabar KS, Rezeiq M, Gretch DR (2001) Elevated levels of interleukin-8 in serum are associated with hepatitis C virus infection and resistance to interferon therapy. J Virol 75: 6209-6211.

96. Bataller R, Brenner DA (2005) Liver fibrosis. J Clin Invest 115: 209-218.

97. Gale M Jr, Blakely CM, Kwieciszewski B, Tan SL, Dossett M, et al. (1998) Control of PKR protein kinase by hepatitis C virus nonstructural 5A protein: molecular mechanisms of kinase regulation. Mol Cell Biol 18: 5208-5218.

98. Gale MJ Jr, Korth MJ, Katze MG (1998) Repression of the PKR protein kinase by the hepatitis C virus NS5A protein: a potential mechanism of interferon resistance. Clin Diagn Virol 10: 157-162.

99. Williams BR (2001) Signal integration via PKR. Sci STKE 2001: 2.

100. Witherell GW, Beineke P (2001) Statistical analysis of combined substitutions in nonstructural 5A region of hepatitis C virus and interferon response. J Med Virol 63: 8-16.

Citation: Akhtar H, Akhtar S, Raheel U, Faheem M, Arshad M, et al. (2013) Interferons as Immune Regulators: A Rivalry between HCV and Interferons. J Clin Cell Immunol 4: 136. doi:10.4172/2155-9899.1000136