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Review

Understanding the molecular mechanism(s) of hepatitis C virus (HCV) induced interferon resistance

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ABSTRACT

Hepatitis C virus (HCV) is one of the foremost causes of chronic liver disease affecting over 300 million globally. HCV contains a positive-stranded RNA of ~9600 nt and is surrounded by the 5′ and 3′untranslated regions (UTR). The only successful treatment regimen includes interferon (IFN) and ribavirin. Like many other viruses, HCV has also evolved various mechanisms to circumvent the IFN response by blocking (1) downstream signaling actions via STAT1, STAT2, IRF9 and JAK-STAT pathways and (2) repertoire of IFN Stimulatory Genes (ISGs). Several studies have identified complex host demographic and genetic factors as well as viral genetic heterogeneity associated with outcomes of IFN therapy. The genetic predispositions of over 2000 ISGS may render the patients to become resistant, thus identification of such parameters within a subset of population are necessary for management corollary. The ability of various HCV genotypes to diminish IFN antiviral responses plays critical role in the establishment of chronic infection at the acute stage of infection, thus highlighting importance of the resistance in HCV treated groups. The recently defined role of viral protein such as C, E2, NS3/NS4 and NS5A proteins in inducing the IFN resistance are discussed in this article. How the viral and host genetic composition and epistatic connectivity among polymorphic genomic sites synchronizes the evolutionary IFN resistance trend remains under investigation. However, these signals may have the potential to be employed for accurate prediction of therapeutic outcomes. In this review article, we accentuate the significance of host and viral components in IFN resistance with the aim to determine the successful outcome in patients.

Contents

Abbreviations: HCV, hepatitis C virus; UTR, untranslated regions; IFN, interferon; ISG, interferon stimulatory genes; IRES, internal ribosome entry site; IFNAR, IFN-α receptor; STAT, signal transducer and activator of transcription; TLR3, toll like receptor 3; DsRNA, double stranded RNA viruses; IRF3, interferon regulatory factor 3; NF-κb, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; REST, repressor element-1 silencing transcription factor; RE-1, repressor element-1; ISRE, IFN-stimulated response elements; GAS, gamma interferon activation site; GT, genotype; SOCS, suppressor of cytokine signaling; Th, T-helper; CD, cluster of differentiation; SVR, sustained virological response; PI, protease inhibitor; BOC, boceprevir; TVR, telaprevir; IR, insulin resistance; ISDR, interferon sensitivity determining region; IRRDR, interferon and ribavirin resistance determining region; PKR, protein kinase R; eIF2α, eukaryotic initiation factor 2α; PePHD, phosphorylation homology domain; ER, endoplasmic reticulum; UPR, unfolded protein response; SNP, single nucleotide polymorphisms.

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1. Introduction

Chronic Liver Disease (CLD) is a foremost clinical burden and hepatitis C virus (HCV) is one of the major causes of liver diseases. HCV infection with the disease severity varies from asymptomatic chronic infection to life threatening cirrhosis and hepatocellular carcinoma (Saito et al., 1990). *HCV* is a *single*-stranded *RNA virus* that encodes a distinct polypeptide through internal ribosome entry site (IRES)-mediated translation. Translation product is processed by a combination of cellular and viral proteases to settle into at least 10 components; structural proteins (Core, E1, E2, and p7) and nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) (Bartenschlager and Lohmann, 2000; Kato, 2000; Moradpour et al., 2007; Penin et al., 2004). Using a variety of methods, six genotypes of HCV and various subtypes has been identified (Simmonds et al., 2005). Treatment options are limited and resistance associated with treatment is a major problem and in most of the cases the end stage liver disease often requires liver transplantation. Therefore, the existing treatment option with maximum outcome results is urgently required to alleviate the suffering of millions of individuals with chronic hepatitis C.

Interferon alpha (IFN-α) or Interferon gamma (IFN-γ) in combination with other antiviral drugs are routinely used to treat HCV infection (Cooksley, 2004). More than 50 years ago, IFNs were identified and are classified into three major types IFN-I, II and III which bind to specific IFN receptors. Type I bind to a cell surface receptor complex called IFN-α receptor (IFNAR) comprising of IFNAR1 and IFNAR2 chains. Type I is present in humans as IFN-α, IFN-β and IFN-ω. Type II IFN (IFN-γ) interacts to IFNGR that consists of IFNGR1 and IFNGR2 chains. Type III IFN bind to a receptor complex consisting of IL10R2 (CRF2-4) and IFNLR1 (CRF2-12) (De Weerd et al., 2007; Liu, 2005). While all three classes of IFN bind to specific receptors they mediate their actions through common denominator such as STAT1/2. The widespread use of IFNs in viral infected individuals have led to serious resistance problems and understanding these resistance mechanisms is imperative to develop an alternative therapeutic strategy to clear the infection.

2. Induction and activation of interferon

The initiation of IFNs production occurs in response to infection which then activates signal transducer and activator of transcription (STAT) complexes for initiation of the classical Janus kinase-STAT (JAK-STAT) signaling pathway (Platanias, 2005). Furthermore, Toll Like Receptor 3 (TLR3) is an important feature for IFNs induction in response to the occurrence of double-stranded RNA viruses (dsRNA) (Dunlevy et al., 2010). The TLR3 will then activate interferon regulatory factor 3 (IRF3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which bind to response elements IFN type I and III promoters (Heim, 2012). A complex array of cytokines, such as interleukins (IL-1, IL-2, IL-12), TNF are also shown to augment interferon production (Haller et al., 2007).

The binding of IFNs to its receptor induces a cascade of signaling event resulting in the activation of STAT1 and STAT2 which together with IRF-9 form the particular ISGF3 complexes. It is well established that a putative ISRE sequence in the STAT1 promoter is inducible by type I IFN and binds the IFN-α/β-induced complex, ISGF3. Several studies have described distinct promoter, enhancer and repressor regions in the regulatory fragment of hSTAT1 gene extending in the second intron. Intracellular amplification of STAT1 expression is shown to be dispensable for increasing cell responsiveness to the IFNs. How HCVmay repress transcription from the STAT1 gene regulatory region remains to be investigated. Upon activation, the newly formed ISGF3 complexes then translocate to the nucleus where they bind to IFN-stimulated response elements (ISRE) in various IFN stimulated genes (ISGs) such as IRF7, MX1, and OAS1 (Donnelly and Kotenko, 2010) and failure to do so lead into resistance. The response to IFN may depend on various STAT homodimers and/or heterodimers during IFN signaling and these STAT dimers launch transcription by binding to Gamma Interferon Activation Site (GAS) elements in gene promoters. Type I IFN can induce gene activation with both ISRE or GAS elements, while type II IFN dependent activation only recruits GAS element (Platanias, 2005). The interplay of viral proteins with such regulatory elements has not been characterized.

3. HCV genotypes (GT) and the development of IFN resistance

HCV is classified into six genotypes (GT-1 to GT-6) and each GT behaves differently during IFN treatment (Table 1), however, the molecular basis of differential responses to treatment in HCV genotypes is not fully understood. HCV genotypes diverge in their nucleotide sequence by ∼30–35%, and furthermore each genotype has a class of different subtypes that differ in their nucleotide sequence by ∼20–25% (Simmonds, 2004). The heterogeneous populations of HCV genomes that coincide in an infected individual due to replication errors are termed as quasispecies (Heim, 2012), thus making it difficult in the predicament of IFN resistance. Therefore viral genetic diversity and its association with induction of chronic liver diseases and treatment response determination still remains to be completely understood.

Several lines of evidence support the notion that IFN resistance plays a role in the establishment of chronic infection at the acute stage of infection (Meier and Ramadori, 2009). In recent years, the mechanisms of viral RNA recognition and RNA virus-triggered sig-

Table 1
Representative percentage of HCV genotypes associated IFN non responders.

HCV genotype	% IFN non-responders
1	61
2	10
3	20–30
4	40

Jamal et al. (2008); NIH consensus statement (2002); Sharieff et al. (2002).