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Review

Hepatitis C virus-related resistance mechanisms to interferon α-based antiviral therapy

Wolf Peter Hofmann, Stefan Zeuzem, Christoph Sarrazin*

Universitätsklinikum des Saarlandes, Klinik für Innere Medizin II, Homburg/Saar, Germany

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Abstract

Only 50–60% of the patients chronically infected with the hepatitis C virus (HCV) achieve a sustained virologic response to the current standard antiviral therapy consisting of pegylated interferon α in combination with ribavirin. The definite reasons for virologic response or non-response to interferon α-based therapy are unknown. Besides host and treatment efficacy factors, it is presumable that HCV is able to antagonize the antiviral activity of interferon α. So far, among the different HCV proteins, the envelope (E)2 protein, the non-structural (NS)3/4A protein, and the NS5A protein have been associated with interferon α resistance mechanisms in vitro. The clinical significance of amino acid mutations within these HCV proteins in HCV isolates from patients who did or did not respond to interferon α-based therapy was investigated in multiple studies. Within the E2 (HVR2, CD81 binding sites, PePHD) and the NS3/4A proteins no specific mutations in correlation with virologic response to interferon α-based therapy were observed. For the NS5A protein, mutations within the interferon sensitivity determining region (ISDR) and the complete NS5A protein may be of importance for response to interferon α-based treatment in patients infected with HCV subtype 1a/b.

Keywords: E2; Hepatitis C; Interferon-α; ISDR; Mutations; NS3A; NS4A; NS5A; Resistance mechanisms

Contents

1. Introduction

Although substantial improvements have been made for the treatment of patients with chronic hepatitis C virus (HCV) infection, the current standard antiviral therapy consisting of (pegylated) interferon α in combination with the nucleoside analogue ribavirin leads to sustained virologic response rates in only 38–63% of the patients (McHutchison et al., 1998; Manns et al., 2001; Fried et al., 2002; Poynard et al., 1998; Hadziyannis et al., 2004). Multiple studies focusing on host and viral factors associated with different treatment outcomes were published. HCV is a single positive stranded RNA virus

* Corresponding author. Tel.: +49 6841 16 23233; fax: +49 6841 23583.
E-mail address: Christoph.Sarrazin@uniklinik-saarland.de (C. Sarrazin).

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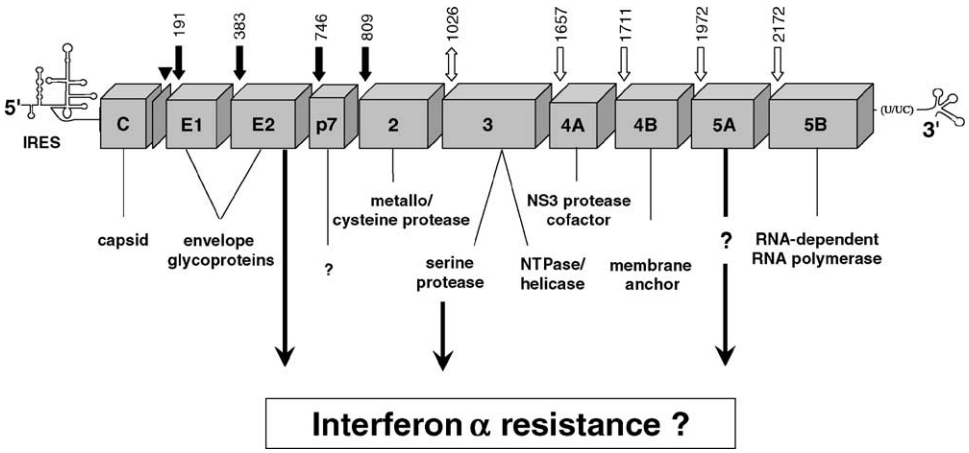

Fig. 1. HCV genome organization. The envelope (E)2 protein, the non-structural (NS)5A protein, and the NS3/4A serine protease were suggested to contribute to resistance mechanisms to interferon α-based therapy. IRES, internal ribosome entry site. Black arrows indicate sites cleaved by host proteases. White arrows indicate the cleavage sites of viral encoded proteases. Numbering according to HCV 1b prototype HCV-J (Kato et al., 1990).

belonging to the family of *flaviviridae*. Due to the lack of a proof-reading activity of the HCV RNA-dependent RNA polymerase, different HCV genotypes have evolved. The different genotypes share amino acid sequence homology of ~70% (Simmonds et al., 1993). Remarkably, the response to antiviral therapy highly depends on the HCV genotype. Patients infected with the HCV genotype 1 show response rates of 38–52%, whereas patients infected with genotypes 2 or 3, achieve a sustained virologic response in up to 90% (McHutchison et al., 1998; Fried et al., 2002; Manns et al., 2001; Poynard et al., 1998; Hadziyannis et al., 2004; Zeuzem et al., 2004). Therefore, it is presumable that the difference of virologic response between the different HCV genotypes beside potential host and treatment efficiency factors are mainly determined by the HCV genome.

2. HCV E2, NS3/4A, and NS5A proteins antagonize interferon α action in vitro

So far, among the different HCV proteins, the envelope (E)2 protein, the non-structural (NS)3/4A serine protease, and the NS5A protein have been suggested to antagonize the antiviral effect of interferon α (Gale et al., 1997; Taylor et al., 1999; Foy et al., 2003) (Fig. 1). Both the E2 and the NS5A proteins were reported to inhibit the interferon α-inducible, double-stranded RNA-dependent protein kinase (PKR) in vitro.

Within the carboxyterminal part of the E2 protein, a 12 amino acid sequence analogous to the phosphorylation site of the PKR and the eukaryotic translation initiation factor (eIF)2α, termed the PKR/eIF2α phosphorylation homology domain (PePHD) was described in HCV 1a/b isolates (Fig. 2). Binding of HCV subtype 1a/b derived PePHD to the PKR abolished its kinase activity and blocked its inhibitory effect on protein synthesis in vitro, while these effects were not detectable for PePHD sequences based on HCV genotype 2 and 3 isolates, respectively. It was hypothesized, that the interaction of the PePHD with the PKR may result in a relatively enhanced resistance of HCV-1 isolates to interferon α-based antiviral therapy (Taylor et al., 1999, 2001).

Within the carboxyterminal part of the NS5A protein, a PKR binding domain covering a 66 amino acid sequence was identified in HCV genotype 1 isolates (Fig. 3). Binding of the NS5A protein to the PKR resulted in inhibition of protein synthesis in vitro. Moreover, this inhibitory action was reversible after insertion of mutations in the PKR binding domain of the NS5A protein (Gale et al., 1998).

Recently, it was shown that the HCV NS3/4A protein blocks the phosphorylation and nuclear translocation of the interferon regulatory factor 3 (IRF-3) resulting in a significant reduction of the transcription of interferon α-inducible genes (Foy et al., 2003).

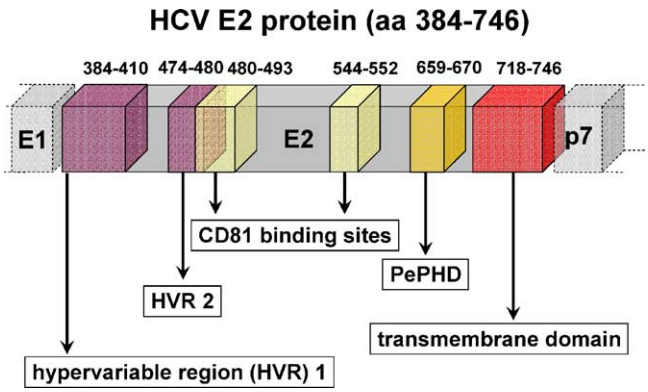

Fig. 2. E2 protein (aa 384–746) with potential functional regions. PePHD, PKR/eIF2α phosphorylation homology domain. Numbering according to HCV 1b prototype HCV-J (Kato et al., 1990).