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Review Article

Interferon signaling in the liver during hepatitis C virus infection

Zuzanna Makowska [a], Markus H. Heim [a,b,*]

[a] Department of Biomedicine, Hepatology Laboratory, University of Basel, Basel, Switzerland
[b] Division of Gastroenterology and Hepatology, University Hospital Basel, Basel, Switzerland

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ABSTRACT

Hepatitis C virus is a global health concern, estimated to infect 2–3% of the world's population. Inter-individual differences in the course of infection and response to therapy, highlighted by recent genomewide association studies, point to the crucial role of the host immune system in the efficient control of infection. Ongoing progress in the studies of the role of innate immunity during hepatitis C virus infection has improved our understanding of the intricacies of the host-virus interactions. In this review, we summarize and discuss the current knowledge concerning interferon signaling in the liver during acute and chronic hepatitis C virus infection and its implications for the outcome of interferon-α-based antiviral therapies.

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1. Hepatitis C

1.1. Hepatits C virus

Hepatitis C virus (HCV) infection is a considerable health burden worldwide, affecting an estimated 170 million individuals [1]. HCV infects only humans and chimpanzees. The main target of HCV are hepatocytes. However it has been reported that the virus can also infect immune cells. [2]. HCV is a positive-strand RNA virus whose life cycle is completed in the cytoplasm of the host cell. The uptake of the viral particles depends on the expression of four obligatory entry factors: CD81, claudin, occludin and scavenger receptor BI [3–6]. Upon virus entry and uncoating, the internal ribosome entry site (IRES)-dependent translation of HCV proteins is initiated on the template of the viral genome. The HCV genome encompasses 9.6 kb and encodes a single open reading frame. Translation of the viral polyprotein followed by a series of cleavage events yields three structural and seven non-structural HCV proteins [7]. HCV non-structural proteins assemble into replication complexes on the membranes of the endoplasmic reticulum, inducing formation of specific structures known as the membranous web [8,9]. Newly synthesized viral RNA translocates to the surface of the lipid droplets, where the virion assembly is thought to occur [10–14]. The viral particles leave the cell in a complex with lipids making use of the very-low-density lipoprotein secretion pathway [15–17].

1.2. Natural history of hepatitis C

HCV infection is transmitted by exposure to contaminated blood. HCV viremia can be first observed 1–2 weeks after transmission (Fig. 1A) [18]. Adaptive immune response to the infection is activated only later, and elevations of serum ALT levels are observed 2–8 weeks after the onset of infection, usually accompanied by a decrease in viral load [18,19]. Viral clearance occurs in approximately 30% of infected individuals [18,20,21]. In the remaining 70% of the infected population the immune system fails to clear the virus and a chronic persistent infection is established. In the chronic phase of HCV infection spontaneous clearance is a rare event [22]. Chronic HCV infection, when untreated, persists and in the course of time may lead to liver pathology including fibrosis, cirrhosis and hepatocellular carcinoma (Fig. 1A) [23,24]. It is estimated that over the course of 20–40 years 20–30% of the patients with chronic hepatitis C progress to liver cirrhosis [25]. Among patients with cirrhosis and active hepatitis C 2–5% a year develop hepatocellular carcinoma. End-stage liver cirrhosis associated to chronic HCV infection is a leading cause of liver transplantation in developed countries.

1.3. Therapy

The current standard of care for chronic hepatitis C consists of weekly injections of pegylated interferon (peg-IFN)-α2 combined

Abbreviations: HCV, hepatitis C virus; IRES, internal ribosome entry site; ALT, alanine aminotransferase; IFN, interferon; IFNAR, interferon α/β receptor; IFNGR, interferon γ receptor; Jak-STAT, Janus kinase-signal transducer and activator of transcription; GAS, gamma-activated sequence; ISRE, interferon-stimulated response element; pDC, plasmacytoid dendritic cell; PAMP, pathogen-associated molecular pattern; SNP, single nucleotide polymorphism; peg, pegylated.

* Corresponding author at: Department of Biomedicine, University of Basel, Zentrum für Lehre und Forschung, Hebelstrasse 20, 4031 Basel, Switzerland. Tel.: +41 61 265 33 62; fax: +41 61 265 38 47.
E-mail address: markus.heim@unibas.ch (M.H. Heim).

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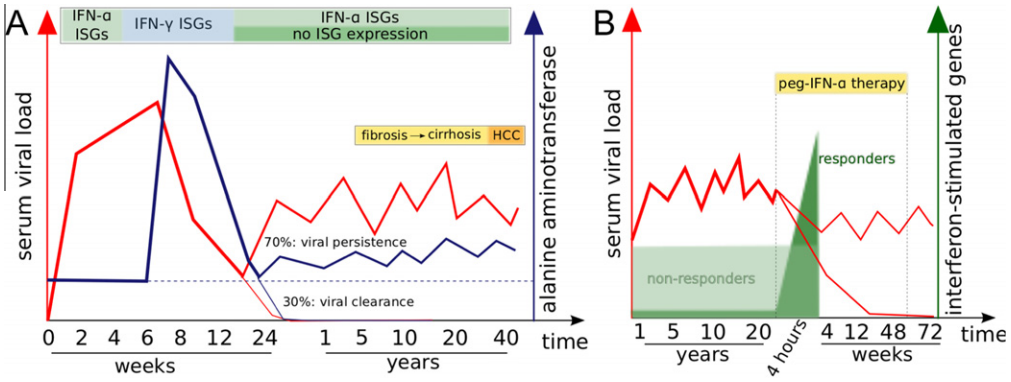

Fig. 1. (A) Natural course of hepatitis C virus infection. Changes in serum HCV load, ALT levels, IFN-stimulated gene expression in the liver as well as the development of liver disease are shown as a function of time from transmission. The dashed line shows the upper limit of normal ALT levels. (B) Treatment of chronic hepatitis C with peg-IFN-α and ribavirin. Changes in serum HCV load and IFN-stimulated gene expression in the liver are shown as a function of time from transmission or initiation of peg-IFN-α and ribavirin therapy.

with orally administered unspecific antiviral drug, ribavirin. For HCV genotype 1 this regimen is complemented by HCV-specific antivirals (boceprevir or telaprevir [26,27]) which act by inhibiting the viral NS3-4A protease, an enzyme essential for the HCV replication cycle [28].

Among patients with chronic hepatitis C response rates to the peg-IFN-α 2 combined with ribavirin vary from about 50% for HCV genotypes 1 and 4 to approximately 80% for viral genotypes 2 and 3 [29,30]. Recent progress in research on IFN signaling in the liver has improved our understanding of the molecular mechanisms behind the non-response to IFN-based therapies observed in a significant proportion of chronic hepatitis C patients.

2. Interferon signal transduction pathway

2.1. Interferons and their receptors

IFNs are immune response mediators that constitute the first line of defense against viral infections. They are classified as type I, II or III IFNs based on their use of specific receptors (Fig. 2) (rev in [31]). Human type I IFNs include 12 highly similar members of IFN-α family, a single IFN-β as well as IFNs-ε, -κ and -ω. The members of type I IFN family bind to a common, ubiquitously expressed IFN-α/IFN-β receptor (IFNAR) which consists of two major subunits, IFNAR1 and IFNAR2 (rev in [31]). Type I IFNs are produced in response to the viral infection [32,33].

The only type II IFN, IFN-γ, is produced primarily by NK and T cells in response to stimulation with antigens or mitogens [34–36]. IFN-γ binds to heterodimeric IFN-γ receptor (IFNGR), which, similarly to IFNAR, is expressed in a ubiquitous manner [37].

The recently discovered type III IFNs include IFN-λ1, -λ2 and -λ3 (also referred to as IL29, IL28A and IL28B, respectively) [38]. The receptor for the IFN-λ family consists of the IL10R2 chain, which is shared with the interleukin 10 receptor, and a unique IFN-λ chain, IL28Rα [38]. Contrary to IL10R2, IL28Rα is expressed in a tissue-specific manner, restricting the activity of IFN-λs to the cells of epithelial origin [39].

All IFNs signal through the Janus kinase-signal transducer and activator of transcription (Jak-STAT) pathway to regulate the expression of their target genes in the nucleus. IFN-γ-induced signaling involves phosphorylation of STAT1, which assembles into homodimeric complexes and translocates to the nucleus where it binds to promoter regions containing a specific gamma-activated sequence (GAS) to activate the transcription of downstream genes [40,41]. Stimulation of cells with type I and III IFNs leads to STAT1 and STAT2 phosphorylation and assembly of two types of transcriptional activators: homodimeric phospho-STAT1 complex and heterotrimeric complex composed of phospho-STAT1, phospho-STAT2 and IRF9 [42,43]. This heterotrimeric complex drives the expression of genes whose promoters contain specific interferon-stimulated response elements (ISREs) [44]. The sets of genes induced by type I and III IFNs are almost identical,

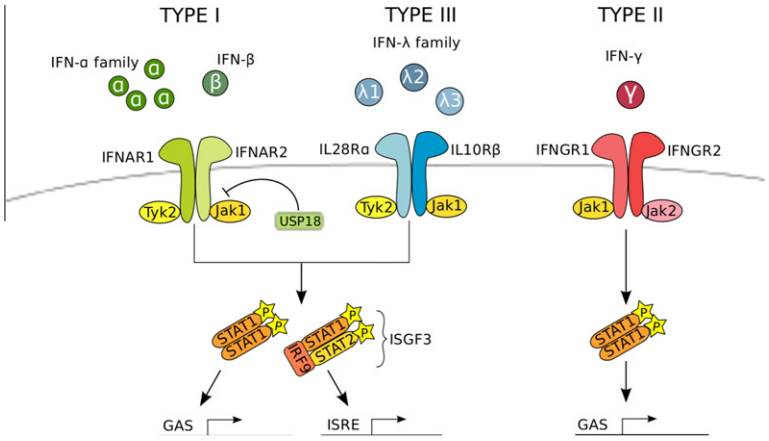

Fig. 2. Type I, II and III interferon signaling through the Jak-STAT pathway. Type I and III IFNs bind to distinct receptors, but activate the same downstream signaling events, inducing almost identical sets of genes through the activation of ISGF3 and STAT1 homodimers. IFN-γ treatment leads to activation of STAT1 homodimers, but not ISGF3, inducing a distinct gene signature which partly overlaps with type I and III IFN target genes.

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