

## WJG 20<sup>th</sup> Anniversary Special Issues (2): Hepatitis C virus

# Transmission of hepatitis C virus: Self-limiting hepatitis or chronic hepatitis?

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## Abstract

It has been suggested that hepatitis C virus (HCV) is selectively transmitted to a new host as an infectious clone from multiple HCV variants (quasispecies) in the donor. Most individuals with HCV infection develop chronic hepatitis, but approximately 15%-40% of them clear the virus spontaneously and the hepatitis is resolved in a self-limiting manner in the acute phase of infection. This difference in the outcome of acute hepatitis C is attributable to both viral characteristics and genetic regulation of infection. In particular, the evolutionary dynamics of the infecting virus and host genetic polymorphisms pertaining mainly to the immune system, including polymorphisms in the region of the Interleukin 28B gene encoding interferon- $\lambda$ -3, are associated with susceptibility to HCV infection.

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**Key words:** Hepatitis C; Spontaneous clearance; Interleukin 28B; Single nucleotide polymorphism; Interferon- $\lambda$

**Core tip:** Most individuals with hepatitis C virus (HCV)

infection develop chronic hepatitis, but in some the hepatitis is resolved in a self-limiting manner in the acute phase of infection. What factors are responsible for this difference in the outcome of hepatitis C? The evolutionary dynamics of the infecting virus and host genetic polymorphisms pertaining mainly to the immune system, including the Interleukin 28B gene, as well as susceptibility to HCV infection, are important in determining the outcome of infection.

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## INTRODUCTION

Hepatitis C virus (HCV) infection is a major threat to public health, and about 170 million people are estimated to be infected worldwide with a potential risk of progression to cirrhosis and hepatocellular carcinoma<sup>[1,2]</sup>. This review summarizes the two current topics of HCV study: the transmission mode of HCV with multiple variants (quasispecies) and the factors associated with susceptibility to HCV infection, with special reference to viral characteristics and host genetic variation.

## MODE OF HCV TRANSMISSION: HOW IS HCV WITH MULTIPLE VARIANTS TRANSMITTED?

HCV shows significant genetic heterogeneity among isolates, and the degree of variability is unevenly distributed throughout the viral genome: some regions are conserved and some are highly variable<sup>[3]</sup>. In particular, the hyper-

variable region 1 (HVR1) of the *HCV* E2 gene encoding a putative envelope glycoprotein mutates at a high rate, resulting in a wide spectrum of mutants referred to as “quasispecies” during infection<sup>[4,5]</sup>. Some virions may contain defective RNA genomes, which also affect the infectivity and replicability of the virus<sup>[6]</sup>. The mixture of clones present determines the biological and immunological properties of the virus.

How is HCV with multiple variants (quasispecies) transmitted to the new host? Does the status of transmitted HCV consist of multiple clones or a selected single clone? The transmission mode of HCV has been investigated by sequencing of the recovered viral genome from both donor and recipient<sup>[7,8]</sup>. HCV infection in human communities has occurred sporadically because no effective neutralizing vaccine against HCV has been developed. In particular, HCV infection in health-care workers through exposure to patient's blood due to a needle stick accident or accidental droplet transmission is a serious problem<sup>[9-12]</sup>. We previously reported a case of HCV infection resulting from a needle stick accident, and had an opportunity to investigate how HCV variants from the donor are transmitted to the recipient by comparing the HCV HVR1 genome encoding the envelope E2 protein recovered from the serum of both the donor and recipient<sup>[7]</sup>. In this case, we had observed the recipient before the onset of hepatitis and collected serum samples after obtaining informed consent. Thus, we were able to compare the HCV HVR1 genome between the donor's HCV at inoculation and the recipient's HCV just after onset of viremia. Interestingly, a minor subset of the donor's HCV clones was selectively transmitted to the recipient, and this selection determined the predominant clone in the new host. Several clones that appeared to stem from the recipient's predominant clone had one amino acid change within the HVR1 region during this short period. This particular case progressed to chronic hepatitis, and the same phenomenon has been demonstrated in the case of acute, self-limiting hepatitis<sup>[8]</sup>. These data suggest that a minor clone of the donor's HCV is transmitted and adapts to the new host. The precise mechanism of this viral selection in the initial phase of transmission has not been elucidated.

The simplicity of the transmitted viral strain in the initial phase of infection may explain some of the important clinical manifestations. Anti-viral therapy using interferon elicits a favorable response in the acute phase of HCV infection<sup>[13-16]</sup>. In addition, if a single strain is transmitted selectively in the initial phase of infection, this specific strain may be one of the factors determining disease activity. In fact, a study using a model of HCV transmission has demonstrated that a specific HCV strain recovered from a patient with fulminant hepatitis caused unusually severe hepatitis in a chimpanzee to which it was transmitted<sup>[17]</sup>. At present, the specific strain of HCV responsible for progressive liver disease cannot be discriminated from viral quasispecies in contaminated blood. Further investigation would be useful for clarifying the

specific viral strain responsible for the disease, and such efforts would be important for planning future strategies for the development of an effective therapeutic vaccine.

## SELF-LIMITING HEPATITIS OR CHRONIC HEPATITIS? HOW IS SUSCEPTIBILITY TO HCV DETERMINED?

### *The spontaneous clearance rate of HCV in the acute phase of infection*

Most individuals with HCV infection fail to clear the virus and develop chronic hepatitis with a risk of progression to cirrhosis and hepatocellular carcinoma. However, a small proportion of individuals are known to show resolution of the infection in a self-limiting manner. The rate of spontaneous viral clearance in acute HCV infection is reported to be approximately 15%-40% of all HCV-infected individuals<sup>[18-20]</sup>. Although differences in study populations such as race may influence the clearance rate in each cohort, a systematic review of 31 studies has estimated this rate to be 26%<sup>[20]</sup>. We have previously reported a Japanese population-based cohort study of the natural history of HCV infection in an area where community-acquired acute hepatitis C is endemic; here, the spontaneous viral clearance rate was estimated to be approximately 20%<sup>[21,22]</sup>. What is the difference between self-limiting resolution of hepatitis and progression to chronic hepatitis? Comparative studies of this issue have focused on both viral characteristics and genetic regulation.

### *Viral characteristics influencing the outcome of acute hepatitis C*

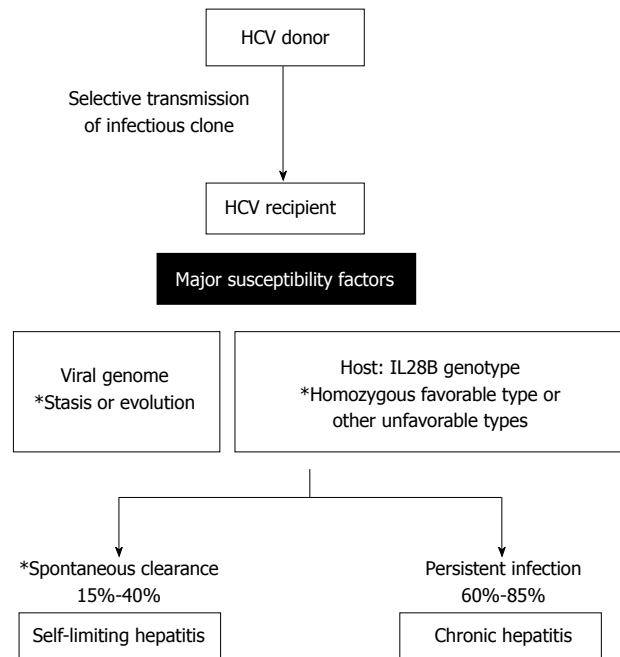
After the establishment of HCV infection, the viral genome mutates at a high rate, especially in the HVR1 of the HCV E2 region. The evolutionary dynamics of the infected virus are associated with the outcome of acute hepatitis C; genetic stasis and a high rate of evolution of HCV HVR1 are associated with resolution of infection in self-limiting hepatitis and progression to chronic infection, respectively<sup>[23]</sup>. The case we experienced progressed to chronic infection and 8 of 30 homogeneously predominant HCV HVR1 clones recovered from the recipient developed one amino acid mutation within this region during a short period of only 6 wk after infection<sup>[7]</sup>. As for the relationship between the viral load at the time of infection and the outcome of acute HCV infection, a recent study has shown that a high viral load in the initial phase of infection is associated with spontaneous viral clearance, leading to self-limiting resolution of hepatitis<sup>[24]</sup>. A high viral load may trigger strong innate immunity in the acute phase. However, it has also been reported that viral clearance may occur after a low infectious dose of HCV has been transmitted<sup>[25]</sup>. In addition, spontaneous viral clearance rarely occurs in the chronic phase of HCV infection where a low viral load is associated with spontaneous clearance<sup>[26]</sup>. The spontaneous clearance of HCV may thus depend on the immune system of indi-

viduals rather than the viral load. Further studies using a greater number of cohorts are needed to clarify the relationship between spontaneous viral clearance and the initial viral load, as well as the degree of induction of the innate immune response.

### Genetic regulation of HCV infection

HCV-specific humoral and cellular immune responses are detectable in infected individuals, and a strong immune response against HCV favors viral clearance<sup>[18,27]</sup>. Genetic variation in host genes involved in immune response is likely to account for the difference in outcome. In particular, induction of natural killer (NK) cells in the innate immune response during the acute phase of infection plays a crucial role in resolving HCV infection. We have previously reported differences in genetic variations between HCV-infected individuals with and without viremia in the Japanese population<sup>[22]</sup>, where a single nucleotide polymorphism (SNP) of transforming growth factor (TGF)- $\beta$ 1, which suppresses the proliferation and cytotoxicity of NK cells (the -509CC genotype or -509C allele), was associated with high HCV clearance rates and low transcriptional activity of TGF- $\beta$ 1<sup>[28]</sup>. The killer cell immunoglobulin-like receptor (KIR) and its human leukocyte antigen (HLA) have been reported to influence the outcome of HCV infection. Combinations of genotypes involving genes encoding the inhibitory NK cell receptor KIR2DL3 and HLA-C1 ligand directly influence HCV clearance in Caucasians and African Americans with an expected low infectious dose of HCV<sup>[25]</sup>. These data suggest that a diminished inhibitory effect of NK cells resulting from such gene regulation confers protection against HCV.

In a recent genome-wide association study, SNPs in the region of the Interleukin 28B (*IL28B*) gene encoding interferon- $\lambda$ -3 were shown to be closely associated with the virologic response of HCV to antiviral therapy<sup>[29-31]</sup>. Patients carrying an *IL28B* homozygote for the major alleles of rs12979860 (CC genotype)<sup>[29]</sup> or rs8099917 (TT genotype)<sup>[30]</sup> show a greater propensity to achieve a sustained virologic response to pegylated interferon- $\alpha$  and ribavirin therapy than those carrying an *IL28B* heterozygote or homozygote for its minor allele. This SNP (rs12979860) also influences the outcome of HCV infection in the context of natural history; the CC genotype enhances resolution of HCV infection with spontaneous clearance among individuals of European and African ancestry<sup>[32]</sup>. This CC genotype has also been reported to be associated with a higher rate of spontaneous clearance in Asian populations<sup>[33]</sup>. In addition, a recent study has demonstrated that SNPs in the region of *IL28B* (rs12979860) and HLA class II (rs4273729) are independently associated with spontaneous resolution of HCV infection in individuals of European and African ancestry<sup>[34]</sup>. A prospective follow-up study of patients who developed acute hepatitis C also revealed a strong correlation between the *IL28B* C allele at rs12979860 and clearance<sup>[24]</sup>. Taken together, the SNP of *IL28B* (rs12979860) can be a marker



**Figure 1** Transmission of hepatitis C virus, and the significance of viral and host factors for predicting the outcome of infection. HCV: Hepatitis C virus; IL28B: Interleukin 28B.

for indicating whether immediate antiviral treatment needs to be started in patients with acute hepatitis C<sup>[35]</sup>. Recently, upstream of the *IL28B* gene, a dinucleotide variant ss469415590 (TT or  $\Delta$ G), in which ss469415590 ( $\Delta$ G) activates the *IFNL4* gene encoding interferon- $\lambda$ -4 protein through a genome frameshift, has been reported to be more strongly associated with HCV clearance in individuals of African ancestry than the SNP of *IL28B* (rs12979860), but comparable to that in Europeans and Asians<sup>[36]</sup>. This variant is in high linkage disequilibrium with rs12979860, and further investigations are expected to elucidate the functional role of ss469415590 ( $\Delta$ G) that activates the *IFNL4* gene in association with the innate immune response to HCV.

## CONCLUSION

Both the viral characteristics of an infecting clone and genetic regulation of infection by the host determine differences in the outcome of acute HCV infection (Figure 1). The evolutionary dynamics of the virus and genetic polymorphisms in the host pertaining mainly to the immune system influence susceptibility to HCV. In particular, the discovery of SNPs in the region of the *IL28B* gene has led to the characterization of a novel genetic marker of hepatitis C that is able to predict self-limiting viral clearance in the acute phase of infection as well as the response to antiviral therapy.

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