

Hepatitis C

Liz Highleyman

Host Genes and HCV

The 2002 National Institutes of Health (NIH) consensus statement on the management of hepatitis C recommended that more research should be conducted on the role of genetic factors in the pathogenesis of HCV. Several recent journal articles look at such genetic influences.

According to a study by Salim Khakoo, Mary Carrington, and colleagues published in the August 6 issue of *Science*, individuals with certain gene patterns may be more likely to clear HCV without treatment. About 15-20% of people infected with HCV spontaneously clear the virus; the rest develop chronic hepatitis C. In previous studies of chimpanzees, animals that spontaneously cleared HCV appeared

to mount a stronger natural killer (NK) cell response. Khakoo and colleagues analyzed DNA from 1,037 HCV-infected subjects, 352 of whom cleared the virus without treatment, examining the gene sequences that code for “killer cell immunoglobulin-like receptors”—or KIR receptors—on NK cells and their corresponding human leukocyte antigen (HLA) molecules. KIR receptors are a type of inhibitory receptor that suppresses the activity of NK cells. When the immune system detects an invading virus, it must override the KIR receptors in order for the NK cells to mount an attack. The researchers found that individuals who spontaneously cleared HCV were twice as likely to have a specific KIR/HLA combination than those who developed persistent infection. The beneficial

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Executive Director
Editor-in-Chief,
HCSP Publications
Alan Franciscus

Contributor:
Liz Highleyman

Managing Editor, Webmaster
C.D. Mazoff, PhD

Design/Production
Alan Franciscus

Contact Information:
The Hepatitis C Support Project
PO Box 427037
San Francisco, CA 94142

www.hcvadvocate.org

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combination appears to be “weaker,” and thus more easily “turned off,” allowing NK cells to become active against virus-infected cells. This apparent genetic protection was only seen in individuals who were initially infected with a relatively small amount of HCV (such as from a needle-stick) and not in those who initially received a large inoculum of virus (such as from a blood transfusion). The results of this research raise the hope that gene therapy or immune-based therapy may help prevent chronic HCV infection. In an accompanying editorial, Peter Parham from Stanford University pointed out that one type of leukemia is already treated by releasing NK cells associated with a specific KIR receptor, and suggested that a similar strategy may one day be developed for hepatitis C. According to Carrington, “It’s possible that if we could activate NK cells in the liver after infection, maybe that could enhance clearance of the virus.”

Turning to existing therapies, Hermann Wasmuth and colleagues reported in the August issue of *Hepatology* that variants of the RANTES gene influence response to antiviral treatment in patients with

chronic HCV. RANTES is a chemokine that attracts immune cells such as T cells and NK cells to sites of inflammation. The researchers analyzed three linked RANTES single nucleotide polymorphisms (genetic variants or mutations)—403 G/A, *In1.1* T/C, and 3’222 T/C—in 297 Caucasian HCV patients and 152 healthy control subjects. Haplotypes (nucleotide combinations on a single chromosome) containing these gene variants were then constructed. Haplotypes carrying the *In1.1C* and 3’222C variants were seen more often in nonresponders than in patients with a sustained response to HCV therapy. This association was strongest in patients with HCV genotypes 1 or 4, which respond less well to treatment than genotypes 2 or 3. In laboratory studies, the *In1.1C* variant has been shown to down-regulate RANTES activity; previous research has found an association between this variant and accelerated HIV progression as well, especially in people of African descent. Wasmuth and colleagues concluded that their analysis supports the hypothesis that nonresponders to HCV therapy have a diminished Th1 type immune response.

Viral Genes Matter, Too

Maria Pascu and colleagues from Berlin reported in the September 2004 issue of *Gut* that in patients with genotype 1b HCV, the number of mutations within the “interferon sensitivity determining region” of the viral NS5A gene—as its name suggests—has an impact on how well patients respond to interferon-based therapy. The researchers analyzed data from 1,230 genotype 1b chronic HCV patients, mostly from Japan (655 subjects) or Europe (525 subjects). They found that the Japanese patients were about twice as likely to have wild-type (nonmutated) ISDR sequences (44% vs 25%), and also more likely to have highly mutant sequences (18% vs 12%); the Europeans, however, were more likely to have intermediate sequences (63% vs 38%). HCV that had more mutations in the ISDR sequence was more susceptible to interferon, and patients with more highly mutated virus were more likely to achieve a sustained virological response (SVR), regardless of geographical region. In the Japanese patients, however, each additional ISDR mutation markedly increased the likelihood of SVR; in the Europeans, this relationship

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was less pronounced. Among patients with low pretreatment viral loads (less than 6.6 log copies/mL), Japanese subjects with ISDR mutant HCV had an SVR rate of 97%—remarkably high for genotype 1 patients—compared with 53% among Europeans. “These data support the concept that mutant-type ISDR strains may represent a subtype within genotype 1b with a more favorable response towards [interferon] therapy,” the authors concluded.

HCV Treatment and Normal ALT

In the August 2004 issue of *Gastroenterology*, Andrew Holt and Stephen Zucker presented an overview of hepatitis C treatment in patients with normal alanine transaminase (ALT) levels, a group that comprises about 30% of patients with chronic HCV. Although most such individuals appear to have mild liver disease, some do progress to advanced fibrosis and cirrhosis. Experts differ on whether patients with normal ALT should routinely receive liver biopsies and HCV treatment. The 1997 NIH hepatitis C consensus guidelines recommended that individuals with persistently normal ALT should not receive

HCV therapy, because treatment with interferon monotherapy was effective only in a minority of patients, prognosis without therapy was generally good, and interferon was associated with newly elevated ALT in some nonresponders (up to 25%). The advent of more effective ribavirin combination therapy and pegylated interferon, however, has led to reconsideration of this recommendation. The 2002 consensus guidelines do not recommend that patients with normal ALT either should or should not be treated, concluding instead that all cases must be considered on an individual basis.

Holt and Zucker commented on a report by C-K Hui and colleagues in the November 2003 issue of *Gut* on the largest study to date of patients with normal transaminase levels. The researchers retrospectively evaluated the responses of 52 chronic HCV patients with normal ALT and 53 subjects with elevated ALT, all treated with standard interferon plus ribavirin. They found that SVR rates were similar in both groups (about 40%). In addition, the incidence of newly elevated ALT in nonresponders who entered the study with normal levels was uncommon, occurring in just three pa-

tients (9%). Holt and Zucker note that with Hui’s study, “[t]he preponderance of evidence” now indicates that HCV patients with normal ALT are as likely to achieve a sustained response to interferon/ribavirin as those with abnormal ALT, and that there is “a reasonably low likelihood of disease exacerbation in those unfortunate individuals who fail to respond.”

Nevertheless, the decision about whether to treat patients with normal ALT remains “thorny.” Opponents argue that given the side effects and cost of therapy, as well as the small risk of worsening the underlying disease in nonresponders, treatment should be reserved for those most likely to benefit. Those who favor treatment note that some patients with normal ALT do develop advanced liver damage, and with SVR rates now in the range of 50% or better, all patients who might benefit should be offered therapy. Holt and Zucker recommend that when considering treatment of patients with normal ALT, “liver biopsy would seem a prudent approach to help determine if treatment is needed, and therapy should be offered to patients with signs of progressive liver damage.”

