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RESEARCH NEWS

Hepatitis C Virus: The Advantages of Diversity

A review of: Farci P, Shimoda A, Coiana A, Diaz G, Peddis G, Melpolder JC, Strazzera A, Chien DY, Munoz SJ, Balestrieri A, Purcell RH, Alter HJ 2000 The Outcome of Acute Hepatitis C Predicted by the Evolution of the Viral Quasispecies. Science 288:339–344

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HEPATITIS C VIRUS (HCV) is a common cause of viral hepatitis. Whereas the acute disease caused by this agent is usually benign, even sometimes asymptomatic, HCV will establish a chronic infection in as much as 85% of infected patients (1). The long-term consequences of the infection can be devastating, including chronic active hepatitis that culminates in cirrhosis in up to 20% of cases, and hepatocellular carcinoma (1). A persisting enigma in HCV research is the mechanism by which HCV can maintain a chronic infection. A related mystery is the lack of protection against re-infection following successful clearance of the infection, in both human and chimpanzees, in spite of the development of both humoral and cell mediated immune responses (2, 3).

The genetic heterogeneity of HCV has long been suspected as an important factor in the pathogenesis. There are several genotypes of HCV (4), which is expected to be an additional complication in the production of a vaccine. Even more relevant to the problem at hand is the "quasispecies" nature of HCV in a given patient, *i.e.* the presence of several distinct, but closely related, mutants of HCV, constantly changing (because of the low fidelity of the RNA polymerase) and presumably constantly generating immune escape mutants (4, 5). In that regard, a 31 amino acids region at the NH_2 terminal of the E2 glycoprotein has received much attention since most mutations accumulate in this region, which has been named the hypervariable region 1 (HVR1). Indeed, mutations in HVR1 are correlated with spectacular changes in its predicted secondary structure (6). HVR1 also contains epitopes for neutralizing antibodies (7).

However, a convincing demonstration of a role of the quasispecies complexity in HVR1 in the pathogenesis remained elusive. In this elegant and thorough study, Farci and coworkers analyzed longitudinal samples collected from patients with acute resolving, chronic slowly progressing, and chronic rapidly progressing hepatitis C, and demonstrated that the outcome can be predicted by the change in quasispecies complexity in HVR1 at the time of seroconversion. Patients whose quasispecies complexity increased following seroconversion became chronically infected, whereas a decrease in complexity was associated with resolution of the infection.

A second valuable insight provided by this study comes from the method used to quantify the complexity of the quasispecies The authors cloned the amplicons obtained by PCR from longitudinal samples, sequenced several clones at each time point in the analysis, and used the "Hamming distance," defined as the number of different amino acids between two sequences. For a mix of sequences (as in a quasispecies) they used the average of the Hamming distances calculated between pairs in the mix. This study underlines the importance of amino acids changes in the HVR1 and supports the hypothesis of immune escape mutants. Thus, the outcome of HCV infection is apparently decided relatively early, depending on whether or not the immune system can contain the viral variation.

Of course HVR1 may not be the only factor accounting for viral persistence. For example, mutations providing escape from cellular immunity have been documented in other regions of the HCV genome (8). Nonetheless, the predictive power of this measurement appears striking; it may well find its place among other molecular markers required to follow HCV infection, such as the determination of the genotype and of the viral load.

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