Mutations within a conservative region of HCV affects the therapy

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At least 200 million individuals are currently infected with hepatitis C virus (HCV) worldwide. Approximately 30%-50% of patients respond to interferon/ribavirin combination therapy. Response to interferon therapy depends mainly on viral and host genetic factors. The HCV is continually mutating which allows the virus to evade the immune system and overcome interferon treatment.

The 5'untranslated region (UTR) of the viral genome is the most conserved region within the viral RNA, and its structural/thermodynamic stability is a key factor for efficient binding to host ribosomes for initiating viral polyprotein translation. It is believed that more than 100 host proteins bind to this region of the virus that is termed IRES (internal ribosome entry sequences). Specific mutations in this region would alter the structure stability of viral RNA, its protein translation efficiency and consequently its ability to replicate, and thus response to therapy. Although several mutations have been observed in different HCV genotypes, no studies have investigated mutations in IRES of HCV genotype 4a; the predominant HCV genotype in Egypt and whether such mutations correlate to therapeutic response.

A research team led by Dr. Hassan M Azzazy from Egypt addressed this issue and their study will be published on March 28, 2009 in the World Journal of Gastroenterology.

In this study, HCV RNA was extracted from 19 chronic HCV 4a patients receiving interferon/ribavirin therapy who showed dramatic differences

in their response to combination therapy after initial viral clearance. IRES domain 3 was cloned and 15 clones for each patient were sequenced. The obtained sequences were aligned with genotype 4a prototype using the ClustalW program and mutations scored. Prediction of stem-loop secondary structure and thermodynamic stability of the major quasispecies in each patient was performed using the MFOLD 3.2 program with Turner energies and selected constraints on base pairing.

Analysis of RNA secondary structure revealed that insertions in domain 3 altered Watson-Crick base pairing of stems and reduced molecular stability of RNA, which may ultimately reduce binding affinity to ribosomal proteins. Insertion mutations in domain 3 were statistically more prevalent in sustained viral response patients (SVR, n = 14) as compared to breakthrough (BT, n = 5) patients.

The results of this study suggest that the presence of single nucleotide polymorphisms (SNPs) in certain positions had direct effect on the response of HCV patients to interferon therapy. Taking into consideration the positions of these mutations, different real-time PCR or other assays can be developed for detection of the SNPs to allow the prediction of the response to interferon therapy as a step for identification of patients who are more likely to respond to therapy.

More information: El Awady MK, Azzazy HM, Fahmy AM, Shawky SM, Badreldin NG, Yossef SS, Omran MH, Zekri ARN, Goueli SA. Positional effect of mutations in 5'UTR of hepatitis C virus 4a on patients' response to therapy. *World J Gastroenterol* 2009; 15(12): 1480-1486 www.wjgnet.com/1007-9327/15/1480.asp

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