Hepatitis C Virus E2 glycoprotein genetic variability in patients subjected to interferon-ribavirin therapy

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Hepatitis C Virus (HCV) is one of the most serious public health threats. It is estimated that approximately 1-2 % of the world's population is infected with the virus, resulting in approximately 242 000 deaths per year and 1.5 million new infections each year. Until 2011, combination therapy with pegylated interferon and ribavirin remained the standard of care for HCV infection. However, many years of research work have led to the development of drugs that target viral proteins directly, so-called direct acting anti-viral drugs (DAAs). These therapies have a very high success rate (above 90%). However, the high cost of providing therapy with DAAs, its limited availability, and the emergence of treatment-resistant variants are major obstacles to effectively controlling the spread of HCV infection. There is therefore still a great need to develop a prophylactic vaccine. However, this task is hampered by the high genetic variability of the virus, as well as the lack of a thorough understanding of the mechanisms of induction of the immune response against hepatitis C virus.

The envelope glycoproteins E1 and E2, which form a heterodimer on the surface of the HCV virus and are responsible for the entry of the virus into the host cell, are the main target for neutralizing antibodies. The ectodomains of both these proteins are highly glycosylated - glycans account for one-third of the mass of the E1E2 heterodimer. Despite high genetic variability, the N-glycosylation sites are highly conserved, which may suggest their important role in HCV glycoprotein function. Moreover, literature data indicate the involvement of N-glycans in the escape of viral variants from the host immune system, both in vitro and in vivo. Thus, it can be inferred that the N-glycosylation pattern of E1E2 glycoproteins may play a key role in the induction of neutralizing antibodies response by potential vaccine candidates.

The aim of the present study was to search for a relationship between genetic variation of the E2 glycoprotein of hepatitis C virus (HCV) and the response to pegylated interferon alpha and ribavirin therapy in children. During the course of the study, an association between mutations in the N-glycosylation pattern of the E2 protein and reduced recognition of epitopes by neutralizing antibodies was documented.

The models used in the study were chimeric heterodimers of HCV glycoproteins E1E2 consisting of proteins obtained from the reference strain H77c of HCV (glycoprotein E1) and proteins obtained from material from patients of the Department of Infectious Diseases and Child Neurology of the Karol Marcinkowski Medical University in Poznań (glycoprotein E2). An important aim of the study was to analyze the role of the presence/absence of sugar residues on the surface of glycoprotein E2 in the recognition process by neutralizing antibodies. Importantly, variants of E2 glycoprotein carrying changes in the N-glycosylation pattern present prior to treatment became the predominant variants in the patient's organism as a result of selection pressure.

The research conducted has provided important insights into the potential mechanism by which HCV escapes from the host immune system, which may contribute to the development of an effective vaccine against hepatitis C virus.