Review article

THE ROLE OF HEPATITIS C VIRUS IN HEPATOCELLULAR CARCINOMA PATHOGENESIS – A PROBLEM OF A MODERN MAN

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People with hepatitis C virus (HCV) have a 2% annual risk, and 7% to 14% five-year risk for development of hepatocellular carcinoma, a tumor with an estimated median survival of 4.3 to 20 months after making the diagnosis. HCV is the cause of: acute hepatitis in 20% of cases, chronic hepatitis in 70%, liver cirrhosis in 40%, hepatocellular carcinomas (HCC) in 60%, and is indication for liver transplantation in 30% of cases. HCC is the fifth most common cancer worldwide, and is one of the most frequent causes of death, accounting for 6% of all carcinomas. There is a heterogeneous distribution of HCC worldwide. It develops after mutations in cell machinery, causing the cell to reproduce faster and/or to avoid apoptosis. Current researches include the search for the genes that are dysregulated in HCC, protein markers, and other predictive biomarkers. As similar research is yielding results in various other malignant diseases, it is hoped that identifying the aberrant genes and the resultant proteins could lead to the identification of pharmacological interventions in HCC. *Acta Medica Medianae 2009;48(2):32-36.*

***Key words**: hepatitis C virus, hepatocellular carcinoma*

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Definition

Hepatitis has been a problem of humanity for centuries. After the discovery of Australia antigen called hepatitis B surface antigen or HbsAg by-Baruch Blumberg in 1960, knowledge in this area has been rapidly expanding. Today, there are at least six major viral agents, called hepatitis viruses A,B,C,D,E and G. They are extremely widespread. These six viral agents are causing viral hepatitis; the knowledge on this subject and disease they cause is expanding (1).

At the beginning of the new millennium, it is estimated that more than 2 billion people were, or currently are infected with some viruses that cause hepatitis, with over 350 million carriers of hepatitis virus without manifestation of the disease. Approxi-mately 25% of these patients will soon die of chronic liver disease or hepatocellular carcinoma (HCC), with the rate of one million deaths annually. This high incidence is attributed to the aforesaid mentioned viruses. As a result, 2.4 to 4 times more people are going to die of hepatitis caused by B or C virus than from HIV (human immunodeficiency virus) (2).

People infected with hepatitis C virus (HCV) have a 2% annual risk and a 7-14% five-year risk for development of hepatocellular carcinoma. Estimated median survival for patients with this type of tumor is 4.3 to 20 months after making the diagnosis (3).

This shows that viral infections have been and continue to be a significant cause of hepatitis and hepatocellular carcinoma (1).

These alarming statistical data, especially since 1989, when hepatitis C virus (HCV) was identified, motivated many authors and research teams to deal with hepatitis C from the aspect of frequency, severity and its consequences as well as diagnostic and therapeutic dilemmas. Research has resulted in many new insights, many of which have been theoretically and practically confirmed, whiles some remained at the level of hypothesis (2). Medical science is obliged to seek answers to current dilemmas.

The discovery of HCV and gained knowledge about its epidemiological, biological, clinical and serological features gives hope in achieving progress in prevention and treatment of different clinical forms of liver disease (4).

History - discovery of hepatitis C virus

During the World War II viral hepatitis was divided into two different diseases that were called infectious hepatitis and serum hepatitis (5). Later on, the terms hepatitis A (HA) and hepatitis B (HB) began to apply, and infectious agents associated with these diseases were named hepatitis A virus (HVA) and hepatitis B virus (HBV). The Australia antigen was discovered in 1960, later named hepatitis B surface antigen (HBsAg) (6). In 1968, it was associated with

hepatitis B, which more clarified the story of viral hepatitis (7, 8).

During the mid-1970[s], Harvey J. Alter, chief of the Section of Infectious Diseases in the Department of Transfusion Medicine at the National Institute of Health, and his research team demonstrated that most post-transfusion cases of hepatitis were not caused by hepatitis A and B viruses. Despite this discovery, international attempts to identify the virus, initially called non-A non-B hepatitis (NANBH), were not successful in the next decade (9).

In 1971, the test of radioimmune precipitation developed antibodies to HBsAg and its sensitivity contributed to detection of all patients who were previously infected with HBV (10).

Prince A.M. in 1978 was the first who began with experimental researches on chimpanzees infected by plasma from patients with NANBH; after a long period of incubation they were very ill (11,12,13).

Using electronic microscopy, Zuckermann revealed smooth deformation of endoplasmatic reticulum of tubular and network-like structure, with the length of about 15 nm in chimpanzee hepatocytes infected with NANBH after its long incubation (14).

In 1987, Micahel Houghton et al. in the Chiron Corporation, in collaboration with Dr. DW Bradley, developed a new approach in cloning and identification of an unknown organism (9, 15, 16). During 1988, the virus was confirmed by Altera and verified as NANBH. In April 1989, the virus was discovered, and it was called hepatitis C virus (HCV), as published in journals (17).

In 2000, doctors Alter and Houghton Laskerovu received the award for clinical medical research for "pioneering work that led to the discovery of the virus that causes hepatitis C and developed screening methods, which reduced the risk of infection caused by blood transfusion in the USA from 30% in 1970 - to 0% in 2000" (18).

Hepatitis C virus - basic structure and organization of the genome, morphology and genotypes

Hepatitis C virus is a member of the family Flaviviride. The virus is small (30-80 nm), icosahedral capsid symmetry, with a lipid envelope (19). Viral genome is a positive single-stranded RNA about 9500 nucleotides of the 5' end contains a secondary structure, and the 3' end of poly A or poly U tract, depending on viral genotype (20).

Genomic structure (large translational open-reading frame ORF), covers almost the entire RNA genome, encodes the synthesis of polyprotein of 3000 amino acids (21). Genome is divided into structural-S (core and shell), non-structural-NS and the two terminal regions 5 'and 3', which are not translated and do not participate in the encoding viral proteins (22). Structural and non-structural region of RNA genome, with the corresponding genes, consists of a sequence encoding ("coding sequence") viral proteins.

The low level of virus in plasma samples and problems of cultivation in vitro made visualization of the virus difficult, however, virus-like particles can be identified using electron microscopy (23).

HCV smear shows extensive heterogenety of the genome, although the variation is not uniform throughout the smear. Relatively well-preserved region of the HCV genome (core, E1 and NS5) have been extensively studied and used as the basis for the classification of isolated parts in six different genotypes (1 - 6) and more than 50 subtypes (1a,1b,1c ...) (24). Yet, there is no classification of HCV based on serotypes.

Preponderance and distribution of HCV genotypes varies globally. For example, in North America, genotype 1a is predominant, followed by 1b,2a,2b and 3a. Genotype 1b is predominant in Europe, genotype 2a, 2b, 2c and 3a follow. Genotypes 4 and 5 are located exclusively in Africa. Genotype is of great clinical importance in determining potential response to interferon therapy and the required length of such therapy. Genotypes 1 and 4 less correspond to interferon therapy than other genotypes (2,3,5 and 6) (25).

Immune response

The virus reaches the liver through the blood. Pathogenic mechanisms that lead to degeneration and necrosis of hepatocytes in patients with HCV infection are not fully understood. Results of previous studies prove that cytotoxic CD8 + T cells have a dominant role in the pathogenesis of lesions of hepatocytes and the elimination of the virus.

Humoral immune response in acute HCV infection is characterized by the appearance of antibodies to capsid C protein, glycoprotein E1, E2 and other non-structural viral proteins (26).

Cellular immune response also determines the outcome of HCV infection, but the dynamics of such responses and their relationship to the purity and viral persistence are poorly studied. It is believed however, that HCV does not destroy cells and immune events play a significant role in the pathogenesis of infection. Mechanisms by which HCV causes acute and chronic hepatitis are still unclear. However, it was shown that the beginning of viral infection and liver disease coincides with the beginning of CD8 + T cell responses and entry of viral specific CD8 + T cells in the liver. Primary induction failure in T cell responses, or exhaustion, or strong T cell response, is associated with viral resistance (27, 28). It is important that the destruction of infected cells by CD8 + T cells is probably not the only way to eliminate the virus, because viral infections can occur in the absence of liver disease as long as CD8 + T cells are present and produce antiviral cytokines such as IFN-. The fact that the virus can persist despite multispecific response of CD4 + and CD8 + T cells, using mutation avoidance response of T cells, further indicates the importance of the immune response

to viral infection and pathogenesis of the disease during HCV infection.

In conclusion, HCV infection is associated with sharp induction and widespread response of T cells, which effectively leads to the liver and produces IFN-γ. In contrast, T cell response is significantly reduced in patients who become chronically infected, many of which show evidence of viral mutation beg that may occur early in acute infection. CD8 + T cell response can be detected in chronically infected individuals and is often functionally impaired, and in terms of its ability to accumulate in the liver and its ability to produce IFN- γ (29).

Clinical aspects of hepatitis C

The liver is the primary target. Hepatocytes are target cells, although different lymphoid populations, particularly B cells and dendritic cells can be infected, but at much lower levels (30). Main features of HCV infection is chronicity, at least 70% of acute infection becomes persistent. Chronic infection is often associated with significant liver disease, especially chronic active hepatitis, cirrhosis and Hepatocellular carcinoma (31).

Source of infection is a man with acute or chronic (clinically manifest or asymptomatic) infection. Virus can be found in blood, saliva, semen, vaginal secretions, milk and other body fluids. Transmission of hepatitis C virus can be: parenteral (through blood, blood products, transplanted organs and blood-contaminated objects), sexual and vertical.

HCV is sensitive to organic solvents, formalin, and beta-propiolakton and UV rays. It is resistant to high temperature, so it can retain infectivity at temperature of 60 °C up to 10 hours. HCV can become completely inactive only at temperature of 100 °C after 5 minutes.

The C virus is a cause of acute hepatitis in 20% of cases, chronic hepatitis in 70%, liver cirrhosis in 40%, Hepatocellular carcinoma (HCC) in 60% and is an indication for liver transplantation in 30% of patients.

Hepatitis C virus as the cause of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver. This cancer is also known as "hepatoma" or "liver cancer cells". HCC is the fifth diagnosis of cancer in the world, but is the leading cause of mortality. There is a heterogeneous distribution of HCC worldwide. The highest incidence is in countries in Africa and Middle East, secondary caused by hepatitis B viral (HBV) infection-which is the most common cause of HCC worldwide. HCC caused by the hepatitis C viral (HCV) infection is increasing in the USA. Men are more frequently infected than women, with a rate of 2:1 to 4:1. Despite resection, recurrence rate ranges from 50% to 70% (32,33).

Hepatocellular carcinoma accounts for 6% of all cancers and is most widespread in the world as the primary tumor of the liver. In terms of geography, the incidence is increasing in the Far East, Southeast Asia and sub-Sahara Africa (90 cases per 100,000 people vs. 2.4 cases per 100,000 people in the United States). It includes important risk factors like liver cirrhosis, hepatitis B and C (33).

Hepatitis C is a viral infection that is transmitted by blood derivatives. In America, more than 4 million are infected, about 36,000 cases have acute hepatitis C; every year about 85% of cases turn into chronic infection. Chronic hepatitis C is often asymptomatic but can lead to liver cirrhosis, as well as Hepatocellular carcinoma. Prognosis of patient with cirrhosis depends on development of hepatic decomposition or HCC occurrence. Patients with chronic HCV infection have a 10-year survival, about 50% without complications from cirrhosis. Chronic hepatitis C is the leading indication for liver transplantation. Every year in America about 8.000-10.000 people die from HCC (34).

The nature of HCC is progressive with provoking pain, hepatomegaly, jaundice, weight loss and the formation of ascites as the predominant clinical traits. Cause of death can be spontaneous tumor rupture with massive intraperitoneal bleeding, which corresponds to the characteristics of hypervascular tumors. However, the factors responsible for neovascularisation processes and subsequent growth and spread of these tumors are not fully identified (35).

Hepatitis C is a major cause of chronic liver disease in Japan, Europe and the U.S., where the relatively low rates of HBV infection are found. Antibodies to HCV were found in 76% of patients with HCC in Japan and Europe and 36% of patients in the United States. HBV and HCV infection were independent risk factors for the development of HCC, but may act synergistically when an individual is infected with both viruses. Although the nature of the history of HCV infection is still unclear, it appears as a chronic infection with a benign early course that ultimately develops into cirrhosis and HCC. HCV is RNA virus that does not integrate into the host genome, and therefore HCC pathogenesis which is related to HCV might be more associated with chronic inflammation and cirrhosis than direct carcinogenesis.

The true association between cirrhosis and HCC is very difficult to understand, and suggestions on the causes remain speculative. Cirrhosis is not an obligatory result of cirrhosis. The relation between cirrhosis and HCC is further complicated by the fact that they share common links. What's more, some links (HBV infection, chemochromatosis) are associated with high risk of HCC, whereas the others (alcohol, primary biliary cirrhosis) are associated with a lower risk of HCC. Research has shown that cirrhotic liver with a higher rate of DNA replication is associated with the development of HCC (36).

Hepatocellular carcinoma, like any other cancer, develops when mutations arise in the

cellular machinery that cause cell to divide faster and / or the resulting cells to avoid apoptosis. Chronic infection with hepatitis B and / or hepatitis C may contribute to development of HCC by constantly causing the immune system to attack the liver cells, some of which are infected with the virus, and also others in environment. This constant cycle of damage followed by repair can lead to errors during the repair, which in turn leads to carcinogenesis. This hypothesis may be more applicable, for the present, in case of hepatitis C. In case of HBV, integration of viral genome into infected cell is the most common factor for malignancy factor. Alternatively, continuous consumption of large amounts of ethanol may have a similar effect. Aflatoxin from Aspergillus fungi is a carcinogen and contributes to HCC carcinogenesis- accumulating in the liver. Mixed high presence of aflatoxin and hepatitis B in countries such as China and West Africa has led to relatively high rates of HCC in these regions. Other viral hepatitis, such as hepatitis A, have no potential to become chronic viral infection and therefore are not associated with HCC (37).

What are the chances of modern man in fighting against HCV and HCC?

Microscopically, there are four architectural and cytological type of hepatocellular carcinoma: fibromelar, pseudoglandular (adenoid), pleomorphic (giant cells) and clean cell. In different forms, tumor cells resemble hepatocytes, form trabecula, ribbons and nests that may contain billiary pigment in the cytoplasm. In poorly limited forms, malignant epithelial cells are pleomorphic, anaplastic and giant. Tumor has meager stroma and central necrosis due to poor vascularisation (38).

Staging and prognosis-important traits for treatments are: size, expansion, vascularisation, presence of tumor capsule, presence of extrahepatic metastasis, presence of daughter nodules, relationship with the vascular elements of the liver.

Treatment: liver transplantation, surgical resection, percutaneous ethanol injection (PEI), transcatheter arterial chemoembolization (TACE), focused radiotherapy, radio frequency ablation (RFA), the intraartery administration iodine-131-lipodola directed high-intensity ultrasound (HIFU), hormonal therapy, chemotherapy, palliative therapy, cryosurgery (39).

Future directions

Current research includes the search for genes which are irregular in HCC (40), protein markers (41), and other predictive biomarkers (42, 43). Since similar researches have already contributed to better outcomes in the treatment of various other malignant diseases, we hope that identification of aberrant genes and resulting proteins will lead to the identification of pharmacology agents for HCC treatment (44).

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ULOGA HEPATITIS C VIRUSA U PATOGENEZI HEPATOCELULARNOG KARCINOMA-PROBLEM SAVREMENOG ČOVEKA

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Osobe zaražene hepatitis C virusom (HCV) imaju godišnji rizik od 2%, a 7-14% je petogodišnji rizik za nastanak hepatocelularnog karcinoma (HCC), tumora čije se preživljavanje procenjuje od 4.3 do 20 meseci nakon dijagnoze. Virus hepatitisa C uzročnik je: 20% svih akutnih hepatitisa, 70% hroničnih hepatitisa, 40% slučajeva ciroze jetre, 60% slučajeva hepatocelularnog karcinoma (HCC) i 30% indikacija za transplantaciju jetre. Hepatocelularni karcinom je peti po proširenosti karcinoma u svetu, ali je vodeći uzročnik smrtnosti širom sveta i predstavlja 6% svih karcinoma. Prisutna je heterogenska distribucija HCC širom sveta. Razvija se kada nastane mutacija u ćelijskoj mašineriji koja izaziva ćeliju da se reprodukuje brže i/ili rezultuje da ćelije izbegavaju apoptozu. Trenutna istraživanja uključuju potragu za genima koji su disregulisani u HCC-u, proteinskim markerima i ostalim prediktivnim biomarkerima. Dok slična istraživanja doprinose rezultatima kod raznih drugih malignih bolesti, nadamo se da će identifikacija aberantnih gena i rezultirajućih proteina dovesti do identifikacije farmakoloških intervencija za HCC. *Acta Medica Medianae 2009;48(2):32-36*.

Ključne reči: *hepatitis C virus, hepatocelularni karcinom*