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EDITORIAL
Hepatocellular carcinoma pathogenesis: Does PPAR alpha polymorphism have a role in hepatocarcinogenesis associated with HBV and HCV infections?

Hepatosellüler karsinoma patogenezi: PPAR alpha polimorfizmi HBV ve HCV infeksiyonu ile birlikte olan hepatokarsinogeneziste rol oynayabilir mi?

See article on TJG 19 (4): 245-249

Hepatocellular carcinoma (HCC) is one of the most common solid tumors worldwide, representing the third cause of mortality among deaths due to cancer. Despite its significance, there is only an elemental understanding of the molecular, cellular and environmental mechanisms that drive the disease pathogenesis.

HCC affects all segments of the world population, although significant differences in HCC incidence in various countries reflect the regional differences in the prevalence of specific etiological factors as well as ethnicity. The most prominent factors associated with HCC include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and aflatoxin-B1-contaminated food. Other risk factors include primary hemochromatosis and cirrhosis of different etiologies, such as alcoholic cirrhosis. In addition, gender can also influence the risk and behavior of HCC, with males accounting for a larger fraction of cases.

There are two major hepatitis viruses that may be associated with the development of HCC. HBV affects approximately 400 million individuals worldwide and causes an estimated 320,000 deaths annually. Approximately 30–50% of HBV-related deaths are attributable to HCC. HCV influences approximately 170 million people in the world. Approximately 20% of chronic HCV cases develop liver cirrhosis and 2.5% develop HCC. The viral–associated mechanisms in hepatocarcinogenesis are complex and involve both host and viral factors.

Chronic HBV infection has been shown to be strongly associated with HCC. At least three different mechanisms have been proposed for HBV–mediated hepatocarcinogenesis. First, studies have shown that HBV DNA can integrate into the host genome to induce chromosomal instability. HBV genome integration has been associated with host DNA microdeletions that can target cancer-relevant genes, including telomerase reverse transcriptase (TERT), platelet–derived growth factor receptor–B (PDGFRB), and mitogen activated protein kinase (MAPK1). Second, HBx transcriptional activation activity can alter the expression of growth–control genes, such as SRC tyrosine kinases, Ras, Raf, MAPK, ERK, JNK and others. Finally, HBx can bind and inactivate the tumor suppressor p53 *in vitro,* therefore increasing cellular proliferation and survival and compromising DNA–damage checkpoints. The hepatocarcinogenic potential of HBx has been genetically validated in HBx transgenic mice, of which 90% developed HCC.

HCV genome is a positive–stranded RNA molecule that encodes non-structural proteins (NS2, NS3, NS4A, NS5A and NS5B). Both viral and host factors are thought to contribute to HCC development in the setting of HCV infection. HCV increases HCC risk by promoting fibrosis and ultimately cirrhosis. Once HCV–related cirrhosis develops, annual incidence of HCC has been estimated to be 1% in these patients. In chronic HCV infection, host and environmental factors are more important than viral factors in progression to cirrhosis. These factors include older age, age at infection, male gender, and alcohol intake. Unlike HBV, HCV is an RNA virus that does not integrate into the host genome. However, host–viral protein interaction seems to be the major pathway of hepatocarcinogenesis. The proteins reported to be associated with HCV–mediated hepatocarcinogenesis

are core, NS3 and NS5A proteins, which have all been shown to inhibit p21 WAF1 expression post-transcriptionally.

Methylation of cancer–relevant genes. Aberrant DNA methylation patterns have been reported in HCC. Methylation has been detected in the earliest stage of hepatocarcinogenesis, and the greater extend in tumor suppression. Specific hypermethylation events in HCC have targeted p16, E-cadherin, COX2, apoptosis–associated speck–like protein (ASC) and deleted in liver cancer 1 (DLC1), among others. The biological significance of the hypermethylation of some of these genes in hepatocarcinogenesis has been evaluated in HCC lines. The epigenetic silencing of key cancer genes seems relevant to hepatocarcinogenesis.

Molecular mechanisms inducing hepatocarcinogenesis at the cirrhosis stage are not clear. Liver cell proliferation is increased during chronic hepatitis, but cirrhosis is characterized by decreasing hepatocyte proliferation. At the cirrhosis stage, we can mention three basic mechanisms that could accelerate carcinogenesis. Telomere shortening leads to an activation of the cell cycle and apoptosis checkpoints that restrain the proliferative capacity of liver cells and in turn select for hepatocytes carrying deletions of checkpoints genes. In addition, telomere shortening induces chromosomal instability, which can be accelerated further by loss of checkpoint functions. Cirrhosis is also associated with microenvironment alterations induced by stellate cell activation and inflammatory signaling and macroenvironment alterations induced by loss of liver mass and toxic metabolites. Both alterations could stimulate liver cell proliferation, thus leading to a further selection of malignant clones.

Telomere shortening and activation of cell cycle checkpoints impair hepatocyte proliferation during cirrhosis. Four major checkpoints are affected in HCC, including p53 pathway, Rb pathway, p27 pathway and transforming growth factor B insulin-like growth factor 2 receptor pathway. p53 pathway is a major tumor suppressor pathway that limits cell survival and proliferation in response to telomere shortening. P53 protein induces cell cycle arrest in response to oncogenic activation and protects genome integrity.

Activation of developmental and oncogenic pathways in hepatocarcinogenesis is a heterogeneous process. Oncogen activation may occur late in hepatocarcinogenesis as a result of chromosomal instability induced by telomere shortening and checkpoint dysfunction. Four major pathways are activated in HCC, including Akt, myc, B–catenin, hedgehog and the met pathways. In addition, telomerase activation is a very frequent event in HCC. It is an essential step during the immortalization of tumor cells.

Do peroxisome proliferators–activated receptors (PPARs) have a role in the development of HCC? Studies on the relationships between PPARs and hepatocarcinogenesis have reported conflicting results. Although experimental studies in the rodent liver have demonstrated that PPARa may have a role in hepatocarcinogenesis, implication of these findings is not clear. PPARs are nuclear hormone receptors that mediate the effects of fatty acids and their derivatives at the transcriptional level. Through these pathways, PPARs can regulate cell proliferation, differentiation and survival, thus controlling carcinogenesis in various tissues. However, the mechanisms that underlie the role of PPARs in hepatocarcinogenesis are still unclear. Peroxisome proliferators are chemically non–related molecules that include naturally occurring steroids and lipids, as well as xenobiotics such as fibrates, industrial plasticizer, pepticides and solvent. Their main target is the liver. PPARa was the first PPAR identified. PPARa–null mice are resistant to acute effects and as well as development of HCC.

In the current issue of this journal, and colleagues have investigated the frequency and effect on clinical outcome of PPARa L162V polymorphism in patients with HCC caused by hepatitis viruses. They included 90 patients with HCC in the study. Eighty–seven patients (97%) had liver cirrhosis. The investigators detected PPARa L162V polymorphism by using RFLP method. PPARa L162V polymorphism was demonstrated in only six patients, all of them infected with HBV. Five of six patients had advanced liver disease. Based on these findings, they suggested that there may be a relationship between this polymorphism and HCC developing in the cirrhotic liver due to chronic HBV infection. They also suggested that PPARa polymorphism is associated with advanced HCC.

The frequency and significance of single nucleotide polymorphisms of different genes such as p53, tumor necrosis factor (TNF)-a and cyclin D1 genes, in hepatocarcinogenesis have been investigated in many studies. All studies published by different investigators have demonstrated that TNF-

a promoter polymorphism was frequently associated with HCC. However, in other gene polymorphisms, a strong link between polymorphism and HCC could not be shown.

In this study, the reported polymorphism rate is very low. Although significant advances have recently been made in the understanding of biological effects of PPARs, the mechanisms concerning PPARa that lead to hepatocarcinogenesis remain unclear. Another challenge regarding mechanisms of hepatocellular carcinogenesis is the presence of liver cirrhosis. Liver cirrhosis is a premalignant status. As mentioned above, liver cirrhosis is associated with telomere shortening. Telomere shortening may lead to chromosomal instability and ultimately liver cancer. Liver cirrhosis is also associated with developmental and oncogenic pathways.

In this study, the key question is whether HBV can cause PPAR alpha L162V polymorphism. Or does HBV have a role in the development of PPAR alpha polymorphism? Currently, it is difficult to answer this question, especially in patients with advanced liver disease due to chronic HBV infection.

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