Perspective

Hepatitis B virus and host factors

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Primary liver cancer is the third most common cause of cancer-related deaths worldwide, with a particularly high incidence in Asian countries. Hepatocellular carcinoma (HCC) accounts for 85-90% of primary liver cancers, and is responsible for approximately 660,000 deaths worldwide each year (1). Hepatitis B virus (HBV) is the most common cause of infectious liver diseases. About 400 million people suffer from chronic HBV infection worldwide, and approximately 60% of HCC cases each year are related to chronic HBV infection (2). It has been suggested that viral factors (e.g., HBV-DNA levels, genotypes, and genomic mutations), host factors (e.g., age, sex, race, and immune status), and unhealthy lifestyles might contribute to the progression of liver diseases (3).

Hepatocarcinogenesis is a multi-factorial process in which genetic and epigenetic factors contribute to abnormal activation or inactivation of multiple cellular signaling pathways that result in malignant transformation (4). Integration of HBV into the host's genome and transactivation of HBx protein promotes and enhances multiple cellular signaling genes (5). For example, this process activates oncogenic genes (e.g., c-myc and c-fos), inactivates suppressor genes (e.g., p53), activates transcriptional factors (e.g., AP-1 and NF-κB), and induces the loss of heterozygosity.

Recent technological advances have revealed that several genetic factors are associated with cancers. Genome-wide association studies (GWAS) have identified numerous single nucleotide polymorphisms (SNPs) that are associated with various cancers. With respect to liver cancers, SNPs in numerous candidate genes were reported to be associated with HCC in case-control and retrospective studies. *Table 1* summarizes the results of GWAS identifying genetic factors implicated in HCC. In 2009, Kamatani *et al.* first reported that SNPs in the human leukocyte antigen (HLA)-DP region were associated with chronic HBV in a study of 188 Japanese patients with chronic HBV infection and 934 controls (6). The HLA gene is located in the region 6p21.3 and plays an important role in antigen presentation. Polymorphisms in this region were also reported in Chinese patients (8,12). In 2010, Zhang *et al.* reported that SNPs in several tumor suppressor genes located in the region 1p36.22, including KIF1B, UBE4B, and PGD, were putatively associated with HCC (7). However, no data from other countries in Asia, or globally, have been published to confirm these associations. GWAS may result in some discrepancies because of differences among ethnicities. Most of the studies published to date were conducted in Asian countries, particularly China and Japan (*Table 1*). Therefore, it is necessary to confirm these associations in other countries and ethnicities.

It is also important that such studies include samples from patients and controls. Several studies identified candidate SNPs by comparing the SNPs present in asymptomatic HBV carriers and HCC patients. However, other factors, including age, sex, viral load, and viral mutations, are often clinically very different between these two groups, and may confound the analyses. Therefore, to precisely analyze genetic factors, it is essential that the patients and controls are well matched for these factors to limit possible confounding. Several studies have also enrolled patients with chronic HBV infection and controls without HBV infection. The results of these studies imply that several SNPs are associated with persistent infection and HBV clearance. Functional analyses are necessary to confirm these results.

Chronic hepatitis B (CHB) normally progresses through five phases: immune tolerance, immune clearance, inactive carrier, reactivation, and recovery. However, the duration and underlying hepatitis disease activity vary considerably

Table 1 SNPs associated with chronic HBV infection and HBV-related HCC

Chr	SNP region	rs./region	Ethnicity	Cases/Control	OR	Reference
6p	HLA-DPA1 HLA-DPB1	rs3077 rs9277535	Japanese	786 CHB /2201 controls	1.45-2.31	Kamatani 2009 (6)
1p	UBE4B-KIF1B-PGD	rs17401966	Asian	1962 HBV-HCC/1430 CHB	1.63	Zhang 2010 (7)
6p	HLA-DP		Han Chinese	521 CHB/819 control	1.98	Guo 2011 (8)
6p	HLA-DPA1 HLA-DBB1	rs3077 rs9277535	European	651 liver tissue samples/ Ref. (6)		O'Brien 2011 (9)
6p	HLA-DPA1 HLA-DPB1 HLA-DQB1 HLA-DQB2	rs3077 rs9277535 rs2856718 rs7453920	Japanese	458 CHB/2056 controls	1.98 1.95 1.59 2.20	Mbarek 2011 (10)
16p	GRIN2A	rs11866328	Chinese	1944 progressed carriers/ 854 asymptomatic carriers	1.65-1.73	Liu 2011 (11)
6p	HLA-DPA1 HLA-DPB1 HLA-DQB1 HLA-DQB2	rs3077 rs9277535 rs2856718 rs7453920	Chinese	1300 HCC/1344 CHB/ 1344 controls with natural clearance	0.29-1.89	Hu 2012 (12)
8p	DLC1	rs12682266 rs7821974 rs2275959 rs1573266	Chinese	95 HBV-HCC/ 97 HCC without HBV	1.38 1.33 1.31 1.39	Chan 2011 (13)
6p	HLA-DPB1	rs9277535 rs9277534	European-American African-American	241 CHB/421 recovered from HBV	0.39 0.37	Thomas 2012 (14)
1p	KIF1B	rs8019 rs17401924 rs17401966	Chinese	473 CHB/ 580 controls	No association	Zhong 2012 (15)
1p	KIF1B	rs17401966	Japanese, Korean, Chinese	580 HBV-HCC/ 1351 CHB	No association	Sawai 2012 (16)
6p	HLA-DPA1 HLA-DPB1	rs3077 rs9277542	Japanese, Korean, Chinese, Thai	181 CHB/184 controls	0.42 0.42	Nishida 2012 (17)
6p 21q	HLADQA1/DRB1 GRIK1	rs9272105 rs455804	Chinese	1538 HBV-HCC/ 1465 CHB	1.30 1.86	Li 2012 (18)
1p	KIF1B	rs17401966 rs12734551 rs3748578	Saudi Arabian	660 CHB/584 controls	No association	Al-Qahtani 2012 (19)

between each phase. Additionally, the clinical course differs between patients. HBV itself is not usually cytopathogenic. Instead, the liver injuries in patients with chronic HBV infection are considered to be the result of the host's immune responses against HBV. For example, an HLA-class I antigen-restricted, cytotoxic T lymphocyte-mediated response to the HBV antigen expressed on hepatocytes results in apoptosis and necrosis (20). Viral and host factors are associated with viral clearance, persistent infection, and clinical course. It was reported that HLA-DP variants were associated with chronic persistent hepatitis following HBV infection. The HLA-DP molecule plays an important role in antigen presentation to cytotoxic T cells. Therefore, functional differences in HLA-DP might contribute to differences in host sensitivity to the virus.

Li *et al.* identified a susceptibility gene within the HLA region, and the SNP identified in their study may influence HLA function. GWAS provide abundant information on a variety of diseases (18). However, the generalizability of the results should still be discussed because the data may differ according to ethnicity and other confounding factors. The pathogenesis of HCC involves multifactorial processes. Further studies are needed to determine whether the susceptibility gene reported by Li *et al.* shows clinical generalizability, and to determine the importance of this gene in the progression of HCC.

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