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REVIEW ARTICLE

Virus-induced hepatocellular carcinoma with special emphasis on HBV

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Abstract Hepatocellular carcinoma (HCC) is a common malignant tumor with high lethality, and the hepatitis B virus (HBV) is a chief cause. HBV can accelerate HCC via multiple mechanisms. First, HBV induces immune reactions that lead to repeated hepatic inflammation, fibrosis and a deficient immune microenvironment. Subsequently, HBV can modify host genes near the insertion point through DNA integration to cause host cell genome instability and to generate carcinogenic fusion proteins. Additionally, HBV expresses diverse active proteins, especially HBx and HBs, which have a range of transactivation functions such as regulation of apoptosis, interference with intracellular signaling pathways, and alteration of epigenetics. Currently, primary prevention measures for HBV-induced HCC focus on vaccination and antiviral treatment. Here, we report the epidemiology, the molecular mechanism and the progress in therapeutic strategies for controlling HBV-induced HCC.

Keywords Hepatocellular carcinoma · Hepatitis B virus · HBV-induced HCC

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Introduction

HCC is a malignant tumor with a high global incidence: there are more than 600,000 new cases annually. Furthermore, HCC is the 5th most common tumor in the world and the 2nd leading cause of cancer mortality (killing ~75 million yearly) [1, 2]. More than 80% of HCCs occur in sub-Saharan Africa and East Asia (>20 per 100,000). Southern European countries (such as Spain, Italy, and Greece) tend to have mid-incidence levels (10.0–20.0 per 100,000), whereas North America, South America, northern Europe, and Oceania have a low incidence of HCC (5.0 per 100,000) [3]. The major risk factors include chronic virus infection with hepatitis B virus (HBV), hepatitis C virus (HCV), cirrhosis, alcohol, aflatoxin-contaminated food, certain hereditary conditions such as hemochromatosis, and various metabolic disorders [4]. Although HBV vaccine is available, safe, and effective [5], cirrhosis caused by HBV remains a main cause of HCC especially in Asia, Africa and Latin America. Studies indicate that the HCC incidence for HBV carriers is 25–37 times that of uninfected people [6, 7]. HBV infection also contributes to the development, invasion and metastasis of HCC. We review the epidemiology, the molecular mechanism and the therapeutic approach of HBV-related HCC.

HBV infection and epidemiology of HBV-related HCC

HBV infection is the leading cause of chronic liver disease worldwide. Although there is a safe vaccine against HBV, it remains a severe public health issue. HBV infection is geographically disparate, dependent on different infection routes (Table 1). HBV is differentiated into many

Table 1 HBsAg seroprevalence, distribution of genotypes and HBsAg seroprevalence in HCC among countries

Country	Prevalence (%) of HBsAg	Genotype of HBV	Prevalence of HBsAg in HCC (%)	References
China	7.18	B, C	69.9	[76, 85]
Tainan	13.7	B, C	50.9	[77, 85]
Japan	1.02	A, B, C, H	15.3	[78, 79, 85]
Korea	4.36	C	72.8	[78, 80, 85]
Singapore	4.09	B	52.2	[78, 80, 85]
Indonesia	4.60	B, C	21.3	[81, 85]
India	1.46	A, C, D	53.5	[78, 80, 85]
America	0.27	A, C, D, G	7.6	[78, 82, 84, 85]
Germany	0.70	A, G	20.9	[78, 82, 84, 85]
France	0.26	A, G	15.3	[78, 82, 84, 85]
Canada	0.76	A, B, C, D	6.2	[78, 83, 85]

genotypes, according to genome sequence. To date, ten genotypes (A–J) of the HBV genome have been defined. Many researchers have reported that different genotypes show different geographical distributions (Table 1), and are related to disease progression, clinical progression, response to antiviral treatment, and prognosis [8].

Chronic HBV infection (CHB) has a well-known association with HCC [9]. A strong geographic correlation has been demonstrated between the prevalence of chronic HBV infection and the incidence of HCC. Globally, it has been estimated that 54% of HCC can be attributed to HBV infection [10]. Most HBV-related HCC occur in low- and middle-income countries. In high-income countries, with much lower HCC incidence, less than a quarter of HCC are attributed to HBV (Table 1).

Among patients with HBV infection, risks of HCC vary by several factors, the major one being HBV–DNA levels. The REVEAL-HBV study (1991–1992) explored the relationship of HBV–DNA load with the risk of occurrence of HCC in patients with CHB. Data showed that HBV–DNA load was positively correlated with the risk of HCC. The risk of occurrence of HCC increased significantly when the HBV-DNA load was $\geq 10^4$ copies/ml. Compared to patients with HBV–DNA load below the lower limit of detection (<300 copies/ml), the risk of HCC in patients with viral loads of 10^4–10^5 copies/ml increased two times and the risk of HCC in patients with viral loads $\geq 10^5$ copies/ml increased six times [11]. Studies have suggested that HBV genotype C increased the risk of occurrence of HCC. When compared to genotype B, HBV genotype C has been shown to be an independent risk factor for HCC development [12]. More recent data also indicate high serum HBsAg levels to increase the risk of HCC development, especially among patients with intermediate HBV DNA levels [13]. Furthermore, risk factors among patients with HBV infection include host factors (male, older age, Asian or African ancestry, family history of HCC, exposure to aflatoxin, and alcohol or tobacco abuse), other viral factors (longer duration of infection, co-infection with HCV, human immunodeficiency virus, or hepatitis D virus) and clinical factors (cirrhosis) [9].

Molecular mechanisms of HBV-induced HCC

HBV promotes HCC through immune-mediated inflammation

Numerous studies show that the persistently existed and amplified inflammatory response is one of the most important factors leading to tumor occurrence or promoting tumor development (Table 2). More than 25% of malignant tumors are induced or promoted by inflammation [14], which contributes to the formation, progression, escape, proliferation, invasion, angiogenesis and metastasis of tumor cells. Among inflammatory aspects, activation of nuclear transcription factor NF-κB contributes to inflammation-induced tumors. Also, tumor-suppressor genes (TSGs) with specific mutations or abnormal expression can activate NF-κB and increase the possibility of immune escape, which can promote HCC development [15]. Research shows that expression of serine/threonine kinase 4(STK4) is reduced in macrophages during external bacterial infection, and that IRAK1 cannot be phosphorylated and degraded, thus it persistently activates the downstream NF-κB signaling pathway and inhibits IRF-3 activation. This subsequently leads to up-regulated expression of inflammatory cytokines and down-regulated expression of IFN-β, and facilitates inflammation-induced HCC processes [16].

Immune CD4+ T cell subset Th1 and CD8+ T cells can effectively inhibit tumor cell growth and promote apoptosis

Table 2 Immune-mediated inflammation in HBV-related HCC

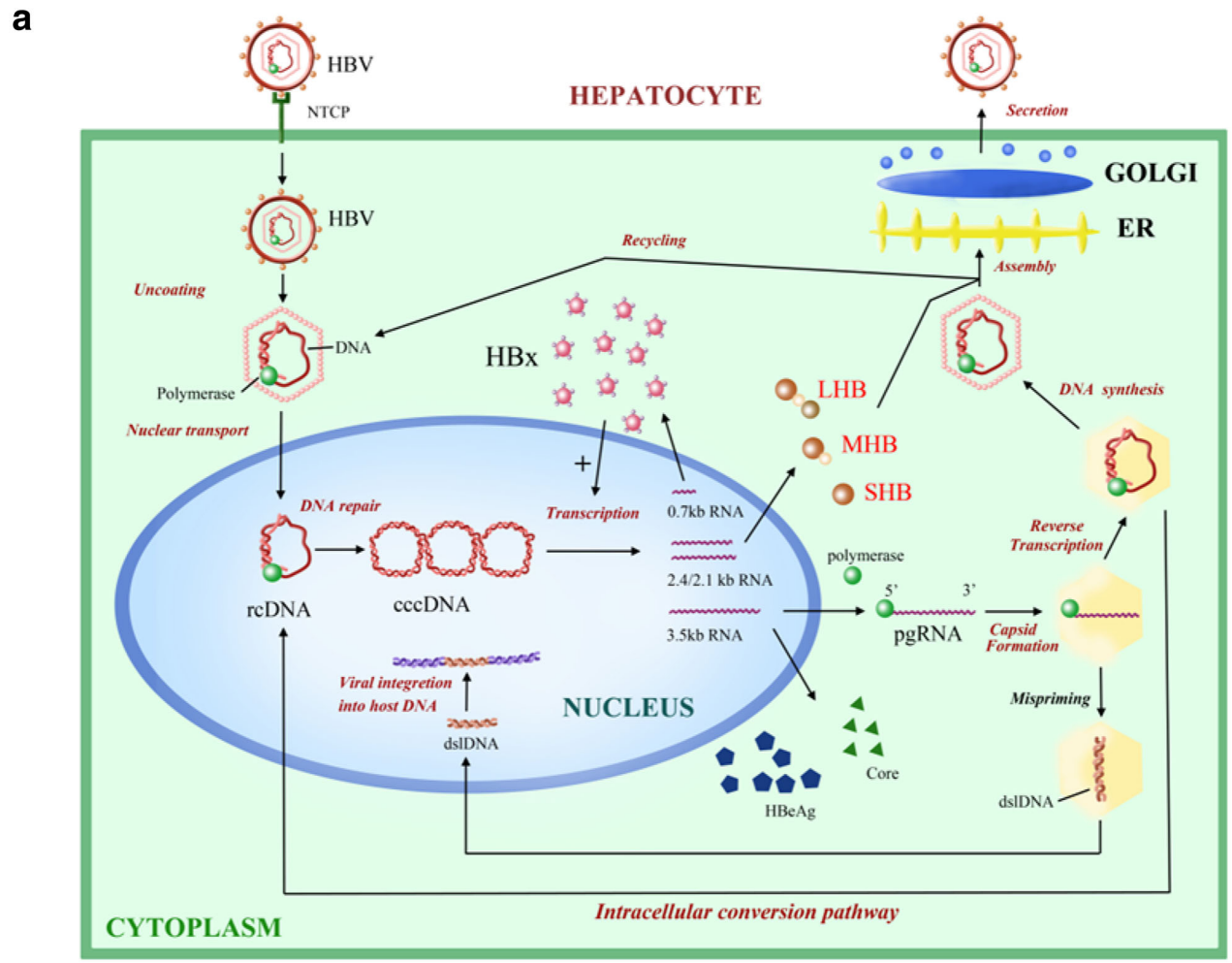
	Immune cells or cytokines	Mechanism	References
Promotion	Treg	Block immune response against HCC and suppress immune surveillance	[20]
	NF-κB	Increase immune escape and promote HCC development	[15]
	Fgl2	Promote HCC proliferation and angiogenesis	[24]
Suppression	Thl	Inhibit tumor cell growth	[17]
	CD8+ T	Mediate cytotoxic effect against tumor cdf s	[17]
	γδT	Recognize tumor antigens and kill tumor cells	[21]

[17]. Li et al. [18] showed that the Tim-3/galectin-9 signaling pathway mediates T cell senescence in HBV-related HCC. Treg cells induce host immune tolerance to change the course of HCC development and contribute to TNM stage (T: tumor, N: node, M: metastasis) [19]. Treg cell infiltration often occurs in HCC, and if Treg cells are more abundant than CD8+ T cells, poor prognosis is indicated [20]. After Treg cell functional amplification and strengthening, the immune response against HCC is blocked and immune surveillance against liver cancer is suppressed [21]. Recently, Treg cells have been noted to affect the functions of γδT cells through TGF-β and IL-10. γδT cells are T cells with innate immune functions and can recognize cancer antigens and kill cancer cells [22].

Fibrinogen-like protein 2(FGL2), which directly generates thrombin from prothrombin without activation of the conventional coagulation cascade, has been shown to be overexpressed in various human malignant tumors [23]. Previous study demonstrated that HBc and HBx initiate the transcription of FGL2 through the c-Ets-2 transcription factor, dependent on the activation of ERK and the JNK signal pathway, respectively [24]. FGL2 was overexpressed in HBV-related HCC tissues and colocalized with fibrin deposition. FGL2 can induce ERK and p38 pathway activation in a thrombin-dependent manner, and subsequent PAR1 and PAR3 activation, or JNK phosphorylation through PAR2 activation, which promote HCC proliferation and angiogenesis [25]. Down-regulation of FGL2 expression might be an alternative strategy for the management of HCC [26].

HBV DNA integration promotes the occurrence of HCC

Integration of HBV DNA into the host hepatocyte genome is key to HCC (Fig. 1). Whole-genome sequencing indicates that the integration of HBV DNA into the host hepatocyte genome can be detected in 80–90% of cancer cells and ~30% of liver tissue adjacent to the tumor [27], and that this integration appears prior to the occurrence of HCC [28]. HBV DNA, after integration into the human host cell genome, can affect the function of host genes as a *cis*-acting element, and activate proto-oncogenes or silence tumor-suppressor genes. Compared to HBV integration in hepatic tissue with hepatitis and cirrhosis, HBV DNA integration with HCC regularly occurs near a special chromosome position, and the amount of integrated HBV DNA is significantly greater [29]. An analysis of breaking points in the integration region showed that 40% of breakpoints are near to the 1800th nucleotide of the HBV genome, which contains an enhancer, an X gene and core promoters of the HBV genome. These special HBV DNA fragments can facilitate viral fusion with the human gene and destroy the tumor-suppressor gene or affect expressions of downstream genes through a *cis*-regulatory effect [30]. Telomerase reverse transcriptase (TERT) is an inserted gene for HBV integration and HBV DNA is integrated near TERT, which activates overexpression of the TERT gene to promote the conversion of tumor cells and cause HCC [30]. In addition to TERT, myeloid/lymphoid or mixed-lineage leukemia 4(MLL4) and cyclin E1(CCNE1) are also commonly inserted genes for HBV integration. Sung's group [27] used parallel sequencing in liver cancer tissue and normal adjacent tissues in 81 patients positive for HBsAg and 7 patients negative for HBsAg, and reported that HBV DNA integration of three genes (TERT, MLL4 and CCNE1) were 23.7, 11.8 and 5.3% respectively, accounting for 40.8% of all inserted genes. In addition, HBV integration sites may occur in genes for which coding sequences are related to growth, development and cell signaling, such as cyclin A, mitogen-activated protein kinase 1, tumor necrosis factor receptor-associated protein 1, SUMO1/sentrin-specific peptidase 5, Rho-associated protein kinase 1 and fibronectin 1 [31]. In addition, HBV DNA integration can also cause host genome instability, and research suggests that chromosomal copy numbers at HBV integration sites near them are significantly higher. HBV integration can cause genetic alterations in the liver cell genome, increase genomic instability and induce mutations, chromosomal deletions, and rearrangements [27]. Fujimoto's group [32] found that HBV DNA integration can cause mutations in chromosome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HBV
NTCP
HEPATOCYTE
Secretion
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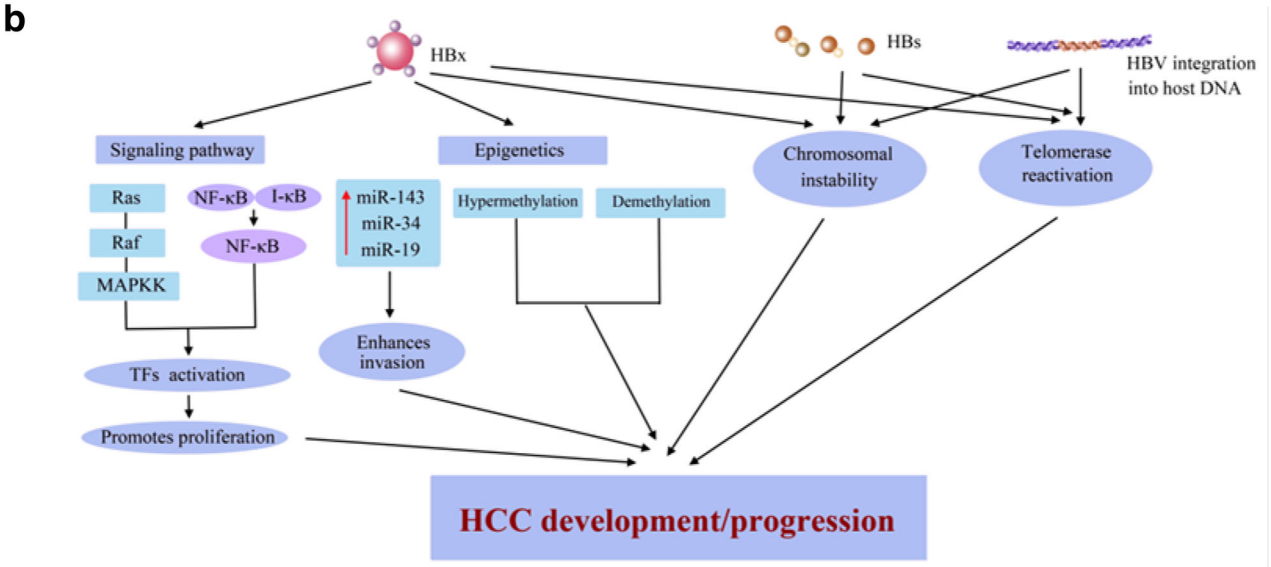
Recycling
Assembly
Uncoating
DNA
HBx
Polymerase
LHB
DNA synthesis
Nuclear transport
MHB
SHB
DNA repair
Transcription
0.7kb RNA
Reverse Transcription
polymerase
2.4/2.1 kb RNA
5'
3'
rcDNA
cccDNA
3.5kb RNA
pgRNA
Capsid Formation
Viral integretion into host DNA
NUCLEUS
Mispriming
dslDNA
Core
HBeAg
dslDNA
Intracellular conversion pathway
CYTOPLASM


b
HBx
HBs
HBV integration into host DNA
Signaling pathway
Epigenetics
Chromosomal instability
Telomerase reactivation
Ras
NF-κB
I-κB
miR-143
miR-34
miR-19
Hypermethylation
Demethylation
Raf
NF-κB
MAPKK
Enhances invasion
TFs activation
Promotes proliferation
HCC development/progression

◀**Fig. 1** HBV life cycle, its main causing factors and mechanisms in HCC development and progression. **a** Scheme of HBV life cycle, including virion entry, nucleocapsid uncoating, nuclear import, cccDNA formation, viral RNA transcription, viral protein translation, capsid formation, viral replication, virion assembly and secretion. **b** Mechanisms of main causing factors in HBV life cycle leading to HCC development and progression. *cccDNA* covalently closed circular DNA, *dslDNA* double-stranded linear DNA, *ER* Endoplasmic reticulum, *HBeAg* hepatitis B e-antigen, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *HBx* hepatitis B x protein, *LHB* large hepatitis B surface protein, *MHB* middle hepatitis B surface protein, *NTCP* sodium taurocholate co-transporting polypeptide, *pgRNA* pregenomic RNA, *SHB* small hepatitis B surface protein, *rcDNA* relaxed circular DNA

regulatory genes such as ARID1A, ARID1B, ARID2, MLL, and MLL3 genes, effecting chromosomal deletion, amplification, breakage, inversion, translocation or copy number variations.

HBx protein and HCC

HBx can not only regulate HBV replication and affect peripheral blood viral load and infectiousness but also interfere with cellular oxidative stress and DNA repair response, signal transduction, cell cycle progression and apoptosis (Fig. 1). HBx is often highly expressed in HBV-related HCC and promotes the occurrence of HCC through *trans*-action by multiple mechanisms such as regulating the interactions between cell survival and proliferation-related genes with intracellular proteins, modulating diverse signaling pathways and inducing abnormal epigenetic changes [33].

HBx can regulate transcription factor activity by interacting with specific proteins, changing the response of normal cells to DNA damage, interfering in the progression of the cell cycle S-phase and causing genomic instability and cell transformation via interactions with DNA damage response-related proteins such as UV DNA damage binding factor [34, 35]. HBx can also interact with p53 to prevent its transactivation and expression of target genes related to apoptosis via p21, Bax and Fas [34].

HBx can modify many cell signaling pathways and promote HCC via altering oxidative stress, DNA repair, proliferation, apoptosis and differentiation [34]. For example, NF-κB, JAK2/STAT3, Ras-Raf-MAPK, Wnt/β-catenin and PKC signaling pathways can up-regulate the expression of tumor-related factors or inhibit expressions of apoptotic molecules and promote HCC [36, 37].

HBx modulates host epigenetics (Table 3). The HBx protein induces epithelial cell adhesion molecule (EpCAM) expression via activating DNA demethylation of the CpG dinucleotides flanking NF-κB half-sites, which is directed by transcription factor RelA in complex with methyltransferase EZH2 and TET2 [38]. The HBx protein promotes P3 transcript expression of the insulin-like growth factor 2(ILGF2) gene via inducing hypomethylation of P3 promoter in HBV-related HCC [39]. RNA helicase DDX5 regulates Polycomb repressive complex2(PRC2)/long noncoding RNA HOTAIR function in HBV infection and hepatocarcinogenesis. The helicase activity of DDX5 stabilized the SUZ12(core subunit of PRC2) and PRC2-mediated gene silencing by displacing the RNA-binding E3 ligase Mex3b from HOTAIR [40]. The HBx protein induces trimethylation of histone H3 lysine 9(H3K9) on the tumor-suppressor p16 promoter via the decrease of demethylase jumonji domain-containing protein 2B expression and thus promotes the repression of p16 gene expression to enhance HBV-associated hepatocarcinogenesis [41].

HBx can regulate the expression of non-coding RNAs (ncRNA), and the imbalance of ncRNA induced by HBx is closely related to the formation, metastasis and prognosis of HCC. MiR-143, miR-34 and miR-19, which were regarded as oncomirs, are abnormally regulated in patients with HBV-related HCC, and studies show that up-regulated expression stimulates the tumor invasiveness and down-regulated expression of Let-7a (regarded as anti-oncomir) mediated by HBx protein promotes tumor cell proliferation [42]. In addition, miR-221, miR-101, miR-18a, miR-18b and miR-106a are critical for the development of HCC [43]. With more research, more miRNAs will likely be tied to HBV-related HCC.

HBsAg and HCC

Expression products of pre S1, S2 and S genes of HBV are components of the HBV surface antigen (HBsAg), which is an important marker of HBV infection and reflects transcriptional activity of cccDNA. The preS/S mutation is widely regarded as a precancerous lesion of HCC, and preS/S mutations in different tissues can induce HCC via different mechanisms (Fig. 1). For example, the preS/S mutation mediates the formation of liver cancer by changing the activity of transcription factors or the inflammatory response [44]. Accumulation of HBsAg in the endoplasmic reticulum (ER) can induce ER and oxidative stress, which lead to DNA damage, cell proliferation and invasion changes in survival and apoptosis-related signaling pathways [45]. Truncated pre-S2/S sequences are often found in HBV DNA integration sites of HCC patients, and truncated pre-S2/S proteins specifically activate the MAPK signaling pathway to activate transcription factors such as AP-1 and NF-κB, and thus promote abnormal proliferation of liver cells [45]. Pre-S2 protein of HBV can be used as a *trans*-activating factor and can interact with the hTERT promoter and increase telomerase activity. The pre-S2 protein can also act on the

Table 3 The modulation of HBx on epigenetic modification in hepatocarcinogenesis

Epigenetic mechanism	Outcome	References
CpG islands demethylation	EpCAM up-regulation	[38]
P3 promoter hypomethylation	ILGF2 up-regulation	[39]
H3K27 trimethylation	EpCAM up-regulation	[40]
H3K9 trimethylation	Tumor-suppressor p 16 down-regulation	[41]

EpCAM epithelial cell adhesion molecule, *ILGF2* insulin-like growth factor 2, *H3K27* histone 3 lysine 27, *H3K9* histone H3 lysine 9

AP-1 binding site of the FoxP3 core promoter to induce transcriptional activation of the main regulatory factor, FoxP3, of $CD4^{+}CD25^{+}$Treg cells [46].

Prevention and treatment of HBV-related HCC

HBV vaccination

HBV vaccination is a primary prevention strategy for HCC, and has been the most successful in reducing its incidence. WHO recommends that all neonates receive the HBV vaccine regardless of the presence or absence of the mother's infection. A large randomized controlled trial (RCT) in China demonstrated the efficacy of HBV vaccination in reducing primary liver cancer (0.16; 95% CI, 0.03–0.77) over a 25-year period [47]. After universal HBV immunization in Taiwan, the incidence of HCC has reduced in children. A follow-up study reported that the average annual incidence of HCC in children 6–14 years of age reduced from 0.70 of 100,000 between 1981 and 1986 to 0.57 between 1986 and 1990 and to 0.36 between 1990 and 1994 ($p < 0.001$) [48]. In addition, the incidence of HCC among children in the 6- to 19-year age group was significantly decreased in the vaccinated cohort (64 HCC in 37,709,304 person-years), compared with that in the non-vaccinated cohort (444 HCC in 76,496,406 person-years) [49]. A recent study from Taiwan also confirmed that HBV vaccination reduces their risk of developing HCC as children and young adults. HCC incidence per 105 person-years was 0.92 in the unvaccinated cohort and 0.23 in the vaccinated birth cohorts. The RRs for HCC in patients 6–9-years old, 10–14-years old, 15–19-years old, and 20–26-years old who were vaccinated versus unvaccinated were 0.26 (95% CI, 0.17–0.40), 0.34 (95% CI, 0.25–0.48), 0.37 (95% CI, 0.25–0.51), and 0.42 (95% CI, 0.32–0.56), respectively [50]. Similarly, a significant reduction in HCC incidence was observed in Thailand and in native Alaskan children who received HBV vaccination in the neonatal period [51, 52]. In recent years, great progress in the implementation of HBV vaccination has been made, especially in countries with a high prevalence of hepatitis B; however, continued effort is needed to increase implementation of global vaccination.

Early surveillance of HCC

Early surveillance of HCC greatly increases the chances for successful treatment and a decrease in mortality. One randomized controlled trial of 18,816 HBV-infected patients in China demonstrated that surveillance consisting of measurement of alpha-fetoprotein (AFP) and ultrasound every 6 months was associated with a 37% reduction in HCC-related mortality [53]. In America, a recent retrospective cohort study of patients with HCC showed that patients who received surveillance were significantly more likely to have early stage disease HCC (27.2 vs. 11.6%) and receive potentially curative (20.9 vs. 11.6%) or palliative (59.2 vs. 45.5%) treatments compared to those without HCC surveillance. Receipt of HCC surveillance was associated with 38% reduction in mortality risk (0.62, 95% CI 0.54–0.71) that declined to 20% (0.80, 95% CI 0.69–0.94) after adjusting for HCC stage and treatment, compared to those without HCC surveillance [54]. AASLD, EASL, and APASL guidelines recommend screening patients who are at risk for HCC, including patients with cirrhosis of any causes or without cirrhosis if the HBV carriers are Africans older than 20 years or Asians older than 40 years or at any age if they have a family history of HCC. There are some differences in the guidelines regarding screening methods, particularly regarding surveillance intervals. The AASLD HCC 2010 guideline recommended ultrasound with or without AFP at 6-month intervals in at-risk patients [55], and the EASL 2012 guideline agreed with this view [56]. In Asia, however, where the etiology of HCC is generally different from the west, the APASL 2010 guideline recommended ultrasound with AFP at 6-month intervals [57].

Antiviral treatment

For patients with CHB, sustained suppression of viral replication with antiviral treatment can effectively prevent HBV-related complications and reduce the risk of HBV-induced HCC [58]. Meta-analyses have confirmed that

antiviral treatment with IFN-α and NAs can significantly reduce HCC incidence for patients with CHB. Sung's group studied 2742 patients with CHB from 12 studies, and divided them into IFN-α treatment and control groups. Data showed that IFN-α treatment reduced HCC by 34%. Also, 2289 patients with CHB from another five studies were divided into NA treatment and control groups and HCC in the NA treatment group decreased by 78% [59].

Currently, treatment of HBV-related HCC is surgical, but ~70% of patients will have HCC recurrences within 5 years [60]. Research shows that a high HBV viral load after HCC surgery is significantly and positively correlated with HCC recurrence [61]. Therefore, standardized antiviral treatments can improve therapeutic effects, preventing tumor recurrence and enhancing overall survival [62]. Zhang's group [63] conducted a meta-analysis of recent studies to assess the effect of IFN on HCC of caused by HCV and HBV recurrence after surgery or ablation, and noted that IFN can reduce HCC-related mortality and early recurrence. In a 7-year clinical study, 181 patients with newly discovered primary liver carcinoma who underwent transarterial chemoembolization (TACE) treatments were randomly divided into a TACE and TACE + lamivudine group. Data show that TACE + lamivudine group were significantly superior to TACE group alone and 1- 2- and 3-year survival was 83, 69, and 58%, respectively, for TACE + lamivudine and 60, 48 and 48%, respectively, for TACE alone. Thus, TACE plus antiviral treatment can significantly prolong survival periods of HCC patients [64]. For HCC patients undergoing radiofrequency ablation treatment, postoperative antiviral therapy with entecavir can significantly reduce the occurrence and recurrence of new HCC lesions [65]. For patients with HBV-related HCC who require liver transplantation, NAs are often used before transplantation to reduce HBV–DNA as much as possible to decrease the risk of post-transplant HBV recurrence, and antiviral treatment is extended to prevent the recurrence of HBV [66].

Current management and recent advances of HCC

Several therapeutic options are available for HCC, depending on liver function, size and number of tumors, macrovascular invasion or extrahepatic spread. The Barcelona clinic liver cancer staging system (BCLC) is a common means to assess prognosis and select appropriate therapy for HCC [67]. In general, patients with single or 3 nodules ≤3 cm each are classified as having early-stage cancer and benefit from tumor resection, liver transplantation, or ablation. Those with a greater tumor burden, confined to the liver, and who are free of symptoms are considered to have intermediate-stage cancer and can benefit from chemoembolization if they still have preserved liver function. Those with symptoms of HCC and/or vascular invasion and/or extrahepatic spread are considered to have advanced-stage cancer and could benefit from treatment with the kinase inhibitor sorafenib. Patients with end-stage HCC have advanced liver disease that is not suitable for transplantation and/or have intense symptoms. In these individuals, pain and symptom control to improve their quality of life should be the primary focus [68, 69].

Biological treatment of HCC is gaining attention and includes targeted therapy, immunotherapy and gene therapy. Sorafenib is currently the only approved targeted drug for the treatment of HCC, and it inhibits the RAF/MEK/ERK signaling pathway to directly inhibit tumor growth as well as indirectly block tumor growth by obstructing angiogenesis via inhibiting vascular endothelial and platelet-derived growth factor receptors. Sorafenib has been demonstrated survival benefits in patients with advanced-stage HCC compared to placebo (10.7 vs. 7.9 months) [70]. In clinical practice, these results have been confirmed by several retrospective and prospective cohort studies [71]. Sorafenib is not eligible as adjuvant treatment for HCC, which has been recently reported in the STORM trial. In this phase III trial, sorafenib did not show an improvement in progression-free survival. Therefore, adjuvant treatment with sorafenib should not be recommended in patients after complete resection or ablation [72]. Additionally, the programmed death receptor 1(PD-1) inhibiting antibodies have been effective against cancers, and preliminary findings from patients with HCC have been encouraging [73].

In recent years, a large number of molecular targeted agents have been tried both in first-line and second-line trails. However, none of the agents, e.g., sunitinib, brivanib, and linifanib, or the combination of sorafenib and erlotinib, were superior to sorafenib in terms of overall survival or toxicity; second-line trails with brivanib, everolimus and ramucirumab have also failed to show benefits compared with placebo [74]. Moreover, a recent work has shown that sodium-dependent taurocholate cotransporter polypeptide (NTCP), which has been identified as a specific functional receptor of HBV, was down-regulated in HCC tumor tissues. The down-regulated NTCP expression by cyclin D1 was associated with poor prognosis and lower HBV cccDNA level in HCC patients [75]. These efforts might expand the therapeutic options for the management of HCC.

Conclusion

HBV is a primary risk factor for HCC. Great progress in understanding how HBV-induced HCC occurs has been made but the mechanisms remain to be explored. Antiviral

treatment of HBV infection has been widely applied and novel therapies are being studied. Given the facts, there are few efficacious approaches for HBV-induced HCC, and control of disease progression in patients with CHB will be the most effective means for the management of HBV-induced HCC.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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