

Review

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Review

Crosstalk Between Hepatitis B Virus and Aflatoxins in Hepa-Tocellular Carcinoma: Epidemiology and Mechanisms

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Abstract: Hepatocellular carcinoma (HCC) is a significant burden on global public health, being one of the main causes of cancer mortality worldwide. This type of cancer has been closely linked to viral and environmental factors, particularly hepatitis B virus (HBV) infection and exposure to aflatoxins, produced by fungi of the genus *Aspergillus*. Aflatoxins are known carcinogens found in contaminated foods, such as grains and nuts. In the presence of chronic HBV infection, they can function as cofactors in liver carcinogenesis. The synergistic interaction between HBV and aflatoxins is crucial for understanding the molecular complexity of HCC. Multiple studies have shown how the simultaneous presence of these carcinogens significantly increases the risk of developing HCC. The complexity of these mechanisms highlights the urgent need for targeted preventive and therapeutic strategies, ranging from improvements in food safety and aflatoxin regulation to widespread HBV vaccination in high-prevalence areas. Understanding the molecular interactions between these environmental and viral factors is crucial not only for the diagnosis and treatment of HCC, but also for the effective implementation of public health policies that re-duce the global burden of this devastating liver disease. A multifactorial approach is essential to effectively address the increasing prevalence of HCC worldwide and improve health outcomes for affected populations.

Keywords: HBV; hepatocellular cancer; aflatoxin

1. Introduction

Cancer has a major influence on mortality and life expectancy worldwide. According to the World Health Organization (WHO) in 2019, this disease is listed as the main or second cause of death in many countries and occupies a prominent position on the list of diseases that reduce life expectancy before the age of 70 [1]. For cancer to develop, cells need to acquire a series of initial changes that promote uncontrolled proliferation. These changes include genetic mutations and epigenetic modifications essential for the oncogenic process [2,3]. Subsequently, changes occur that are associated with tumor progression and are involved in metastasis [4].

Hepatocellular carcinoma (HCC) ranks sixth in terms of global incidence among all types of cancer. Furthermore, it is the third leading cause of cancer death worldwide and it is estimated that there were 865,269 new cases of HCC worldwide in 2022 and around 757,948 deaths from HCC in the same year. These statistics highlight the significant public health burden of HCC globally [5]. Hepatitis B virus (HBV) has been established as one of the causative agents of HCC, once the infection has progressed with a chronic persistence model [6]. However, evidence have suggested that persistent viral infections require cofactors for the development of cancer [7–9]. For instance, exposure to aflatoxin B1 (AFB1) is strongly associated with an increased risk of HCC, especially in areas with high prevalence of HBV infection [10]. Aflatoxins are xenobiotics produced by certain

fungi, which are prevalent in some foods, worldwide. Aflatoxin B1 (AFB1) is the most important oncogenic aflatoxin characterized as Class I carcinogen by the International Agency for Research on Cancer (IARC). In this review, the epidemiological and mechanistic background regarding the cooperation between HBV and aflatoxins for the development of HCC is presented.

2. Hepatitis B Virus: Structure and Replication

HBV is an enveloped hepatotropic virus belonging to the Hepadnaviridae family with icosahedral symmetry and a relaxed-circular DNA (rcDNA) genome of approximately 3.2 Kbp in length, with a complete negative strand and an incomplete positive strand [11,12]. It is composed of a nucleocapsid containing the HBV core antigen (HBcAg), a DNA polymerase-reverse transcriptase, the viral genetic material, and host proteins. In addition, HBV has an envelope composed mainly of three types of surface antigens (HBsAg), essential for the diagnosis of infection [13] (**Figure 1**). The infection predominates in hepatocytes and can trigger a variety of immune responses, from asymptomatic infections and liver inflammation to acute or chronic hepatitis, liver cirrhosis and HCC in chronic cases [14]. Three main types of particles are found in the serum of patients with HBV infection: Dane particles are 42 nm complete infectious virions containing a lipid envelope with surface antigens (L-HBs, M-HBs and S-HBs) and a nucleocapsid with viral DNA. While the much more abundant 22 nm particles lack a nucleocapsid, and therefore, are not infectious. In addition, other non-infectious particles have been identified, including enveloped particles without viral genome and those containing viral RNA and naked nucleocapsids [15,16]. The replication cycle of HBV is a complex process that initiates with virus entry into hepatocytes. HBV attaches nonspecifically to the cell surface through interactions with heparan sulfate proteoglycans (HSPG) [17–19]. This step is followed by a more specific and high-affinity binding with the Na⁺ Taurocholate Co-transporter Polypeptide (NTCP), which is crucial for viral internalization [20–23]. HBV entry is also facilitated by the Epidermal Growth Factor Receptor (EGFR), which interacts with NTCP, working as a cofactor [24]. After internalization by endocytosis, the virus is transported to the nucleus of the cell via microtubule-mediated transport and the nuclear pore complex [25–27]. In the nucleus, the viral DNA is converted into covalently closed circular DNA (cccDNA), a stable form that serves as a template for transcription of viral genes and genome replication [28–30]. Transcription of cccDNA produces various types of messenger RNA, regulated by hepatic transcription factors and epigenetic modifications such as histone acetylation and methylation [31,32]. The HBx protein is crucial for this stage as it modulates cccDNA activity by counteracting repression mediated by the Smc5/6 complex and other regulatory proteins [33,34]. In the cytoplasm, the encapsidation of viral pregenomic RNA (pgRNA) and DNA synthesis occur with the formation of capsids containing HBc protein and viral polymerase (Pol) [35,36]. The release of virions and subviral particles from the cell occurs through the ESCRT complex; subviral particles follow different secretion pathways depending on their type [37–39].

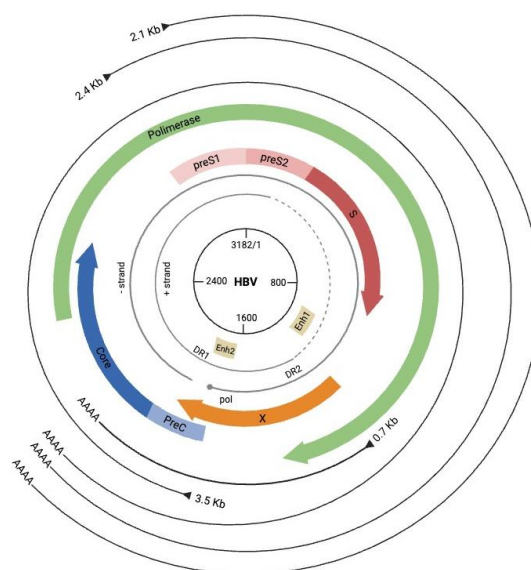


Figure 1. HBV genome organization. Created in BioRender.com.

3. Mechanisms of HBV-Mediated Cancer Development

Hepatitis B virus (HBV) is a significant contributor to HCC, with various mechanisms underlying its role in hepatic carcinogenesis. Chronic HBV infection often leads to unrelenting inflammation in the liver, primarily due to the immune response to the virus. The resulting inflammatory environment contributes to tissue damage, fibrosis, and cirrhosis, ultimately predisposing cells to malignant transformation. Chronic inflammation is intimately linked with carcinogenic pathways, as inflammatory cytokines can stimulate cell proliferation and genetic instability [40,41]. Studies have indicated that cirrhosis, often secondary to chronic HBV infection, significantly increases the risk for HCC, underscoring the importance of inflammation in HBV-related oncogenesis [42]. Additionally, the HBV life cycle involves the delivery of its genome into hepatocytes, where it exists as covalently closed circular DNA (cccDNA). This genomic presence can lead to persistent infection and replication, creating a constant state of viral antigen expression that imposes additional stress on the host's cellular machinery [43]. Importantly, HBV can integrate into the host genome, disrupting normal gene function, leading to chromosomal instability, and inducing mutations in oncogenes and tumor suppressor genes [44,45]. The integration of HBV DNA has been particularly associated with alterations in key regulatory pathways that control cell growth and apoptosis, such as those involving p53 [46].

The HBx protein plays a critical role in promoting HCC. This protein has been shown to interfere with p53, a crucial tumor suppressor, impairing its function and promoting cellular proliferation and survival under otherwise harmful conditions. In fact, studies have shown that HBx binds to p53, disrupting the ability of this protein to activate its target genes that control cell cycle arrest and apoptosis [47–49]. Additionally, HBx has been reported to upregulate MDM2, an E3 ubiquitin ligase, leading to increased ubiquitination and subsequent proteasomal degradation of p53. This Mdm2 upregulation can be mediated by NF- κ B signaling pathway activation, promoting the expression of additional genes involved in cell survival and proliferation [50,51]. Additionally, HBx has been shown to upregulate the mammalian target of rapamycin (mTOR) pathway via the IKK β signaling cascade. This activation enhances cell proliferation and vascular endothelial growth factor (VEGF) production, which are critical for angiogenesis and tumor growth [52]. Similarly, HBx stimulates the CDC42 pathway, facilitating cell migration and wound healing, which could also contribute to the metastatic potential of liver cancers [53].

Another significant HBx function involves the modulation of microRNA (miRNA) expression. Indeed, HBx has been found to upregulate miR-21, a potent oncogenic microRNA which accelerates

hepatoma cell migration by downregulating the tumor-suppressor phosphatase and tensin homolog (PTEN) [54,55]. The ability of HBx to hijack the host's miRNA machinery facilitates a nuanced approach to increasing its oncogenic potential, primarily by demolishing regulatory checkpoints in the cell cycle. Moreover, HBx has been implicated in epigenetic alterations that disrupt normal gene expression patterns. For example, HBx interacts with histone demethylases and acetyltransferases, leading to aberrant modifications of histones that contribute to oncogenic transformation [56,57]. This epigenetic modulation results in the activation of genes associated with proliferation and survival while repressing those involved in differentiation and apoptosis [58,59]. HBx also affects liver regeneration processes that can lead to carcinogenesis if dysregulated. Studies indicate that HBx inhibits liver regeneration by altering the expression of urokinase-type plasminogen activators, which are essential for proper recovery post-injury [60]. The dysregulation of regenerative pathways can create an environment conducive to cancer development, particularly in the context of chronic liver injury. In addition to these mechanisms, HBx has been linked to the upregulation of SIRT1, which contributes to the epithelial-mesenchymal transition (EMT) process—an essential feature in cancer metastasis [61]. The induction of SIRT1 promotes cell migration and invasiveness, providing resistance to chemotherapy, thereby influencing treatment outcomes and cancer progression [61]. Furthermore, HBx's interplay with the Notch signaling pathway has been recognized as a pivotal mechanism in HCC pathogenesis. Notch signaling, when aberrantly activated by HBx, influences cellular differentiation and proliferation, thereby facilitating tumorigenesis [62]. Taken together, these combined effects on various signaling and transcriptional pathways underscore the multifaceted role HBx plays in liver oncogenesis.

Importantly, HBV infection is associated with alterations in cellular metabolism, notably aerobic glycolysis, which can enhance the proliferation of liver cancer cells. This metabolic shift is partly mediated by the regulation of nicotinamide adenine dinucleotide phosphate (NADPH) metabolism, supporting cancer cell survival and growth [63]. Changes in metabolism can create an environment that favors tumor development by providing the necessary substrates and energy for rapidly proliferating cancer cells. Furthermore, HBV can lead to the activation of cellular stress response pathways, including those related to oxidative stress, which is implicated in hepatocarcinogenesis [64]. Indeed, HBx contributes to the development of oxidative stress in hepatocytes through several mechanisms, including the generation of ROS and disruption of mitochondrial functions [65,66]. The resultant oxidative stress not only promotes apoptosis but also fosters a pro-inflammatory microenvironment conducive to liver carcinogenesis [67]. These findings underscore the critical role of HBx in mediating oxidative stress during HCC progression.

4. Aflatoxins and Hepatocellular Carcinoma

Aflatoxins are toxins produced by fungi of the genus *Aspergillus* that can interfere with various biological processes if ingested in sufficient quantities. These toxins pose a serious threat to food safety by contaminating various foods such as grains, nuts, and their derivatives, posing significant risks to public health worldwide [68,69]. Aflatoxins are synthesized by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, which thrive in grain storage environments with high humidity and temperature, coupled with inadequate ventilation [70]. These microorganisms prefer relative humidity of 80-85% or higher and temperatures between 13-42°C, with optimal spore production between 25-37°C [71]. Adverse effects, such as stunting and immune suppression, have been reported mainly in young children exposed to aflatoxins at an early age, especially in West Africa [72]. Effective post-harvest strategies have been identified to reduce aflatoxin exposure in agricultural settings, underscoring the importance of preventing aflatoxin-associated diseases through integrated interventions between agriculture and public health [73]. In addition, aflatoxins and other mycotoxins can activate cellular oncogenes and inhibit genes that function as tumor suppressors, in turn increasing the risk of cancer in humans and animals by promoting genetic mutations [74].

Aflatoxins are responsible for a significant proportion of HCC cases globally, especially in regions with high exposure such as Africa and Asia [75]. Aflatoxin B1 (AFB1) is metabolized to AFB1-

exo-8,9-epoxide, which plays a crucial role in the development of this type of cancer (**Figure 2**). Recent research indicated that AFB1-induced HCC reduced mRNA expression and activity of antioxidant enzymes such as SOD, GPx, catalase, GR, and GST, while increased lipid peroxidation and decreased GSH levels. Moreover, treatment with phosphodiesterase-5 inhibitors (PDE5), such as tadalafil and sildenafil, restored these parameters towards normal values, with sildenafil being most effective in this process. These findings suggest that PDE5 inhibitors might act as anticancer agents by modulating the antioxidant pathway, potentially preventing the development and progression of AFB1-induced HCC [76]. Importantly, AFB1 is involved in HCC development through the generation of DNA adducts [77]. The primary DNA adduct of AFB1 is 8,9-dihydro-8-(N7-guanyl)-9-hydroxyafatoxin B1 (AFB1-N7-Gua), which naturally converts to two secondary lesions, an apurinic site and an AFB1-formamidopyrimidine adduct (AFB1-FAPY). AFB1-FAPY has been found to cause G to T mutations in *Escherichia coli* approximately six times more frequently than AFB1-N7-Gua, and blocks DNA replication, including replication mediated by the bypass polymerase MucAB. These properties underscore the genotoxic and mutagenic potential of AFB1-FAPY, which may contribute to the development of liver cancer [78,79]. Interestingly, in a comprehensive metabolomic analysis after exposing Hep3B cells to AFB1 at two concentrations (16 μ M and 32 μ M), results revealed that AFB1 induces dynamic metabolic reprogramming, altering purine and pyrimidine metabolism and reducing the activity of metabolic pathways involved in producing hexosamine and sialic acid [80].

More than 50% of HCC cases harbor a G to T mutation at the third position of codon 249 of the TP53 gene, which is associated with high exposure to AFB1 (R249S mutation) [81]. This mutation significantly increases the transcription of insulin-like growth factor II (IGF-II) from promoter 4, resulting in the accumulation of the fetal form of IGF-II. Additionally, the TP53 R249S mutation was shown to modulate the binding of transcription factors to the P4 promoter, increasing DNA-protein (Sp1 or TBP) and protein-protein (Sp1 and TBP) interactions. Furthermore, the TP53 R249S mutation stimulates the phosphorylation of the transcription factor Specificity protein 1 (Sp1), which may increase its binding to the P4 promoter, whereas wild type p53 does not show this effect. Expression of the TP53 R249S mutant also inhibits HBx- and TNF-alpha-induced apoptosis, which might favor the survival of transformed hepatocytes. These findings reveal how the AFB1-induced TP53 R249S mutation drives the molecular genesis of HCC [82]. Interestingly, different lysine pretreatments affect the mutation at codon 249 of the TP53 gene in liver cells exposed to AFB1. In fact, pretreating cells with excess lysine for 72 h before exposure to 1 μ g/mL AFB1 inhibited the mutation at this specific locus of the TP53 gene. These results suggest a potential for chemoprevention of AFB1-induced mutations in primary liver cancer [83].

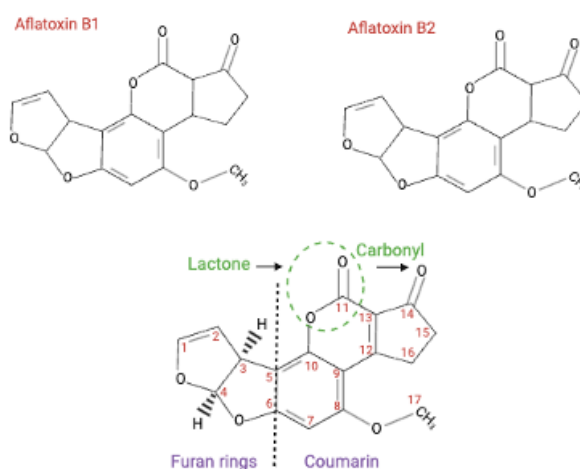


Figure 2. Structure of Aflatoxin 1 (AFB1) and Aflatoxin 2 (AFB2).

5. Epidemiological Associations Between HBV and AFB1 for HCC Development

A Pekin duck model investigating the effects of AFB1 on duck hepatitis B virus (DHBV) replication found that AFB1 may act as a cofactor in hepatitis B pathogenesis, potentially affecting the epidemiology and disease progression in susceptible populations [84]. Interestingly, the TP53 R249S mutation was significantly associated with three single nucleotide polymorphisms (SNPs): ADAMTS18 (rs9930984), WDR49 (rs75218075), and SLC8A3 (rs8022091). Specifically, the TT genotypes of rs9930984 and rs75218075 showed a high association with the R249S mutation. Furthermore, significant differences in ADAMTS18 and WDR49 mRNA expression between tumor and non-tumor tissue were observed, correlated with these SNPs. These findings suggest that the identified SNPs might influence susceptibility to the TP53 R249S mutation in HCC patients exposed to both AFB1 and HBV [85].

A total of 573 chromosomal abnormalities, including 184 gains and 389 losses, were identified in HCC patients divided according to their exposure to HBV and AFB1. Recurrent changes in regions such as 4q13.3-q35.2, 13q12.1-q21.2, and gain at 7q11.2-q35 were observed in the HBV and/or AFB1-exposed groups. Loss of 8p12-p23.2 was associated with advanced tumors and poorer survival. In iTRAQ proteomic analysis, 133 proteins showed differential expression, including AKR1B10, which was elevated in the AFB1-exposed groups, suggesting its role in hepatocarcinogenesis [86]. A synergistic interaction between alpha-tocopherol, alpha- and beta-carotene in the formation of AFB1-DNA adducts was observed in HBsAg carriers, underlining the importance of antioxidant vitamins in modulating AFB1-induced liver carcinogenesis [87].

In Thailand, high concentrations of R249S-mutated DNA (≥ 150 copies/mL) were more common in HCC patients without pre-existing cirrhosis, suggesting a possible association independent of HBV-related cirrhosis [88]. Interestingly, the TP53 R249S mutation might be a result of co-exposure to aflatoxins and HBV, with even modest levels of aflatoxin tripling the risk of HCC in this population [89]. Notably, TP53 gene mutations in HCC are not limited to regions with high aflatoxin ingestion but may also be associated with HBV infection [90–92]. In fact, TP53 mutations in 223 HCCs and 13 adjacent liver tissue samples, but only one normal liver tissue sample, were concentrated in exons 4 to 9, with codon 249 (R249S) of exon 7 being the most affected. Furthermore, TP53 mutations and HBV/AFB1 status independently predicted postoperative tumor recurrence [93]. Additional results showed that 47% of the HCC cases from Guatemala had mutations in the TP53 gene, with the AFB1-associated R249S mutation detected in 24% of cases. No overlap was observed between the R249S mutation and HBV infection in this cohort. Of the analyzed samples, 44% showed some mutation in the TP53 gene and 33% had the R249S mutation. Additionally, other somatic mutations were identified in genes known to drive the development of HCC. These findings suggest that AFB1 might be significantly contributing to the high incidence of HCC in Guatemala, especially in the absence of concomitant HBV infection [94]. Conversely, a study did not find evidence of aflatoxin exposure in 74 HCCs from Mexican Mestizo patients. Indeed, the main risk factors identified were HCV (39%), alcoholism (20%), and HBV (2%). Additionally, the TP53 R249S mutation was not found in any sample, suggesting a low association with aflatoxins in these cases. Interestingly, cases with steatohepatic variants and metabolic conditions such as diabetes and systemic hypertension were observed [95]. The occasional presence of mutations at codon 249 of the TP53 gene in HCC samples might indicate the influence of other environmental carcinogens or the need for prior hepatitis B virus-related hepatitis for the specific induction of these mutations by AFB1 [96]. An association between high aflatoxin intake and a high frequency of the TP53 R249S mutation, independently of HBV, has also been reported [97].

The influence of risk factors such as HBV and AFB1 on chromosomal instability is reflected in higher mutation rates in TP53 (48% vs. 22%, $p < 0.0001$) and lower mutation rates in β -catenin (4% vs. 26%, $p < 0.0003$) [98]. Nine AFB1-induced tumors in non-human primates were analyzed for cyanotoxins (microcystin-LR and nodularin) and TP53 gene mutations. No mutations at codon position 249 of the TP53 gene were found in any of the tumors examined by the targeted analysis. However, a point mutation at codon position 175 was identified in one HCC. These results suggest

that mutations in the TP53 gene are not a necessary event for AFB1-induced hepatocarcinogenesis in non-human primates. HBsAg seropositivity significantly increases the risk of cirrhosis by 58.8% (OR = 8.0), as do the presence of HBeAg (OR = 10.3) and HCV infection (OR = 3.3). Significant associations were also found between aflatoxin exposure, as assessed by high peanut consumption, and the 249 (ser) TP53 mutation in plasma, with the risk of cirrhosis (OR = 2.8 and OR = 3.8, respectively). The interaction between aflatoxin and HBV appears to increase the risk of cirrhosis, although not statistically significantly [99]. The interaction between HBx and AFB1 may synergistically promote hepatic steatosis, as evidenced by changes in liver histology and increased expression of genes and enzymes related to lipid metabolism. Furthermore, treatment with AFB1 reportedly accelerates hepatic hyperplasia in transgenic fish [100].

Elevated levels of aflatoxin M1 (AFM1) in urine have been associated with an increased risk of HCC in chronic HBV carriers. Furthermore, AFB1-N7-guanine adducts in urine also significantly increase the risk of HCC, especially when both types of adducts are present (OR = 10.0, 95% CI = 1.6-60.9) [101]. Aflatoxin-albumin adduct levels in humans and rodents reflect relative susceptibility to AFB1 carcinogenesis. In rodents, rats, which were more sensitive, were found to have higher levels of albumin adducts compared to hamsters, while mice were more resistant. This correlates with human data, where patients with chronic active hepatitis B virus (CAH) showed significantly higher levels of aflatoxin-albumin adducts compared to HBsAg+ carriers and controls. Specifically, in the CAH group, the levels were five times higher than in the control group, highlighting the utility of aflatoxin-albumin adducts as markers of chronic exposure to aflatoxin and its relationship with HBV infection [102,103].

6. Mechanisms of Cooperation Between HBV and Aflatoxins for HCC Development

AFB1 has been suggested to synergistically cooperate with HBV, accelerating HCC development [104]. Evidence supports some mechanisms for such a cooperation.

6.1. Aflatoxin B1 Cooperates with HBV HBx Oncoprotein for Carcinogenesis

HBV-encoded X protein (HBx) is a multifunctional 154-amino-acid HBV protein that acts as a transcriptional transactivator and a viral replication and tumor-driving protein [105]. Evidence shows that the combined action of chronic HBV HBx expression and dietary AFB1 exposure is an important risk factor in the hepatic environment for the development of HCC [106]. Indeed, exposure to AFB1-8,9-epoxide alone induces a low-level of mutation at codon 249 of the TP53 gene, specifically the AGG to AGT transversion (R249S mutation), a frequent event in endemic HCC. However, expression of the HBV HBx protein further increased the frequency of this AFB1-epoxide-induced mutation compared to control cells, suggesting that HBx might increase susceptibility to carcinogen-induced mutagenesis by perturbing the balance between DNA repair and apoptosis, crucial processes in cellular defense against genotoxic stress [107]. Notably, the TP53 R249S mutation does not preserve the ability to activate p53-regulated genes or to bind to its response sequences in HCC cell lines. In cells without functional p53, introduction of mutated R249S p53 did not significantly affect cell proliferation after exposure to cytotoxic stress. Furthermore, in cells expressing mutated p53 and HBV HBx protein, silencing of either p.R249S or HBx slowed cell proliferation, suggesting an interaction between these proteins in the early stages of hepatocarcinogenesis. However, the interaction between p.R249S and HBx does not appear to be crucial for the progression of advanced HCC in patient samples [108]. Interestingly, AFB1 up to 5 μ M was found to reduce HBV replication, suggesting that they do not collaborate to increase AFB1-induced DNA damage in HepaRG cells [80]. In mice, co-exposure to AFB1 and microcystin-LR (MC-LR), a cyanobacteria toxin, increased the risk of liver tumors at 24 weeks, although the combination of AFB1, cyanotoxins, and HBx had a moderate effect on hepatic tumorigenicity at 24 weeks [109].

6.2. AFB1 Exposure Might Favor HBV Integration Events

It has been clearly shown that AFB1 exposure promotes single- and double-strand DNA breaks in HepG2 cells [110,111]. Considering the additional role of the R249S TP53 mutation in inhibiting wild type p53 activity and promoting a defective DNA damage response (DDR), it is possible to suggest that AFB1 can promote the integration of HBV genomes [111]. HBV is known to frequently integrate into the HCC genome, so it is plausible that factors promoting DNA damage can cooperate with HBV to promote HCC. Preliminary findings to assess whether genetic instability, as measured by induced chromatid breaks in cultured lymphocytes, modifies the risk of developing HCC suggested that differences in genetic susceptibility exist in cases with significantly more bleomycin- and benzo(a)pyrenediol epoxide (BPDE)-induced chromatid breaks than in controls (both $P < 0.0001$). Bleomycin and BPDE sensitivity were associated with an increased risk of HCC in multivariate analyses, with odds ratios of 5.63 (95% CI: 2.30-13.81) and 14.13 (95% CI: 3.52-56.68), respectively [112]. These findings suggest that these sensitivities may influence the development of HCC, possibly by affecting HBV integration or increasing vulnerability to carcinogen-induced DNA damage. However, to our knowledge, this hypothesis has not been experimentally demonstrated. Conversely, studies in cell lines suggested that hepatocarcinogenesis associated with p53 mutations does not require the genomic integration of HBV sequences [113].

6.3. HBV Infection Sensitizes Hepatic Cells to AFB1 Effects

HBV infection has been reported to promote the expression of CYP450 enzymes, which are involved in AFB1 biotransformation. In fact, epidemiological data revealed that Gambian children previously infected with HBV (HbsAg positive) showed an increase in aflatoxin-albumin adducts compared to uninfected children [114,115]. However, additional studies from Africa and Asia failed to demonstrate this association between HBV infection and increased aflatoxin-albumin adducts [116,117].

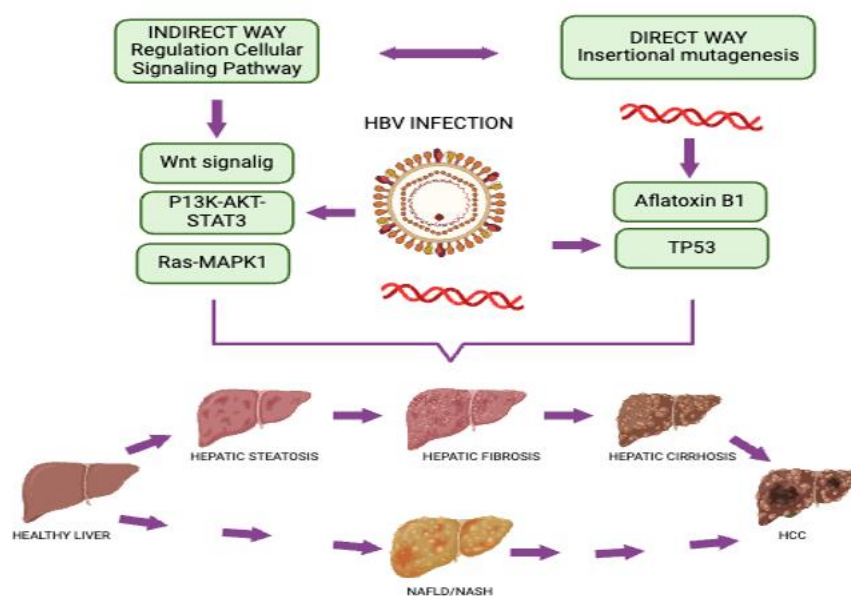


Figure 3. Role of HBV and AFB1 in HCC pathogenesis and progression. The pathogenesis of HCC is closely related to the presence of HBV. The viral agent supports the onset and progression of cancer through consequential events involving genetic alterations, increased reactive oxygen species, and angiogenesis that occur during tumor progression from a healthy to a diseased liver.

7. Conclusions

The interaction between hepatitis B virus (HBV) infection and exposure to aflatoxins, particularly aflatoxin B1 (AFB1), constitutes a significant risk factor for the development of HCC. The cooperation between these two factors amplifies the oncogenic potential in hepatocytes, leading to a higher incidence of liver cancer, especially in regions where both HBV and aflatoxin exposure are prevalent. The interplay between HBV and aflatoxins provides a compelling example of how environmental and biological factors can synergistically contribute to cancer development. Aflatoxin B1 exposure enhances the mutagenic potential of HBV, leading to increased genomic instability and alterations in key tumor suppressor genes such as TP53. This cooperation not only accelerates the progression from chronic hepatitis to HCC but also poses significant public health challenges, particularly in endemic regions where both factors are prevalent. Addressing this dual risk requires comprehensive strategies, including vaccination against HBV and effective management of dietary aflatoxin exposure.

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