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EDITORIAL

Androgen Enhances Aflatoxin-induced Genotoxicity and Inflammation to Liver Cancer in Male Hepatitis B Patients

Hepatocellular carcinoma (HCC) is a male-predominant liver malignancy worldwide. Particularly striking is the male/female ratio in hepatitis B virus (HBV)-related HCC, which increases to 6 to 8:1.[1] One possible explanation for this comes from molecular studies, which have identified androgen receptor response elements in the enhancer I of the HBV genome. These cis-elements are predicted to increases HBV transcription and viral titer, a documented risk for HCC, principally in males.[1] In addition, most HBV-related HCCs contain integrated HBV DNAs in which the retained viral enhancer I elevates the host oncogene transcription. Amplification of these transcripts by testosterone is another mechanism favoring HCC in males.[2]

In addition to HBV infection, environment factors, especially aflatoxin exposure, increases HCC risk among males approximately 3- to 4-fold. Aflatoxin is a well-characterized genotoxic chemical that produced aflatoxin B1-N7-guanine adduct.[3] How HBV and aflatoxin work together to enhance liver cancer in males is a clinically significant topic that merits further study.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Xu et al[4] took advantage of the unique HCC cohort in Qidong (QD), a coastal city with high aflatoxin exposure in China, to investigate the interaction among environmental and male risk factors in HCC. First, the authors studied the somatic mutation profiles and gene expression patterns of male and female QD-HCC patients. The authors found that the male QD-HCC had higher expression of metabolic genes for aflatoxin response (*AHR* and *CYP1A1*), but lower levels of DNA repair factors for nonhomologous end joining (*XRCC4*, *LIG4*, and *MRE11*) than females. Supporting the biologic relevance of these associations, in cultured cell lines with HBV persistence, treatment with testosterone enhanced aflatoxin-induced genotoxicity but reduced cellular DNA repair capacities. In addition, the authors observed increased release of nuclear DNAs into the cytoplasm in the treated cells, which stimulated the cGAS-STING pathway to activate type I interferon (IFN-I) signaling. Significantly, in HCC tissues, the IFN-I pathway was upregulated in males but not in females, and it was accompanied by increased $PD1^+/CD8^+$ T-cell infiltration in male HCC tumor tissues. The authors went on to show that the presence of this immunosuppressive cell infiltrate was recapitulated in murine HCC xenograft models, and that anti-PD-1 therapy against established HCC tumors was synergistically enhanced by pretreatment of tamoxifen. These findings highlight the therapeutic potential of combined checkpoint inhibitor/hormonal therapy for HBV-related HCC males.

In summary, Xu et al[4] present an interesting framework for how HBV, aflatoxin, and androgens interact to amplify aflatoxin-induced DNA damage and a permissive inflammatory response that together enhance liver carcinogenesis. The observation that nuclear and/or mitochondrial DNA activates cGAS-STING pathway in HCC linked to combined HBV and aflatoxin exposure is also innovative and worthy of further investigation. Going forward, 3 additional areas of research deserve attention. The first regards the role of HBV, which was not explored in the current report. HBV X protein has been shown closely to interact with androgen receptor to increase its activity,[1] so its carcinogenic role in aflatoxin-exposed male HBV patients should be investigated. The second involves mechanistic studies to understand how increased IFN-α leads to an immune-suppressive environment. Specifically, the identification of effectors produced by HBV-infected hepatocytes or HCC that mediate $CD8^+$ T-cell chemotaxis. Third, the genetic mutation profiles in QD-HBV-HCC were distinct (eg, only 41% harboring HBV DNA integration, much lower than nonaflatoxin areas in which viral integration is detected in 80% of HBV-related HCC).[2,5] It would be important to determine whether aflatoxin-induced genotoxicity drives carcinogenesis in the absence of HBV DNA integration in some patients. Finally, it would be also interesting to evaluate the efficacy of anti-HBV nucleos(t)ide analogues in patients from the QD region, as compared with low aflatoxin exposure areas, especially in male patients.

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Conflicts of interest
The authors disclose no conflicts.

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