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The Mechanism of APOBEC3B in Hepatitis B Virus Infection and HBV Related Hepatocellular Carcinoma Progression, Therapeutic and Prognostic Potential

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Abstract: Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors globally. Prominent factors include chronic hepatitis B (CHB) and chronic hepatitis C (CHC) virus infections, exposure to aflatoxin, alcohol abuse, diabetes, and obesity. The prevalence of hepatitis B (HBV) is substantial, and the significant proportion of asymptomatic carriers heightens the challenge in diagnosing and treating hepatocellular carcinoma (HCC), necessitating further and more comprehensive research. Apolipoprotein B mRNA editing catalytic polypeptide (APOBEC) family members are single-stranded DNA cytidine deaminases that can restrict viral replication. The APOBEC-related mutation pattern constitutes a primary characteristic of somatic mutations in various cancer types such as lung, breast, bladder, head and neck, cervix, and ovary. Symptoms in the early stages of HCC are often subtle and nonspecific, posing challenges in treatment and monitoring. Furthermore, this article primarily focuses on the established specific mechanism of action of the APOBEC3B (A3B) gene in the onset and progression of HBV-related HCC (HBV-HCC) through stimulating mutations in HBV, activating Interleukin-6 (IL-6) and promoting reactive oxygen species(ROS) production, while also exploring the potential for A3B to serve as a therapeutic target and prognostic indicator in HBV-HCC.

Keywords: hepatocellular carcinoma, hepatitis B virus, APOBEC3B, chronic hepatitis B

Hepatitis B Virus and Hepatocellular Carcinoma

HCC accounts for approximately 80% of all liver cancers, posing a substantial health risk,[1] the majority of HCC cases are diagnosed at an advanced stage, limiting the effectiveness of treatments.[2] HBV and hepatitis C virus (HCV) infections are the primary contributors to HCC. Conversely, in developed countries, the prevalence of non-alcoholic fatty liver disease (NAFLD) is rising while virus-related HCC is declining.[3–5] In adults, HBV infection elicits a rapid immune response, leading to lifelong immunity following acute self-limited infection, whereas, in children, chronic infection with lifelong HBV persistence is more prevalent.[6] Chronic inflammation is a pivotal factor that alters the tumor microenvironment.[7] In the absence of liver cirrhosis, HBV can still induce HCC through host gene mutations. Both HBV replication and host genome mutations contribute to HCC development.[8]

HBV Infection and Chronic Liver Injury

HBV infections can manifest as acute or chronic, varying from asymptomatic or mild cases to severe or rare fulminant hepatitis.[9] Chronic hepatitis B, in particular, presents significant complexity. HBV can prompt immune escape through S gene mutations, resulting in occult hepatitis B infection (OBI). OBI is characterized by the presence of HBV DNA in the liver of HBsAg-negative

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individuals, detectable through current methods (HBV DNA may be detectable in serum (usually<200 IU/mL) or remain undetectable).[10] In such cases, the virus may continuously replicate and harm the liver.

ROS play a crucial role in the progression of CHB and HCC. Studies have demonstrated that HBeAg suppresses the production of Nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) and IL-1b through interference with the nuclear factor kappa-B (NF-κB) signaling pathway, potentially via transverse rectus abdominis myocutaneous (TRAM) and myelin and lymphocyte protein (MAL) blockade. Conversely, it suppresses ROS generation by impeding the translation of the p47-Phox complex and the activation of NADPH oxidase.[11] Additionally, HBx can induce excessive oxidative stress and elevate ROS production.[12] The inflammatory processes within the tumor microenvironment and the intricate interplay between immune cells and cancer cells are pivotal and decisive elements in determining the course of tumor diseases.[12]

HBV Infection and Genetic Mutations

Hepatitis B virus typically induces hepatocellular carcinoma through two mechanisms: integration of HBV into the host genome during reverse transcription, thereby modifying the host genome; and direct impact on cell function or activation of oncogenic signaling pathways via its oncoviral gene proteins (HBx and Pre-S).[13] The Pre-S mutant HBsAg accumulates in the endoplasmic reticulum(ER) and induces ER stress.[14] This ER stress can lead to oxidative stress and DNA damage, ultimately resulting in genomic instability.[14] HBV DNA integration is not crucial throughout the virus life cycle as this process cannot generate replicable viruses, which are found in less than 1% of infected hepatocytes during viral infection, indicating a strong positive selection for hepatocellular carcinoma progression.[15]

HCC patients exhibit significantly more double-stranded linear DNA(dslDNA) integration sites than non-HCC patients.[15] DslDNA integration leads to HCC, involving three main steps: HBV integration reduces the stability of host DNA chromosomes, induces mutations in oncogenes and tumor suppressor genes, and overexpression of mutated proteins such as HBsAg and HBx leads to HCC.[16] The downregulation of tumor suppressor genes and upregulation of oncogenes result from the integration of oncogenic HBV into the host genome.[17] Furthermore, the C-terminal protein fragment of HBx, which integrates the HBV gene, can induce mutations by influencing oncogenic signaling pathways such as TP53, AXIN1, KEAP1, and RB1, inhibiting cell apoptosis and transformation, and promoting tumor metastasis and growth by regulating the expression of various proteins and enzymes.[5]

HBV-Induced Abnormal Proliferation and Angiogenesis of Liver Cells

Cells with pre-S gene deletion mutations are termed ground glass hepatocytes (GGHs), which are categorized into Type I and Type II GGHs.[18] Type I GGHs typically grow in isolation and predominantly express Pre S1 protein within the cell, whereas Type II GGHs tend to cluster and express Pre S2 protein at the cell periphery.[19] The expression of wild-type large surface proteins can initiate GGH formation and sustain their proliferation, while the presence of pre-S deficient proteins can confer substantial growth advantages to GGHs and foster their malignant transformation. The pre-S mutant accumulates as a viral oncoprotein in the endoplasmic reticulum of GGHs.[20] The pre-S mutant can induce endoplasmic reticulum stress signaling, oxidation, DNA damage, and transformation.[21] Therefore, GGHs are considered precursor lesions of HCC,[22] particularly in Type I or Type II GGHs.

Vascular endothelial growth factor-A (VEGF-A) is among the earliest identified angiogenic factors and is the principal regulator of tumor angiogenesis.[23–25] Studies have demonstrated that the induction of ER stress can upregulate VEGF-A expression.[26,27] Consequently, increased expression of VEGF-A stimulates cell proliferation; in essence, hepatocytes, particularly those with pre-S mutants, will bear a heightened risk of cancer.

HBV-Induced Immune Escape

HBV particles or their related antigens may inhibit both innate and adaptive immune responses, especially affecting innate pattern recognition receptors and their downstream signals.[28] This inhibition may be associated with alterations in HBsAg antigenicity. The main hydrophilic region (MHR) of HBV contains a cluster of B cell epitopes known as the "a" determinant cluster, which includes amino acids 124–147, such as T116N, P120S/E, I/T126A/N/I/S, Q129H/R, M133L, K141E, P142S, D144A/E, and G145R/A.[29–31] Changes in the amino acid sequence within the "a" determinant cluster due

to point mutations, deletions, or insertions in the S-domain of S open reading frames (S-ORF) may lead to significant immune and preventive alterations against HBV infections. These changes affect the antigenicity of HBsAg and are sometimes termed "immune-escape" mutations.[32] These mutations have been identified as immune escape mutations, resulting in phenomena related to vaccine and diagnostic escape.[9]

The Mechanism of APOBEC3B in HBV-HCC

Within the APOBEC3 family, the A3B gene significantly contributes to tumor progression. As a DNA cytosine uracil deaminase in the body, the A3B gene serves dual functions: it aids in combating HBV and delaying virus replication, while also inducing C-T mutations in host cell genes, thus accelerating tumor progression. Numerous studies have investigated DNA mutations induced by A3B, revealing the widespread existence of APOBEC3 cytidine deaminase mutation patterns in human cancers including those of the liver, bladder, breast, cervix, and thyroid.[33–41] Research indicates that homozygous deletion of A3B is thought to markedly enhance host susceptibility to HIV-1 infection, Inducing immune suppression and immune escape effects within the host, leading to the development of AIDS.[42] APOBEC3 family is an innate single-stranded DNA cytosine uracil deaminase found in all tetrapods, including primates, and bony fish such as Lampreys. It is located on chromosome 22q13.1 – q13.2.[43] Apolipoprotein B mRNA catalytic editing protein 3B (APOBEC3B) is one of the eleven members of the AID/APOBEC family. APOBEC3B stands as the sole member within the APOBEC3 family that demonstrates significant overexpression in hepatocellular carcinoma (HCC) tissues, potentially acting as a factor in suppressing tumor growth in HCC.[34] The overexpression of A3B in human HCC significantly correlates with the ratio of C-to-A and G-to-T mutations in the genome. In HCC cells, this overexpression fosters cell proliferation, migration, and invasive capabilities in vitro, as well as tumor occurrence and metastasis in vivo, which plays a pivotal role in the suppression of HBV infection and the initiation of HCC.

Influence on Hepatitis B Virus

The Hepatitis B virus is among the smallest enveloped DNA viruses and can lead to both acute and chronic liver diseases, which may advance to liver fibrosis, cirrhosis, and hepatocellular carcinoma.[44] HBV infection may result in liver fibrosis, cirrhosis, and hepatocellular carcinoma. The stages of HBV infection are as follows: initial HBeAg positivity with high serum HBV DNA levels, followed by HBeAg serum conversion and decreased serum HBV DNA levels, and finally, HBeAg negativity with either reduced or undetectable serum HBV DNA levels.[45] The third stage of infection signifies the predominance of HBV in liver cells, significantly heightening the risk of cirrhosis or hepatocellular carcinoma.[46] Common amino acid sequences contain H-X-E-X23-28-P-CX2-4-C, where "X" represents any amino acid.[47] Variations in conserved domain amino acid sequence(CDAS) could be a significant factor contributing to the functional distinctions between A3B and other family members. The genes APOBEC1 (A1), APOBEC3A (A3A), APOBEC3C (A3C), and APOBEC3H (A3H) of AID contain only one Zn2+ binding domain, whereas the genes APOBEC3B (A3B), APOBEC3D/E (A3D/E), APOBEC3F (A3F), and APOBEC3G (A3G),[35] resulting from original gene duplication and contain two zinc-binding domains. Evidence indicates that only the carboxyl-terminal CDA is necessary for suppressing HBV replication.[39] Since its discovery, the A3 gene has primarily been studied for its capacity to inhibit various exogenous viruses, including human immunodeficiency virus (HIV/SIV) and hepatitis B virus.[48–50]

Studies have indicated that the anti-HBV effect of A3B may be associated with the A3B protein's capability to inhibit nuclear HBV DNA, consequently affecting HBV gene expression.[51] A3B could inhibit core-associated HBV DNA and HBV gene expression.[52] A3B expression decreased the nuclear-associated HBV DNA level by 90%, indicating A3B's potential as an effective inhibitor of HBV DNA replication as a nucleocytoplasmic shuttling protein.[53] Consequently, A3B reduces the expression of HBsAg and HBeAg.[52] Being a distinctive nuclear-cytoplasmic shuttle protein, A3B can efficiently bind to the HBV virus capsule due to its nuclear site advantage. Interferon inhibits HBV replication and triggers the expression of an antiviral protein that hampers HBV nucleation, ultimately culminating in the resolution of chronic HBV infection.[54–59]

Covalently closed circular DNA(cccDNA) plays a crucial role in the advancement of CHB and HCC. It directly processes cccDNA in the nucleus by inducing cytosine deamination mutations on DNA or RNA. cccDNA is considered highly stable and long-lived, and therefore, it plays a critical role in sustaining chronic HBV infection.[60] Residual cccDNA may persist in

hepatocytes and serve as the template for HBV replication when immune control of the infection is lost.[61] When in a temporary single-stranded state, A3B deaminates cccDNA, and DNA glycosyl deaminase generates uracil at the AP site. Subsequently, these uracil residues are identified and degraded by AP endonucleases, thereby hindering HBV replication.[60] Another hypothesis suggests that A3B-mediated mutagenesis of viral DNA may lead to an elevated viral mutation load surpassing the threshold for viral viability.[62,63] Within the human APOBEC3 protein family, the interaction between A3B and various heterogeneous nuclear ribonucleoproteins (hnRNPs) is distinct, particularly with hnRNP K, hnRNP I, hnRNP C1/C2, hnRNP H/F, and hnRNP A/B, which are more significant than other proteins in the family.[53] The downregulation of hnRNP K hampers HBV Enhancer II, consequently delaying the replication of HBV DNA.

Retrotransposons, classified as class I mobile elements, move via RNA intermediates.[64,65] They transcribe backward using a copy-and-paste mechanism to increase their copy numbers. These elements include long terminal repetitive retrotransposons of the human endogenous retrovirus (HERV) family and non-long terminal repeat (non-LTR) retrotransposons such as long spacer element 1 (LINE-1s or L1s).[66] A3B strongly inhibits non-LTR reverse transcription factors, such as LINE-1 (L1) and Alu elements, possibly through the inhibition of L1 transposition via a deamination-dependent mechanism.[67] Additionally, A3B can inhibit the expression of neomycin phosphotransferase II by the Simian vacuolating virus 40 (SV40) promoter.[67] Lymphotoxin-β receptor (LTβR) signaling induces cytidine deaminases of the APOBEC family, which then initiates cccDNA degradation through deamination.[67] A3B is involved in the degradation of cccDNA through co-localization or interaction with HBV nuclei in the nucleus. In contrast to activated cytidine deaminase (AID), which primarily edits HBV RNA and single-stranded DNA during reverse transcription, APOBEC3B primarily edits HBV negative and positively stranded DNA. Both can synergistically participate in the anti-HBV process through a common signaling pathway.[35] A3s are single-stranded DNA cytidine deaminases that can restrict viral replication. HBV undergoes a unidirectional phase in its life cycle.[68] Evidence indicates that A3B-mediated HBV clearance does not inflict damage on hepatocytes, a crucial factor in HCC progression.[69] Simultaneously, A3B can induce hypermutation in HBV through its editing activity.[19] The frequency of HBV mutations induced by A3B is 1.5 mutations per 100 bases, with the most prevalent mutation being C to T, followed by G to A.[19]

R-loop occurs when newly formed RNA anneals back onto the transcribed DNA strand, forming a triple strand containing RNA/DNA heteroduplex and translocated non-transcriptional single-stranded DNA(ssDNA) strands. This process is an important source of genomic instability in cancer. An increase in the R-loop triple-strand structure in the core is associated with a decrease in A3B levels. Research has found that A3B can accelerate the dynamic process of the R-loop and alter its distribution throughout the genome through deamination.[70] A3B can deaminate ssDNA cytosines in R-loop structures, leading to the formation of uracil, which then become substrates for multiple competing DNA repair/replication processes,[70] resulting in mutations. The upregulated DExH-Box Helicase 9(DHX9) could interact with A3B, inhibiting the association between A3B/pgRNA and attenuating the anti-HBV efficacy of A3B, consequently contributing to viral DNA replication.[71] In summary, A3B can inhibit HBV virus replication through various pathways, demonstrating strong antiviral effects.

APOBEC3B in HBV-HCC

APOBEC3B exhibited significant upregulation in HBV-infected patients and all tumor hepatectomy tissues.[72] It shows low expression in various normal tissues and organs, functions in catalyzing mutations, and significantly impacts the development of various human diseases.[34] A3B catalyzes the conversion of cytosine (C) to uracil (U) as a cytosine deaminase, leading to DNA sequence mutations in the substrate, indicating poorer clinical outcomes.[73–75] IL-6 has been confirmed to significantly influence the occurrence of HCC. A3B is significantly upregulated in HepG2 cells, inducing IL-6 overexpression by repositioning human antigen R(HuR), enhancing the stability of IL-6 mRNA, resulting in recurrent inflammatory attacks in liver tissue, and accelerating the progression of liver cirrhosis and hepatocellular carcinoma.[1] In summary, these results suggest the crucial role of A3B in the occurrence of HCC.[70] A3B expression has been reported to increase in various tumors, and it is associated with somatic mutations in genes such as P53 and PIK3CA.[32,37,76,77] The characteristic mutations of A3B may serve as potential tumor markers, significantly impacting the identification of tumor resistance, metastasis, or guiding treatment to enhance the survival rate of cancer patients. The mechanisms are summarized in Table 1.

Table 1 Mechanisms of A3B in HCC

Mechanism	Impact on Disease
A3B leads to GC to AT mutation in HBx	Diverse HBV genomic mutations, accelerate inflammatory response and HCC progression
A3B and IL-6 form a positive feedback loop	Persistent inflammatory reactions and APOBEC3B-UNG imbalance facilitate HCC evolution
A3B upregulates chemokine expression	Stimulates tumor cell survival and immune escape

Research has shown that A3B initiates cancer development via uracil DNA glycosylase. Overexpression of A3B in various tumors led to significantly lower OS (overall survival), DSS (disease-specific survival), and PFI (progression-free interval) compared to low APOBEC3B expression.[78] Recent studies have shown that A3B plays a crucial role in innate immunity and is associated with immune cell infiltration in tumors. Similarly, APOBEC3s induce diverse HBV genomic mutations, with HBx mutations being a critical step in the development of liver cancer. This effect mainly occurs during the reverse transcription of hepatitis B virus DNA into RNA. HBV DNA mutations induced by APOBEC3s occur when viral RNA is converted by HBV polymerase into partially double-stranded relaxed circular DNA (rcDNA) through cDNA in the capsid.[79] A3B is not only associated with inducing DNA mutations but also represents an important endogenous source of these mutations by converting DNA cytosine into uracil. Conversion of DNA through a zinc-mediated hydrolysis mechanism, deamination of cytosine to uracil, or conversion of cytosine to guanine (C-to-G). High expression of APOBEC3B in cancer cells is associated with an increased frequency of genome-wide GC to AT mutations.[80] Whole genome sequencing (WGS) studies identified APOBEC3-specific mutational signatures in tumor genomes and observed that the mutations are frequently clustered.[81] The mutated HBx gene can induce overexpression of PLA2R (phospholipase A2 receptor, which could cause a variety of cellular effects),[82] activating the NLRP3 inflammasome (composed of nucleotide-binding oligomerization domain-like receptor protein 3, apoptosis-associated speck-like protein containing card, and pro-caspase-1) in podocytes, leading to the generation of ROS, and accelerating inflammatory response and tumor progression.[83]

The interaction between IL-6 and A3B accelerates tumor progression. Reports indicate a positive feedback loop between the inflammatory factors IL-6 and A3B in liver cells. The prevailing assumption suggests an incremental process where external stimuli induce genetic changes in mature liver cells, leading to cell death, proliferation, and regeneration.[84] A3B induces IL-6 overexpression by modulating HuR (Hu-antigen R, implicated in carcinogenesis and therapeutic options).[85] This action increases IL-6 mRNA stability, triggers classical and non-classical NF kB signaling pathways, and elicits persistent inflammatory reactions and destructive effects in liver cells, promoting chronic hepatitis development into hepatocellular carcinoma.[1] Conversely, IL-6 could upregulate A3B expression via the JAK1/STAT3 pathway, evidence that A3B may be regulated by IL-6 in vivo and in vitro, forming a positive feedback loop.[1] Additionally, IL–6–induced APOBEC3B-UNG imbalance in the proinflammatory microenvironment facilitates HCC evolution. Studies have shown that IL6 significantly increases A3B expression in HepG2 and L02 cell lines while reducing UNG expression.[86] APOBEC3B and UNG significantly increase the risk of HCC development in HBV-infected patients in an inflammatory environment, correlating with HBV mutations and HCC risk.[86] Research demonstrates that A3B overexpression in HCC cells promotes cell proliferation, migratory and invasive abilities in vitro, tumorigenicity, and metastasis in vivo. Conversely, knockdown of A3B suppresses the aforementioned tumor cell functions.[87]

Chemokine expression is another significant factor contributing to HCC. The incidence of HCC is closely related to the chronic inflammatory background, resulting in alterations in the number and function of immune cell subsets (eg, T cells, MDSCs, and macrophages).[88] Previous studies indicated that A3B could promote the upregulation of chemokine expression, leading to the recruitment of MDSCs (myeloid-derived suppressor cells) and TAMs (tumor-associated macrophages). These cells inhibit CD8+T cell function by expressing amino acid I.[89] Amino acid I extracts amino acids, releases oxidative molecules, and stimulates other immunosuppressive cells,[89] increasing the risk of liver cancer occurrence and development.[90] In liver cancer, genetic and epigenetic mechanisms regulate chemokine expression, with polycomb repressive complex 2 (PRC 2) playing a significant role.[90] The research found that PRC2 participates in H3K27 (histone H3 lysine 27) methylation while regulating the expression of specific genes.[91] In breast cancer,

inhibiting H3K27 expression promotes the upregulation of chemokines, including CCL2 and IL-8,[58] potentially explaining A3B's role as an immunomodulatory regulator of chemokine expression.[92] The non-classical NF-kB pathway stimulates the A3B binding promoter via the RelB/p52 complex, increasing A3B transcriptional expression.[86] Increased A3B expression significantly increases CCL2 chemokines, recruiting MDSCs and TAMs to participate in liver cancer development.[86] A3B can bind to the core proteins of PRC2, inhibiting the expression of chemokines including CCL2, a key factor in liver cancer occurrence and development by aggregating monocytes and macrophages into tumor tissue, stimulating tumor cell survival, and immune escape.[93] The non-enzyme-dependent function interfering with A3B inhibits the immunosuppressive microenvironment in tumor tissue, suggesting A3B's potential to inhibit liver cancer occurrence and development.[94]

Discussion

APOBEC3 proteins have been identified as key components of the innate immune response against viral infections.[62] Besides their beneficial roles in innate and adaptive immunity, multiple DNA cytosine deaminases also play a detrimental role in cancer mutagenesis.[95] APOBEC3B has contrasting effects on HBV and HBV-HCC. Previous research indicates that the APOBEC3B gene plays dual roles in the onset and progression of hepatitis B-related hepatocellular carcinomas. Firstly, the APOBEC3B gene can inhibit the replication of HBV virus particles by affecting reverse transcription, thus reducing viral titer, alleviating inflammatory reactions, and preventing or delaying the progression of hepatitis B to hepatocellular carcinoma. Secondly, APOBEC3B's DNA deaminase properties can increase genomic instability through various pathways, such as initiating HBx mutations, activating the IL-6 inflammatory pathway. In recent years, the R-loop triple-strand structure has also been confirmed to be associated with A3B, further supplementing the role of A3B in HBV mutation and the occurrence of HBV-HCC. Genomic mutations are crucial factors contributing to the onset and development of liver cancer. Hence, the challenge lies in balancing the suppression of APOBEC3B gene expression, which leads to increased HBV replication, with the promotion of genomic mutations caused by the APOBEC3B gene. This review delineates the mechanism of action of A3B in the progression of HBV-HCC. It comprehensively summarizes the impact of A3B on HBV infection, drawing upon numerous existing research findings and literature evidence. Additionally, it critically discusses the aforementioned content to furnish valuable insights for subsequent related research. However, owing to the paucity of literature information, this review's limitation lies in its somewhat deficient exploration of A3B's potential value in the early diagnosis and treatment of HBV-HCC.

Current antiviral therapies utilizing interferons and/or nucleotide/nucleoside analogs are unable to directly target HBV cccDNA.[96] Consequently, these treatments do not eradicate HBV infection.[94] Current treatments involve the use of resveratrol and silymarin to inhibit the YY1/MYC/SLC2A1 signaling pathway, which can impede abnormal aerobic glycolysis. Alternatively, curcumin derived from plant sources can inhibit mTOR, thereby blocking abnormal lipid synthesis and achieving a therapeutic effect on hepatocellular carcinomas. Additionally, CAR-T, TCR-T, and MAIT represent potential treatment modalities.[96] Regulating APOBEC3B represents a potential treatment strategy for liver cancer. While inhibiting APOBEC3B may decrease the likelihood of hepatocellular carcinoma, it may also lead to increased HBV replication, further exacerbating inflammation and the progression of liver cirrhosis. Replacing A3B with LT β Up-regulation of R-agonists,[53] processing of cccDNA in the nucleus, and reducing viral load represents a promising strategy for the treatment of HBV. Furthermore, estrogen can inhibit the onset of HCC, while androgens have a supportive effect on HCC, although the association between the APOBEC3B gene and estrogen and androgens remains unclear.[97] The A3B protein exhibits dual functionality with robust deaminase activity and nuclear localization function.[98]

APOBEC-3's highly efficient mutational activity is crucial for host defense against viruses because sublethal mutagenesis may not disable viruses but rather contribute to viral variation, leading to viral immune escape or drug resistance.[99] Knocking out APOBEC3B also increases the sensitivity to several anticancer drugs targeting DNA.[100] One of the most direct methods to mitigate the impact of APOBEC3B is to inhibit the enzyme's deaminase activity using small molecules to create a hypomutator environment in the tumor tissue.[73] Up-regulated expression of A3B could result in increased tumor cell death by enhancing immune surveillance due to increased A3B activity.[101] Studies show that treatment with an NF-κB inhibitor has enhanced efficacy in preventing the emergence of resistance, shedding light on a novel pathway for hepatocellular carcinoma treatment.[47,102] Another report indicates that, compared to stage II or stage I tumors, APOBEC3B exhibits significant

overexpression in tumor-node-metastasis (TNM) stage III tumors in gastric cancer, signifying its association with cancer development, thus proving crucial for predicting cancer prognosis.[47,80] Hence, elucidating the mechanism by which host factors regulate the activity of A3B cytidine deaminase or influence A3B binding to nuclear proteins or viral RNA will also aid in designing and developing new treatment methods for curing HBV infections.

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Disclosure

The authors report no conflicts of interest in this work.

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