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Evo-Dev of hepatitis B virus-induced hepatocellular carcinoma: Role of human APOBEC3 cytidine deaminases on linking inflammation and cancers

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Chronic infection with hepatitis B virus (HBV) contributes to more than three quarters of hepatocellular carcinoma (HCC) cases worldwide. Genetic predispositions of human leukocyte antigens (HLAs) contribute to immune imbalance upon HBV infection, leading to chronic inflammation in liver. HBV demonstrates “mutation-selection-adaptation”, an evolutionary process during hepatocarcinogenesis. Cytokines generated during chronic but active inflammation or antiviral cytokines such as interferons can up-regulate the expression of activation-induced cytidine deaminase (AID) and apolipoprotein B mRNA editing enzyme, catalytic polypeptides (APOBECs). These enzymes efficiently deaminate cytidine to uracil in DNA and/or RNA and generate G to A hypermutations both in viral and host genomes, thus editing HBV genome and increase viral mutation. Following immune/survival selections in the inflammatory microenvironment, the HBV mutants and cancer-initiating cells with somatic mutations such as p53 mutation contribute to the generation of HCC. Chronic inflammation provides “fertile field” for somatic mutation, selection, and adaptation (evolutionary process) during HCC development. Genetic predispositions of inflammatory signaling molecules such as nuclear factor-kappaB (NF- κ B), signal transducer and activator of transcription 3 (STAT3), HLAs, and some miRNAs contribute significantly to the generation of HCC-risk HBV mutations. Genomic variations of HCC caused by different etiological factors might be different but the common genomic variations should be important for the elucidation of HCC evolution. Genome-wide analysis of HBV integrations may help in clarifying the mechanisms of HBV-induced hepatocarcinogenesis and disease progression. RNA sequencing presents additional evidences of epigenetic modification during HCC evolution. Understanding the key genomic variations during HCC evolution might be essential for accurate prognosis prediction and efficient targeted treatment for this fatal malignancy. Prospective cohort studies are indispensable to identify the HBV-infected subjects who are more likely to develop and need specific intervention.

Biography

Guangwen Cao has completed his PhD from Second Military Medical University in 1995 and Postdoctoral training from Baylor College of Medicine in 2002. Currently, he chairs the Department of Epidemiology, Second Military Medical University. He is sponsored by Outstanding Young Scholar fund from NSFC and serves as the chief scientist for a national key basic research project (973-project) in evolution-development of cancers in China. As the corresponding author, he has published more than 100 papers in reputed journals.

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