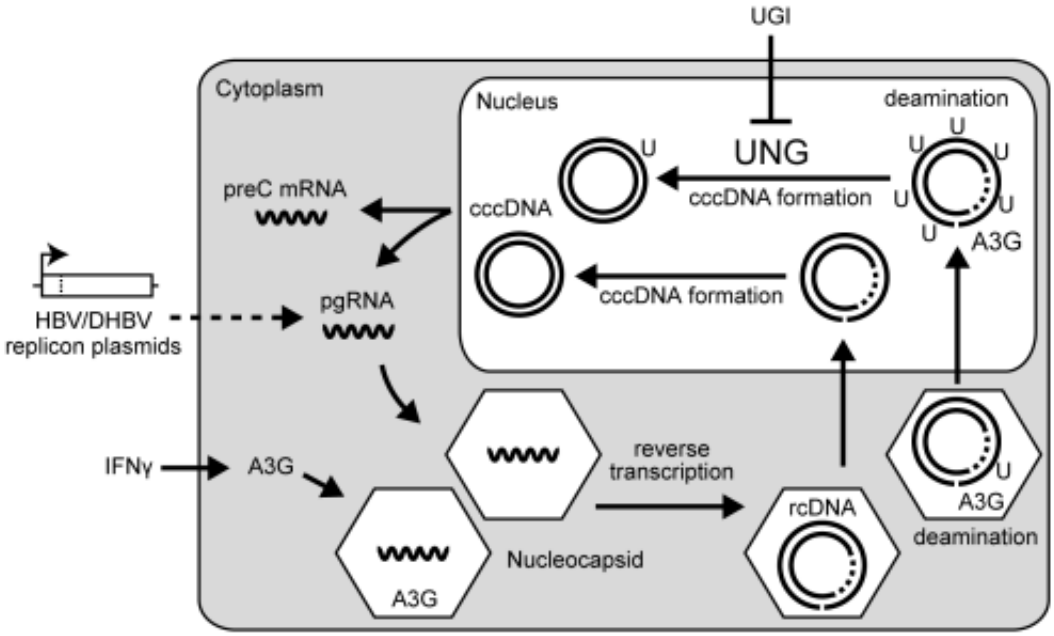
Hepatitis B virus control: Identifying proteins in mutation management

June 25 2013



(Figure S6) Caption: A proposed model to explain how UNGreduces uracil load on cccDNA. Intracellular viral lifecycletogether with possible role of UNG. pgRNA is transcribed fromcccDNA and the replicon plasmid when transfected. NC isassembled in the cytoplasm from core and P proteins together withpgRNA. In human hepatocytes, interferon induces APOBEC-proteins such as A3G. A3G is encapsidated in a subset of NCs andinduces hypermutation predominantly on the minus strand ofrcDNA, resulting in G-to-A hypermutation. In addition, A3Ginhibits minus strand DNA synthesis. After transportation intonucleus, additional hypermutation may be induced by A3G, andUNG repairs them during or after cccDNA formation. WhenUNG activity is inhibited by UGI, the extensive hypermutationremains in cccDNA, disrupting the genetic information for viralreplication. Pre-C mRNA is transcribed from cccDNA but notfrom the replicon plasmid. When hypermutation does not affectany processes required for transcription, hypermutated transcriptssuch as pgRNA and pre-C mRNA are transcribed fromhypermutated cccDNA. The hypermutated pgRNA may beencapsidated to enter a second viral lifecycle.

(Medical Xpress)—Researchers at Kanazawa University Graduate School of Medical Science in Japan have determined how APOBEC proteins mediate hypermutations that inhibit viral replication. They also identify the host factor protein UNG that can repair these mutations. This research is also described in the inaugural June 2013 issue of the *Kanazawa University Research Bulletin*.

The hepatitis B virus (HBV) is a primary cause of chronic liver disease. So far the persistence of the virus has not been fully explained. Recently researchers showed that a group of proteins – apolipoprotein B mRNA editing catalytic polypeptide (APOBEC) proteins – were found to inhibit replication of the virus but the exact mechanism remained a mystery. Now researchers at Kanazawa University Graduate School of Medical Science in Japan have determined how APOBEC proteins mediate hypermutations that inhibit viral replication. They also identify the host factor protein UNG that can repair these mutations.

The HBV genome form is converted into stable covalently closed circular DNA (cccDNA) in the nuclei of liver tissue cells when they are infected. As the authors point out, "cccDNA is not targeted by anti-HBV drugs and thus enables the re-establishment of viral replication after cessation of antiviral therapy." However the lack of an experimental system that can produce cccDNA in sufficient quantities for investigation has limited what is known about the host factors that control cccDNA.

Masamichi Muramatsu and colleagues at Kanazawa University Graduate School of Medical Science used an avian counterpart for HBV – duck HBV (DHBV) – to investigate the role of the host factor UNG in viral hypermutation in cccDNA. DHBV shares many similarities with HBV with an important advantage for experimental investigation; it reproduces cccDNA more efficiently.

Transfection experiments showed that cccDNA hypermutation was enhanced on UNG inhibition in APOBEC3G expressing cells, resulting in a significant decrease in viral production. "We speculate that the balance between AID/APOBECs and UNG activities on mutation frequency decides the consequence to hepadnaviruses: deleterious mutations vs. diversification," suggest the researchers. Their future research will look into the possible role of APOBECs and factors like UNG in the emergence of drug-resistant mutants of HBV and DHBV.

More information: Kitamura, K. et al. Uracil DNA Glycosylase Counteracts APOBEC3G-Induced Hypermutation of Hepatitis B Viral Genomes: Excision Repair of Covalently Closed Circular DNA, *PLoS Pathog* 9(5): e1003361. doi:10.1371/journal.ppat.1003361.