Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA.

Current antiviral agents can control but not eliminate hepatitis B virus (HBV), because HBV establishes a stable nuclear covalently closed circular DNA (cccDNA). Interferon-β treatment can clear HBV but is limited by systemic side effects. We describe how interferon-β can induce specific degradation of the nuclear viral DNA without hepatotoxicity and propose lymphotoxin-β receptor activation as a therapeutic alternative. Interferon-β and lymphotoxin-β receptor activation up-regulated APOBEC3A and APOBEC3B cytidine deaminases, respectively, in HBV-infected cells, primary hepatocytes, and human liver needle biopsies. HBV core protein mediated the interaction with nuclear cccDNA, resulting in cytidine deamination, apurinic/apyrimidinic site formation, and finally cccDNA degradation that prevented HBV reactivation. Genomic DNA was not affected. Thus, inducing nuclear deaminases-for example, by lymphotoxin-β receptor activation-allows the development of...
new therapeutics that, in combination with existing antivirals, may cure hepatitis B.