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Titel des Beitrags: Alteration of Mature Nucleocapsid and Enhancement of Covalently Closed Circular DNA Formation by Hepatitis B Virus Core Mutants Defective in Complete-Virion Formation.

Abstract: Assembly of hepatitis B virus (HBV) begins with packaging of the pregenomic RNA (pgRNA) into immature nucleocapsids (NC), which are converted to mature NCs containing the genomic relaxed circular (RC) DNA as a result of reverse transcription. Mature NCs have two alternative fates: (i) envelopment by viral envelope proteins, leading to secretion extracellularly as virions, or (ii) disassembly (uncoating) to deliver their RC DNA content into the host cell nucleus for conversion to the covalently closed circular (CCC) DNA, the template for viral transcription. How these two alternative fates are regulated remains to be better understood. The NC shell is composed of multiple copies of a single viral protein, the HBV core (HBc) protein. HBc mutations located on the surface of NC have been identified that allow NC maturation but block its envelopment. The potential effects of some of these mutations on NC uncoating and CCC DNA formation have been analyzed by transfecting HBV replication constructs into hepatoma cells. All envelopment-defective HBc mutations tested were competent for CCC DNA formation, indicating that core functions in envelopment and uncoating/nuclear delivery of RC DNA were genetically separable. Some of the envelopment-defective HBc mutations were found to alter...
specifically the integrity of mature, but not immature, NCs such that RC DNA became susceptible to nuclease digestion. Furthermore, CCC DNA formation could be enhanced by NC surface mutations that did or did not significantly affect mature NC integrity, indicating that the NC surface residues may be closely involved in NC uncoating and/or nuclear delivery of RC DNA. Hepatitis B virus (HBV) infection is a major health issue worldwide. HBV assembly begins with the packaging into immature nucleocapsids (NCs) of a viral RNA pregenome, which is converted to the DNA genome in mature NCs. Mature NCs are then selected for envelopment and secretion as complete-virion particles or, alternatively, can deliver their DNA to the host cell nucleus to maintain the viral genome as nuclear episomes, which are the basis for virus persistence. Previous studies have identified mutations on the capsid surface that selectively block NC envelopment without affecting NC maturation. We have now discovered that some of the same mutations result in preferential alteration of mature NCs and increased viral nuclear episomes. These findings provide important new insights into the regulation of the two alternative fates of mature NCs and suggest new ways to perturb viral persistence by manipulating levels of viral nuclear episomes.