Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

Host-targeting agents for treatment of hepatitis B virus infection

Thomas F Baumert[1,2,3,4], Eloi R Verrier[1,2], Michael Nassal[5], Raymond T Chung[4] and Mirjam B Zeisel[1,2]

Hepatitis B virus (HBV) infection is a major cause of chronic liver disease, including liver cirrhosis, liver failure and hepatocellular carcinoma (HCC) — the second leading and fastest rising cause of cancer death world-wide. While *de novo* infection can be efficiently prevented by vaccination and chronic infection can be controlled using antivirals targeting the viral polymerase, the development of efficient antiviral strategies to eliminate the virus and thus to cure infection remains a key unmet medical need. The recent progress in the development of robust infectious HBV cell culture models now enables the investigation of the full viral life cycle, including a more detailed study of the molecular mechanisms of virus–host interactions responsible for viral persistence. The understanding of these virus–host interactions will be instrumental for the development of curative treatments. Host-dependency factors have recently emerged as promising candidates to treat and prevent infection by various pathogens. This review focuses on the potential of host-targeting agents (HTAs) as novel antivirals to treat and cure HBV infection. These include HTAs that inhibit *de novo* and re-infection, synthesis and spread of cccDNA as well as development of immune-based approaches eliminating or curing infected hepatocytes, including the eradication of viral cccDNA.

Addresses
[1] Inserm, U1110, Institut de Recherche sur les Maladies Virales et Hépatiques, 67000 Strasbourg, France
[2] Université de Strasbourg, 67000 Strasbourg, France
[3] Institut Hospitalo-Universitaire, Pôle Hépato-digestif, Nouvel Hôpital Civil, 67000 Strasbourg, France
[4] Liver Center and Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, United States
[5] Department of Internal Medicine 2/Molecular Biology, University Hospital Freiburg, D-79106 Freiburg, Germany

Corresponding author: Baumert, Thomas F (thomas.baumert@unistra.fr)

Current Opinion in Virology 2015, **14**:41–46

This review comes from a themed issue on **Engineering for viral resistance**

Edited by **Albrecht von Brunn**

For a complete overview see the Issue and the Editorial

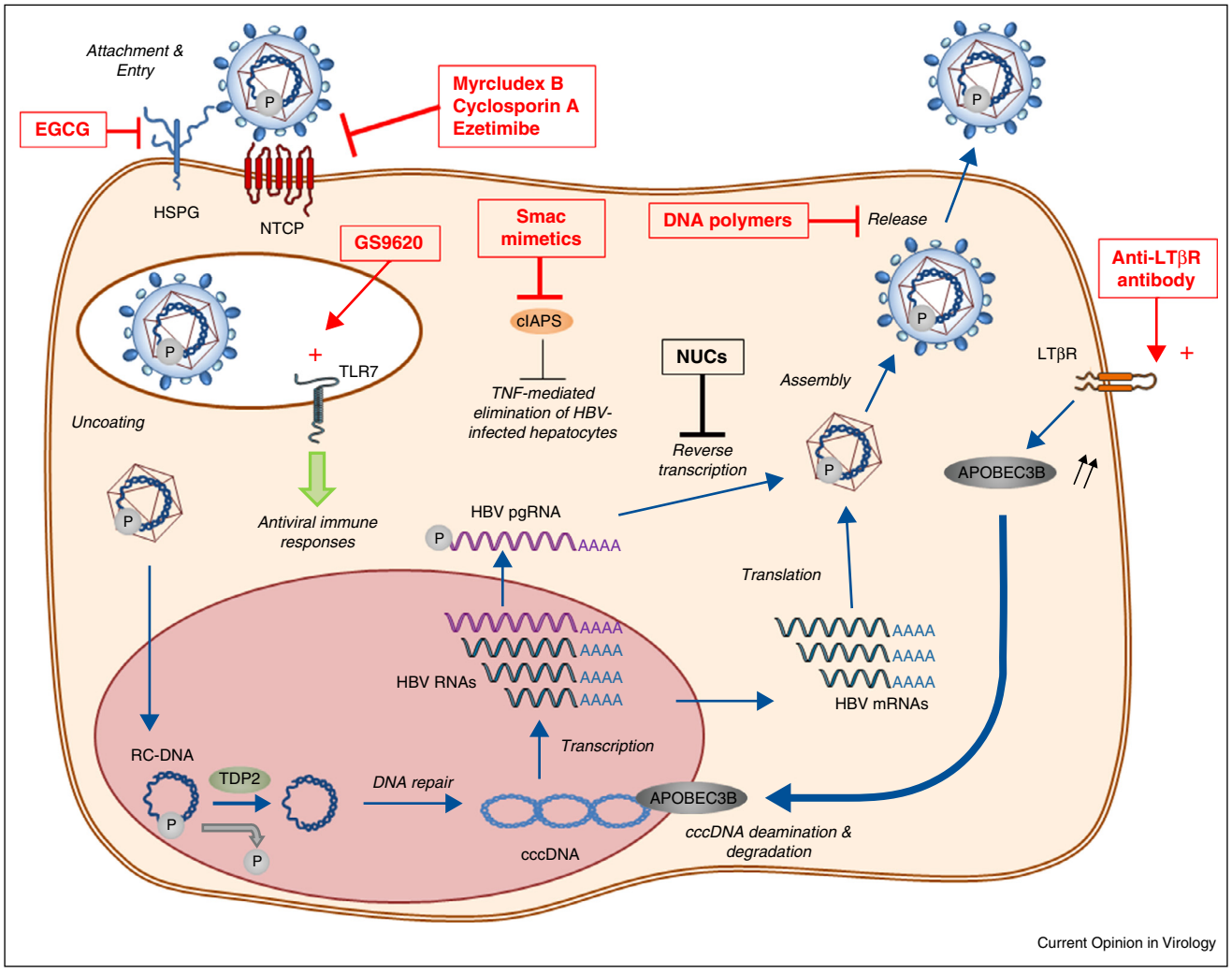
Available online 8th August 2015

http://dx.doi.org/10.1016/j.coviro.2015.07.009

Clinical impact of chronic hepatitis B

Hepatitis B virus (HBV) infection is a major cause of chronic liver disease, including liver cirrhosis, liver failure and hepatocellular carcinoma (HCC) — the second leading and fastest rising cause of cancer death world-wide [1–4]. In spite of the existence of a vaccine, an estimated 2 billion people have evidence of exposure to HBV and approximately 350 million people are chronically infected with HBV worldwide [4]. Because of limited access to vaccination, the high efficiency of vertical transmission and the lack of curative treatment, the prevalence of HBV infection has remained virtually unchanged. HBV-infected patients have an approximately 100-fold increased risk for HCC compared to uninfected patients [5]. Although early-stage tumors can be curatively treated with surgical approaches, efficient treatment options for advanced HCC are limited or absent. Efficient treatment strategies to cure chronic hepatitis B (CHB) are thus greatly needed [6]. A key challenge in the management of CHB patients is the absence of efficient strategies to cure infection. Current treatment approaches can suppress viral replication but have no meaningful ability to cure CHB patients [4,7]. The standard of care consists of one of the nucleos(t)ide analogs (NUCs), which include tenofovir and entecavir, or pegylated interferon (IFN)-α-2a. The goal of current treatment(s) is to suppress HBV replication and to limit disease progression [4,8]. In contrast to NUCs, IFN-α can occasionally produce a durable anti-hepatitis B surface (HBs) seroconversion, but its adverse effect profile limits its widespread use [4,8,9]. Although NUCs reduce progression of the disease, viral cure is not achievable with these agents, which must be administered life-long [7]. The long-term safety of sustained NUC therapy is unknown, with renal failure and bone loss emerging as potential safety concerns. Although NUCs with a high barrier to resistance have been introduced, drug resistant variants can also evolve during long-term treatment and cross-resistance to other NUCs represents a potential challenge for current therapies [10]. Thus, the development of efficient antiviral strategies to eliminate HBV and thus cure infection remains a key unmet medical need [6]. Notably, while 90% of acutely infected adults resolve HBV infection via strong and multispecific T cell responses that eliminate infected cells by both cytolytic and non-cytolytic means [1,11,12], persistent infection is common amongst immune compromised patients or those who acquired their infection via perinatal transmission [1,13,14], highlighting the pivotal role of the vigor and breadth of the host immune response in resolving HBV infection.

Figure 1



Host-dependency factors of the HBV life cycle as antiviral targets. Model of the HBV life cycle and suggested mechanisms of action for host-targeting agents. APOBEC3B: apolipoprotein B mRNA editing enzyme, catalytic polypeptide-Like 3B; cccDNA: covalently closed circular DNA; cIAPS: cellular inhibitor of apoptosis proteins; EGCG: (−)-epigallocatechin-3-gallate; GS9620: TLR7 agonist; HSPG: heparan sulfate proteoglycan; LTβR: lymphotoxin-β receptor; NTCP: sodium taurocholate co-transporting polypeptide; NUCs: nucleoside analogs; P: HBV polymerase; pgRNA: pregenomic RNA; RC-DNA: relaxed-circular DNA; TDP2: tyrosyl-DNA-phosphodiesterase 2; TNF: tumor necrosis factor. Host-targeting agents are shown in red, direct-acting antivirals (NUCs) in black.

Unique features of the HBV lifecycle are responsible for the limited efficacy of therapies to cure infection

HBV is a hepatotropic DNA virus comprised of an outer envelope, which incorporates three HBs antigens (HBsAg) and an internal core or nucleocapsid that contains the hepatitis B core antigen (HBcAg) [13,15–17]. The genome in infectious virions is a 3.2 kb relaxed circular (RC) DNA in which one strand is covalently linked to the viral polymerase. Upon infection, the nucleocapsid is released into the cytoplasm and the genome is transferred to the nucleus where it is converted into cccDNA, the template for all viral transcripts, including the pregenomic (pg) RNA. Following export to the cytoplasm, the viral RNAs are translated and the pgRNA is reverse transcribed into new RC-DNA [18]. The cccDNA persists in the nucleus and is a major determinant of the slow HBV clearance kinetics [3,11,19]. Antiviral NUC therapy neither prevents the initial formation of cccDNA nor does it induce its eradication. Indeed, a few cccDNA copies per liver can reactivate full virus production upon therapy withdrawal. As a consequence, viral relapse is regularly observed after cessation of NUC therapy [4]. Thus, treatment with novel antivirals with different mechanisms of action will be necessary to clear established HBV infection (Figure 1). Given the unique HBV