Challenges and Approaches for Virological Cure of Hepatitis B

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The Approaches for a HBV Cure

• HBV genome, gene products and life cycle
• Current therapies
• Approaches to virological cure: viral vs host targets
• Immunotherapy
HBV Genome and Gene Products
HBV Life Cycle

Xia Y & Liang TJ, Gastroenterology 2019
Approved HBV Therapies

• Six nucleoside analogs: NRTIs
  − Lamivudine (1998)
  − Adefovir (2002)
  − Entecavir (2005)
  − Telbivudine (2006)
  − Tenofovir disoproxil fumarate (2008)
  − Tenofovir alafenimide fumarate (2016)

• Two forms of interferon:
  − Interferon-alfa-2 (early 1990s)
  − Peginterferon-alfa-2 (early 2000s)
Why New Therapies?

Ultimate goals of HBV treatment

• Eradicate HBV
• Reverse liver damage
• Prevent cirrhosis and HCC

Efficacy of existing treatment

• Suppress but not eradicate HBV
• Low rate of HBsAg loss
• Partial reversal of inflammation and fibrosis
• Decrease but not eliminate risk of HCC
• Prolonged therapy, side effect & cost
HBV Life Cycle

NRTIs

Interferons
HBV cccDNA

- Viral replication: recycling of rcDNA-containing nucleocapsid for amplification
- Conversion of rc to cccDNA mediated by host proteins (removal of pol by TDP2)
- Negatively regulated by LHBsAg
- 1-10 copies/cell
- Mini-chromosomes: histones, nonhistone proteins and viral proteins (core, HBx)

Levrero et al, J Hepatol 2009; Koniger et al, PNAS 2014
HBV cccDNA

- Transcriptional regulation by hepatocyte-specific factors (HNF1, 3 & 4) and other transcriptional factors (RXR, PPAR-α, etc)
- Epigenetic regulation: histone (H3 and H4) acetylation (↑) and methylation (↓)
- IFN and TNF-α induce APOBEC3A to degrade cccDNA
- HBx exerts an epigenetic regulation of cccDNA transcription by targeting degradation of viral restriction factor SMC5/6

HBV cccDNA

- Long half-life, stable in quiescent cells; mechanism of turn-over unknown

- Loss of cccDNA controlled by
  - Cell death: immune cytolytic mechanism
  - Dilution by cell proliferation: liver regeneration
  - Cell cure: immune non-cytolytic mechanism, IFNs & other cytokines

- Persistence of low-level cccDNA in hepatocytes, even in long-term treated patients

HBV Life Cycle

Entry inhibitors
HBV Entry Inhibitors

Urban et al, Gastroenterology 2014

Myrcludex B; cyclosporin analogs; Ezetimibe; proanthocyanidin

Broadly neutralizing antibodies
HBV Life Cycle

Secretion inhibitors
Host Targeting Antivirals

• Limited viral targets
• Host factors requisite for productive viral infection
• High barrier for drug resistance
• Potential toxicity
  • Redundancy
  • Differential sensitivity
Targeting cccDNA?

• Prevent cccDNA formation: NRTIs, CAMs, TP/RNase/TDP2 inhibitors

• Silence cccDNA activity: Epigenetic modifying agents; anti-HBx; HBV-specific transcription inhibitors

• Accelerate cccDNA degradation: APOBEC3A activator?

• High-throughput screen of large diverse compound libraries
HBV