HBV-TAG

2021 CONFERENCE

Thoughts on Treatment Approaches for Chronic HBV Infection by Targeting HBsAg from cccDNA or Integrates

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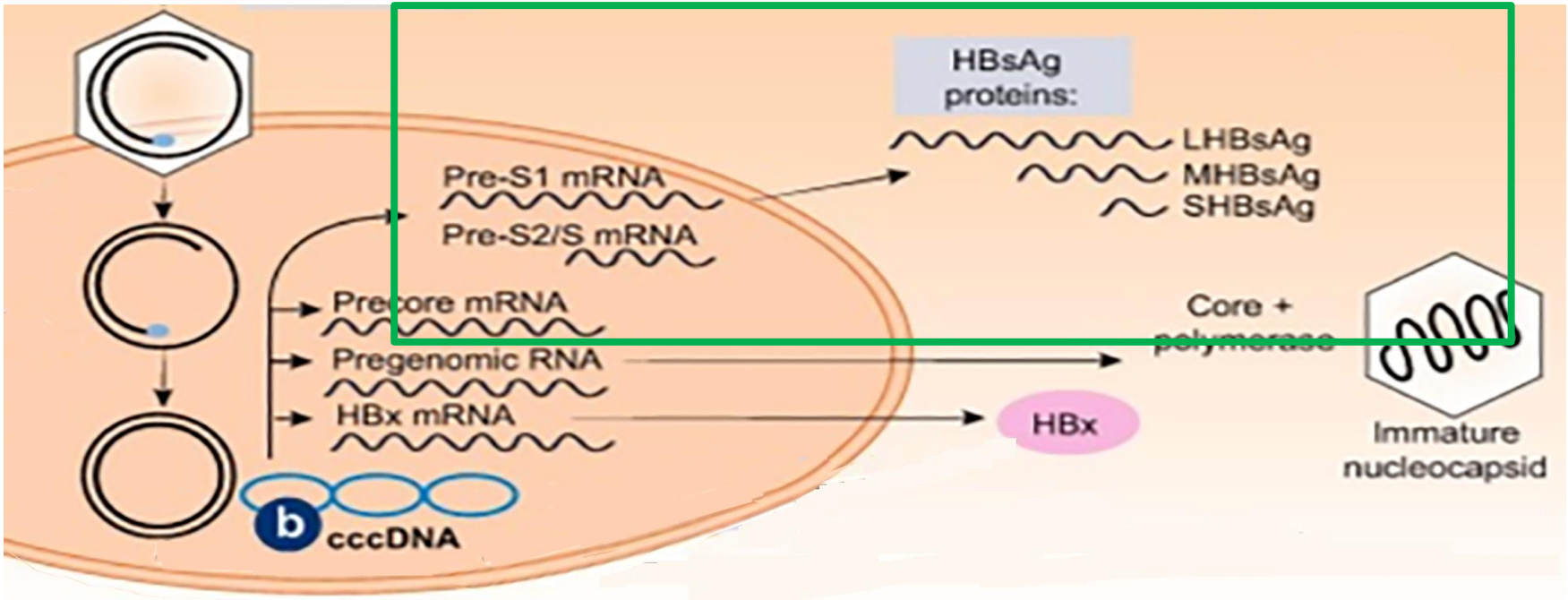
The Problem

- Current anti-HBV therapies are highly effective at viral suppression, but relapse rates are high as well.
- The reasons for this are complex, but a major factor appears to be high levels of circulating HBsAg.
- HBsAg - essential component of the virus, mediates viral attachment and uptake.
- Serum levels - often high with no correlation to replication.
- The postulated pathogenic effect of excess HBsAg production - antigen-specific immune tolerance preventing induction of an adequate immune response.
- Current anti-HBV therapies – not very effective in decreasing HBsAg levels.

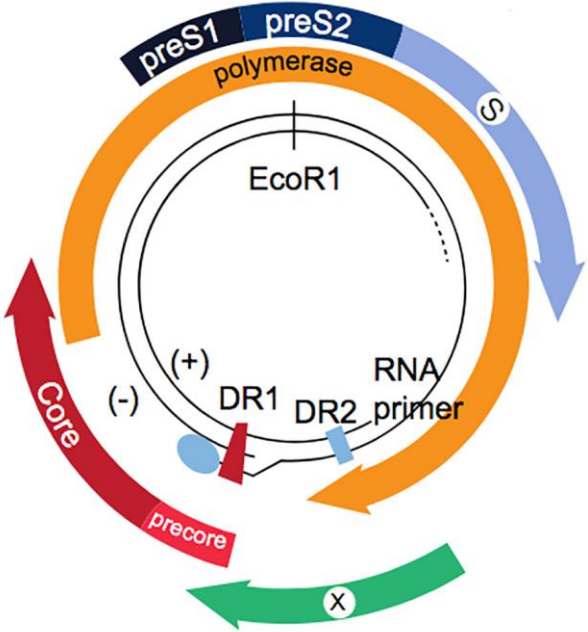
Potential Sources of HBsAg

1. cccDNA through various mRNA transcripts



Two separate mRNA species: PreS1 mRNA, and Pre S2/S mRNAs are translated into various forms HBsAg.

Regulation of HBsAg production further complicated by different translational start sites



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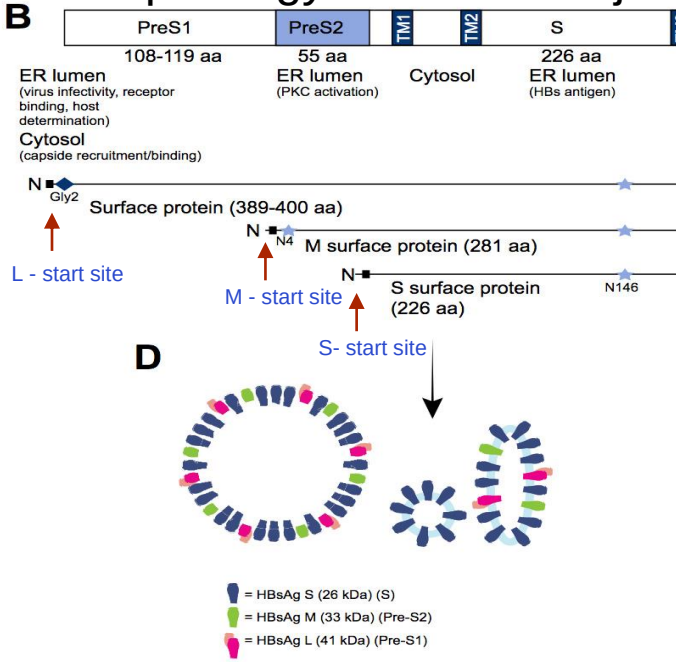
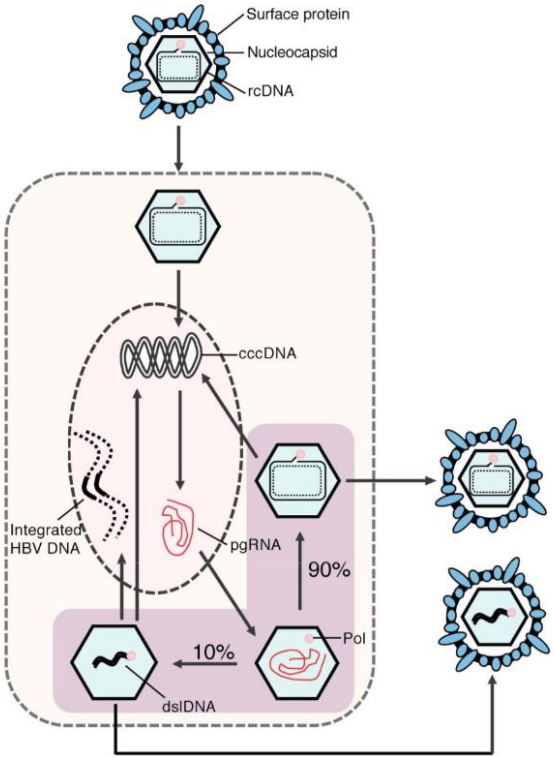


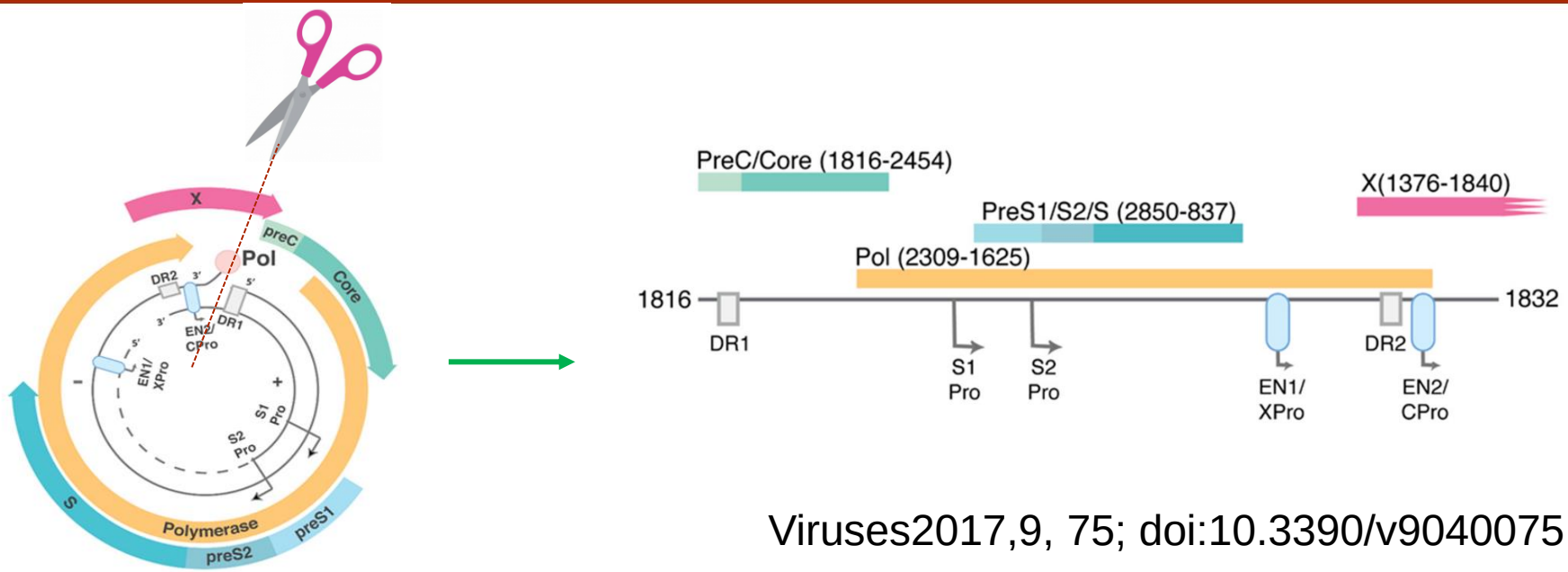
Large, major, and small HBsAg - different translational start sites. HBsAg combinations incorporated into various subviral particles - circulate and interact with the immune system

Potential Sources of HBsAg
2. Integrated DNA

- Integrated HBV DNA can occur by infection of particles containing double-stranded linear DNA or from reverse transcription of pre-genomic RNA.
- Integrated HBV gene expression can be altered, but not eliminated without eradication of the host cells.
- In both cases, sites of linearization of HBV DNA appear to be random.



Preservation of HBsAg Reading Frames



Viruses2017,9, 75; doi:10.3390/v9040075

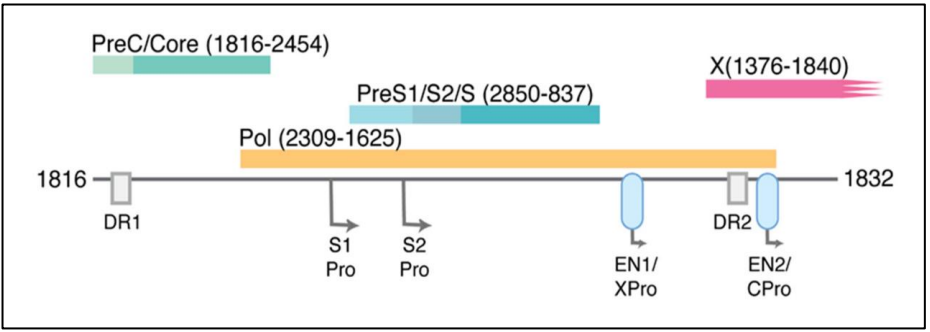
- If linearization preserves HBsAg reading frames, HBsAg can be generated by the integrant within the host chromosome.
- However, because of overlapping reading frames, linearization of cccDNA usually disrupts reading frames of other vital genes.

Integration

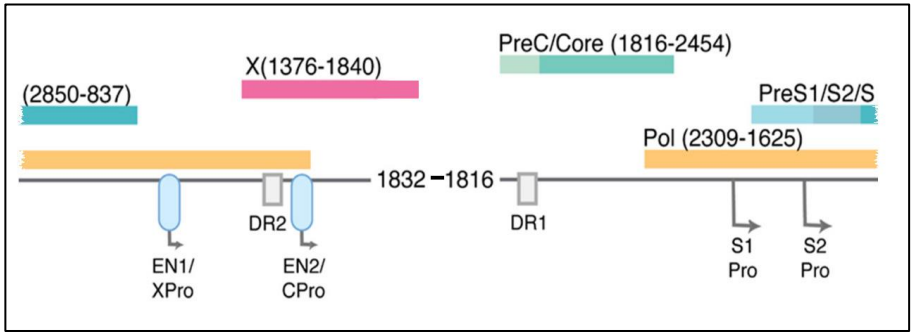
- Therefore, integration – usually a terminal event for HBV replication.
- Even if HBsAg is produced, the absence of other critical viral components would prevent viral production.
- However, if a cell contains many integrants, it is possible for viral replication to occur through *trans*-complementation – integration sites at different locations or even different chromosomes could supply all viral proteins required for viral replication.
- The main point is that integrants, independent of cccDNA, can produce HBV surface antigens, sub-viral particles, and maintain immune tolerance, as well as support HBV replication.

Trans-Complementation

Integrant 1



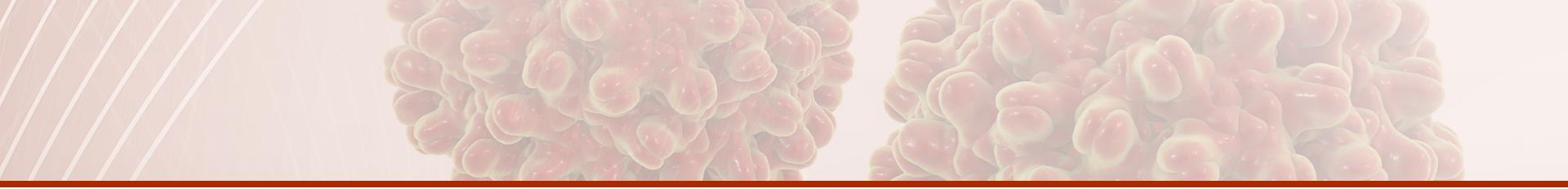
Integrant 2



Integrant 1 retains expression of pol, HBsAg, core proteins, but lacks X

Integrant 2 lacks expression of HBsAg, pol, but retains X

If the integrants are in the same cell, HBsAg and various subviral particles, as well as all protein components of the virus can be provided for replication.

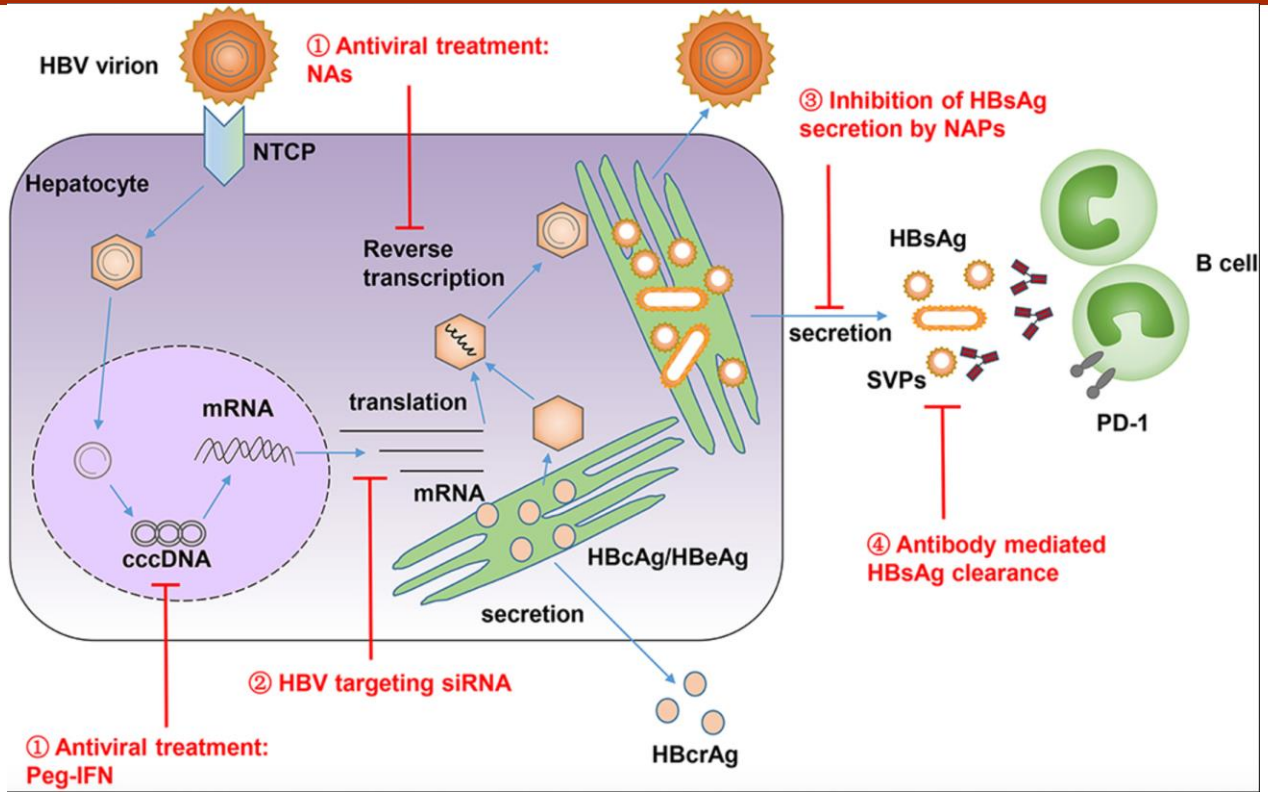


- The longer the duration of HBV infection, and the higher the level of viral replication, the higher the probability of integration.

- Early and effective elimination of viral replication may decrease the number of integrants and the likelihood of *trans*-complementation.

- What anti-HBV strategies are under investigation to decrease HBsAg levels?

Strategies to Eliminate/Minimize HBsAg Levels



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Brief Summary of Clinical Studies on HBsAg Levels

A. Direct-acting Agents

- Nucleo(s)tide analogues (NUC) – low cccDNA, minimal effect on HBsAg levels, very low SVR.
- Capsid Assembly Molecules (CAM) inhibitors – minimal effect on cccDNA, no effect on HBsAg levels, rapid relapse even in combination with NUC.
- RNAi – low cccDNA, low HBsAg in HBeAg (+), but not HBeAg (-) patients.

Brief Summary of Clinical Studies on HBsAg Levels (Cont.)

- Nucleic acid polymers (NAP) – monotherapy decrease HBsAg and HBV DNA, but low rates of functional cure; in combination with NAs and PEG IFN – >50% HBsAg seroconversion and significant (39%) functional cure at 3 yr follow up.

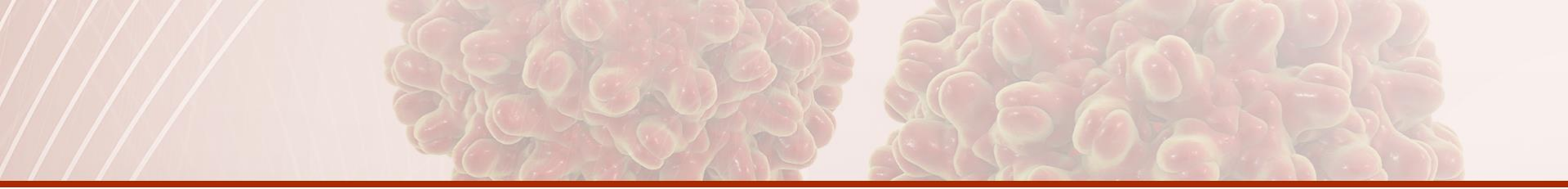
B. Indirect-acting Agents

- Interferons - low cccDNA, decrease HBsAg levels, but high relapse rates, and many side effects.

- Therapeutic vaccination – PreS1/PreS2/S vaccine in combination with NA – transient HBsAg suppression, but no SVR reported.

Conclusions

- HBV has evolved a complex and highly effective set of mechanisms to elude elimination by the host.
- These include high replication rates, high mutation rates, integration, overproduction and secretion of antigens/subviral particles, the latter preventing induction of an adequate immune response.
- Combinations of agents that address different mechanisms of action to suppress HBsAg production, suppress viral replication/re-infection, and eliminate infected cells will likely be required for sustained virological response and functional cure.
- Tolerability as well as safety and efficacy will be major issues, but the progress to date is promising.



Thank You