Molecular and immunological mechanisms of occult hepatitis B virus infection and pathogenesis

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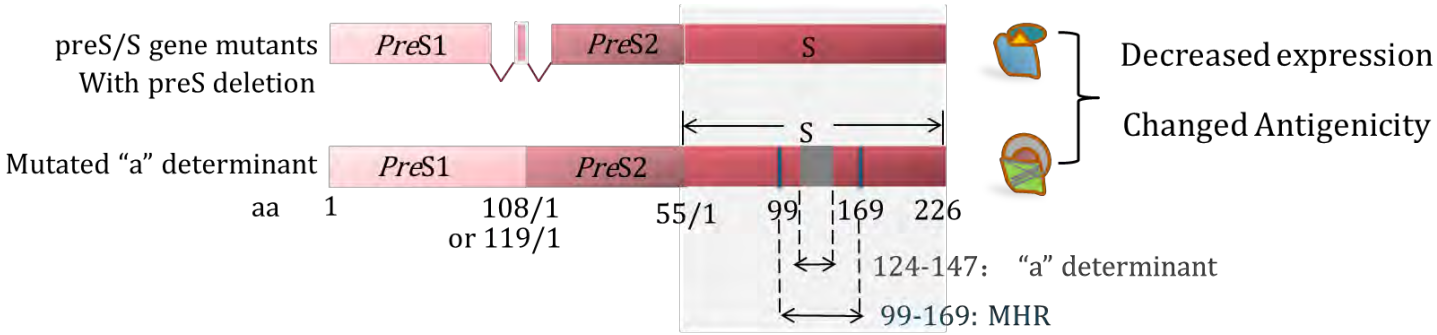
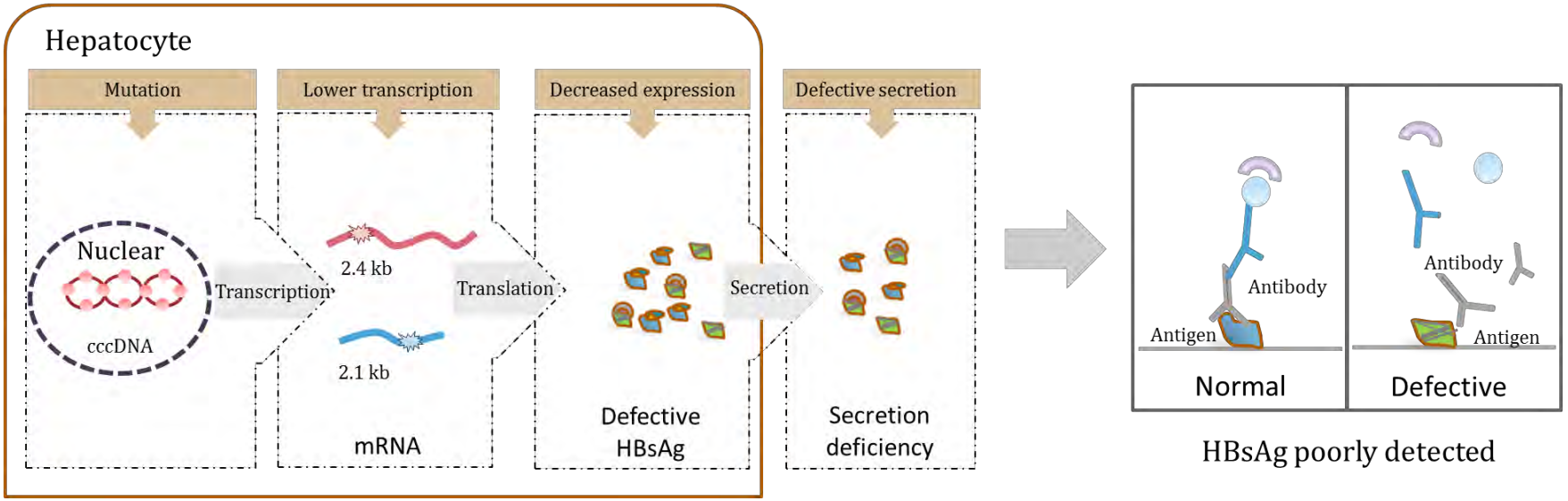
Occult HBV infection: HBsAg-/HBV DNA+

- **Viral and host factors known to influence the state of HBV infection:**
  - **Replication competence and activity**
  - **Genetic variability: detectibility of HBsAg, secretion deficiency**
  - **Innate and adaptive immunity**
  - **Host restriction factors**

The expression of defective HBV surface antigens and OBI infection

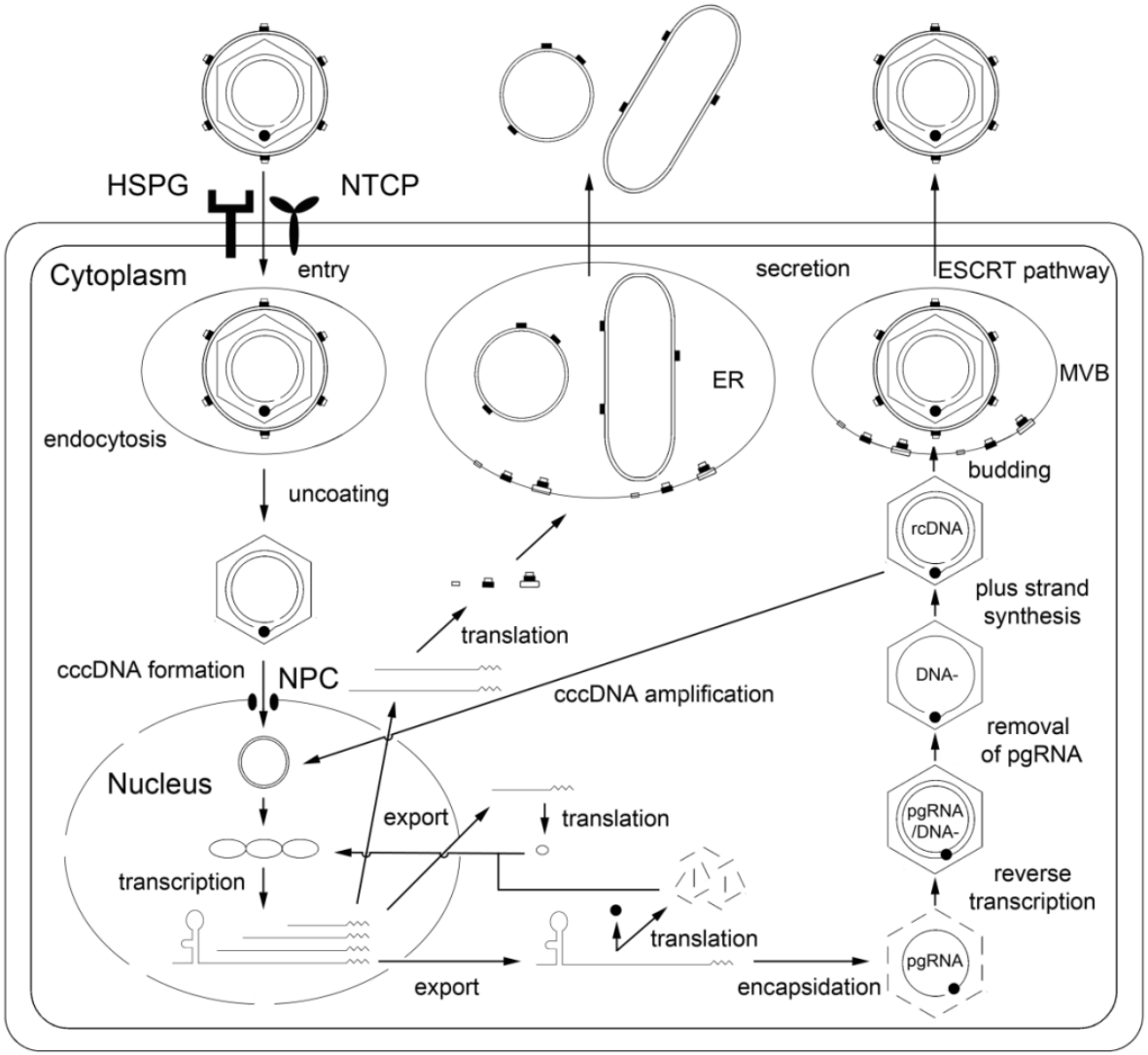




A mechanistic explanation of the status of OBI

- **Two interdependent pathways of HBsAg and virion formation: ER-Golgi pathway and autophagy-MVB pathway**
- **Relationship between OBI and liver pathogenesis: positive feedback cycle lncldуing HBV mutations, ER-stress, viral replication and HBsAg/virion formation, resulting in enhanced host T cell responses and hepatocyte loss**

Life cycle of hepatitis B virus

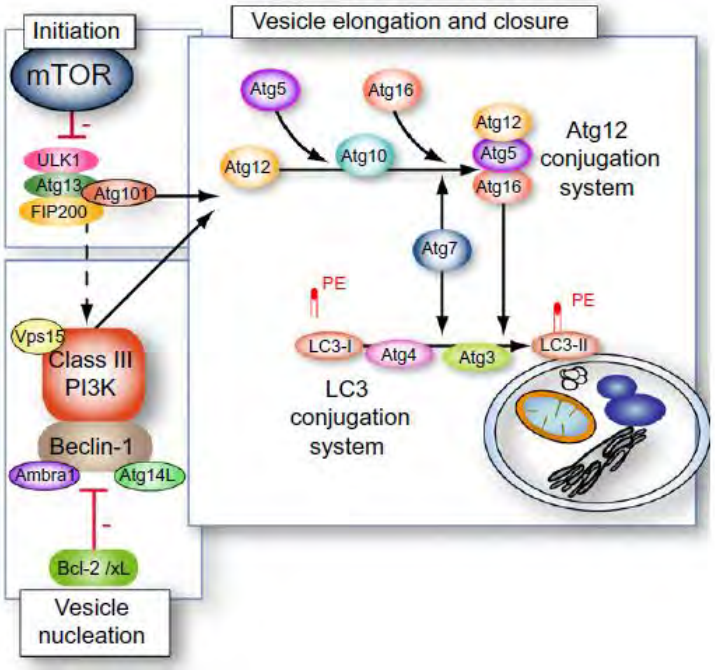


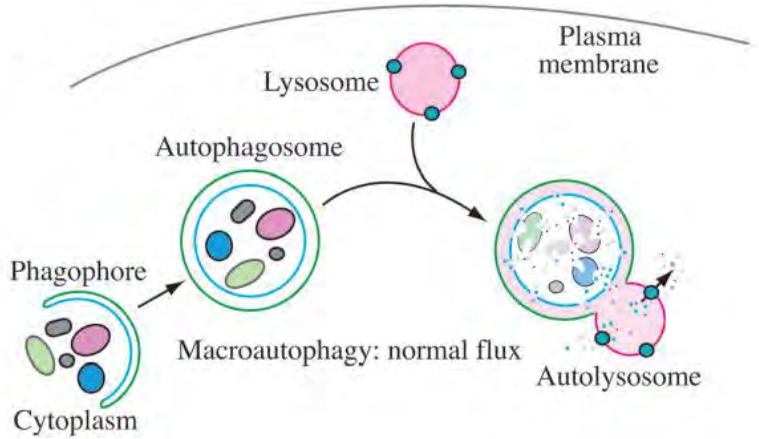
Yang et al., ASC Infect Dis., 2019

Autophagy

Autophagy is a conserved catabolic process mediating the degradation of cargos.

Complete autophagy comprises the formation of autophagosomes and their fusion with lysosomes and cargo degradation in the lysosomes.

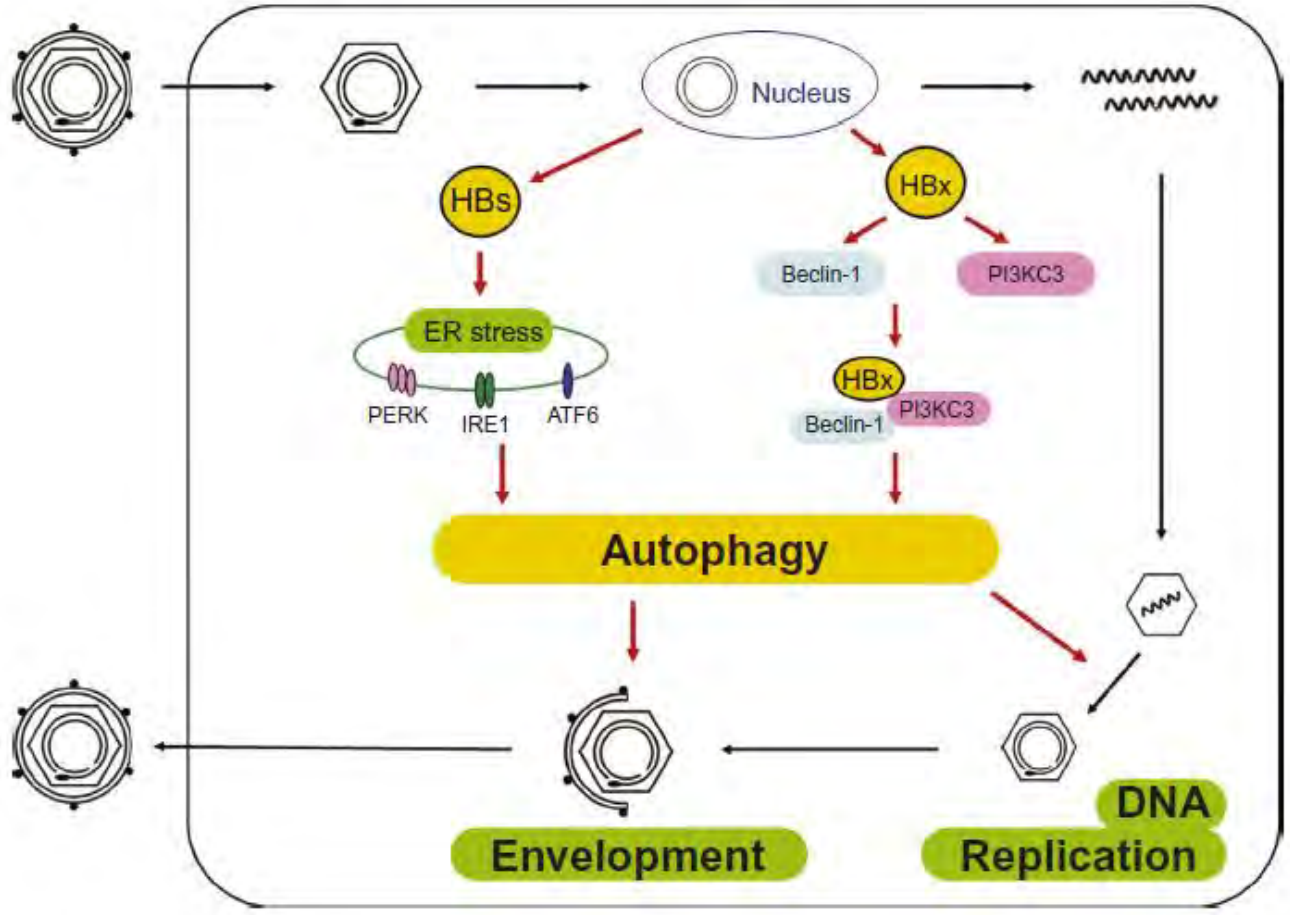




Mizushima D J., et al. Cell. 2011 *Klionsky D J., et al. Autophagy. 2012*

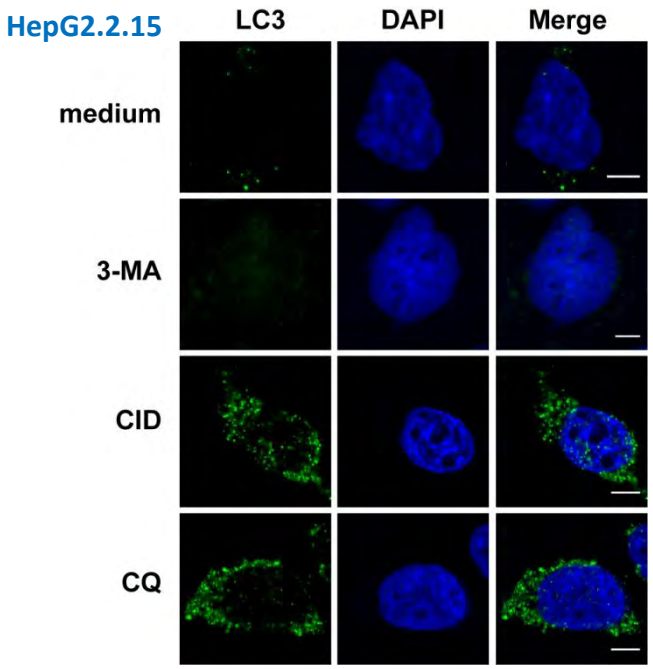
Autophagy and HBV

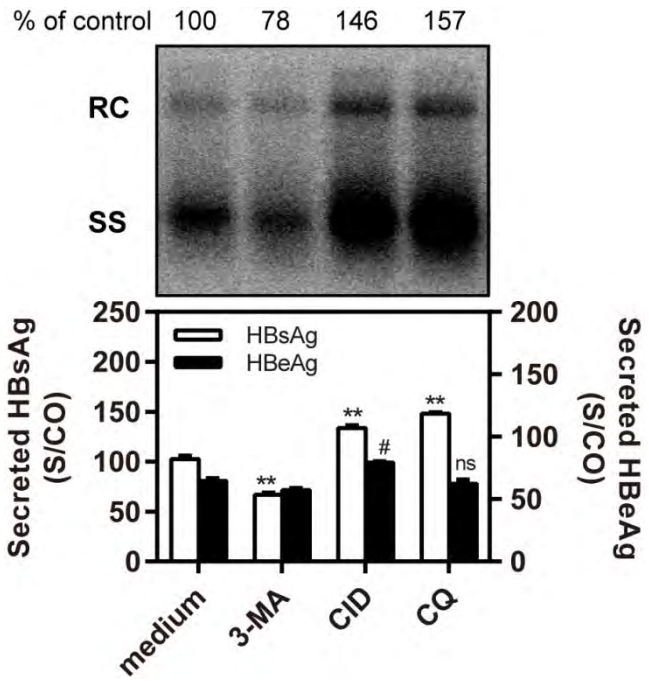
- **HBV modulates autophagic flux.**
- **Autophagy plays an important role in HBV production.**

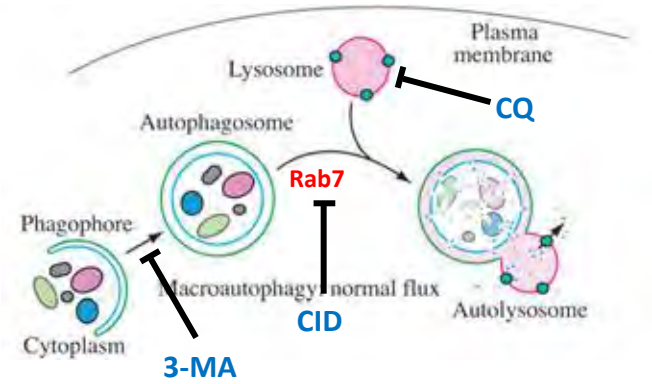


Sir et al., PNAS, 2010 *Li et al., J Virol, 2011* *Lin Y., et al. Cell Microbiol. 2017*

Different autophagic phases inversely affect HBV production





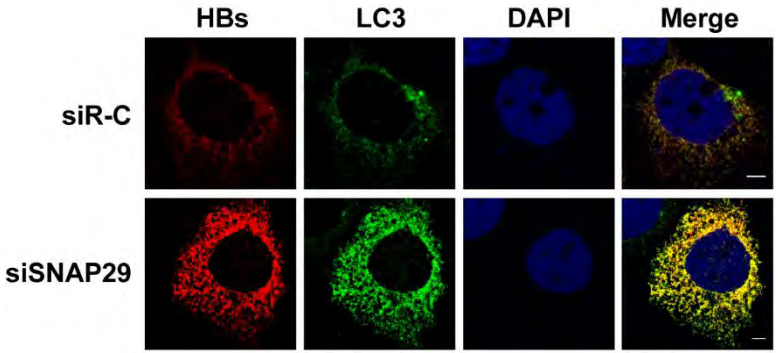


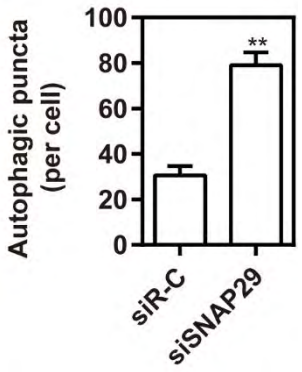
Inhibition of early autophagy decreases HBV replication and HBsAg production, but inhibition of late autophagy increases HBV production.

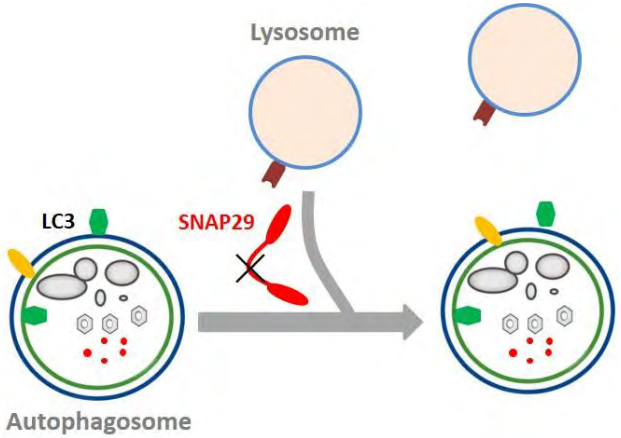
Lin Y., et al. Protein Cell. 2018

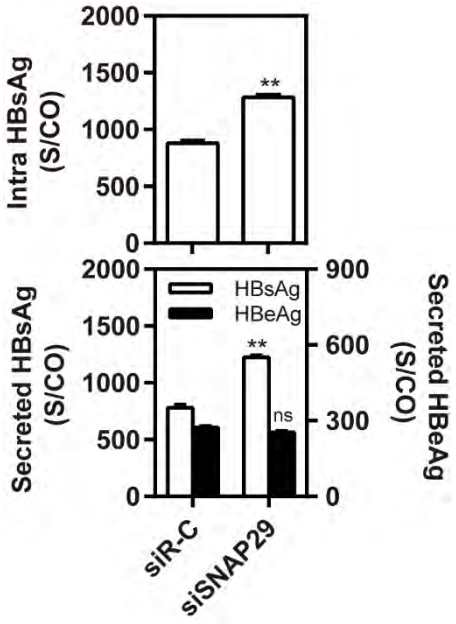
3-MA: autophagy inhibitor
CID: CID1067700, Rab7 inhibitor
CQ: chloroquine, inhibitor of lysosomal acidification

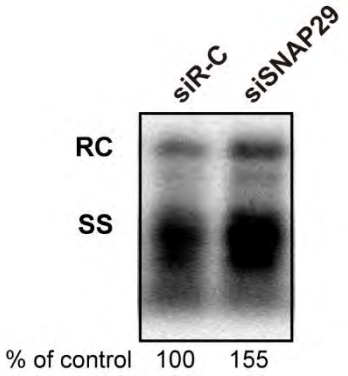
SNAP29 silencing increases autophagosome numbers in hepatoma cells







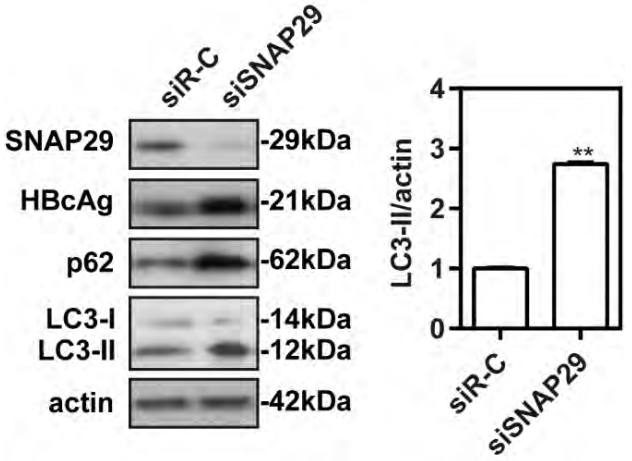




HBV DNA RIs:

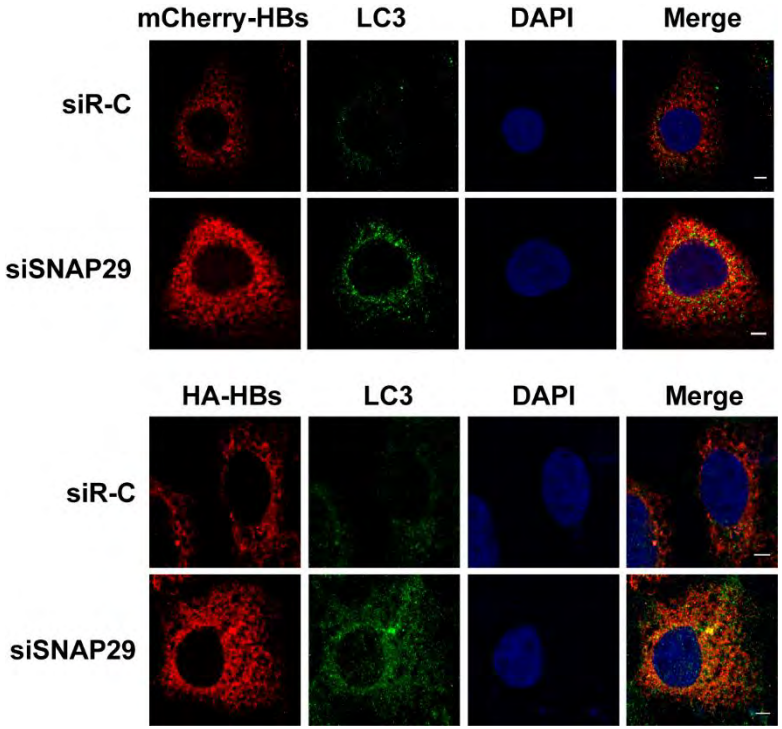
RC: relaxed circle

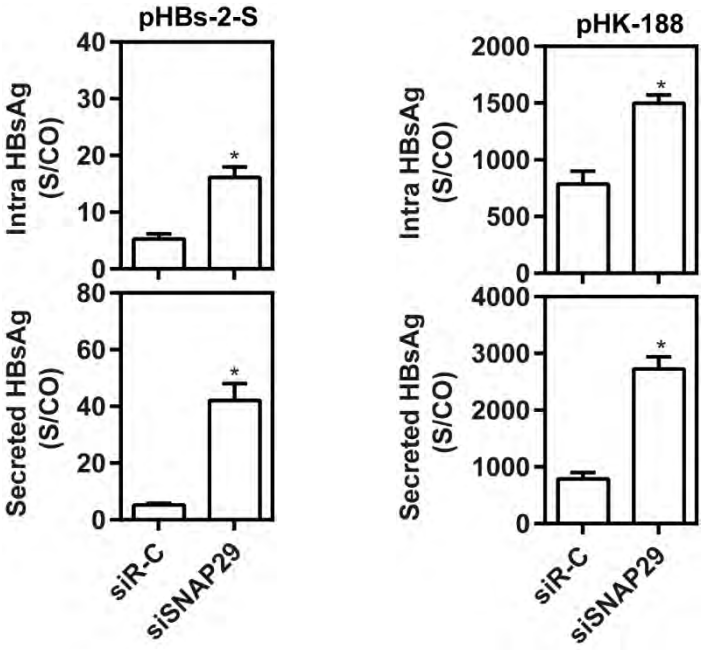
SS: single strand



Lin Y., et al. FASEB J, 2019

SNAP29 mediates autophagic degradation of HBsAg





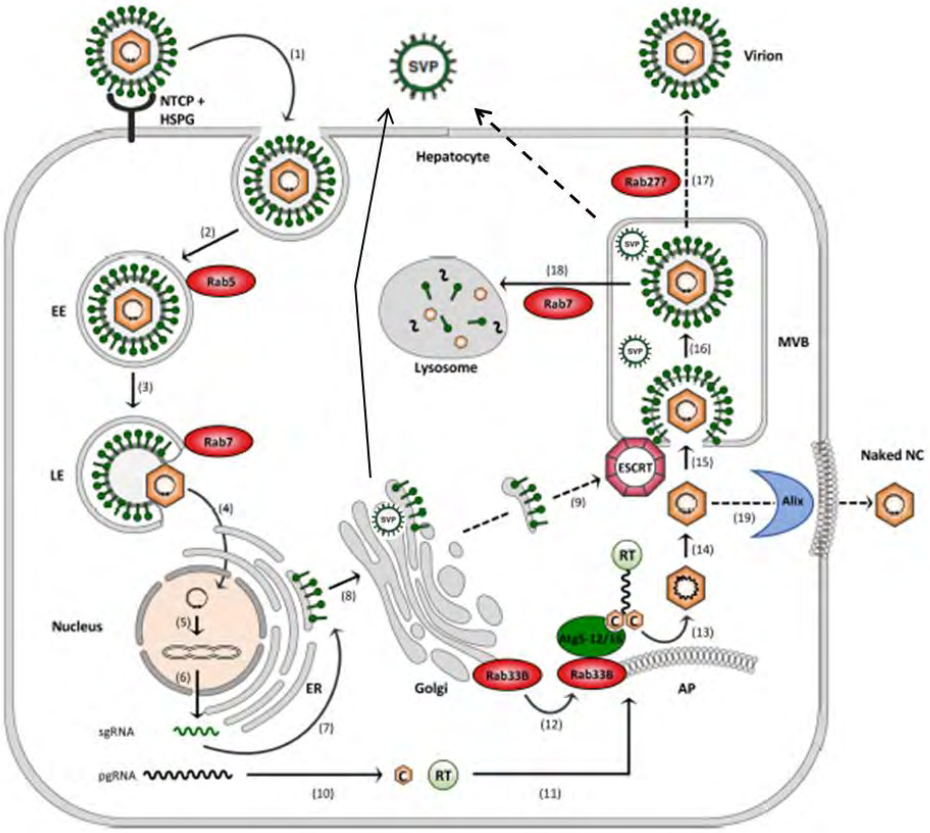
HA-HBs: expressing HBsAg with a HA-tag
mCherry-HBs: expressing HBsAg with a mCherry-tag

pHBs-2-S: expressing middle and small HBsAg
pHK-188: expressing small HBsAg

Lin Y., et al. FASEB J, 2019

HBsAg and HBV virion production

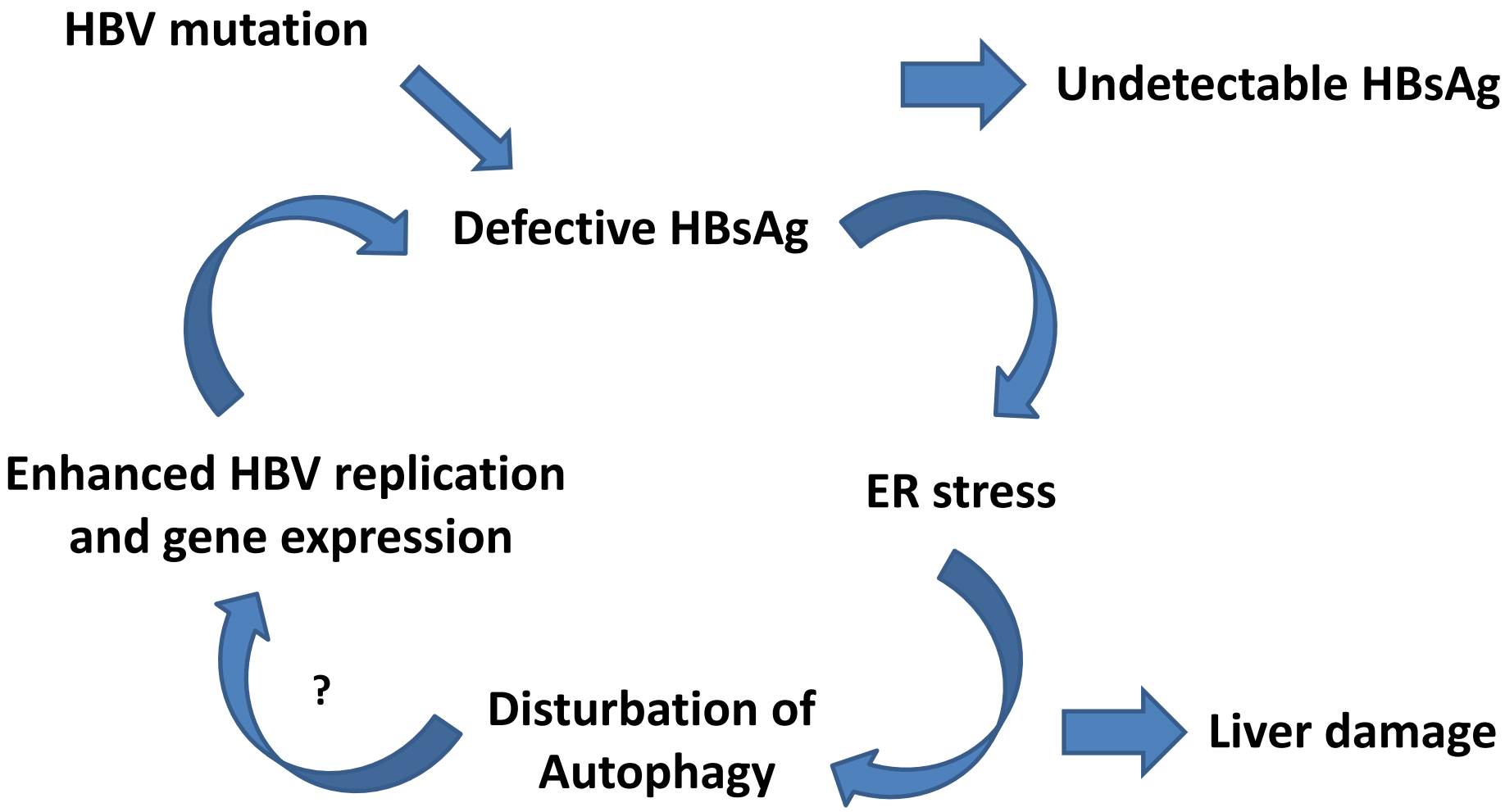
- **Two processes with overlap**
- **HBsAg via ER-Golgi pathway**
- **HBV virion via autophagy-MVB pathway**



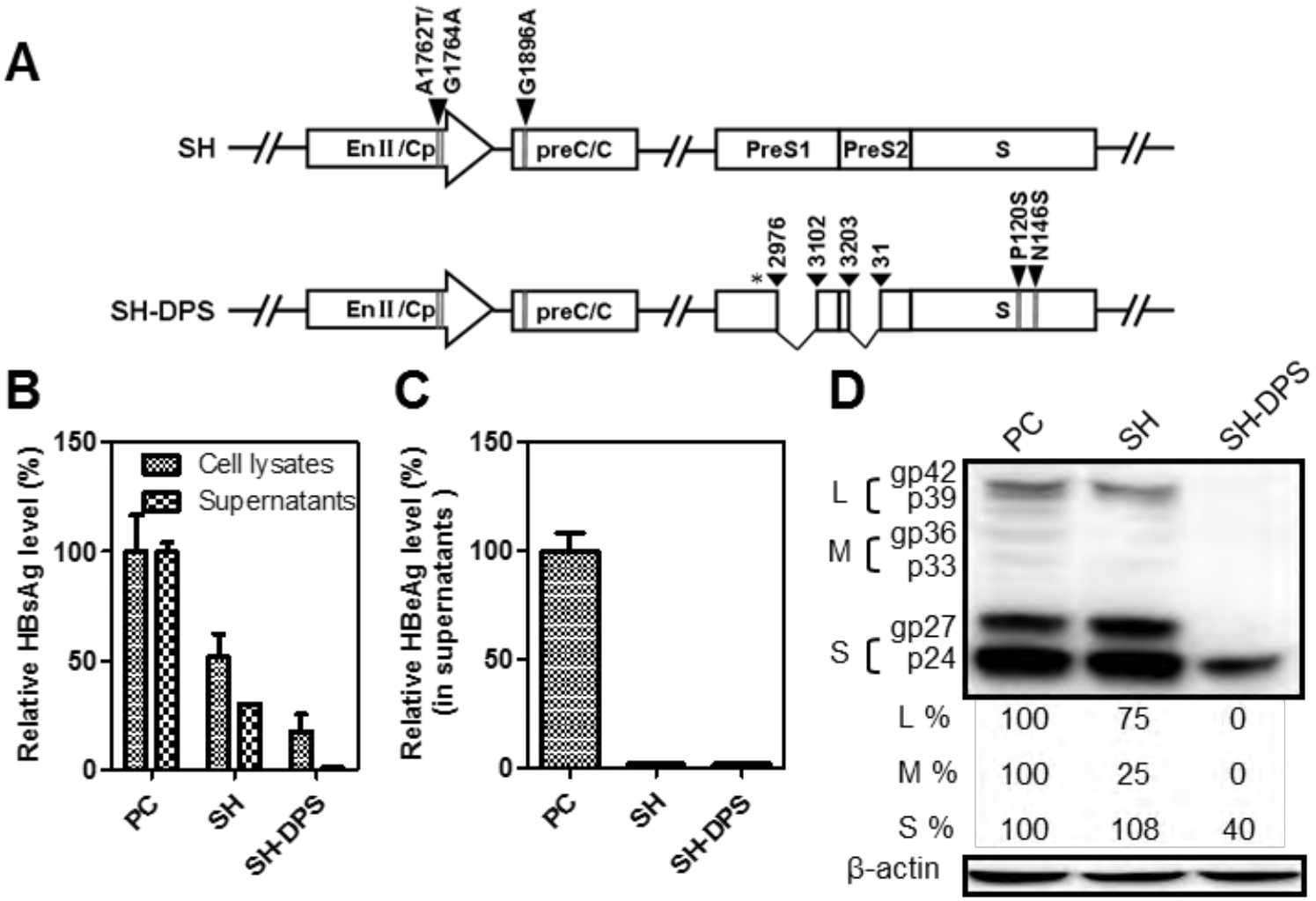
Modified after Prange, 2018

- **This fact suggests that even a complete stop of HBsAg secretion via ER-Golgi pathway does not exclude the continuous production of virions independently through autophagy.**

Possible link between HBsAg negative status and pathogenesis

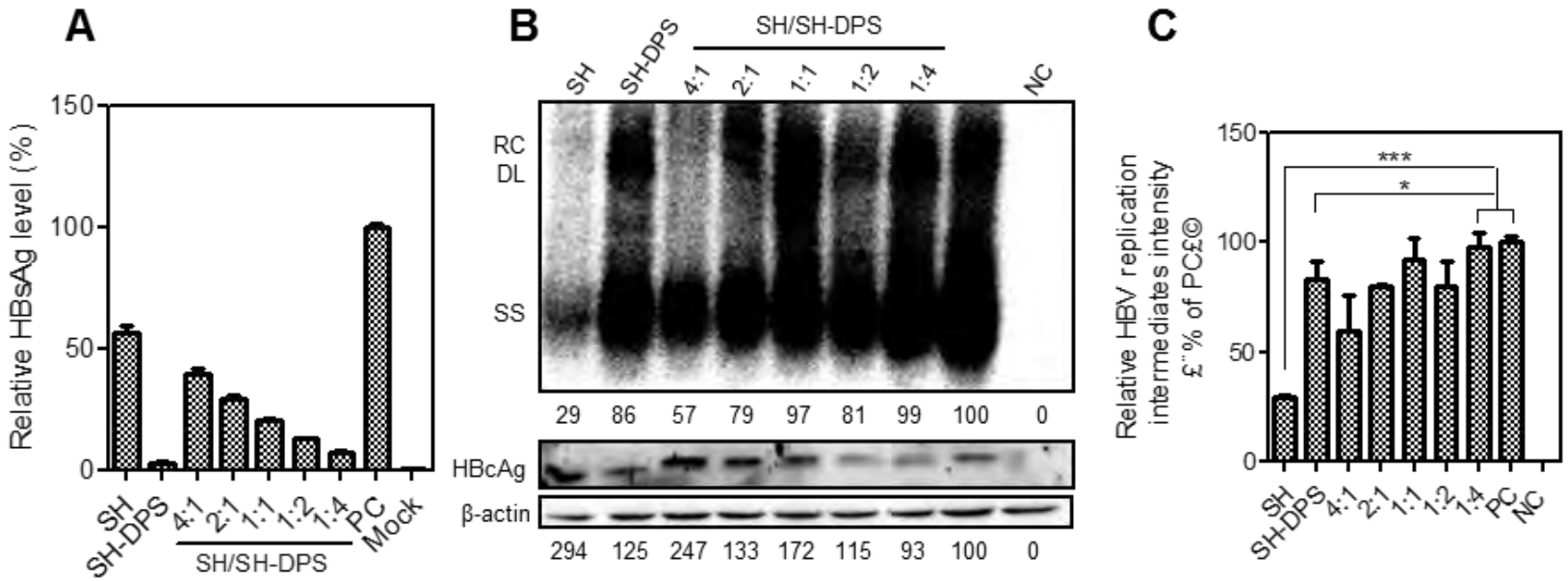


Co-existence of HBV genomes expressing wild type and defective HBsAg in patients



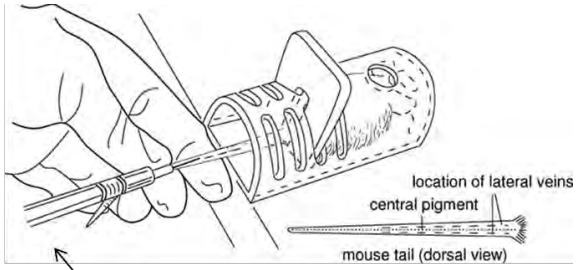
Cao L., et al. J Virol., 2014

Co-replication of HBV genomes expressing wild type and defective HBsAg

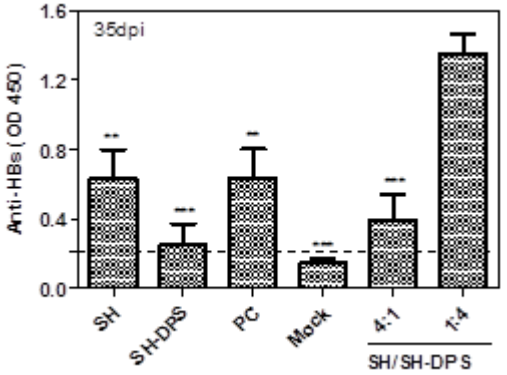


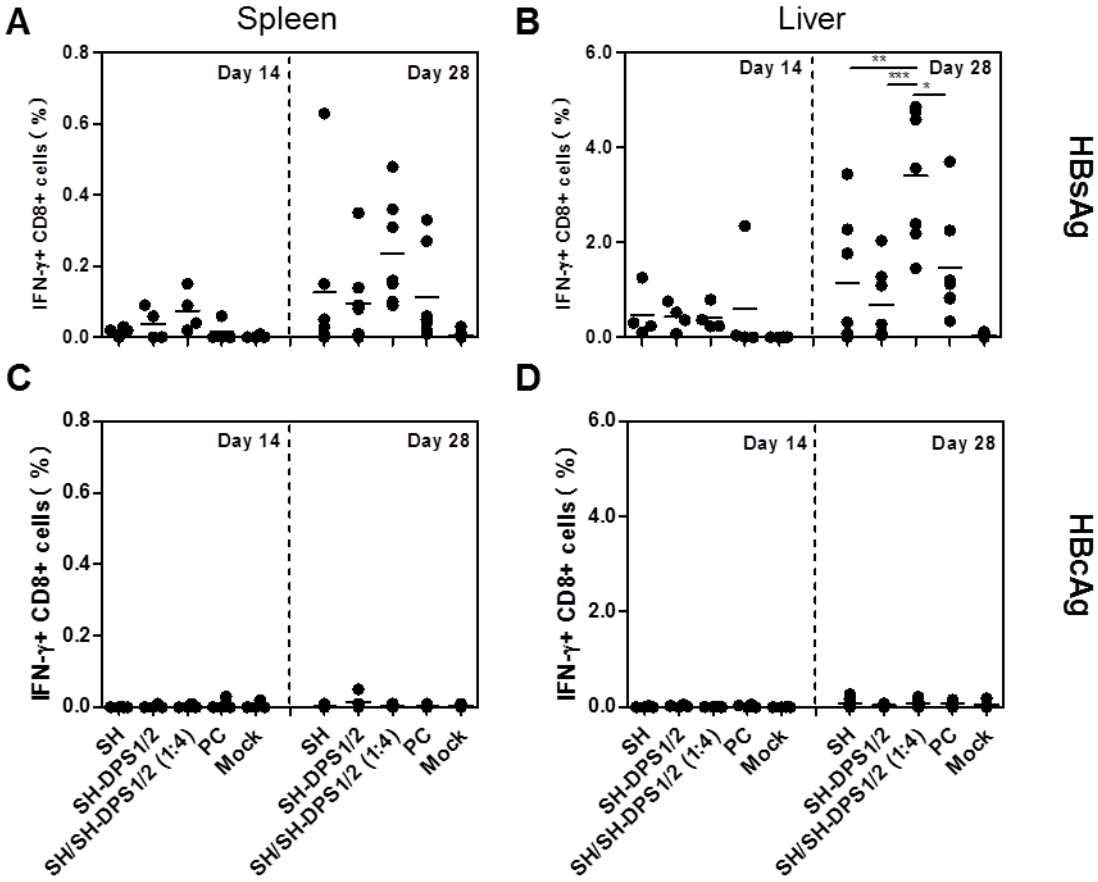
Co-application of wild type and defective HBV genomes induces enhanced host immunity

Hydrodynamic injection (HI)
HBV mouse model

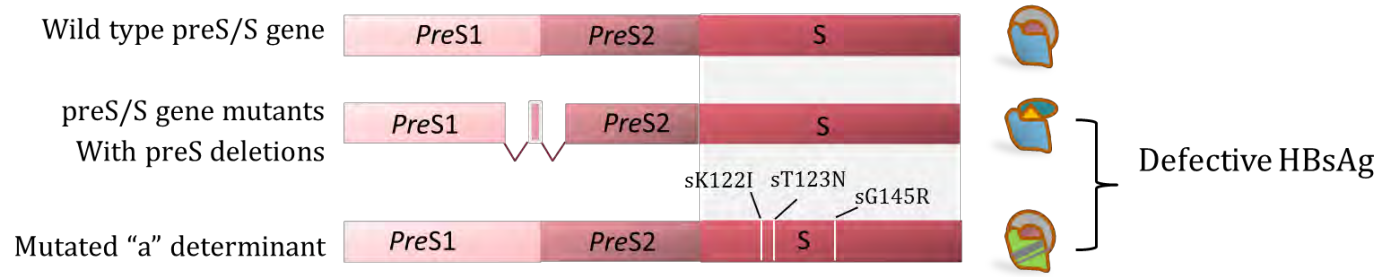


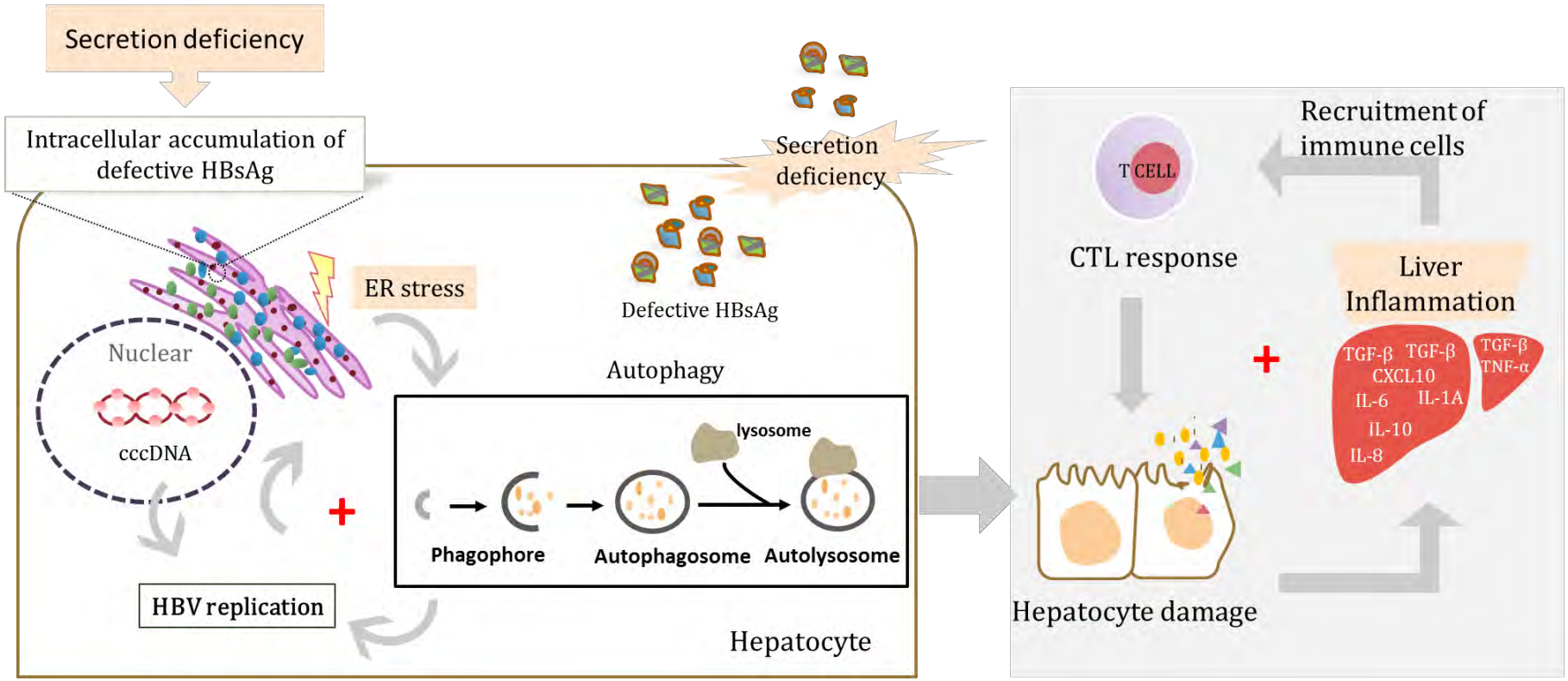
HBV replication-competent plasmid





The role of defective HBsAg in pathogenesis of chronic HBV infection





Conclusion and future research

- **OBI = HBsAg -/HBV DNA status may be facilitated by the interdependent pathways of HBsAg and virion formation .**
- **HBV mutants contribute to liver pathology by defined molecular mechanisms that need to be dissected for different types of mutations, for that mutants may interfere with autophagy in different ways. Better surveillance and detection of HBV mutants may be helpful.**
- **Antiviral therapy may further reduce HBV replication in OBI and therefore limit the co-existence of wild type and mutant HBV genomes and pathological consequences.**
- **We need to be aware that many drugs may interfere with cellular signaling pathways and thereby modulate HBV replication. It is useful to find a way to control ER-stress that may play a major role in HBV replication and liver pathology.**

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