HDV Virology

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Outline

• Brief overview of:

  HDV virology and life cycle
  
  preclinical potential targets for future therapeutic interference
  
  targets of agents in clinical development
Hepatitis delta virus (HDV)

- HDV is found in every country except:
  -- where people don’t test for HDV, or
  -- their anti-HDV tests don’t work

Hepatitis Delta Virus
Requires HBsAg from HBV for Viral Assembly / Packaging

- HDV makes HBV disease worse
- HDV is worst form of human viral hepatitis
- Rapid progression to cirrhosis; HCC; ↓ survival
- ~ 15-20 million world-wide; ~ 100K in U.S.
- No FDA-approved therapy
The HDV Life Cycle

Attachment and entry

Transport to Nucleus

Replication

Assembly

Release of Progeny

HDV genome

small HDAg

large delta antigen

large HDAg

Prenylation

HBV surface antigen

HBsAg

small HDAg

large HDAg

prenylated LHDAG

prenyl moiety
- Na-taurocholate cotransporting polypeptide (NTCP)
  - On surface of hepatocytes

- Receptor for bile acids and HBV/HDV virus entry

The HDV Life Cycle

1. **Attachment and entry**
   - HDV genome
   - Small delta antigen

2. **Transport to Nucleus**
   - HDV genome

3. **Replication**
   - Large HDAg
   - Prenylation

4. **Assembly**
   - Large HDAg
   - Preyalted LHDAg

5. **Release of Progeny**
   - HBV surface antigen
   - HBsAg

**Key Proteins**:
- Small HDAg
- Large HDAg
- Preyalted LHDAg
- Prenyl moiety
- HBsAg
Double rolling circle model of HDV genome replication

→ Multiple potential host cell targets
RNA editing generates two types of delta antigen

delta antigen isoform: small

- 195 a.a.
- Required for replication

large

- 195 + 19 a.a.
- Inhibits replication
- Required for packaging with HBsAg

ADAR1
Prenylation of large delta antigen is required for HDV assembly

Prenylation site = "CXXX box"

Prenylation -- site-specific lipid modification of proteins

Mevalonate → Isoprenoids (prenyl lipids)
- Farnesyl (C15)
- Geranylgeranyl (C20)
large antigen:

Ser 211 large antigen:
(Cys→Ser)

farnesyl transferase

CXXX

CXXX

SXXX

SXXX
Multiple HDV-host interactions = potential preclinical targets

Caveat: require further confirmation of druggability and acceptable therapeutic index

RNA transcription:
RNAP I, II, III
DIPA, YY1
Histones, RNA splicing /processing factors

Intracellular transport:
clathrin
microtubule and centrosomal

Nuclear import and export:
importin

Prenylation

delta antigen protein modifications:
phosphorylation by kinases
ERK 1, 2, PKR, PKC, Casein kinase II
sumoylation
methylation
acetylation

> 100 reported delta antigen interaction factors

Multiple HDV-host interactions = potential preclinical targets

Caveat: require further confirmation of druggability and acceptable therapeutic index
Targets of therapies in advanced clinical development
The HDV Life Cycle

Attachment and entry

Transport to Nucleus

Replication

Assembly

Release of Progeny

Entry Inhibitors (i.e. Myrcludex-b)

HDV genome

large delta antigen

small delta antigen

Prenylation

HDV genome

small HDAg

large HDAg

prenylated LHDAg

prenyl moiety

HBsAg

HBV surface antigen
The HDV Life Cycle

Attachment and entry

Transport to Nucleus

Replication

Assembly

Release of Progeny

Nucleic Acid Polymers (i.e. REP 2139)

Cytoplasm

HDV genome

large HDAg

prenylated LHDAg

prenylated LHDAg

prenyl moiety

HBsAg

HDV genome

small HDAg

large HDAg

prenylated LHDAg

prenyl moiety

HBsAg
The HDV Life Cycle

Attachment and entry

Transport to Nucleus

Replication

Assembly

Release of Progeny

Prenylation Inhibitors (i.e. lonafarnib)

Cytoplasm

HDV genome
- small HDAg
- large HDAg
- prenylated LHDAg
- prenyl moiety
- HBsAg

HBV surface antigen

HDV genome

HBV
- surface antigen

large delta antigen

prenylated LHDAg

LHDAg

small delta antigen

RSV genome

release of progeny
The HDV Life Cycle

Attachment and entry

Transport to Nucleus

Replication

Assembly

Release of Progeny

HDV genome

large delta antigen

small delta antigen

Prenylation

lambda Interferon

Lambda Interferon Receptor

ISG Induction

Antiviral Activity

HDV genome

small HDAg

large HDAg

prenylated LHDAg

prenyl moiety

HBsAg
Conclusions

• HDV—found everywhere; % of HBV patients co-infected with HDV varies by country

• HDV--fascinating collection of biology and important cause of human viral hepatitis; most severe form

• Study of HDV life cycle has identified many potential host targets for antiviral intervention; several form the basis for drugs in clinical development (entry, prenylation, HBsAg secretion, IFN lambda signaling)

• Complementary mechanisms of action offer potential for combination therapy