Hepatitis D (delta) Virus

- one of the 5 major hepatotropic viruses
- infection only in HBsAg +
- worldwide epidemiology, 15-20 millions infected
- severe liver disease
ADVENTURE

“a risky undertaking”

“an unusual and exciting experience”
HEPATITIS B VIRUS

HBsAg

HBcAg

HBeAg
Complement fixing hepatitis B core antigen immune complexes in the liver of patients with HBs antigen positive chronic disease

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SUMMARY One hundred and fifty-two biopsies from serologically HBsAg positive and negative patients with liver disease were studied in immunofluorescence for the presence of the surface (HBs) and the core (HBc) antigenic determinants of the hepatitis B virus, of immunoglobulins and complement (C) deposits, and for the capacity to fix human C. Circumstantial evidence is presented suggesting that HBc immune-complexes are a relevant feature in the establishment and progression of chronic HBsAg liver disease. C fixation by liver cells was shown in all HBc positive patients with chronic hepatitis; an active form was present in every case, except two with a persistent hepatitis, an inverse ratio of HBc to C binding fluorescence being noted between active chronic hepatitis and cirrhotic patients. HBc without C fixation was observed in only three patients in the incubation phase of infectious hepatitis. IgG deposits were often found in HBc containing, C fixing nuclei. No C binding or IgG deposits were observed in acute self-limited type B hepatitis, in serologically positive patients with normal liver or minimal histological lesions, with and without HBs cytoplasmic fluorescence in their biopsy, or in serologically negative individuals.
HEPATITIS B VIRUS

HBsAg

HBcAg

HBeAg

delta ?
Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

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John Gerin
Robert Purcell
James Shih
HDV Chimps Experiments

CHIMP n° 32

HDAg positive cells
HBsAg

HEPATITIS

µg/ml

0 1 2 3 4 5 6 7

0 8 9 10 11 12 13 14 15 16 17 18

(Weeks)

↑ L.M.Undil

HDAg
HDV Chimps Experiments

- CHIMP n° 29
  - HDAg positive cells
  - HbsAg

- CHIMP n° 32
  - HDAg
  - Infectivity: $10^{-6}$ serum dilutions
  - Infectivity: $10^{-11}$ serum dilutions

- L.M. Undil
  - (Weeks)
HEPATITIS DELTA VIRUS

Classification: Genus Deltavirus
Virion: 36 nm, enveloped (HBsAg)
Genome: 1.7 Kb RNA single-stranded,
HDV-RNA: structure

native

denatured
HDV RIBOZYME

- Extensive Base-Pairing
- Self-cleaving of RNA

- only ribozyme encoded by a human pathogen
- < 100 nucleotides
- crystallized, complex three-dimensional architecture
Attachment of HDV through HBsAg

Pre S1 sequence in L protein
HDV transferred to nucleus

- **HBsAg**
- **HDV**

- hepatocyte

- nucleus
HDV transferred to nucleus
Replication of HDV-RNA

HOST RNA polymerase II, I, III

HDV Ribozyme

Cell Ligase HDV Ribozyme?

= genomic HDV-RNA

= antigenomic HDV-RNA
Assembly of HDV virions

- HBsAg
- HDV

Virion assembly

hepatocyte

nucleus
Life cycle of HDV directed by post-translational modification of HDAg

- Transfer
- Replication
- Virion Assembly

HDAg:
- Acetylation
- Farnesylation
- Methylation
- Phosphorilation
- Sumoylation

= HBsAg
= HDV

nucleus
Corollaries

- HDV latency, theoretically HDV may survive in the absence of HBV as helper virus

- Hepatitis D therapy, no replicative target for antivirals
Latency of HDV

- Survival of HDV monoinfection for up to 38 days in woodchucks
  
  Netter HJ, 1994

- HDV monoinfection persisting in mice for at least 6 weeks before conversion to HBV/HDV infection by HBV rescue

  Giersch K, 2014

- In vitro and in vivo HDV survives liver regeneration, propagates and amplifies among cells, despite absence of HBV

  Giersch K, 2015
HDV: unique features

- Smallest infectious agent in man: 1700 nt
- Circular, single stranded-negative polarity
- Infectious at 10-11 serum dilutions in HBsAg +
- Rolling circle mechanism of replication
- Self-cleaving ribozyme
- Transcription by host-RNA polymerases
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* in helper virus coat
HDV origin

HDV evolved from a viroid-like RNA that captured the m-RNA encoding the HD-Ag protein

Taylor, 2010
Hammerhead and HDV-like self-cleaving ribozymes ubiquitous, expressed along the tree of life (worms, mosquitos, see urchins, plants...)

Webb C-HT, 2009
HDV 2016

- Infection, present and ominous throughout the world
- Hepatitis D, only viral liver disease in search of a cure
- HBV vaccination best and cheaper antidote
- HDV-RNA, a continuing biological surprise
ADVENTURE OF DELTA

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“an unusual and exciting experience”