Hepatitis research in Hungary: from identification to treatment

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Elimination of Viral Hepatitis in Hungary: Lessons learnt and the way forward

Budapest, Hungary
30-31 October 2019
Several cytokines are released after in vivo and in vitro after virus infection.

Schaff Z et al.  
*Cancer Research* 32: 2696-1972,  
*Lab Invest* 29:577-586 1973,  
*JNCI* 51:293-297 1973,  
*JNCI* 51:1751-60 1973,  
*J Invest Derm* 63:407-410 1974,  
*Int J Cancer* 18: 697-702 1976,  
*Ultr Path* 3:169-173 1982,  
*Lancet* 1:1336 1983,  
*Hepatology* 6:966-970 1986
Chemical and virus-induced hepatocarcinogenesis

DEN-induces foci in rat liver
GGT reaction

MC-29 induced turkey hepatoma

PATHOLOGY OF INCIPIENT NEOPLASIA

Second Edition

Chapter

LIVER

ZSUZSA SCHAFF, KAROLY LAPIS, AND DONALD EARL HENSON

Epidemiology of Hepatocellular Carcinoma

1983), 53 years in American blacks, and 61 years in American whites. HCC among chil-
Etiology of Cancer

- 15%
  - Viruses
  - Bacteria
  - Paracytes
Cancer Incidence and Mortality Worldwide

New Tumor cases in 2018: 18,1 million
Mortality 2018: 9,6 million
New Tumor cases in 2013: 14,9 million
Mortality in 2013: 8,2 million
New tumor cases in 2008: 12,7 million
Mortality in 2008: 7,6 million
New tumor cases in 2002: 11 million
Mortality in 2002: 7 million

GLOBOCAN 2008 (IARC 2010), JAMA Oncol.2015, CA Cancer J.Clin. 2018 Sept
Pathomechanism of virus-induced liver cancer (HCC)

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Metabolic</th>
<th>Toxic</th>
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<tbody>
<tr>
<td><strong>HBV</strong></td>
<td>Cell death, proliferation, inflammation</td>
<td>Immune response, cytokines, oxidative stress, fibrosis, ECM</td>
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<tr>
<td>Immune response, cytokines</td>
<td>10%</td>
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<td>Oxidative stress</td>
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<td>Fibrosis, ECM</td>
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<tr>
<td>Growth factors (TGFα, TGFβ, HGF, IGF II, etc)</td>
<td>80%</td>
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<td>HBV DNA integration</td>
<td></td>
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<tr>
<td>Viral proteins (HBx, PreS₁,₂, LHBS)</td>
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<tr>
<td>Genetic instability</td>
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<td>Chromosomal alterations</td>
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**HBV**

- Genetic instability
- Chromosomal alterations

**HCV**

- Immune response, cytokines
- Oxidative stress
- Fibrosis, ECM

**Growth factors** (TGFα, TGFβ, HGF, IGF II etc)

**Clonal expansion**

**HCC**

- No integration, No RT
- Viral proteins (core, E1, E2, NS2,3,5A,B)
- Genetic instability
- Chromosomal alterations

**Chronic inflammation** (CH, cirrhosis)

- Cell death, proliferation
- Oxidative stress
- Genetic instability
- Genetic alterations, mutations
- Cellular gene transactivation

**Cell death, proliferation**
HBV
10%
Chronic inflammation
Cirrhosis
Hepatocellular carcinoma (HCC)

10-20 yrs
- 257 million chronic HBV infected patients
- 3.5% of the world population

WHO Global Hepatitis Report 2017
Interferon therapy in CH-B *Hepatology* 6:966-970 1986

IFN treatment induces increased expression of HLA class I antigens leading to elimination of infected hepatocytes (*Hepatology* 6:349-353 1986)
"Ground-glass" hepatocytes

HBsAg by immunohistochemistry

Chronic Non-A, Non-B Hepatitis

#922

#930

Broken Pipette

Non-A, Non-B hepatitis

Lancet 1978 8062: 463-466
Additional evidence for more than one agent of human non-A, non-B hepatitis
Transmission and passage studies in chimpanzees

E. Tabor, P. Snoy, D. R. Jackson, Z. Schaff, P. M. Blatt and R. J. Gerety

Evidence supporting the existence of two agents of human non-A, non-B hepatitis was obtained by the inoculation of chimpanzees sequentially with serum from a chronically infected human (Inoculum I) and with fibrinogen prepared from pooled plasma (Inoculum IV), each of which had transmitted non-A, non-B hepatitis to humans. Passage inoculations of serum samples obtained during the acute stages of chimpanzee infections transmitted by either the agent in Inoculum I or IV also transmitted non-A, non-B hepatitis to additional chimpanzees. Transmission and passage of the agent in Inoculum IV were conducted in chimpanzees which previously had recovered from infection by the agent in Inoculum I. Cytoplasmic tubules in hepatocytes, which have been described during non-A, non-B hepatitis, were observed by electron microscopy in liver biopsies obtained during all infections transmitted by the agent in Inoculum I. These cytoplasmic tubules were not detected in liver biopsies from chimpanzees infected by Inoculum IV, except in one chimpanzee inoculated by Inoculum IV without prior exposure to the agent in Inoculum I. The cytoplasmic tubules observed in this study were found to be composed of transverse bands arranged with a periodicity of approximately 17 nm. These studies suggest that two different agents or distinct serotypes of human non-A, non-B hepatitis may have been present in these inocula, although reactivation of latent infection or reinfection could not be ruled out completely. TRANSFUSION 1984;24:224-230.
Ultrastructural alterations in nonA-nonB hepatitis vírus infection

Schaff et al. Virchow’s Arch 45: 301-312  1984
Membran-associated replication complex

Virális proteinek
Replikálódó virális RNS
Alterált celluláris membránok
Bradley DW, Cook EH, Gravelle CR, McCaustland KA, Maynard JE, Miller MF, Schaff Zs:
Non-A, non-B hepatitis in experimentally infected chimpanzees: Comparative morphology of virus-induced ultrastructural changes
Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome

1. QL Choo,
2. G Kuo,
3. AJ Weiner,
4. LR Overby,
5. DW Bradley,
6. M Houghton

See all authors and affiliations

Science 21 Apr 1989:
Vol. 244, Issue 4902, pp. 359-362
DOI: 10.1126/science.2523562
Localisation of HCV by immunofluorescence

H. Alter, K. Krawczinsky, D. Bradley, Zs. Schaff
HCV-core (IEM)

Hepatitis C virus core protein shows a cytoplasmic localization and associates to cellular lipid storage droplets


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Communicated by William Rutter, University of California, San Francisco, CA, December 5, 1996 (received for review April 10, 1996)
HCV core protein/Apo All
Double transgenic mice

HCV

Hepacivírus
Flaviviridae
ssRNS
Great genomic variability
(7 genotypes, >100 subtypes)
HCV prevalence worldwide

Hepatitis C prevalence, 1999
HCV Genotypes

DEVELOPED COUNTRIES

AMERICAS + WESTERN EUROPE

SOUTH AFRICA

MIDDLE EAST
NORTH AFRICA

IVDU

ASIA

+ 7

IVDU=intravenous drug user.
Simmonds P. J Hepatol. 1999;31(suppl 1):54-60.
HCV genotypes in Hungary 2000-2017
(based on 5917 patients)

- 1a: 5.6%
- 1b: 84.6%
- 1a+1b: 5.1%
- 3: 1.8%
- Mixed: 1.6%
- Not differentiated: 1.1%

Eder G., Schaff Zs. FAS antigen (APO1/CD95) expression in experimental HCV infection in chimpanzees Hepatology 24:218A 1996
Structure of HCV polyprotein

Direct-acting antivirals, DAAs

5’ NTR
Capsid
Capsid glycoproteins

Envelope
Capsid

Structural proteins
Capsid
Envelope glycoproteins

Non-structural proteins
Metalloprotease
Serine protease
RNA helicase

Cofactors

3’ NTR
RNA polimerase

Protease inhibitors
Paritaprevir (ABT-450)
Telaprevir
Boceprevir
Simeprevir
Faldaprevir

NS5A inhibitors
Ombitasvir
Daclatasvir
Ledipasvir
GS-5816
ACH-3102

Polimerase inhibitors
Nucs
Sofosbuvir
VX-135
IDX-20963
ACH-3422

Non-Nucs
Dasabuvir
Deleobuvir
BMS-791325
PPI-383

**Figure 1:** Changes in standard of care for HCV, and improvements in numbers of sustained virological responses

Data from references 9-12. PI = protease inhibitor.
HCV: „Báránybőrbe bújt farkas”
(„wolf in lamb’s clothing – wolf in sheep’s clothing”)

- Milder and more prolonged (15-30 yrs)
- Transmission: transfusion, sexual (rare), perinatal (rare)
- 71 million infected
- 80% progression into chronicity
- No vaccine
National Hepatitis Elimination Board
2018. December 13th, Budapest