Virology and Immunology of Hepatitis C Virus Infection

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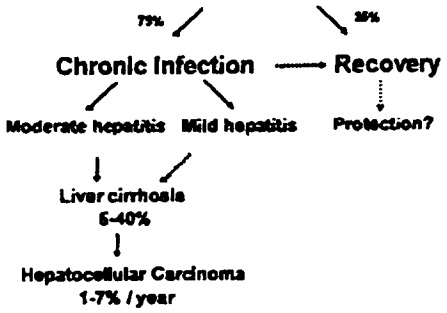
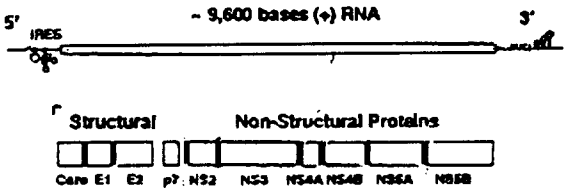
Hepatitis C Virus Infection



Hepatitis C Virus



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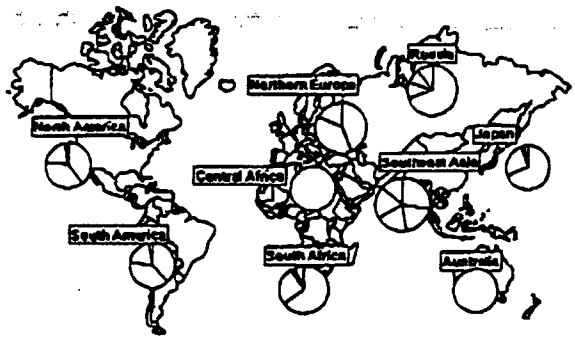
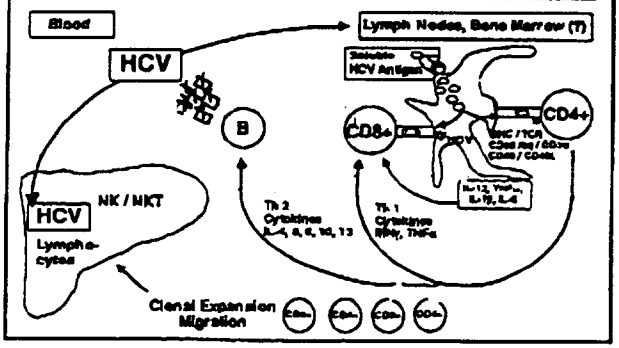
HCV Genotypes



Determinants of the Outcome of Infection

- Virus
- Innate Immune Response
- Humoral Immune Response
- Cellular Immune Response

Immune Response In Hepatitis C



Evidence for a Role of the Humoral Immune Response

- Clinical Studies - Resolution of acute hepatitis C
  - HVR 1 — Ziebert et al., Hepatol. 1997
  - non HVR 1 — Lechner et al., Virology 1998
  - Resolution of chronic hepatitis C
  - NOB — Ishii et al., Hepatology 1997
- Neutralization studies, chimpanzee model
  - antiHVR I — Farci et al., 1996
  - human Ig — Krawczynski et al., AASLD 1999
- Vaccine studies
  - E1/E2 — Choo et al., PNAS, 1994

Evidence for a Role of the Cellular Immune Response

Resolution of infection in the absence of antibodies in

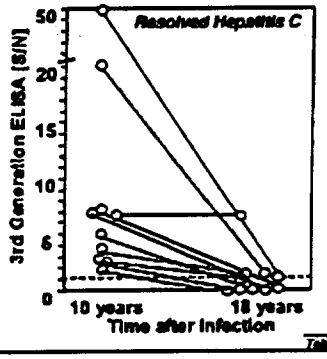
- hypogammaglobulinemic patients
  - Bjoro et al., NEJM 1994
  - Christie et al., Clin. Exp. Immunol., 1997
  - Adams et al., Pediatr. Infect. Dis. 1997
- chimpanzees
  - Cooper et al., Immunity, 1999
  - Bassett et al., J. Virol. 1999

Immune Response to HCV

	Cellular	Humoral
Chronic	+	+ +
Recovered	+ + +	+ → -

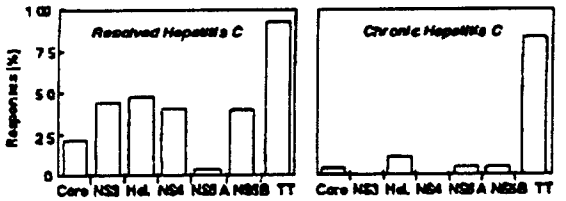
References: *Lechmann et al., Hepatology 1996; 24: 790*
Cramp et al., Gut 1999; 44: 424
Bassett et al., J. Virol. 1999; 73: 1118
Takaki et al., Nature Medicine 2000; 6: 578

Circulating Antibodies Decrease After Recovery

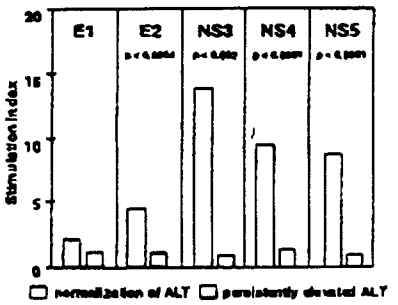


Takaki et al., Hep. Res. 2000

Proliferative T cell Response

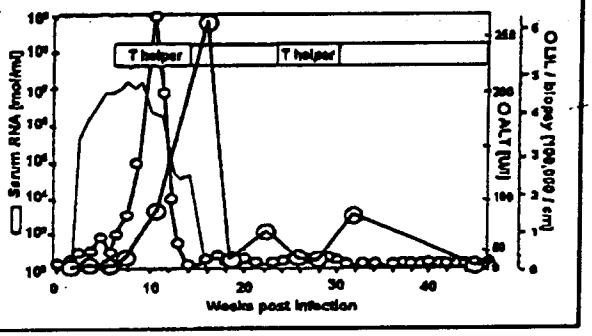


T Helper Cell Response in Acute Hepatitis C



Missale et al., J Clin Invest, 1996

Acute, Self-limited Hepatitis C in a Chimpanzee



Methods to Study T Cell Responses

Quantitative Assays
Frequency

- MHC-I Tetramer
- ELISPOT
  Intracell. cytokines

Qualitative Assays
Effector function

- Proliferation
- Cytotoxicity
- Cytokine release

IFNγ Production by HCV Peptide Specific T cells After Recovery From Hepatitis C

Elispot Assay

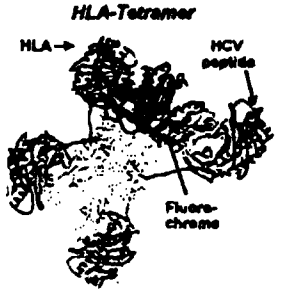
IFNγ spots / 3 x 10^5 PBL

Medium

HCV peptide (NS3 1073)

CMVpp65 peptide

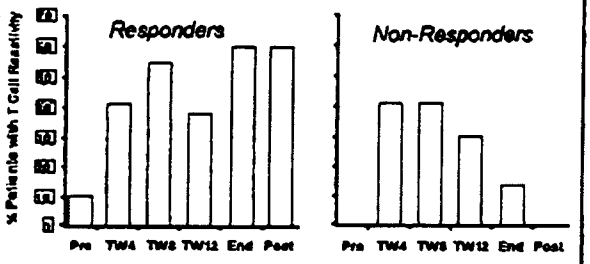
Low Frequency of HCV Specific T Cells in Chronic HCV Infection



Blood: 0.01-0.5 % CD8+ T cells
Liver : 30 x higher frequency
all cells express
activation markers

J Clin Invest 1994; 98:1432
PNAS 1993;96; 6682
Viral Immunology 2001;14:53

Cellular Immune Response During IFN / Ribavirin Therapy



Cramp et al., Gastroenterology 2000

Cellular Immune Response in Acute Self-Limited Hepatitis C

- A vigorous, multispecific and sustained CD4+ and CD8+ T cell response is associated with recovery from hepatitis C and needs to be maintained to ensure viral clearance.
- After recovery, circulating HCV specific antibodies decrease while Th1 and Tc1 cells remain detectable in the blood for decades.

Potential Mechanisms of HCV Persistence

- Lack or loss of neutralizing antibodies
- Low frequency of HCV specific T cells
- HCV sequence variations, quasispecies
- HCV may interfere with antigen processing
- HCV may not be susceptible to T cell cytokines
- HCVcore may alter T cell induced apoptosis
- Sequences within HCV E2 and NS5A proteins interfere with activation of the interferon-inducible PKR