Kinetics of hepatitis B surface antigen specific immune responses in acute and chronic hepatitis B

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Overview

1. The HBV and its envelope
2. HBV immunopathogenesis
3. Envelope specific antibody production
4. Envelope specific T cells in *acute* hepatitis
5. Envelope specific T cells in *chronic* hepatitis B
6. Summary and Conclusion
The Hepatitis B Virus (HBV)

- large HBs antigen (preS1/2 + sHBs)
- major HBs antigen (sHBs)
- polymerase
- middle HBs antigen (preS2 + sHBs)
- lipid layer
- dsDNA genome
- nucleocapsid antigen
CTL and Th cell epitopes

HBV envelope protein

- PreS1
- PreS2
- HBs

MHC class I
MHC class II

400 aa

HBV nucleocapsid protein

- Precore
- Core

MHC class I
MHC class II

212 aa

Chisari and Ferrari
Ann Rev Immunol 1995
Pathogenesis of HBV infection

Hepatocytes

HBV

Dendritic cells

HLA-I
HLA-II

IFN-α
TNF-α

CTL
Th cells

HBV

B cells
(HBs specific)

neutralisation
viral spread
IC diseases

Regulation of immune response

Lysis of infected cells
noncytopathic pathway

anti-HBs antibodies

Neutralisation viral spread IC diseases
Anti-HBs abs: virus neutralisation

active (HBs) vaccination

passive (HBIg) vaccination

Szmunes SW et al., N Engl J Med 1980

Terrault NA et al., Hepatology 1996
Anti-HBs antibody response: selflimited vs. chronic infection
Anti-HBs/pre\text{S}_{1/2} \text{ in HBV infection}

- 5-10% positivity for \textbf{anti-HBs antibodies} in chronic hepatitis B (Mishra, 1992)
  -> super-/co-infection with different HBV subtypes or mutants
  (i.e. HBsAg subtype \textit{ad} or \textit{ay} and anti-HBs subtype \textit{-ay} or \textit{-ad})
  (Tabor, J Immunol 1977; Wang, J Gastro 1999)

- seropositivity of \textbf{anti-preS antibodies} in acute (45%) and in chronic hepatitis B (14%) correlate with preS-antigenemia and viremia
  -> indicator of HBe seroconversion (Budkowski, 1992)
Anti-envelope ICs in *chronic* hepatitis B

Maruyama T et al., J Clin Invest 1993
Anti-HBVEnv in *chronic* hepatitis B

<table>
<thead>
<tr>
<th>ALT (U/l)</th>
<th>45 ± 30</th>
<th>104 ± 70</th>
<th>415 ± 214</th>
<th>98 ± 88</th>
<th>38 ± 38</th>
</tr>
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<tbody>
<tr>
<td>HBsAG/ICs</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>0</td>
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<tr>
<td>HBV DNA</td>
<td>672 ± 1828</td>
<td>16 ± 320</td>
<td></td>
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<tr>
<td>HBcAg</td>
<td>26.4 ± 23.6</td>
<td>0.9 ± 1.7</td>
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</table>

Maruyama T et al., J Clin Invest 1993
HBs specific B / Th cells in acute hepatitis B

HBsAg       +              +               +                              + +                -
HBV-DNA                 +                                           +                                - (PCR -)
anti-HBs     - - - - - 70 U/l

stimulation index (SI)

Böcher WO et al., Hepatology 1999
HBs specific B cells in acute and chronic HBV infection

![Graph showing HBs-ASC levels in acute, resolved, and chronic HBV infections.](image_url)

- **Acute HBV**: Higher HBs-ASC levels compared to resolved and chronic HBV.
- **Resolved HBV**: Lower HBs-ASC levels.
- **Chronic HBV**: Intermediate HBs-ASC levels.

Statistical significance: p<0.02

Böcher WO et al., Hepatology 1999
Enrichment of HBs specific B cells in bone marrow

Böcher WO et al., Hepatology 1999
HBV specific Th cells in acute hepatitis B

Ferrari C et al., J Immunol 1990
Correlation of HBc specific CTL and Th cells with HBV clearance in acute infection

Webster G. et al., Hepatology 2000; (also Maini M. et al., Gastroenterology 1999)
Envelope specific Th cells in chronic hepatitis B

Böcher WO et al.,
Clin Exp Immunol 1996
HBV specific CTL in *chronic* hepatitis B
HBV specific CTL during treatment with lamivudine

Boni C et al., Hepatology 2001
Summary:

• **in acute hepatitis B:**
  - high frequencies of circulating anti-HBs secreting B cells before HBs seroconversion, migrating to lymphoid organs later on
  - weak envelope specific CTL and Th cell responses during seroconversion

• **in chronic hepatitis B:**
  - correlation of complexed anti-HBs and anti-preS antibodies with inflammatory activity
  - weak envelope specific Th cell activities, no correlation of envelope specific CTL with virus control
Correlation of HBc specific Th cells with HBV clearance

Ferrari C et al., J Immunol 1990
HBV clearance is mediated by HBc specific T cells after adoptive transfer

8 patients with chronic HBV and BMT from HLA matched sibling with immunity to HBV (aHBs+, aHBc+)

flares (week 24) in 8/8 recipients, sustained HBsAg seroconversion in 6/8:
weak HBs strong HBc specific T cell activities in recipients (Lau 2002)
no elimination after transfer from HBs vaccinated donors (Lau 1998)
Conclusion: HBV envelope antigens

• strong B cell antigens in *acute and chronic* HBV infection
  - virus neutralisation
  - viral spread \(\downarrow\), protective immunity

• weak Th cell and CTL antigens in acute and chronic infection
  - limited role in immune control of HBV replication
  - core and polymerase specific T cell immunity critical

• suitable as protective vaccine or adjuvant for therapeutic vaccine