Hepatitis virus immunity

Mar 9, 2005
Rehermann and Nascimbeni review
Crispe review
HBV & HCV infection outcomes

- Both viruses cause immune-mediated active and chronic hepatitis
- **HBV**
  - Vertical transmission = chronic hepatitis
  - Adult infection = protective immunity
- **HCV**
  - Adult infection = 60-80% chronic hepatitis
# Clinical features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>350 million infected</td>
<td>170 million infected</td>
</tr>
<tr>
<td>United States</td>
<td>1 million infected</td>
<td>4 million infected</td>
</tr>
<tr>
<td>Vertical transmission</td>
<td>Mother to neonate Chronic hepatitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Horizontal transmission</td>
<td>IV drug use, parenteral, sexual</td>
<td>IV drug use, parenteral, sexual</td>
</tr>
<tr>
<td></td>
<td>Recovery</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
## Molecular virology

<table>
<thead>
<tr>
<th>Feature</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>42 nm enveloped partially dsDNA</td>
<td>50 nm enveloped +stranded RNA</td>
</tr>
<tr>
<td><strong>Family</strong></td>
<td>Hepadnaviridae</td>
<td>Flaviviridae</td>
</tr>
<tr>
<td><strong>Receptor</strong></td>
<td>Unknown</td>
<td>Includes CD81</td>
</tr>
<tr>
<td><strong>Mutation rate</strong></td>
<td>Low (10⁻⁵/base)</td>
<td>High (10⁻³/base)</td>
</tr>
<tr>
<td><strong>Genotypes</strong></td>
<td>8; low divergence</td>
<td>6 with &gt;50 subtypes</td>
</tr>
</tbody>
</table>
Image removed for copyright reasons.

Source: Figure 1 in Rehermann, B., and M. Nascimbeni. "Immunology of hepatitis B virus and hepatitis C virus infection." *Nature Review Immunology* 5, no. 3 (2005).
HBV molecular virology

- Relaxed circular 3.2-kb genome
  - Full-length negative strand, 5´ viral RT
  - Partial positive strand, 5´ oligoribonucleotide
- cccDNA template for transcription of 4 viral RNAs in nucleus
  - Exported to cytoplasm and translated
  - Longest RNA also serves as template for HBV replication in nucleocapsids in the cytoplasm
  - Some DNA and nucleocapsids return to nucleus
  - Others bud into ER & are secreted via golgi
HCV molecular virology

• ssRNA (+) 10K nucleotides
• Single long ORF flanked by 2 UTRs
• Replicates in the cytoplasm
  - Translation initiated by internal ribosomal entry site in 5’ UTR
• Polyprotein processed into structural and non-structural proteins
  - Combine with viral RNA to form membrane-associated replication complexes
  - Nucleocapsids bud into cytoplasmic vesicles
Acute HBV infection in adults

- HBV DNA is detectable in circulation within 1 month of infection
  - Remains at a low level \((10^2-10^4\) genome equivalents/ml\) for up to 6 weeks
  - HBeAg and HBsAg reach peak levels
  - HBcAg-specific IgM appears early and IgG persists for life, regardless of outcome

- T cell-mediated liver damage begins to be apparent 10-15 weeks after infection
  - Most viral DNA is cleared by this time
Acute HBV infection in adults

• >90% of acutely infected adults resolve all clinical signs, develop HBeAg- and HBsAg-specific antibodies, clear HBeAg and HBsAg from circulation, and maintain lifelong protective immunity

• Despite complete clinical recovery, trace amounts of HBV DNA persist and are controlled by humoral and cellular immune responses
Acute HCV infection in adults

• HCV reaches high levels in serum within 1 week after infection
  - Cellular immune response takes 1 month and humoral immune response 2 months
  - Clinical signs associated with T cell-mediated liver damage are rare

• Liver enzymes indicating tissue damage are detectable 8-12 weeks after infection
  - Viral RNA declines
  - Development of HCV-specific Ig is variable
Acute HCV infection in adults

• HCV-specific antibodies do not indicate the outcome of infection
• Most individuals develop chronic hepatitis with relatively stable viral titers (2-3 logs below that in the acute phase)
• Only a small proportion of patients recover and test negative for viral RNA
• Whether complete eradication occurs is controversial
Protective immunity to HBV

- Clinical recovery is associated with lifelong protective immunity
  - Trace amounts of virus persist
  - Reactivation with immunosuppression
  - Transmission via organ transplantation
  - Trace virus may maintain immune response

- Controversy regarding need to boost to maintain vaccine-induced HBsAg-specific immunity
Protective immunity to HCV

- Recovery is associated with HCV-specific T cells
  - B cell responses are variable, and may not persist
- Whether HCV is completely eradicated or trace amounts remain is controversial
- Protective immunity is not believed to be completely protective or lifelong
  - But data in humans are limited
Liver tolerance

- Portal blood is rich in bacterial products and food-derived antigens
- *Malaria, HBV, and HCV* all persist
- Allogeneic liver grafts can be established and maintained without immunosuppression
- Local presentation of Ag causes T cell inactivation, tolerance, and apoptosis
Immune cells in the liver

• Resident macrophages = Kupffer cells
  - Can sometimes be effective APCs
  - Also seem to be involved in tolerance

• Intrahepatic lymphocytes
  - CD8+ > CD4+
  - NK and NKT populations are enriched
Figure by MIT OCW.
NK cells in the liver

- Important role in T cell recruitment
- In response to type 1 IFN, Kupffer cells produce CCL3 (MIP-1)
- Once activated by Kupffer cell IL-12, produce IFN-\(\gamma\)
- Induces other cells to secrete CXCL9 (MIG)

Figure by MIT OCW.
DC trafficking in the liver

- Also in response to Kupffer cell CCL3, immature DC respond via CCR1
- Downregulate CCR1 and CCR5, upregulate CCR7 and become responsive to CCL21
- Migrate to lymphoid aggregates in portal tracts and to LN

Figure by MIT OCW.
T cell tolerance in the liver

Figure by MIT OCW.
Overcoming baseline tolerance

- Hypothesis that type 1 IFN allows liver sinusoidal endothelial cells to produce IL-12
- Promotes differentiation of Th1 cells
- IL-15 serves as a survival factor for CD8+ T cells

Figure by MIT OCW.