Chronic Viral Infection: challenges and new opportunities

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To discuss
- Overview of the problems
- What we think might be going on….
- Novel pathways
- Novel treatments
Co-infection: A Significant Problem

- HIV affects 40 million globally and about 1 million in the U.S.
- HCV affects 200 million globally and 4 million in the U.S.
- Prevalence of co-infection varies from 4% to greater than 90% depending on the population
- In IV drug users and hemophiliacs, the prevalence has been as high as 98%
- MSM sexually-acquired HCV appears to occur in the setting of high risk exposures (STDs, traumatic intercourse)


HIV and HCV: more similar than you might think

<table>
<thead>
<tr>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>ssRNA retrovirus</td>
</tr>
<tr>
<td>Transmission</td>
<td>Sexual/IVDU</td>
</tr>
<tr>
<td>Viral kinetics</td>
<td>Massive production</td>
</tr>
<tr>
<td>Viral load</td>
<td>Correlates well with disease</td>
</tr>
<tr>
<td>Major target</td>
<td>T cell</td>
</tr>
<tr>
<td>Latency</td>
<td>Yes</td>
</tr>
<tr>
<td>Goal of therapy</td>
<td>Viral suppression</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>Occurs</td>
</tr>
</tbody>
</table>

WHY PERSISTENCE?

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New Targets for chronic viral infection: the negative immunoreceptors

Immune exhaustion

PD-1 and HIV

- PD-1 expression on HIV-specific T cells is associated with T cell exhaustion and disease progression (Day et al. Nature 2006; 443: 350-354)
- Immune dysfunction was reversible in HIV-specific CD8+ T cells (Trautmann et al. Nat Med 2006; 12:1198-1202.)

PD-1 and HCV

PD-1 modulates regulatory T cells and suppresses T-cell responses in HCV-associated lymphoma.


New Targets: the Tim-3 story

Fig. 5. TIM-3 engages APC during the priming phase to stimulate the innate immune system to produce inflammatory cytokines that drive T-effector responses. In the effector phase, Th1 cells secrete Tim-3 and produce TNF-α, which drives effector T cells. Galactose-9 inhibits the infiltration of Th1 effector responses through TIM-3. TIM-3+ T cells can regulate Th2 responses and enhance Th1 responses. APC, antigen-presenting cell; TNF-α, tumor necrosis factor-α; Th1 cell, T helper type 1 cell.
Differential expression of TIM-3 on the surface of T cells regulates susceptibility to viral infection or development of autoimmune injury.


HCV and Tim-3: T cells
- Up-regulation on HCV-specific T cells
- Blockade is associated with improved CD4+ and CD8+ functions
- Dual expression of Tim-3/PD-1 on T cells has been described in co-infected patients and correlates with progression of liver disease


**Tim-3 in monocytes**, **HCV infection**
Defining an Initial Virologic Response

- **RVR**: HCV RNA Undetectable at Week 4

- **EVR**: HCV RNA ↓ ≥ 2 logs or Undetectable at Week 12

### Initial Treatment of Chronic HCV - Predicting SVR Over Time

**No matter what genotype, achieving RVR is crucial for a SVR**

HCV monoinfection: Sustained Virologic Response With Peg-interferon and Ribavirin Combination Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall</th>
<th>Genotype 1</th>
<th>Genotype 2 or 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a plus ribavirin</td>
<td>56%</td>
<td>46%</td>
<td>76%</td>
</tr>
<tr>
<td>Peginterferon alfa-2b plus ribavirin</td>
<td>54%</td>
<td>42%</td>
<td>82%</td>
</tr>
<tr>
<td>Weight-based dosing</td>
<td>48%</td>
<td>88%</td>
<td></td>
</tr>
</tbody>
</table>


New Targets

STAT-C: Specifically Targeted Antiviral Therapy for Hepatitis C

- IFN + RBV + small molecule agents specifically inhibit HCV life cycle
- achieve RVRs and increase SVRs from 50 to 80%
- Pretreatment quasispecies confer resistance to all classes of inhibitors
- All therapies will still be IFN-based
- Sides effect: skin rash, renal toxicity
Therapies arrived: NS3/4A inhibitors

- The NS3/4a complex acts as a serine protease to process the HCV polyprotein
- Peptidomimetic inhibitors developed (oral)
  - Boceprevir
  - Telaprevir

+McCutshison et al. NEJM 2009; 360:1827.
+Honzaki et al. NEJM 2009; 360:1839-1850.
Summary: Treatment-naïve, Genotype 1
- Addition of protease inhibitor increases SVR by 1.7 fold
  - Boceprevir:
  - Telaprevir:
- 24 (±8) weeks of treatment is effective for many patients
- Adverse events include
  - Boceprevir: anemia, dysgusia
  - Telaprevir: skin rash, anemia
- Effective in African-Americans and patients with cirrhosis
- First line treatment for genotype 1 HCV now

Summary – Treatment-Experienced Patients
- Boceprevir and telaprevir increase SVR for non-responders
  - 48 weeks of treatment
- Probability of SVR depends on prior response to PegIFN/RBV
  - 75 - 85% in relapers
  - 50-65% in non-responders (non-null)
  - 30% in null-responders
- Null responders not optimally served by either drug

Summary
- Protease inhibitor + pegIFN/RBV expected to be the next standard of care for most patients with HCV genotype 1
- Treatment-naïve patients can anticipate SVR rates from 63%-75%
  - Shorter duration for many patients (response-guided therapy)
- Treatment-experienced patients can anticipate SVR rates ranging from 29%-88% depending on response to pegIFN/RBV
- Side effects:
  - Boceprevir: anemia, dysgusia
  - Telaprevir: rash, anemia
- Resistance in patients who don’t respond to pegIFN/RBV
- New agents are promising, probably with pegIFN + RBV
Summary

- HCV and HIV present similar challenging issues and perhaps underlying immunopathology
- Novel treatments for HCV will likely lead to substantial improvements in sustained virologic responses in both mono- and co-infected populations
- Novel pathways that mediate immune exhaustion are potential targets to improve host responses

Thanks....

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Consequences: not just persistence

Vaccine responses in chronic HCV infection

A Vaccine (Failure) Model

Does having HIV make HCV worse?

- Co-infected patients had higher HCV RNA viral loads*
- Co-infected patients had more rapid HCV viral replication and progressed more rapidly and frequently to hepatic fibrosis and cirrhosis than HIV (-) patients with HCV†
- In a large group of hemophiliacs, progression to liver failure was more likely and was inversely correlated with CD4 count‡

HIV/HCV Co-infection
RR for ESLD 6.14
RR for Cirrhosis 2.07

Fig. 1. Adjusted relative risk of decompensated liver disease or histological cirrhosis in patients with HIV/HCV co-infection compared with patients who have HCV infection alone (adapted from meta-analysis published by Graham and colleagues) [6].
