Immunopathogenesis of HIV/HCV Co-infection

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Disclosure Statement for Arthur Kim

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I will discuss the following off-label use in this presentation:
Unapproved direct-acting agents and combinations

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Objectives

• Review what we know (and don’t know) about HCV pathogenesis as it relates to HIV co-infection

• Identify clinical translations related to insights

• Describe the rationale for greater understanding of HCV immunopathogenesis
What is the correct statement regarding HCV pathogenesis?

1. An HCV vaccine is not required due to the availability of antivirals
2. HIV-associated microbial translocation and immune activation protects against liver fibrosis
3. Almost 90% of hepatocytes are infected and productively support HCV infection
4. Spontaneous clearance of the virus is more likely in females compared to males
Outline

Outline- a very broad topic

• Focus on virus-specific T cells and protective immunity
  • Intrahepatic immune responses
  • Immunogenetics, including IL28B
  • Innate immunity, antibody-mediated immunity (not covered)
Heroin use - shifts in demographics

• In 2012, about 669,000 Americans reported using heroin in the past year, compared to 404,000 ten years earlier.

• In 2011 179,000 new initiates of injecting opiates.

• 4.2 million Americans ages 12 or older (1.6 percent of Americans) have used the drug at least once in their lives.

Need for HCV prevention and vaccine!

National Survey on Drug Use and Health (NSDUH), National Institute on Drug Abuse (NIDA), Cicero et al. JAMA Psych 2014
Infectivity of JFH-1 strain of HCV in syringes

Recovery of live virus 8 weeks later

Need for clean injection equipment, universal precautions

Natural outcomes after infection with HIV-1 and HCV

**A** HIV-1
- Initial burst of viremia
- Establishment of viral setpoint
- Progressive HIV-1 infection (∼85-95%)
- Slowly progressive HIV-1 (∼5-15%)
- "Elite" controller (<1%)

**B** HCV
- Initial burst of viremia
- Establishment of outcome
- Chronic HCV infection (50-80%)
- Spontaneous clearance (20-50%)

*Time after initial viremia*
Outcomes of acute HCV

Chance of viral clearance highest (~66% of clearances occur within first 6 months)

More responsive to interferon-based treatments

Most studies define acute HCV as the first 6 months following infection

Rehermann and Nascimbeni. Nat Rev Immunol 2005
Clearance is associated with protection from reinfection

HCV peak viral load (A) and duration of viremia (B) during reinfection

Osburn et al. Gastroenterology 2010
Transmission & early innate immune events

• average 4 transmitted/founder viruses
• Doubling time 7.4 hours
• ~21 days to reach 6.5 log

Innate responses activated to restrict viral replication/spread
• Pathogen-associated molecular patterns activate various receptors
  • Cytokines/chemokines, recruit macrophages, DCs, neutrophils, NK cells
  • APCs—> present antigen to T cells
• HCV protease interferes with RIG-I by cleaving MAVS

Gale, Plenary CROI 2015
Factors associated with HCV clearance

- Female gender
- Younger age
- Symptoms at presentation (particularly jaundice)
- Race (non-African-American)
- Genetic:
  - polymorphisms related to IL28B were associated with interferon-induced clearance and spontaneous clearance
  - Interferon-lambdas use similar pathways to interferon-alfa receptors on hepatocytes and immune cells
  - HLA

Genome-wide association study - polymorphisms associated with HCV spontaneous clearance

- Further work has identified **IFNL4**

**IL28B: rs12979860**

**HLA (class II)**

**Chromosome 1-23**
T cell Responses are Crucial in Spontaneous Control of HCV

- HLA association studies
  - Class I: HLA B*57/B*27, Class II: GWAS reveals rs4273729 (DQB1*0301)
- Chimpanzee CD8+ and CD4+ T cell depletion
- Association of breadth and magnitude of T cell response with viral clearance
- IFN-γ HCV specific CD8+ T cell responses are temporally correlated with reductions in viremia after infection
- T cells are associated with protective immunity with subsequent reinfection

HCV control and T cells

Acute HCV infection

Resolution

Persistence

Why do T cells fail?

Are these responses protective?

Lauer, G., J Infect Dis 2013
Viral peptide in the context of HLA on the surface of infected cells signals to the T cells
Ex-vivo IFN-gamma CD8+ T-cell responses are equivalent during early (<3 months) acute HCV infection but then decline over time if not resolved.

**Breadth of CD8 Response**

\[ p=1 \]

**Strength of CD8 Response**

\[ p=0.86 \]

Unpublished data

Viruses can evolve under external pressure

Selection Pressure (medication or immune system)

Mutant strain (R155K etc)

TLV
BOC
HCV evolving within a population

with restricting allele

without restricting allele
with restricting allele

without restricting allele
HLA-I Associated Mutations Across HCV

Dataset:
- 405 GT1a full length consensus sequences
- Relate frequency of mutations with expression of HLA alleles
- 279 unique HLA-I associated mutations (52 HLA)

Specific immunity likely to be genotype (and subtype?) specific

Variability is a barrier, certain genomic regions have more viral fitness cost

HLA-associated polymorphisms also observed for HBV (Desmond et al. J Virol 2012)
For responses that do not escape: persisting antigen leads to impaired effector functions and reduced memory T cell formation “exhaustion”

Wherry EJ, Nature Immunology 2011
PD-1 is upregulated on HIV and HCV-specific CD8 T cells

T cells become exhausted, but can this be reversed with treatment?

Order of co-infection: HCV before HIV

What is the fate of HCV-specific T cell responses after HIV-1 acquisition?

Do they play a role in pathogenesis of accelerated liver disease?

Are they restored due to antiretroviral therapy?

Are they restored after HCV cure?
Intrahepatic infection and immune responses

Laser-capture microdissection studies

Minority of hepatocytes infected (20-45% hepatocytes) - between 1-100 copies/hepatocytes

Infected and surrounding cells have higher levels of IFN-stimulated genes (ISGs)

Kandathil et al. Gastroenterology 2013
Sheahan et al. Cell Host Microbe 2014
Effect of CD4 depletion on HCV-specific CD8 T cells

Kim et al. Blood 2005
CD4 T cell depletion in the gut is massive during HIV infection and not fully restored by antiviral therapy

Brenchley et al, JEM 2004
Microbial translocation may contribute to liver disease progression

HIV induces:

1. Intestinal villous effacement
2. Mucosal CD4 depletion
3. Immune activation and dysregulation

Bacterial translocation

Enhanced susceptibility to permucosal transmission (?)

LPS

Increased fibrosis progression

Adapted from Balagopal et al. Gastroenterology 2008
Mechanisms of accelerated HCV-related fibrosis in HIV

Suppressive antiretroviral therapy combats liver fibrosis

Curative anti-HCV therapy combats liver fibrosis

Kim and Chung Gastroenterology 2009
What immune factors play a role in pathogenesis of accelerated liver disease? - limitation of cross-sectional studies particularly for HIV/HCV co-infection

As liver fibrosis is a dynamic process involving a variety of influences over decades…

Will cross-sectional studies of plasma cytokines, PBMC or liver-infiltrating lymphocytes capture the cumulative effects over time?

Chronic HCV + HIV-1 → CD4 depletion
Immune activation
Immune dysregulation

Antiretrovirals
CD4 repletion

years to decades

your favorite biomarker or cytokine
Examined ALT elevations, viral kinetics, T cell responses and expression profiling after cART initiation

Sherman et al. Sci Transl Med 2014
CD8 T cell responses are primed and detectable in peripheral blood early in HCV.

Frequency declines as one enters chronic phase.
- Escape mutations
- Upregulation of inhibitory receptors - exhausted phenotype

Subsequent HIV co-infection may have additional effects.
- CD4 depletion
- ART: “immune reconstitution”
- DAAs: ? restoration of exhaustion
What is the fate of T cell responses?

Can they provide protective immunity?

Can protective immunity be preserved with earlier antiviral treatment?
Longitudinal course
Intermittent control of HCV

![Graph showing the longitudinal course of HCV, with markers for HCVAb- and HCVAb+, and measurements for RNA (HCV or HIV), CD4*, ALT, HCV RNA, and HIV RNA over time.](image)
Dynamics of T cell responses in relationship with HCV virus titers
CD4+ T-cell responses during acute HCV infection (HIV negative)

Direct ex vivo enumeration and immunophenotyping of HCV-specific CD4 T cells using class II tetramers
HCV-specific CD4 T cells are primed during acute HCV infection irrespective of outcomes or HIV status but rapidly disappear in progressing HCV infection.

<table>
<thead>
<tr>
<th>HIV-</th>
<th>HIV+</th>
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<tbody>
<tr>
<td><strong>Progressor</strong></td>
<td><strong>Resolver</strong></td>
</tr>
<tr>
<td>N=24</td>
<td>N=16</td>
</tr>
<tr>
<td>67%</td>
<td>100%</td>
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CD4: 898± 203 cells/mm3

CD4: 619 cells/mm3
T cell responses during aHCV in those with HIV

• Studied 19 HIV+ patients with acute GT1 HCV infection: only 1 spontaneously cleared (another treated as he was clearing)

• **CD8 responses were readily detected** early, regardless of CD4 count
  • Escape mutations in T cell epitopes frequent

• CD4 responses were found in 10/19 subjects
  • Viral fluctuations >1 log: detectable CD4 10/10, no CD4 1/9
  • T cells were preserved in clearers (spontaneous or by IFN)
    • In one case re-expanded when challenged with autologous virus

• No defect in priming of responses

**HIV+ persons are candidates for T cell-based vaccine approaches**
04L - A reinfection with another 1b virus

Viral load—ALT

ALT

HCV VL IU/ml

04L Reinfaction

Time (Weeks)

Tx

Reinfection
04L - A reinfection with another 1b virus

Massive memory response of CD4 & CD8 T cells against a reinfecting virus
Summary and Conclusions

- HCV-specific CD4 and CD8 T cells in HCV/HIV-1 coinfection are likely rendered ineffective
  - Escape mutations (class I)
  - Activation and exhaustion
  - CD4 depletion
  - ? deleterious role in immune reconstitution

- CD4 and CD8 T cells are frequently generated in HIV-1 positive persons acquiring HCV
  - Rationale for inducing protective responses via vaccine
  - Possible rationale for early treatment to preserve T cell responses
  - DAAs: Innate and adaptive responses in A5327
Future key questions

• Understanding pathogenesis of accelerated liver disease
• Reversing T cell exhaustion
  • Curing virus but potential for increased immunopathology
  • *Does treatment restore innate or adaptive responses?*
  • *ACTG 5335s substudy of 5329*
• *What are links between the innate and adaptive immune responses?*
• Protective immunity
  • Understanding acute HCV infection
    • *What underlies the dichotomous outcomes of HCV?*
    • *What are effects of illicit drugs on immunity?*
    • *Vaccine?*
Patients!

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