HCV and ‘immune exhaustion’
Lessons from curing hepatitis C

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Disclosures

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  • AbbVie
  • Gilead
  • Merck
  • BMS
  • ViiV

• Academic:
  • Affiliation with Dalhousie University and Nova Scotia Health Authority
  • HCV virology / immunology lover

• Advocacy:
  • HCV and HIV community groups
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Lab crew
Objectives

Review the idea of immune exhaustion and why it is important

Describe changes in immune exhaustion after DAA-associated viral cure

Future directions and why immune exhaustion is still important
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HCV and immunity

HCV exposure

20%
Self limiting disease
Viral clearance

HCV specific adaptive immunity
HCV specific innate immunity

Young and active' immune system

80%
Chronic HCV infection
Chronic immune stimulation

HCV specific adaptive immunity
HCV specific innate immunity

Immune exhaustion / aging

???
Direct acting
anti-HCV
treatment
'cure'
**Immune assessment**

Baseline  
Day 7  
End of treatment *  

**RIBAVIRIN CONTAINING DAA THERAPY**

Immune phenotyping  
Peripheral blood  
Liver  

HCV specific immunity  
Peripheral blood  

T cell  
B cell  
NK cell  

ELISPET enumeration  
Functionality  
IL-2  
IFN-γ  
TNF-α  

* 30/30 viral suppression at end of treatment

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**Methods**

35 chronic HCV-infected patients  
Peripheral blood mononuclear cells  
Collected from patients at baseline, day 7, and end of treatment (EOT)

10 HCV negative individuals

Cryopreserved  
Thawed  
Immediate

**T cell panel**

<table>
<thead>
<tr>
<th>PD-1</th>
<th>Tim-3</th>
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<tr>
<td>CD57</td>
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**NK panel**

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<tr>
<td>CD16</td>
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<td>CD56</td>
<td>p30</td>
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<tr>
<td>CD27</td>
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<tr>
<td>Perforin</td>
<td>G2A</td>
</tr>
<tr>
<td>Granzyme B</td>
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</table>

**B cell panel**

Immature transitional  
Naive  
Resting memory  
Activated memory  
Tissue like memory  
Plasmablast  
(CD10, CD19, CD20, CD21, CD27)
Peripheral blood
Adaptive immunity

T cell phenotype

T cell exhaustion markers decrease with HCV clearance
Peripheral blood
Adaptive immunity

B cell phenotype

B cell abnormalities even with viral suppression
Persistently altered B cell subsets are important

- Activated Memory (AM) & Plasmablasts (PB)
  - Large & activated
  - Prone to extrinsic apoptosis (AM)
- Tissue-Like Memory (TLM)
  - Increased levels of inhibitory receptors
- Resting Memory (RM)
  - Critical for maintaining humoral immunity

Peripheral blood
Innate immunity

NK cell phenotype
Decreased inhibitory KIR expression on NK cells

Fold change (Baseline to EOT)

* *

KIR 2DL3 KIR 3DL1

Peripheral blood
HCV specific immune responses

Adaptive immunity
HCV specific responses
Methods

30 patients
Peripheral blood mononuclear cells
Collected from patients at baseline and end of treatment (EOT)

Cryopreserved

Thawed

6 hour rest

IFN-γ ELISpot assay
250,000-400,000 cells/well; duplicates

CMV pp65 2 ug/mL
PHA 5 ug/mL
HCV peptide pools: 2ug/peptide/well
11-21 pools

Augmented
HCV-specific immunity at EOT
HCV responsive polyfunctional T cells increase at the end of therapy

Pre-treatment

EOT

Neg
IFN-γ
TNF-α
IFN-γ TNF-α

HCV responsive polyfunctional T cells increase at the end of therapy
HCV responsive T cells rarely express exhaustion markers

HCV and immunity

HCV exposure

HCV specific responses
Quality and quantity

T cell exhaustion markers
Slow change in B cells
NK cell KIR expression

Viral inhibition
without interferon
associated with improved immune function
Sustained augmentation after drug therapy

% IFN-γ+ spots

Weeks

DAA therapy

SVR

Relapser

Innate T cell B cell T cell function NK cell function

Relapsers

FB

TD

DP

JS

SVR

MV

FP

VJ

LW

Innate T cell B cell T cell function NK cell function
Immunity after longer course ribavirin containing DAA therapy

- Less exhausted immune phenotype in T and NK cell compartment
- Functionally improved T cells (somewhat sustained)
- Cumulative immune function associates with clearance

Ongoing
- Shorter course multi-targeted DAA therapy and longitudinal post-cure changes
- Vaccine associated responses
- B cell characterization
- Comparison with CMV, HIV and chronologic aging

Does decreased immune senescence and in vitro immunity translate into less HCV reinfection?
Sleepy Hollow

Study design

If:
Five (5) participants have been enrolled and on treatment for at least 6 weeks;
OR there is ANY participant issue with study procedure;
OR The 4th month of enrollment occurs without (a) or (b);
Then:
There will be a 1 month enrollment pause for advisory board review of process and participant issues.
BASIC SCIENCE QUESTIONS

Does improved immunity persist and translate into less reinfection in high risk people?

And could this be a good vaccination time?

Not the same exhaustion in all chronic HCV infection:
Younger, shorter duration of infection, history of recent IDU
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HCV IMMUNITY
DOES IT STILL MATTER?

- Immune function
- Vaccine response
  - Public health
  - HCV specific
- Clinical connections
  - Chronic fatigue and well-being
  - Understanding immune exhaustion in cancer, inflammation and aging

A rapid reversible model of aging??