Altered M1 macrophages may contribute to CD8+ T-cell dysfunction in chronic HCV infection with advanced liver fibrosis

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IMMUNE IMPAIRMENT IN CHRONIC HCV INFECTION

Innate immunity dysfunction
- Monocytes, macrophages, dendritic cells
- Natural killer cells, neutrophils
- Myeloid-derived suppressor cells
- Kupffer cells, hepatic stellate cells

Adaptive immunity dysfunction
- B-cells
- CD8+ T-cells
- CD4+ T-cells
- Tregs

Rehermann, B., and Nascimbeni, M. 2005

GENERALIZED CD8+ T-CELL DYSFUNCTION IN HCV INFECTION

CD8+ T-cells are dysfunctional in HCV+ infection with advanced liver fibrosis
- Cells exhibit overactive, yet inefficient functions compared to HCV+ infection with minimal liver fibrosis or uninfected controls. This dysfunction is not reversed after DAA treatment.
MONOCYTES IN CHRONIC HCV INFECTION

↓HLA-DR
↓TNF-α in response to lipopolysaccharide stimulation
↓ chemoattactant receptors (CCR2, CCR4)  \( \text{Gadd, } V.L. \text{ et al., 2016. PLOS ONE} \)
↑galectin-9  \( \text{Harwood N.M. et al., 2016. J Leuko Biol.} \)

PROGRESSIVE LIVER FIBROSIS IN HCV INFECTION

The liver filters 1/3 of the body’s blood every minute!

Effect of inflammatory, fibrotic environment on circulating immune cells?
Research Objectives

1. Assess the phenotypic differences between macrophage subsets in health and chronic HCV infection.

2. Examine the role of macrophage subsets in altering CD8⁺T-cell function in health and HCV infection.

HYPOTHESIS

M1 macrophage subset increases CD8⁺T-cell function.

Altered M1 cells in chronic HCV infection with advanced fibrosis contribute to generalized CD8⁺T-cell dysfunction.

CHRONIC HCV⁺ PATIENT CHARACTERISTICS

- HCV RNA⁺ > 6 months, HIV⁻, HBV⁻
- Untreated for HCV infection
- Fibrosis scoring (transient elastography)

HCV control, F0-1, < 7.0 kPa, F3-4, > 14.0 kPa
BLOOD MONOCYTE- DERIVED MACROPHAGES PROTOCOL

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Blood Monocyte

M-CSF

48 hours

IFN-γ

IL-4

IL-1β + LPS

IL-10

Blood Monocyte

M1

M2α

M2b

M2c

HIGHER PROPORTION OF CO-STIMULATORY MOLECULE CD86+ ON M0 AND M1 CELLS IN ADVANCED FIBROSIS

M0-CD86, p=0.04

M1-CD86, p=0.01

M2α-CD86

M2β-CD86

M2c-CD86

*p=0.04

*p=0.01
M1 CELLS EXPRESS LESS PRO-INFLAMMATORY TNF-ALPHA AND IL-6 IN ADVANCED FIBROSIS

M2 CELLS EXPRESS MORE TH1-ENHANCING IFN-GAMMA AND IL-12 IN ADVANCED FIBROSIS
ALL MDM SUBSETS PRODUCE MORE IMMUNOREGULATORY IL-10 IN ADVANCED FIBROSIS

EXAMINE THE ROLE OF MACROPHAGE SUBSETS IN ALTERING CD8⁺ T-CELL FUNCTION IN HEALTH AND HCV INFECTION.

Macrophage:T-cell co-culture

CD8⁺ T-cell controls  M0 controls  M0:T-cell co-culture  M0:T-cell co-culture
M1 INCREASES %IFN+ CD8+ T-CELLS IN HEALTH

- Example using this template layout with an illustration or photo
- Next chart provides a variation of a template layout with a photo/illustration
- Ullamcorper suscipit lobortis nisl ut aliquip ex ea commodo consequat

M1 DOES NOT CHANGE LYTIC MOLECULE PRODUCTION BUT INCREASES DEGRANULATION OF CD8+ T-CELLS
M1-INDUCED IFNα CD8+ T-CELLS IS CONTACT DEPENDENT

OMG – that’s amazing!!!

M0 REDUCE %IFN-γ CD8+ T-CELLS IN HCV INFECTION WITH MINIMAL FIBROSIS
MDM subset differentiation is impaired in advanced fibrosis

M0, M2c produce IFN-y in HCV infection, unlike in health

M1 macrophages reduce %IFN-y+ T-cells in a contact-dependent manner in HCV infection: the reverse occurs in health

**TRANSLATE FINDINGS TO THE LIVER?**

Interaction of circulating T-cells with liver-resident macrophages.

- Kupffer cells (liver resident macrophages)?
  - Proximity to circulating cells, as they line the portal tract
  - Ref for KC1, KC2 similar to M1, M2 subsets
  - Challenge: no human KC line
  - Hepatic stellate cells?
LIVER MACROPHAGES

- Kupffer cell/macrophage activation indicated by increased CD163 and CD33 expression

- High expression of CD68 HCV-infected liver tissue; correlated with increased IFN-γ, IL-18.


THANK YOU!