HCV-HIV Coinfection: Pathogenesis of Accelerated Liver Disease Progression

Raymond Chung, M.D.
Director of Hepatology and Liver Center
Vice Chief, Gastroenterology
Kevin and Polly Maroni Research Scholar
Massachusetts General Hospital
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  – Gilead
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Liver disease is the second leading specific cause of death among HIV(+) persons

*D:A:D study*

\[ n=33,308, 180,000 \text{ p/y} \]

HIV’s adverse effects on HCV

- Higher rates of persistence
- Enhanced HCV replication
- Accelerated fibrogenesis
- Increased frequency of liver decompensation and death
- Until recently, diminished response rates to antiviral therapy for HCV
Impact of HIV on HCV-related Liver Disease Progression

Systematic review of natural hx studies


![Graph showing RR of cirrhosis vs HCV]

RR of cirrhosis vs HCV
- HCV/HIV 2.1
- No HAART 2.5
- HAART 1.7

Years

Cirrhosis (%)

HCV (n = 33,121)

HIV/HCV (n = 3567)
Hepatic decompensation is accelerated in HCV-HIV coinfection

(VA: 4280 HCV-HIV, 6079 HCV)

Hepatitis C disease pathogenesis

CD8+ CD4+

Cell killing

Cytokines (TNF-α, TGF-β, PDGF)

Death

Hepatocytes

Kupffer cell

Hepatic stellate cells

TGF-β

Activation

FIBROSIS
Pathways to fibrogenesis

Cytokines: TGFβ, PDGF, TNFα
HIV pathogenesis and interaction with HCV-related liver disease

Chen, Feeney, Chung. Nat Rev Gastro Hep 2014
Determinants of Pathogenesis in HCV-HIV Coinfection

- Effects on HCV-specific T cell responses
- T cell independent effects of HIV on HCV replication
- Cooperative effects on
  - TGF-$\beta$1 secretion
  - Hepatic stellate cell activation and fibrogenesis
  - Hepatic macrophage polarization
  - Hepatocyte apoptosis
- Microbial translocation
HIV Effects on HCV T cell responses
HCV T cell responses in coinfection are blunted compared with HCV monoinfection

CD4+ Proliferative Responses to HCV are dependent on nadir CD4 (n=47)

HIV effects on HCV replication
HIV gp120 directly enhances HCV replication in a full-length replicon (OR6)

HCV directly induces profibrogenic cytokines
HCV induces ROS formation and TGFβ in hepatocytes

Lin et al. Gastroenterology. 2010;138:2509-18
HCV induction of TGF-β1 is ROS-dependent and partially dependent on p38 MAPK, ERK and JNK

Lin et al. Gastroenterology. 2010;138:2509-18
Model of events underlying HCV induction of TGF-β1 production in hepatocytes

Lin et al. Gastroenterology. 2010;138:2509-18
HCV and HIV exert cooperative effects on TGF-\(\beta\)1 secretion
HIV or gp120 increase TGF-β secretion in JFH1-infected or uninfected Huh7.5.1 cells

HIV or gp120 increase TGFβ secretion in JFH1-infected or uninfected Huh7.5.1 cells

This enhancement of TGFβ secretion is also ROS-dependent

HIV and HCV cooperative effects on hepatic fibrogenesis
HIV-1 and HCV cooperatively increase type I collagen secretion in hepatic stellate cells

Lin et al., J Biol Chem. 2011;286(4):2665-74
HIV-1 increases TIMP-1 expression and secretion in HSCs

ROS inhibition blocks HIV-1 and HCV-induced TIMP-1 and collagen mRNA expression in HSCs

Model of HIV/HCV regulation of hepatic fibrogenesis in HSCs and hepatocytes

- HIV
- HCV

- HSC
- Hepatocyte
- ROS

- NFκB
- TGFβ1
- CoL1A1
- TIMP1

Nucleus
Cooperative effects of HCV and HIV on the hepatic macrophage population
The contribution of the macrophage to HCV-HIV liver disease

- Macrophages important reservoirs for HIV and contribute to chronic liver disease (KCs)
- Activated tissue macrophages polarize into
  - pro-inflammatory (M1): CD86, CD80
  - pro-repair/fibrotic (M2): CD163, Arg1, CD206
- M2 polarized macrophages in turn activate HSCs
- Peripheral levels of soluble CD163 associated with
  - liver fibrosis in HCV, HBV, and NASH
  - HIV infection

Kazankov K, Hepatology. 2014 60:521-30
Kazankov K, J Gastroenterol Hepatol 2015
Feeney E et al, AASLD Nov 2014
Chew K et al, OFID 2014 Dec 3
Cooperative effects of HCV and HIV on hepatocyte apoptosis
Extrinsic Pathway

Death Ligand

Death Receptor

FADD

Caspase 8

Caspase 8

↓

Caspase 8 Activation

↓

Caspase 3, 6, 7 Activation

↓

Mitochondria

Cytochrome c

Active Caspase 9

Cell death

Intrinsic Pathway

↓

tBid

Phagocytosis by HSCs \(\rightarrow\) activation
HCV and HIV induce caspase 3/7 activity in Huh 7.5.1 cells

- $p = 0.01$
- $p = 0.004$
- $p = 0.004$
- $p = 0.002$

Jang JY et al, J Hepatol 2011; 54:612-20
HCV and HIV-mediated hepatocyte apoptosis is blocked by caspase inhibitors

Extrinsic Pathway

↑ TRAIL (in HIV)

↑ DR4, DR5

FADD

Caspase 8

↓

Active Caspase 9

Caspase 3, 6, 7

Activation

↑ DR4, DR5

Intrinsic Pathway

Mitochondria

Cytochrome c

Active Caspase 9

Phagocytosis by HSCs → activation

Extrinsic Pathway

Caspase 8 Activation → tBid

↑ TRAIL (in HIV)

Cell death

Phagocytosis by HSCs → activation

Intrinsic Pathway

Mitochondria

Cytochrome c

Active Caspase 9
Microbial Translocation and Pathogenesis

• Evidence for MT with HIV CD4 depletion enteropathy
• Translocated LPS
  – Triggers TNF-α secretion by KCs
  – TLR4 ligand → HSCs → enhanced TGF-β signaling
• Stimulates fibrogenesis
  – Triggers chemokine secretion
  – Enhances HSC senstivity to TGF-β signaling
• Enteropathy is not fully reversed by ART
• ?role for clearance/alteration of microflora
  – probiosis
  – antibiosis

Summary

• HIV cooperatively interacts with HCV to accelerate liver disease through several mechanisms, both direct and indirect
  – increased HCV replication, oxidative stress, TGF-β, M2 polarization, hepatocyte apoptosis, microbial translocation
• Multiple cell types affected by both HCV, HIV cooperatively interact to accelerate fibrosis
• Effective HIV suppression still incompletely removes the profibrogenic environment
• These findings provide a framework for understanding HIV and its contribution to acceleration of other liver diseases (HBV, NASH)
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