HCV-HIV Coinfection: Pathogenesis of Accelerated Liver Disease Progression

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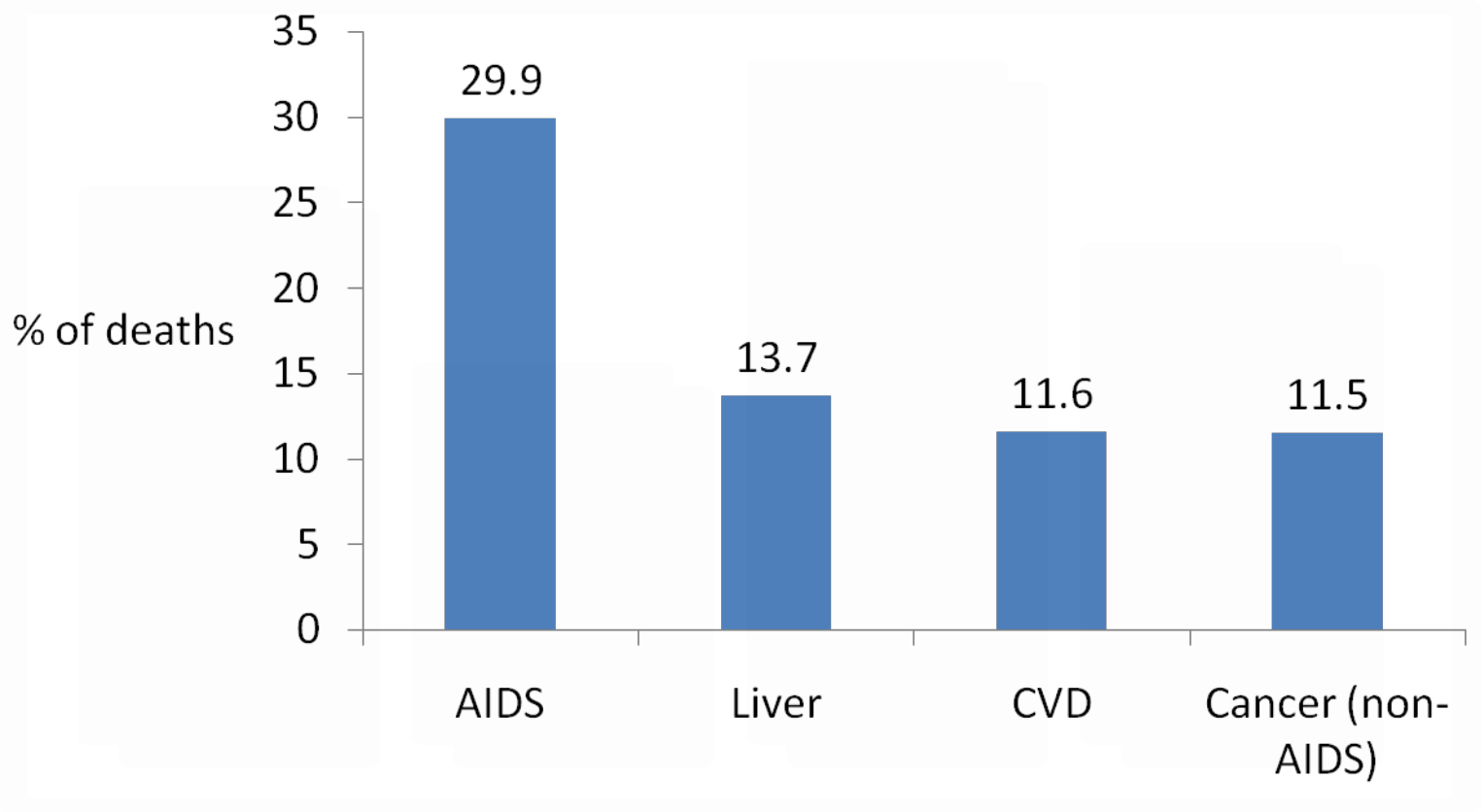
  - Gilead
  - Abbvie
  - Merck
  - BMS
  - Mass Biologics

Liver disease is the second leading specific cause of death among HIV(+) persons

D:A:D study

n=33,308, 180,000 p/y



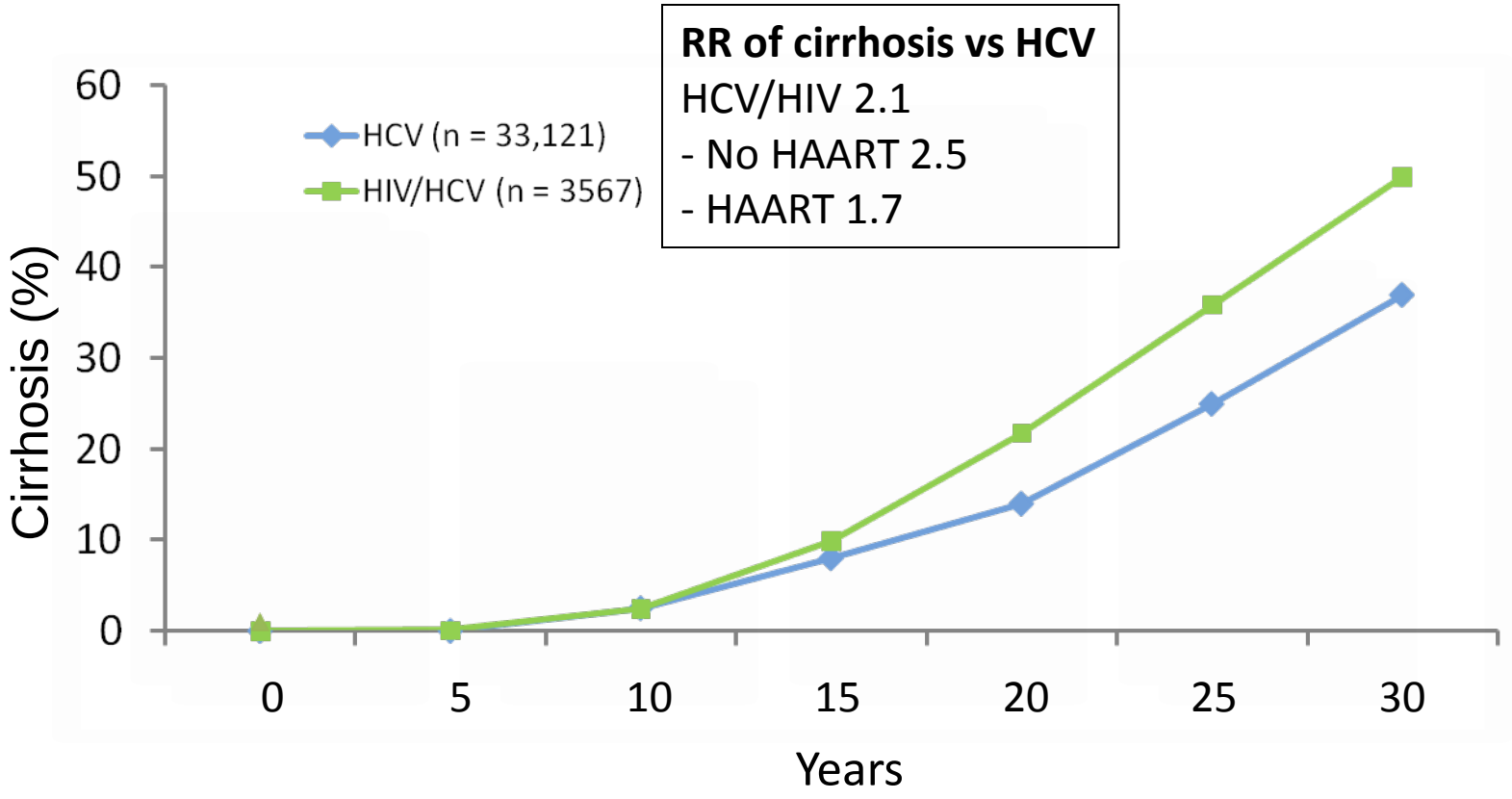
Smith C, et al. *AIDS*. 2010;24:1537-48

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

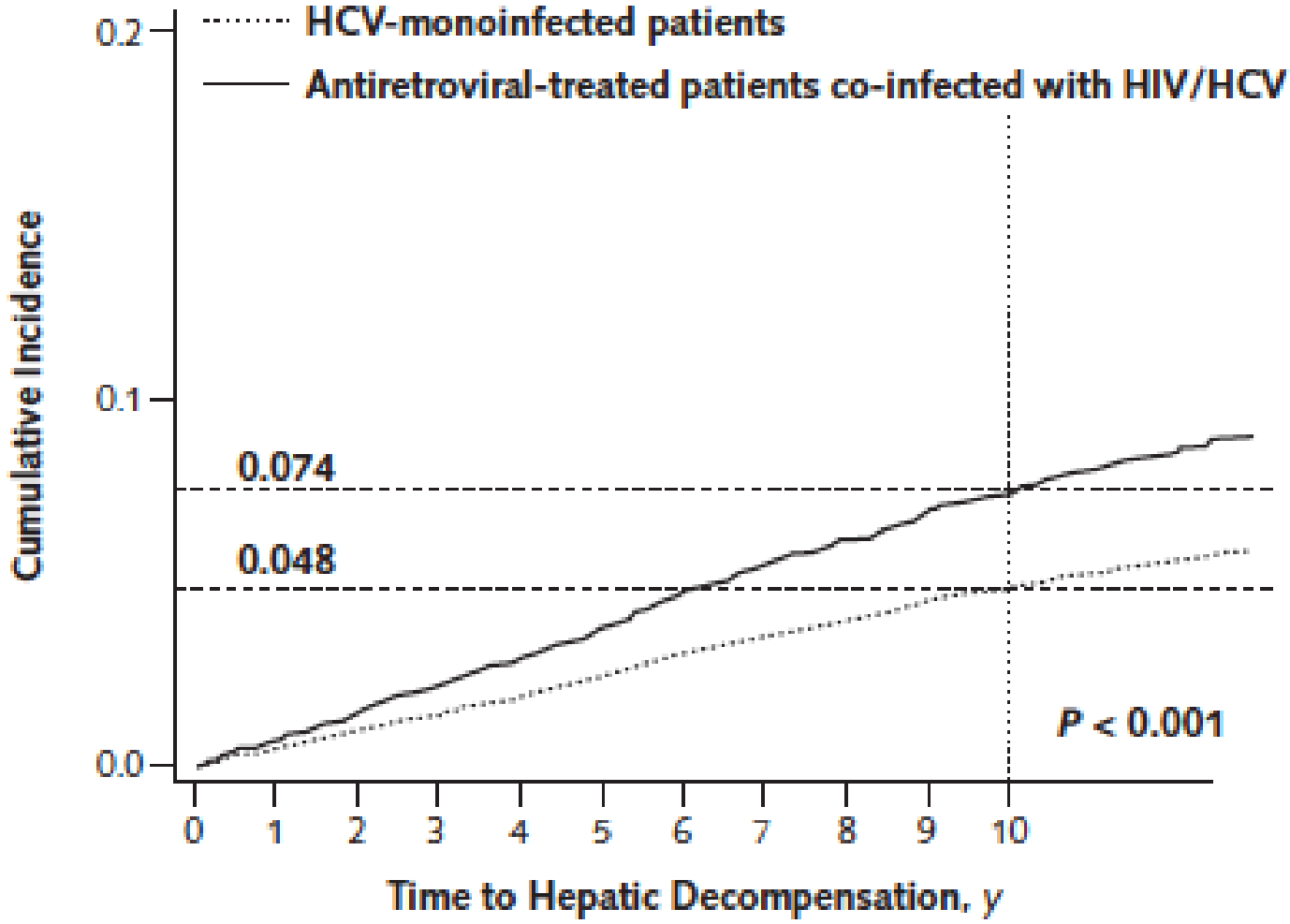
Systematic review of natural hx studies



Thein H-H et al. AIDS. 2008;22:1979-1991.
Thein H-H et al. Hepatology. 2008;48:418-431.

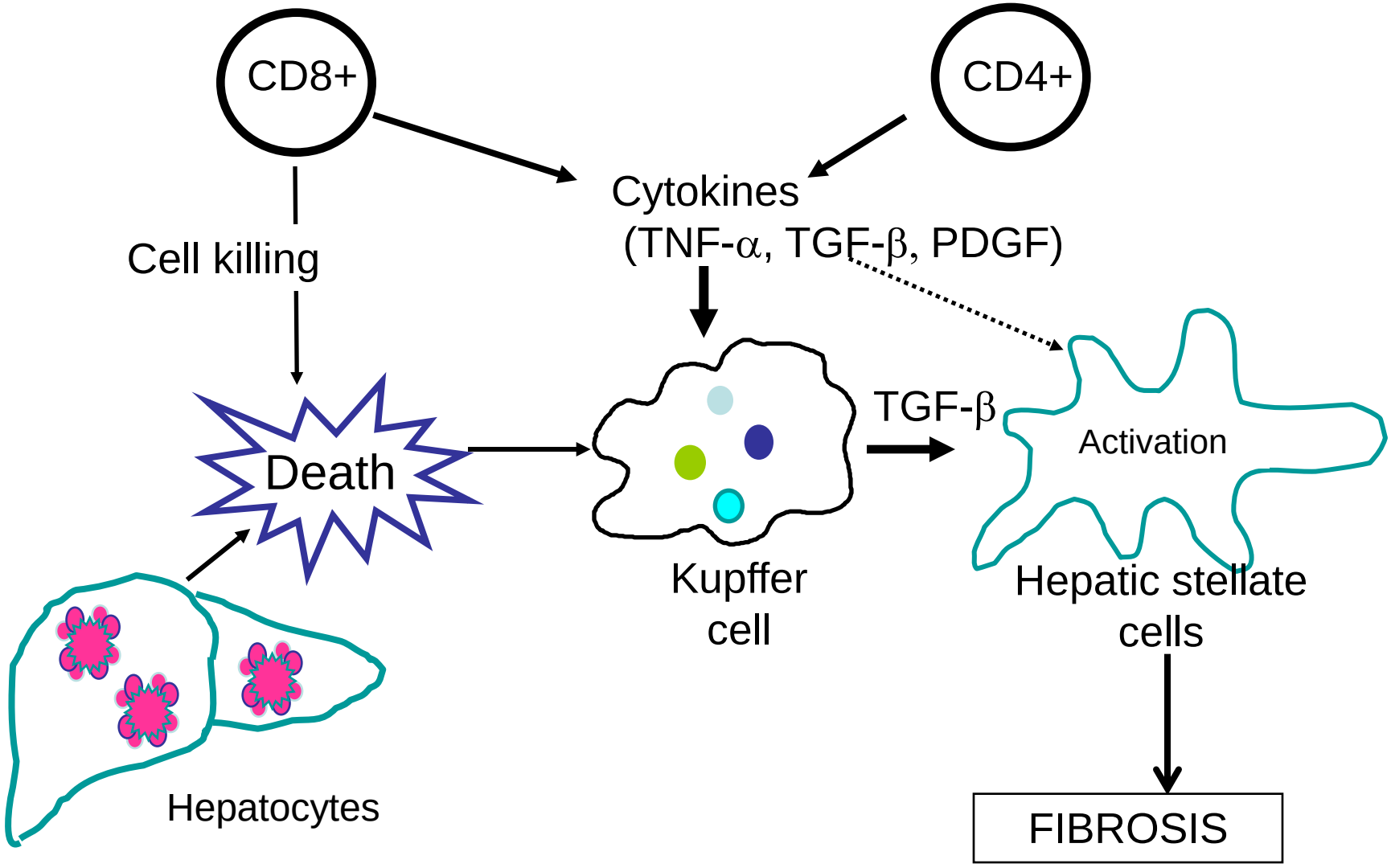
Hepatic decompensation is accelerated in HCV-HIV coinfection

(*VA: 4280 HCV-HIV, 6079 HCV*)

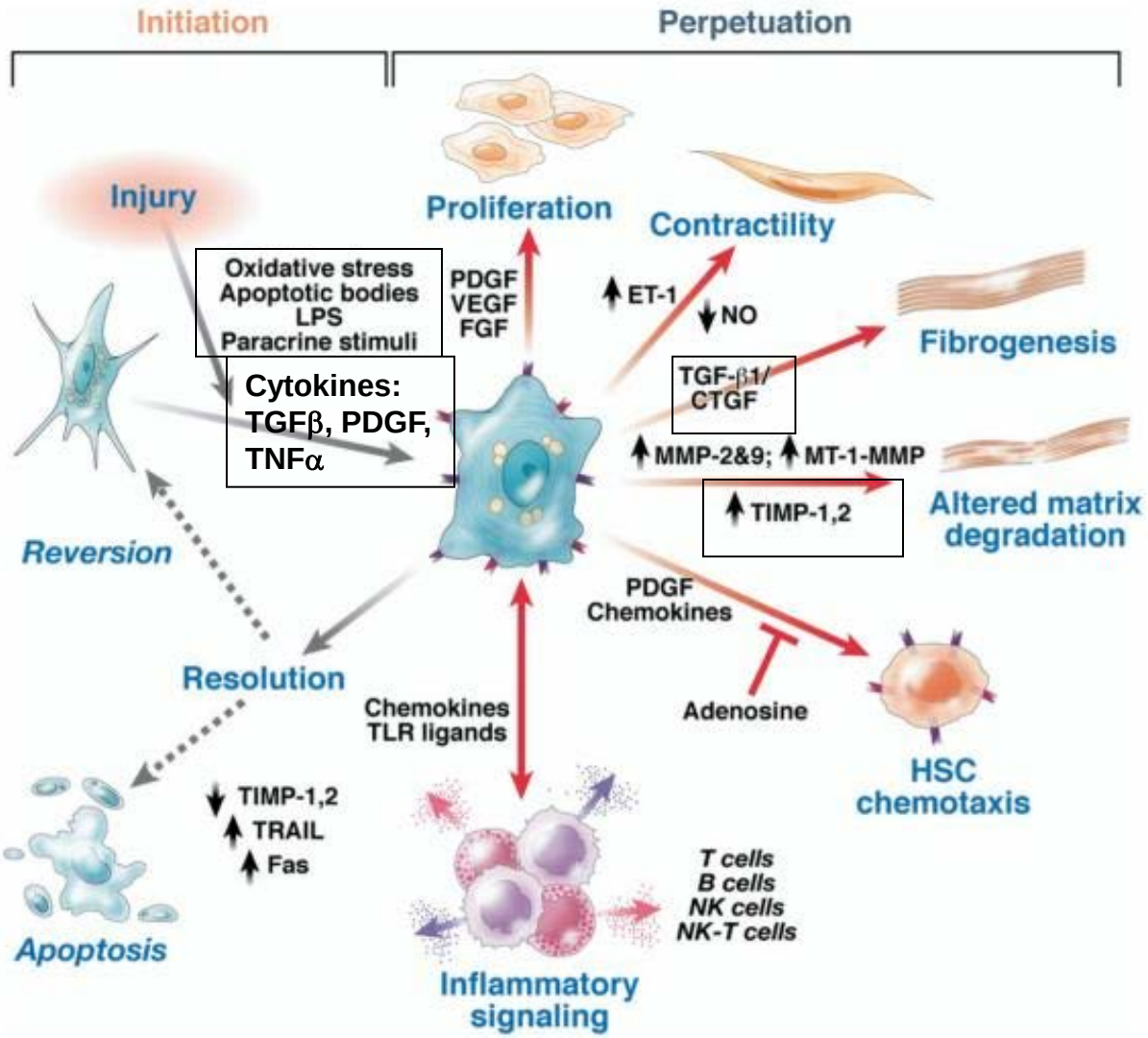


Lo Re V et al. *Annals Int Med* 2014; 160:369

Hepatitis C disease pathogenesis

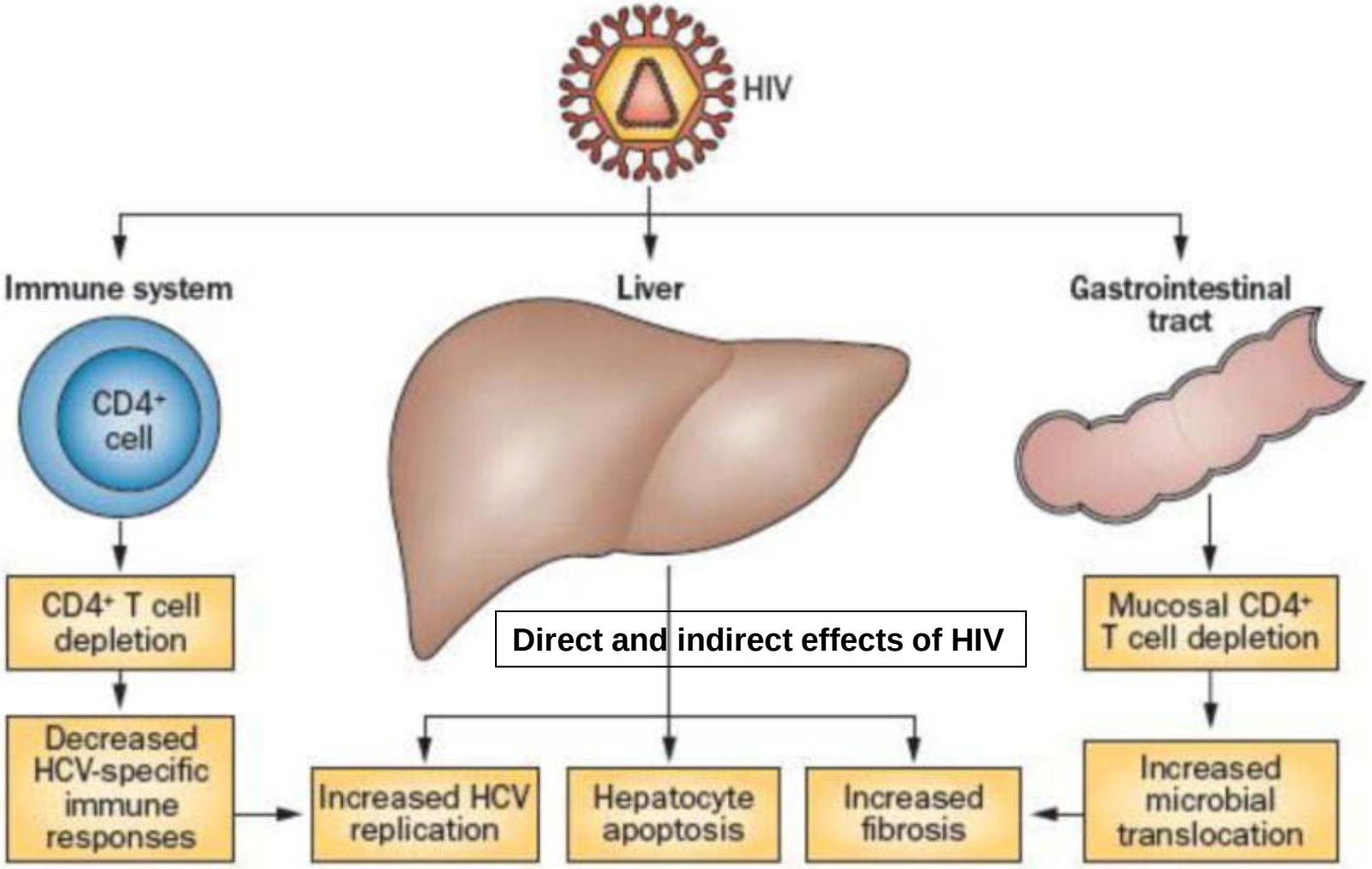


Pathways to fibrogenesis



Friedman SL. *Gastroenterology* 2008;134:1655

HIV pathogenesis and interaction with HCV-related liver disease



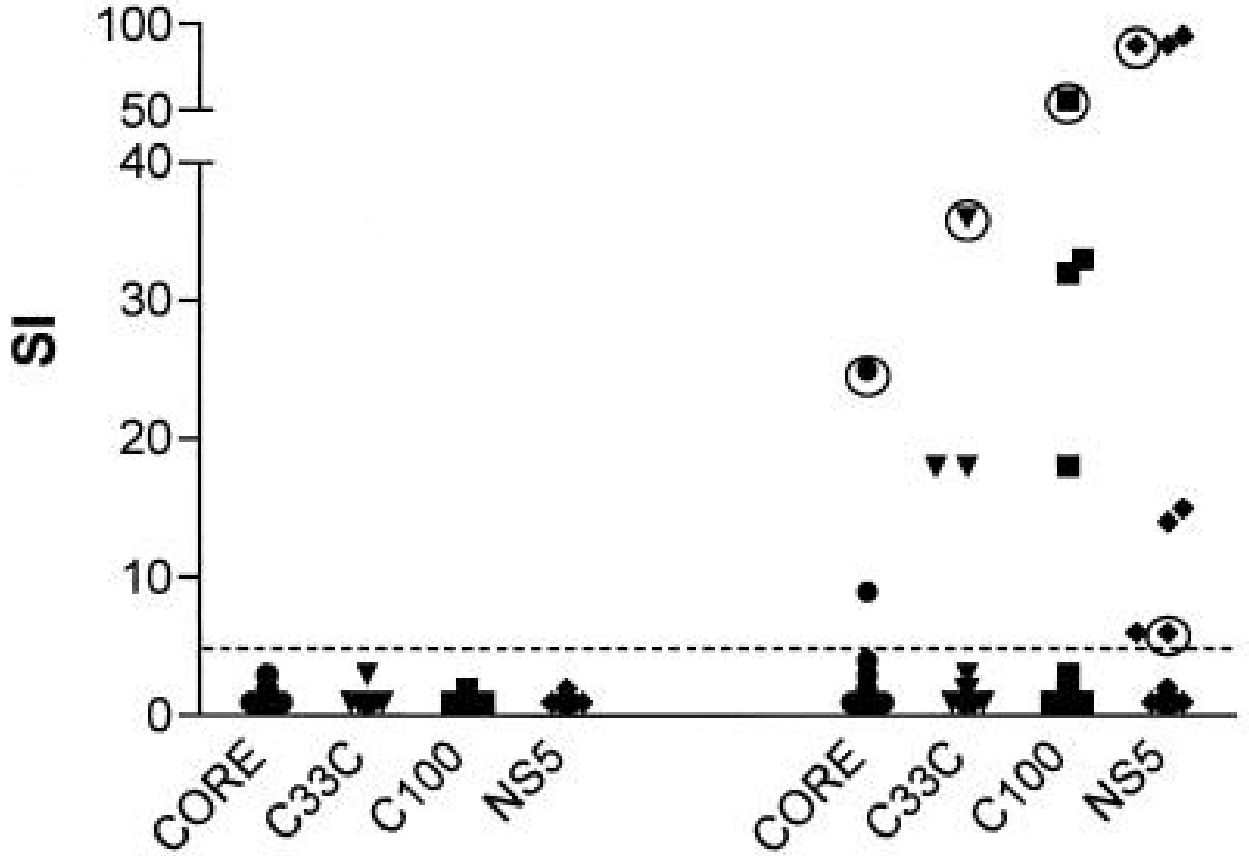
Chen, Feeney, Chung. Nat Rev Gastro Hep 2014

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-β1 secretion
  - Hepatic stellate cell activation and fibrogenesis
  - Hepatic macrophage polarization
  - Hepatocyte apoptosis
- Microbial translocation

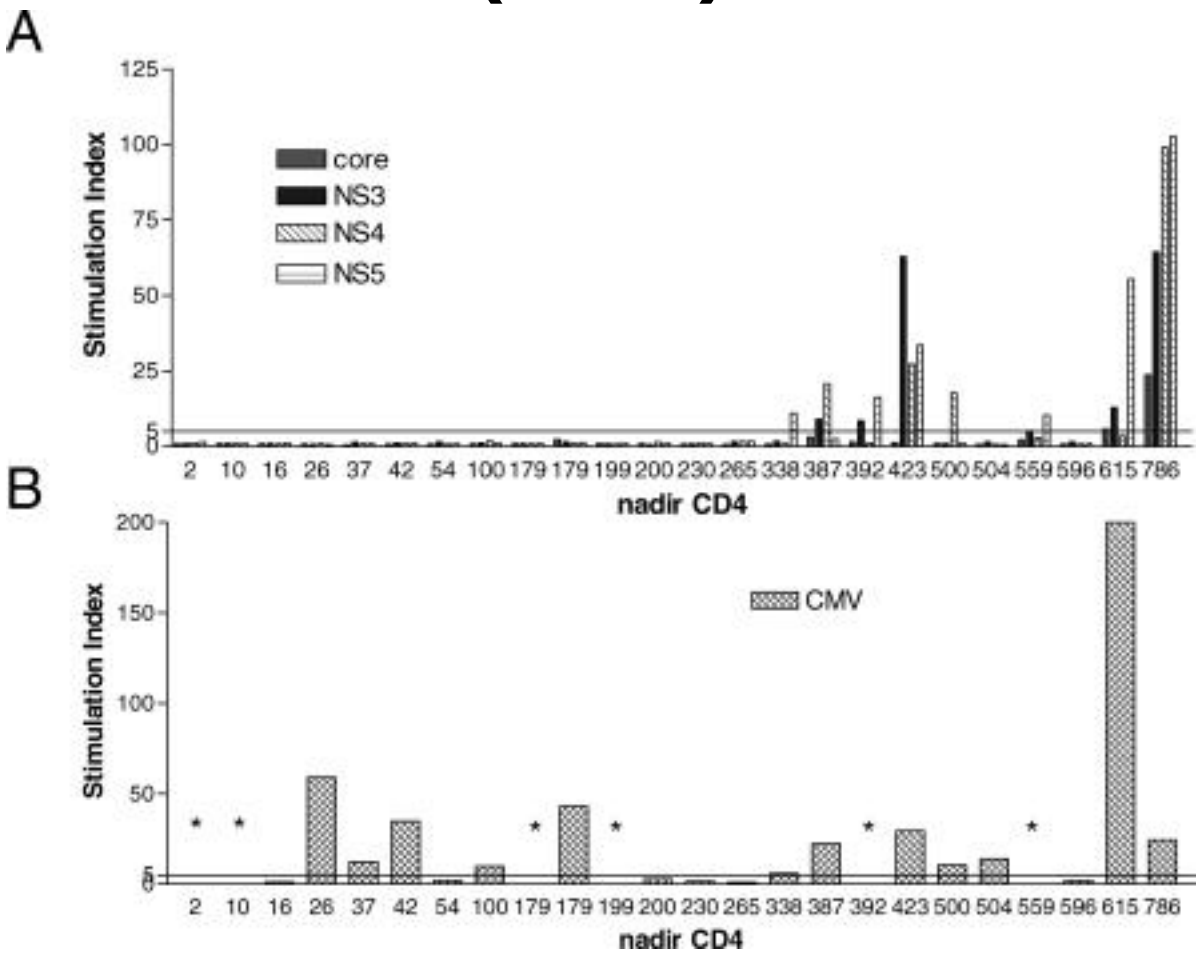
HIV Effects on HCV T cell responses

HCV T cell responses in coinfection are blunted compared with HCV monoinfection



Lauer *et al. J Virol* 2002

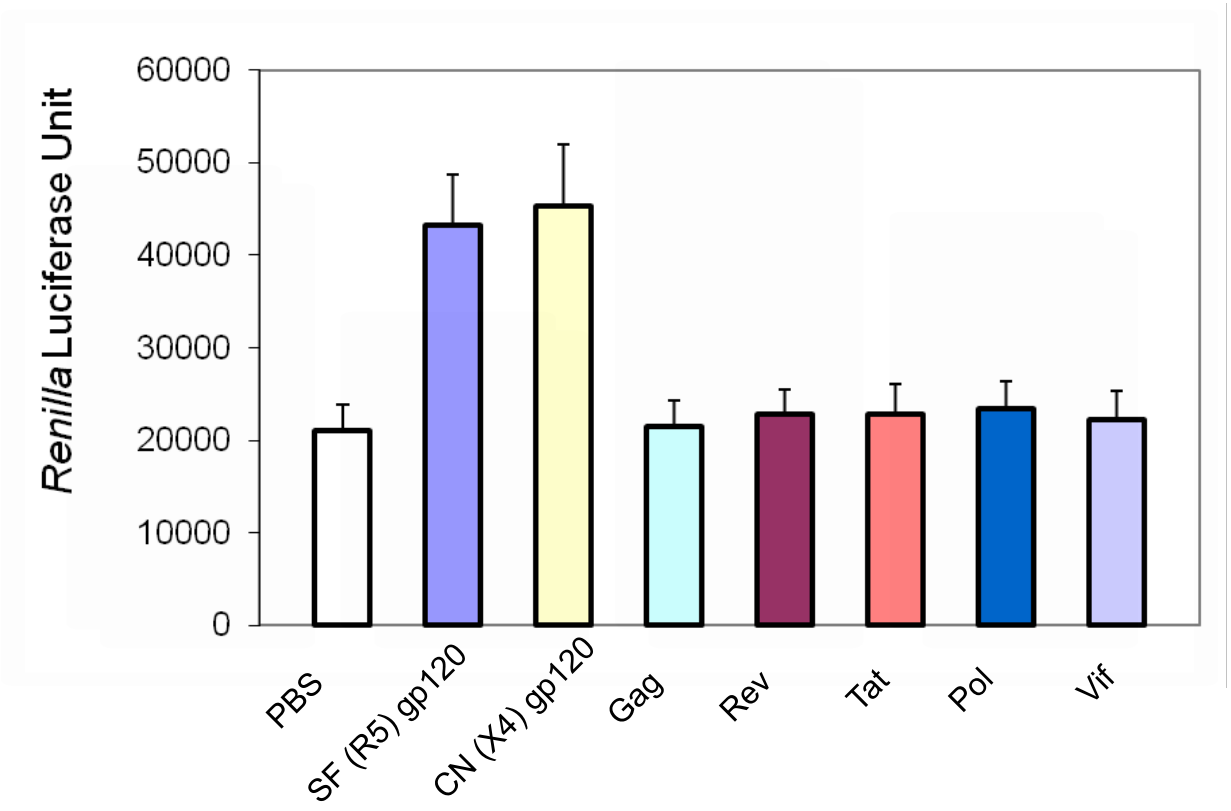
CD4+ Proliferative Responses to HCV are dependent on nadir CD4 (n=47)



Kim *et al. PLoS Med*. 2006

HIV effects on HCV replication

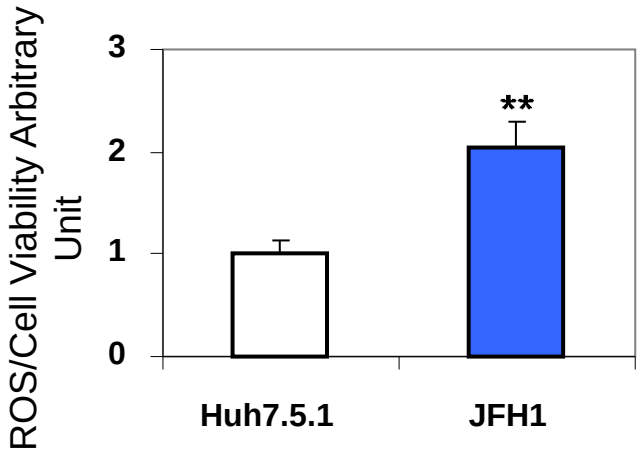
HIV gp120 directly enhances HCV replication in a full-length replicon (OR6)

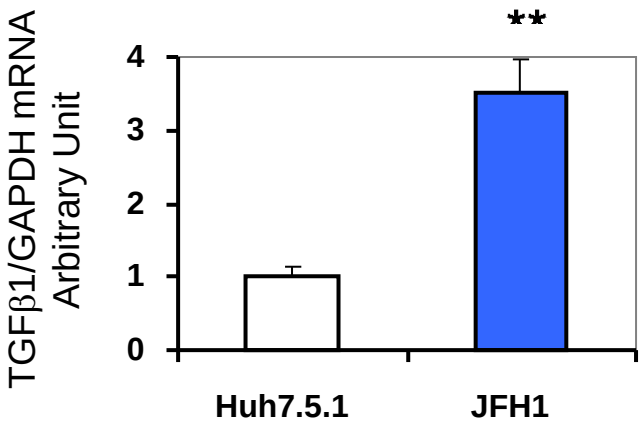


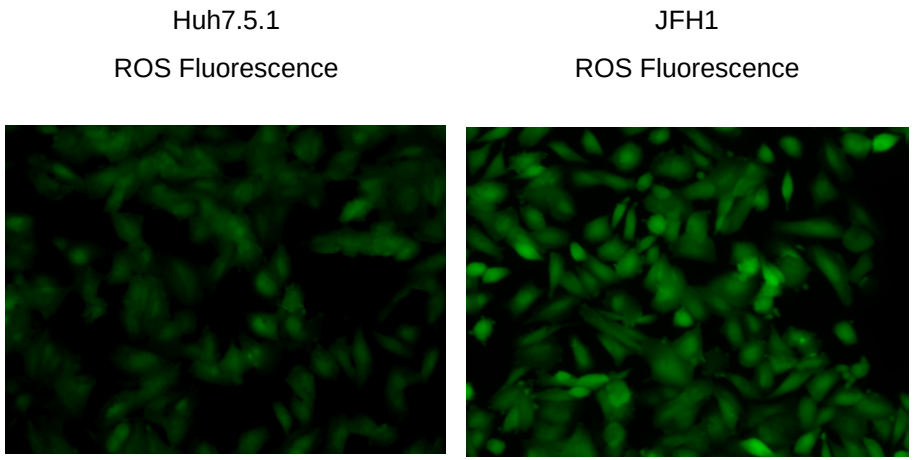
Lin *et al. Gastroenterology*. 2008 Mar;134:803

HCV directly induces profibrogenic cytokines

HCV induces ROS formation and TGFβ in hepatocytes

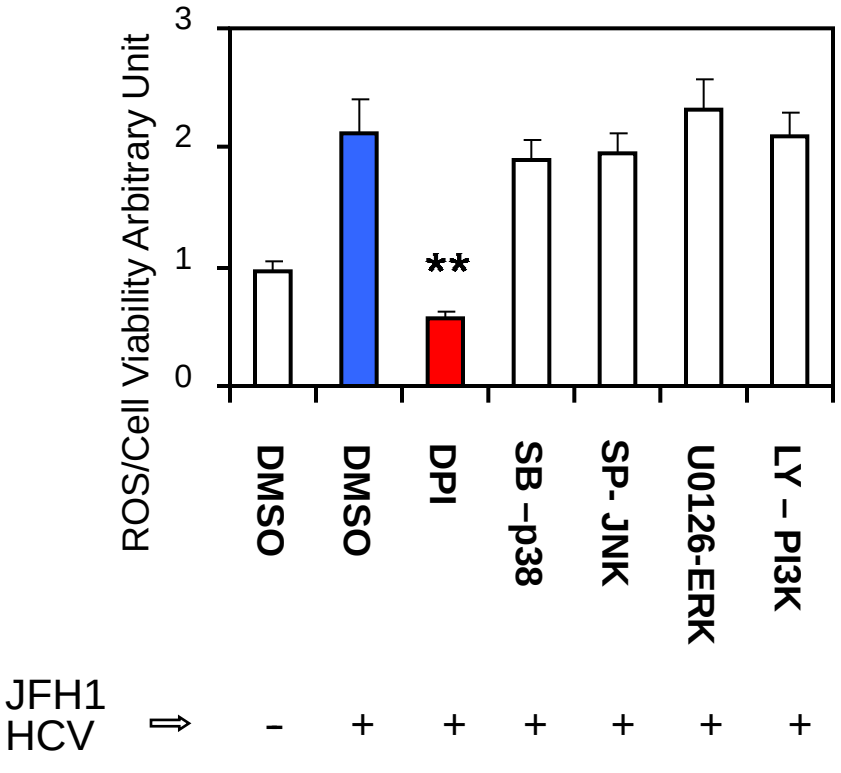


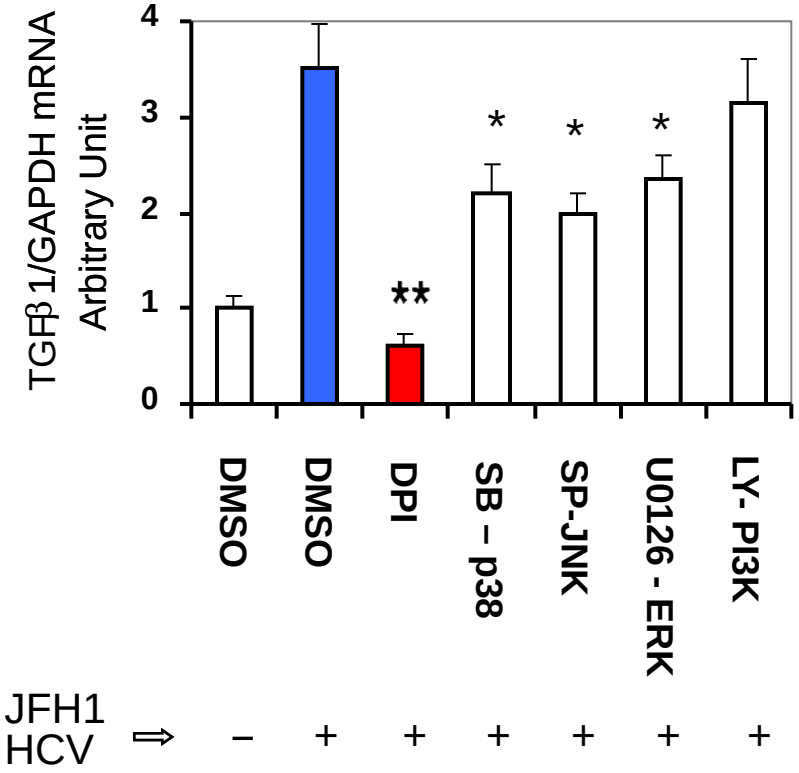




Lin *et al. Gastroenterology*. 2010;138:2509-18

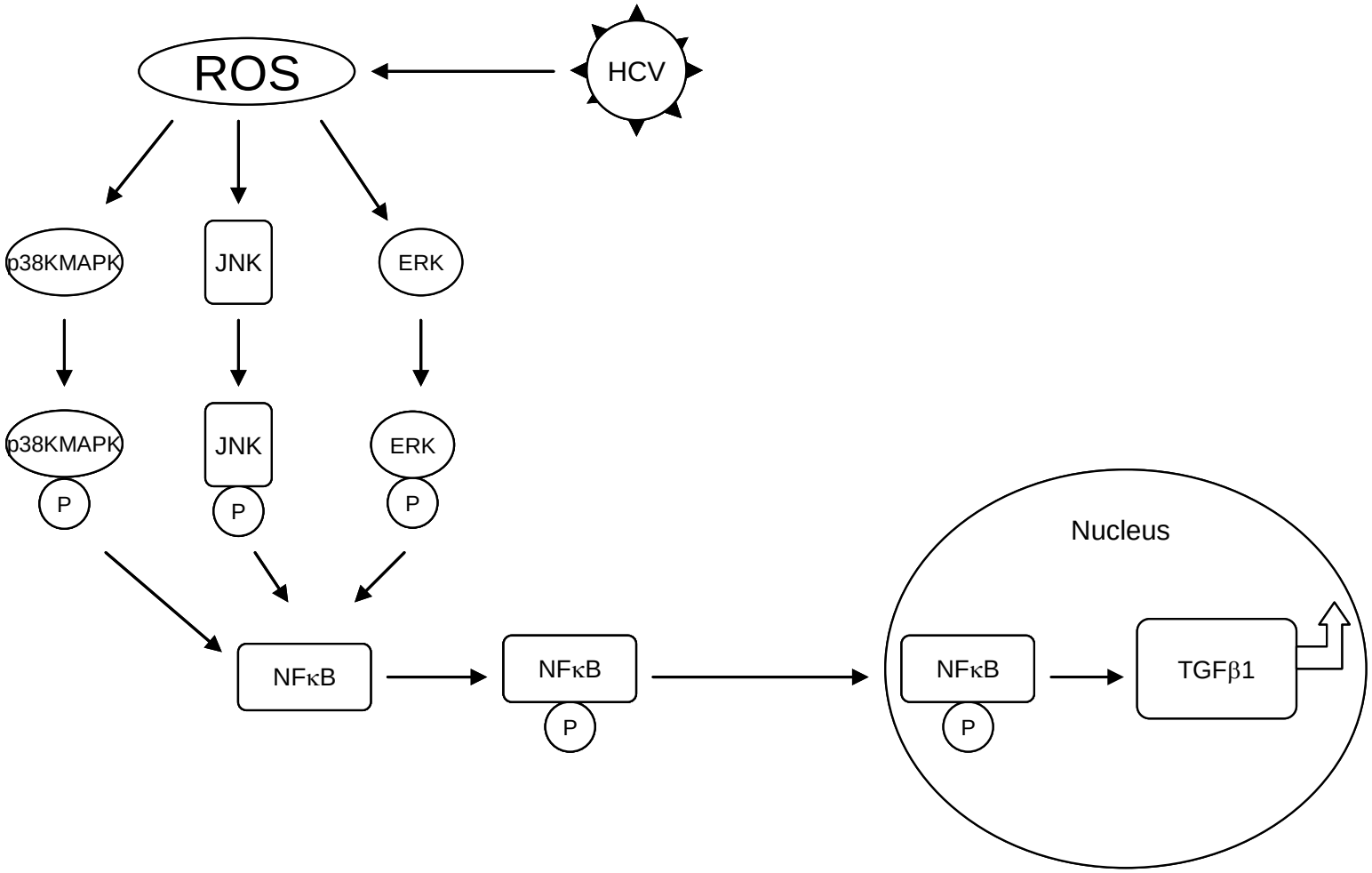
HCV induction of TGF-β1 is ROS-dependent and partially dependent on p38 MAPK, ERK and JNK





Lin *et al. Gastroenterology*. 2010;138:2509-18

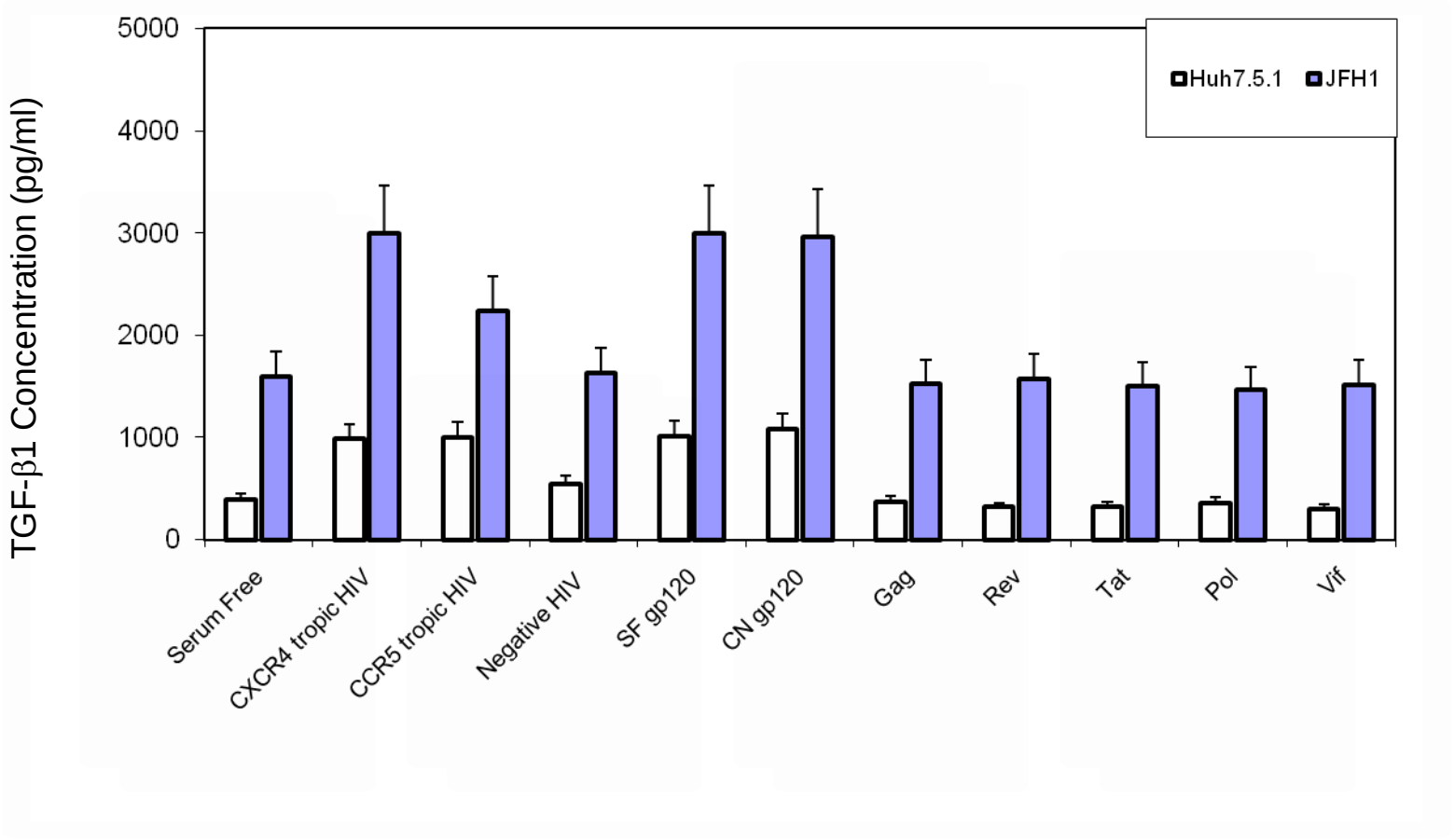
Model of events underlying HCV induction of TGF-β1 production in hepatocytes



Lin *et al. Gastroenterology*. 2010;138:2509-18

HCV and HIV exert cooperative effects on TGF-β1 secretion

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



Lin *et al. Gastroenterology*. 2008;134:803

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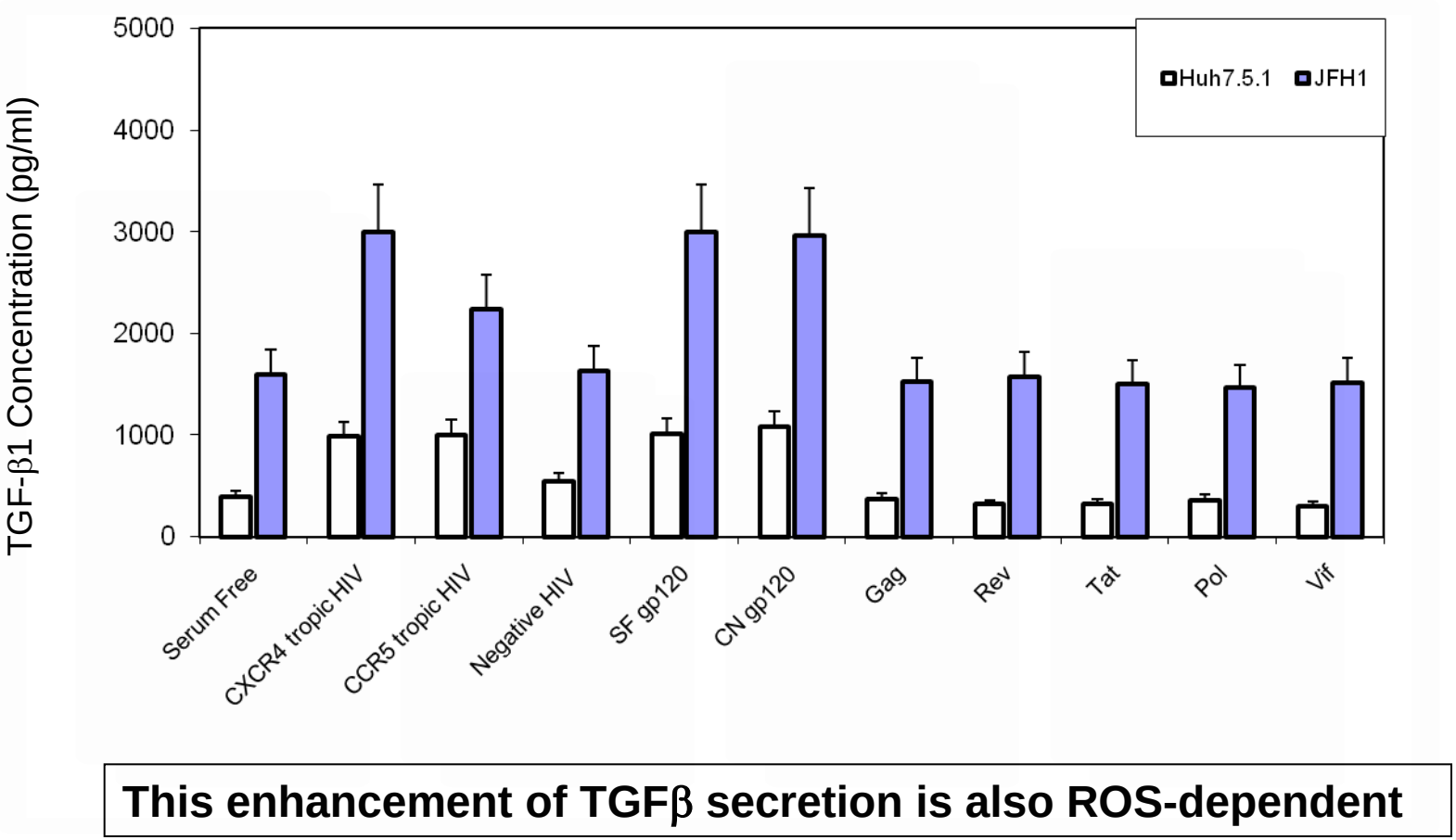
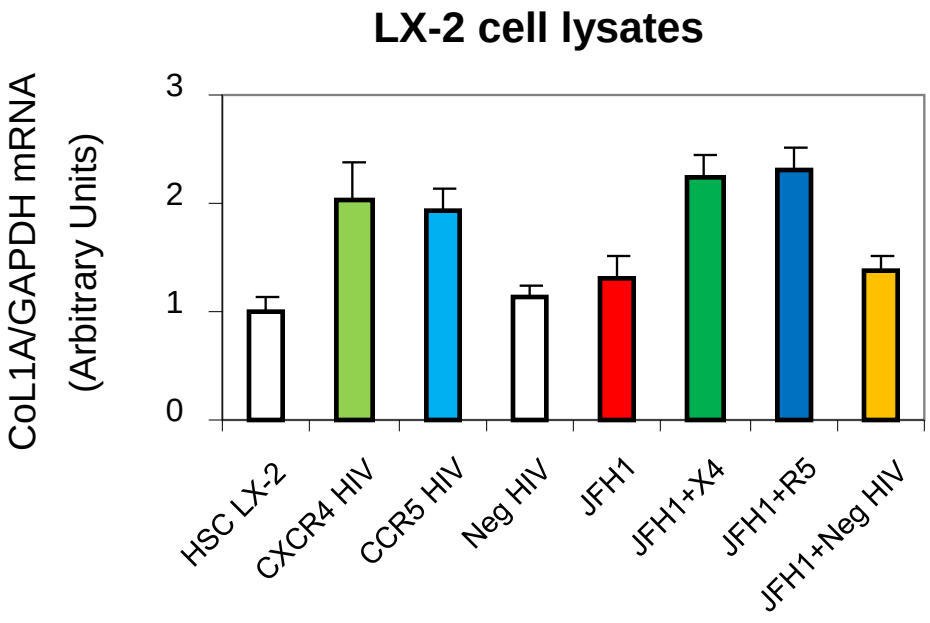


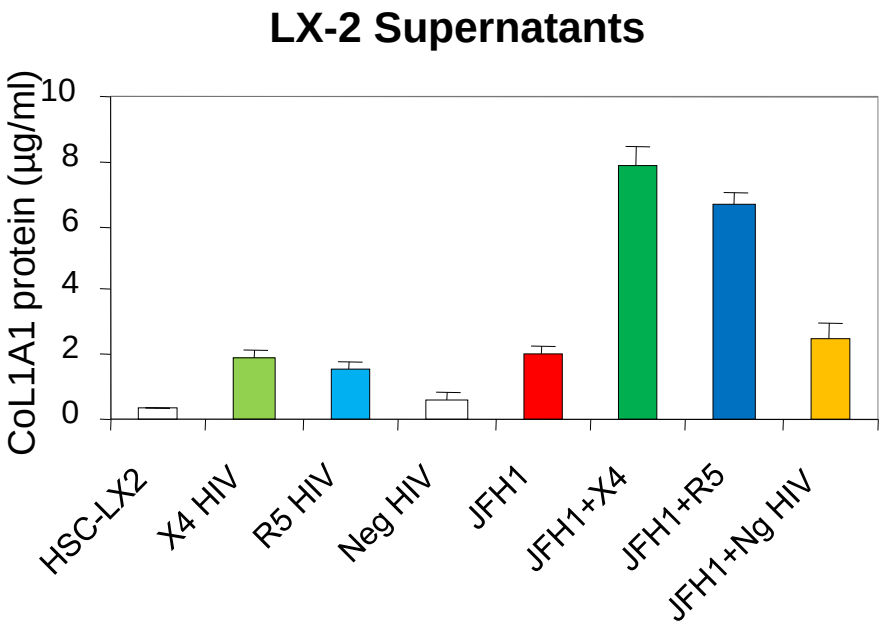
This enhancement of TGFβ secretion is also ROS-dependent

Lin *et al. Gastroenterology*. 2008;134:803

HIV and HCV cooperative effects on hepatic fibrogenesis

HIV-1 and HCV cooperatively increase type I collagen secretion in hepatic stellate cells

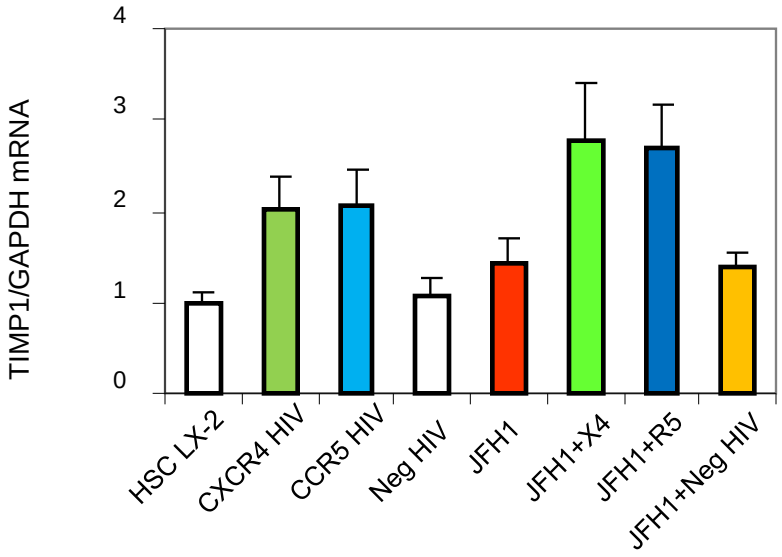




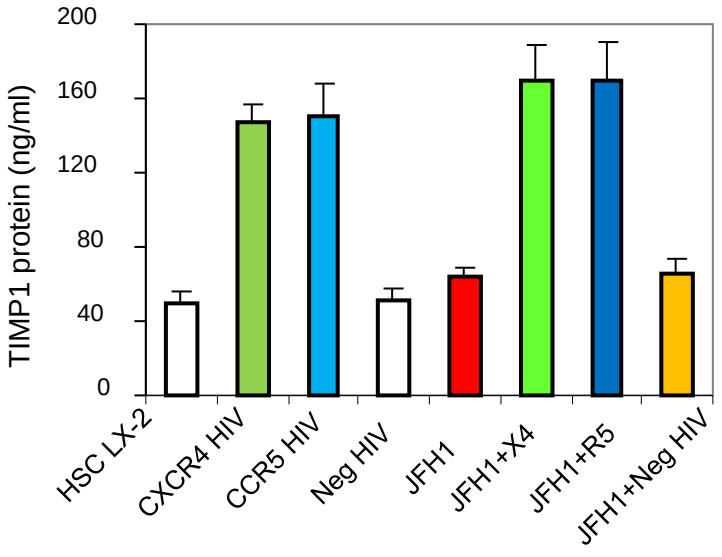
Lin et al., *J Biol Chem*. 2011;286(4):2665-74

HIV-1 increases TIMP-1 expression and secretion in HSCs

LX-2 Cell Lysates



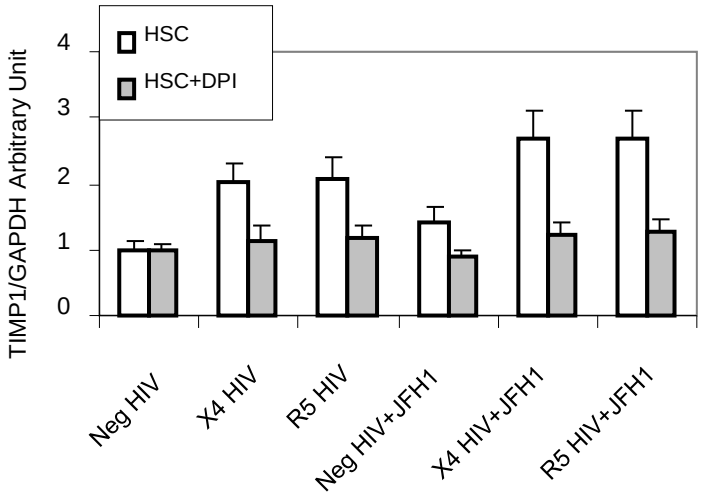
LX-2 Supernatants



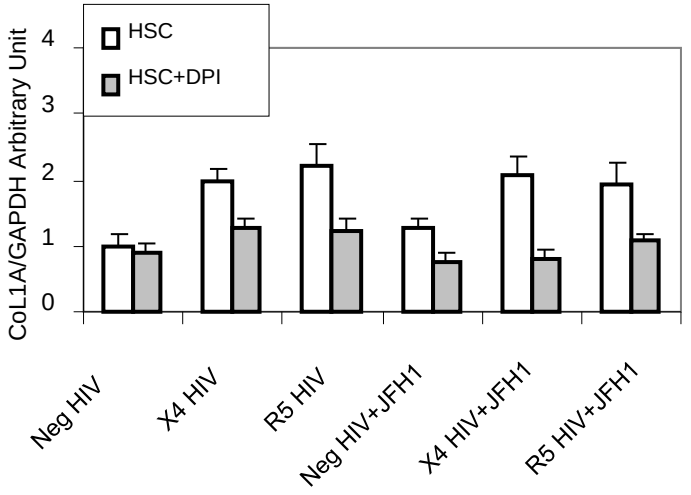
Lin et al., *J Biol Chem*. 2011;286(4):2665-74

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

TIMP-1

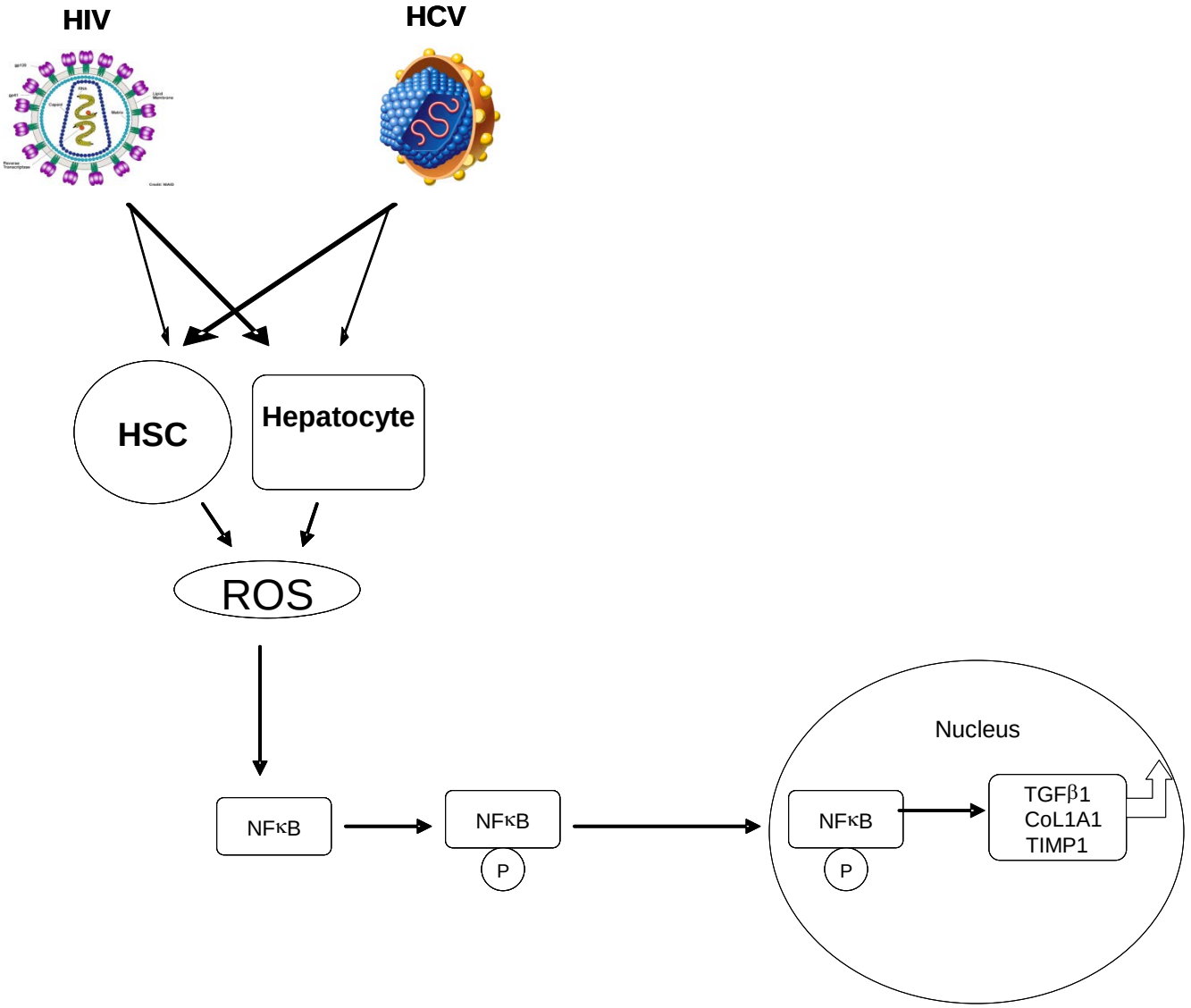


Col1A1



Lin et al., *J Biol Chem*. 2011;286(4):2665-74.

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



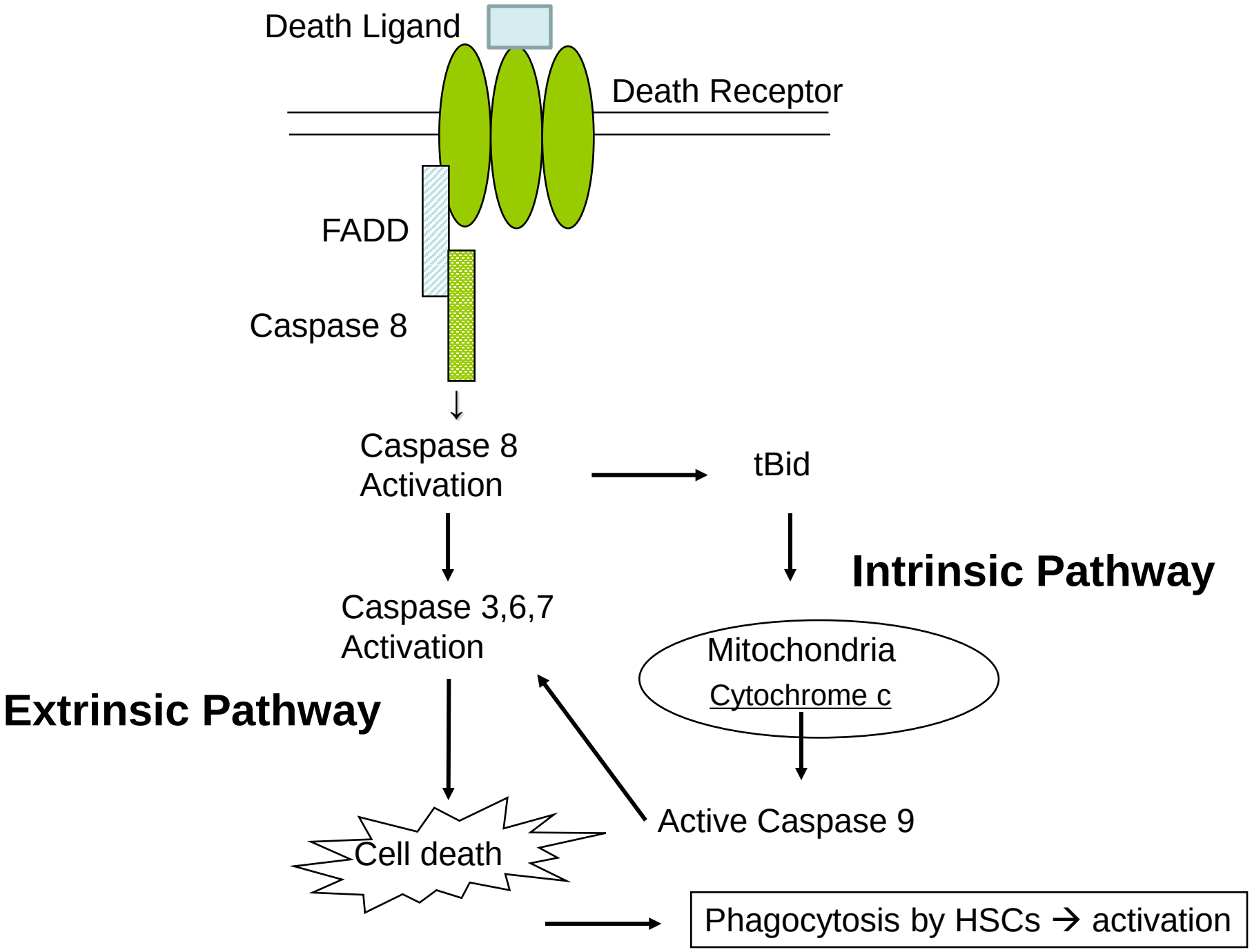
Cooperative effects of HCV and HIV on the hepatic macrophage population

The contribution of the macrophage to HCV-HIV liver disease

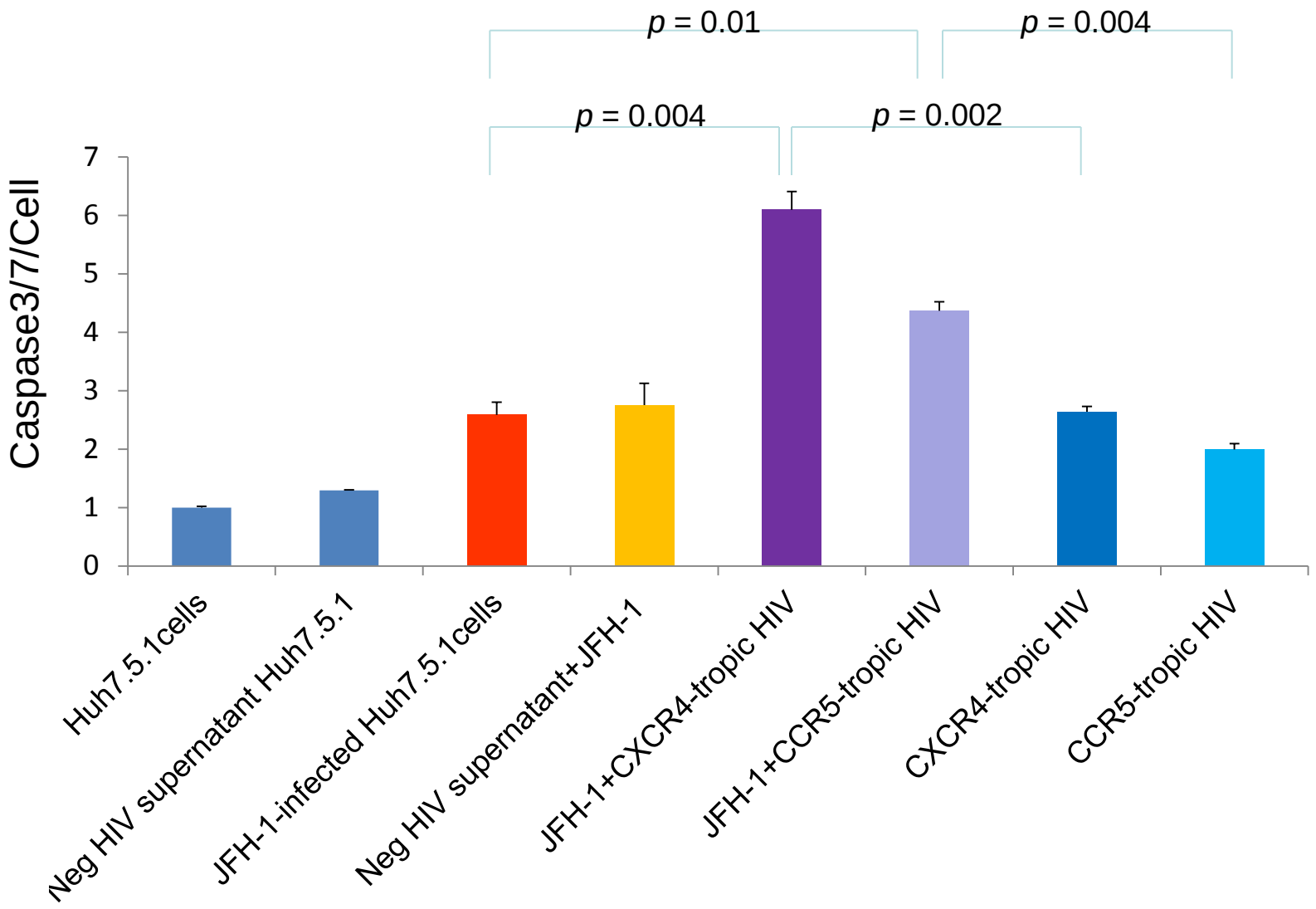
- Macrophages important reservoirs for HIV and contribute to chronic liver disease (KCs)
- Activated tissue macrophages polarize into
  - pro-inflammatory (M1): CD86, CD80
  - pro-repair/fibrotic (M2): CD163, Arg1, CD206
- M2 polarized macrophages in turn activate HSCs
- Peripheral levels of soluble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

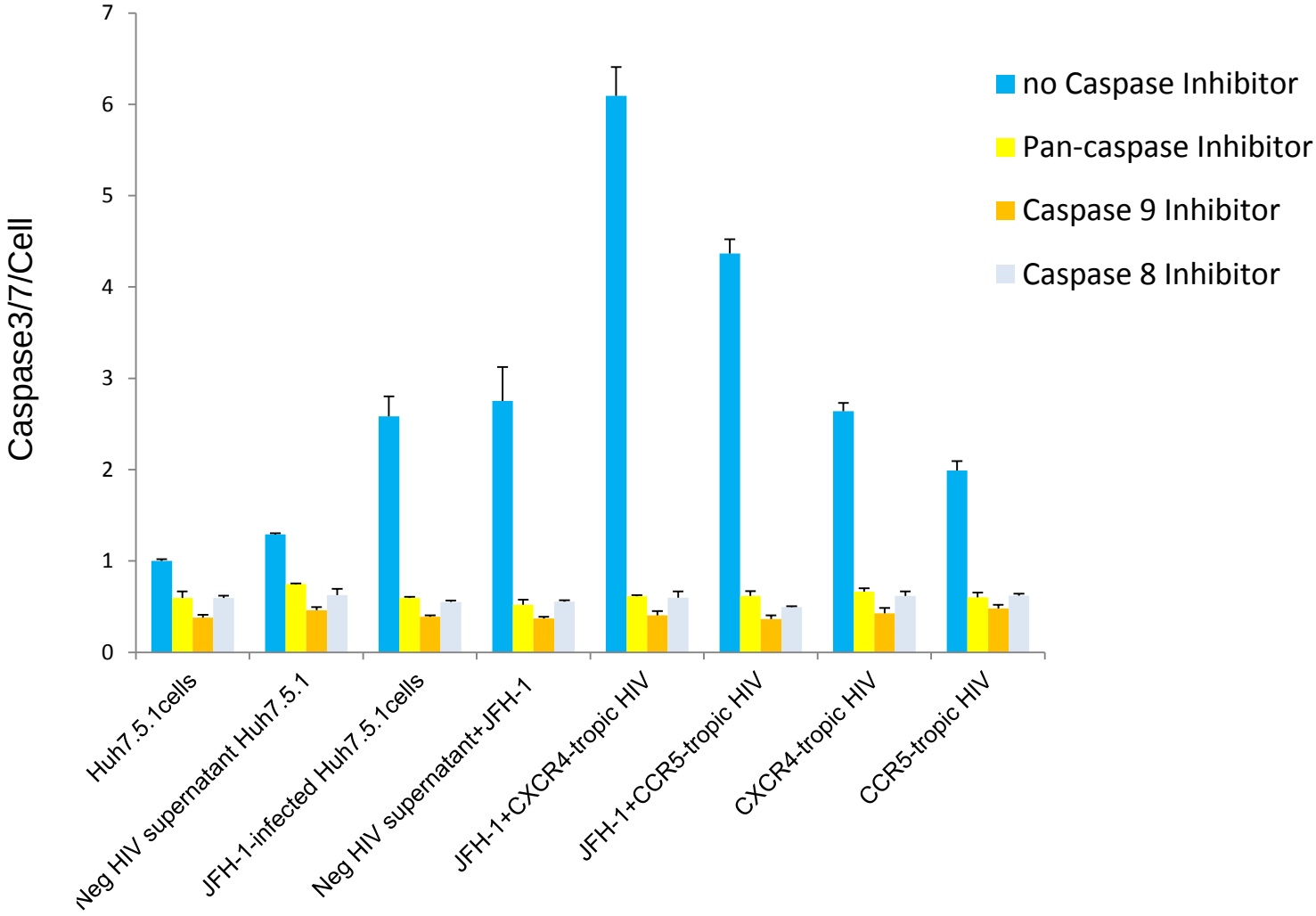

Death Ligand
Death Receptor
FADD
Caspase 8
Caspase 8
Activation
tBid
Intrinsic Pathway
Caspase 3,6,7
Activation
Mitochondria
Cytochrome c
Extrinsic Pathway
Active Caspase 9
Cell death
Phagocytosis by HSCs → activation

HCV and HIV induce caspase 3/7 activity in Huh 7.5.1 cells

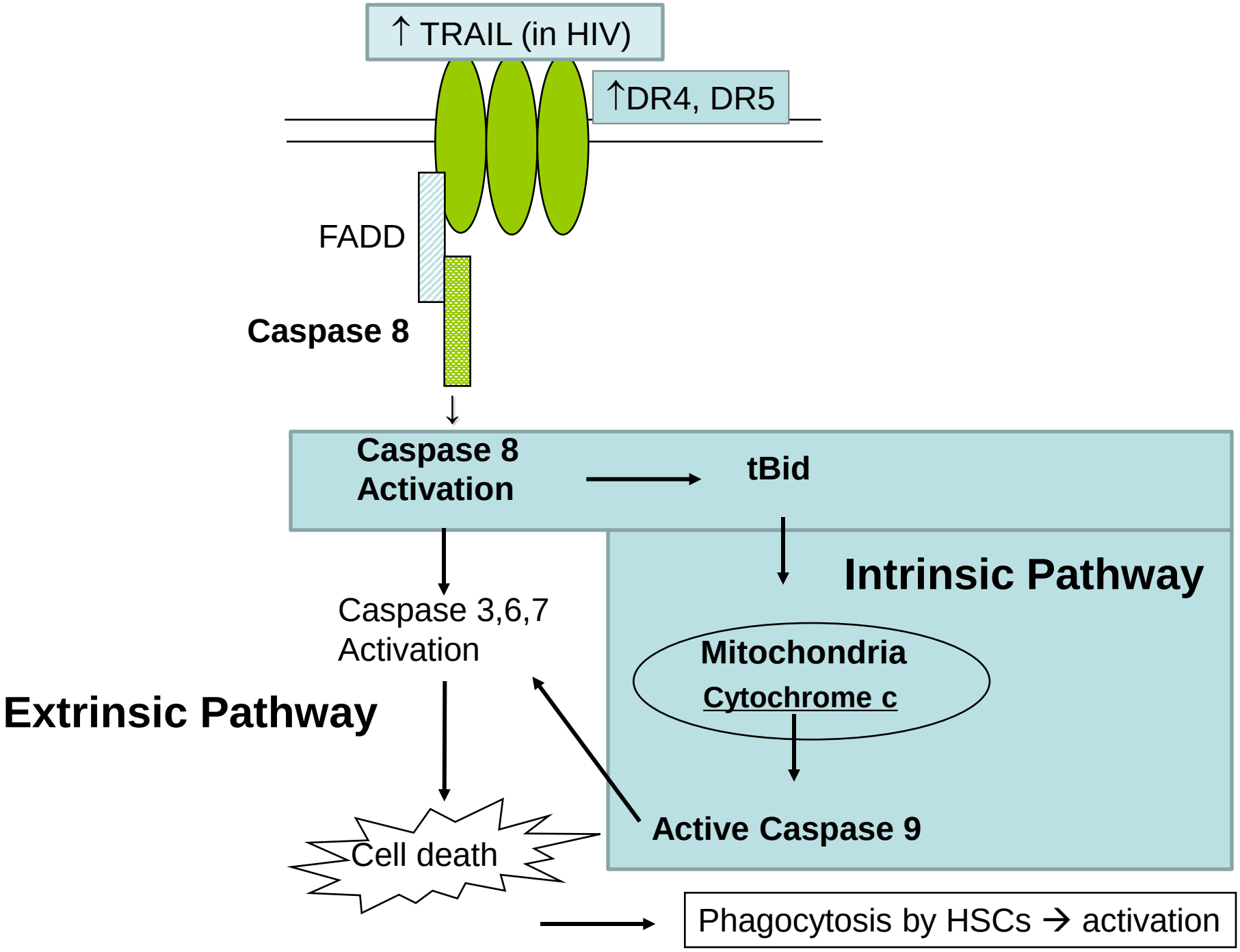


Jang JY et al, *J Hepatol* 2011; 54:612-20

HCV and HIV-mediated hepatocyte apoptosis is blocked by caspase inhibitors



Jang JY et al, *J Hepatol* 2011; 54:612-20


↑ TRAIL (in HIV)
↑DR4, DR5
FADD
Caspase 8
Caspase 8 Activation
tBid
Intrinsic Pathway
Caspase 3,6,7 Activation
Mitochondria
Cytochrome c
Extrinsic Pathway
Active Caspase 9
Cell death
Phagocytosis by HSCs → activation

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

Seki E et al. Nature Med 2007; 13(11):1324
Balagopal A et al. Gastro 2008;135:226-33

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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- Shadi Salloum
- Anna Lidofsky
- Annie Kruger

Ragon Institute

- Mark Brockman

UCSF

- Ma Somsouk
- Steve Deeks
- Peter Hunt

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- Nobuyuki Kato, Okayama (OR6)

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