Understanding acute HCV infection kinetics in humanized mice via an agent-based modelling approach

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1 Introduction

Understanding of HCV early evolution and the interplay between HCV and the mammalian host will help to identify key aspects of early HCV infection that is crucial for the design of an urgently needed prophylactic HCV vaccine. uPA-SCID chimeric mice with humanized livers (SCID-MhL) are a useful tool for studying acute HCV infection in the absence of an adaptive immune response.

2 Aim

To analyse and model the HCV kinetics from inoculation to steady state in the uPA-SCID mouse model, using an agent-based modelling (ABM) approach.

3 Mice

Ten male mice (5 PXB SCID-MhL with hepatocyte donor: JFC [1 year, male Caucasian] and human albumin > 9mg/mL, and 5 SCID mice without humanized livers, SCID-M) were inoculated intravenously with HCV (genotype 1a)-infected serum of 1x10^6 copies/animal. HCV RNA was measured using quantitative real-time PCR (qRT-PCR) as previously reported [1].

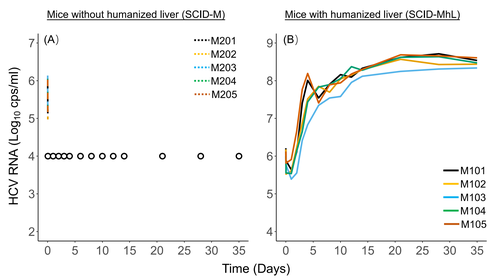

Fig. 1: Kinetics of acute HCV infection in SCID mice. **(A)** HCV kinetics in SCID-M. **(B)** HCV kinetics in SCID-MhL. Empty circles, HCV RNA level lower than quantifiable limit (<6000 copies/mL).

4 Viral kinetics

While in SCID-M HCV was rapidly cleared (**Fig. 1A**), a productive infection was established in SCID-MhL (**Fig. 1B**). After an initial viral decline, the virus resurged, followed by a transient decline (in 4 mice) that eventually stabilized at high steady state levels (**Fig. 1B**). To account for a transient decline, a decrease in viral production was assumed reminiscent of our previous observation of such transient HCV decline seen in chimpanzees [2].

5 Agent-based modeling (ABM)

We modified our recent ABM for hepatitis B virus acute infection that accounts for two types of agents: human hepatocytes and virus in the blood [3]. The ABM simulates a series of infection stages including initial infection of uninfected cells, infected cells in a non-productive viral eclipse phase, and infected cells in a productive infection phase releasing HCV virion, which then proceed to infect additional hepatocytes (**Fig. 2**). The production of new virions follows a stochastic production process (**Fig. 3**).

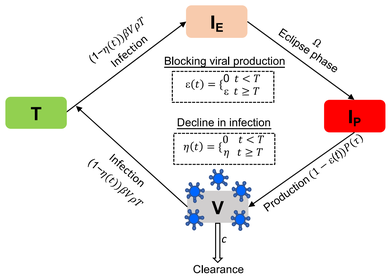

Fig. 2: Schematic diagram of ABM model of HCV infection. T, I_E, and I_P represent cells that are uninfected, in eclipse phase, and in the productive phase of infection, respectively. Free HCV in blood, V, is composed of infectious (ρ) and non-infectious virus (1- ρ). P(τ) represents virion secretion from I_p. Possible blockage of viral production or decline in infection by the innate immune response starting at time t p.i. is modeled with efficacies ε and η, respectively.

Viral production: $P(\tau) = \frac{P_{st}}{1 + e^{-\gamma(\tau-\alpha)}}$

Time interval between production cycle: $l(\tau) = \delta e^{-\omega\tau}$

Parameter definition

- τ: production cycle
- P_{st}: steady state virus production
- γ: steepness of the production curve
- α: number of cycles to reach to 50% of P_{st}
- δ: scaling factor indicating the initial production cycle length
- ω: decay constant

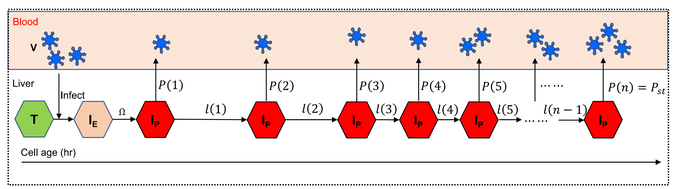

Fig. 3: Schematic diagram of viral production cycle for an individual hepatocyte. P(τ) is the number of virions produced by an infected cell, and $l(\tau)$ is the time interval between production cycle (h).

6 Model calibration

Model parameter fitting was done using a Genetic Algorithm (GA) with with the DEAP Python library [4] and run with EMEWS [5] framework on the Midway2 high-performance computing cluster at the University of Chicago.

7 Results

The ABM quantitatively reproduces the multi-phasic HCV kinetic patterns observed (**Fig. 4**). The ABM predicts that the values for eclipse phase (Ω), infection rate (β), and a number of parameters associated with viral production cycle (**Fig. 3** and **Table 1**) that provides an insights into the multi-phasic HCV kinetics and a transit decline at an early stage of infection.

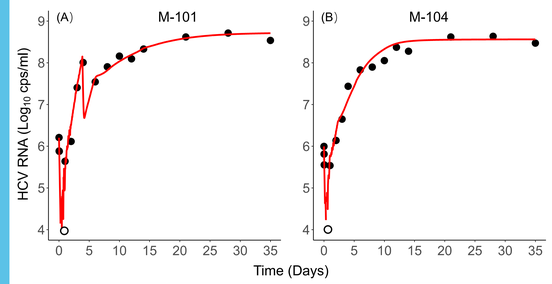

Fig 4: Serum HCV RNA kinetics (circles) and ABM calibration (solid line) in 2 representative SCID-MhL mice. Biphasic viral increase is predicted to happen 5 days p.i. with transient viral decline in between. **(A)** assuming blocking of viral production (ε =98%) and decline in virions infectiousness (η=90%), or **(B)** without assuming blocking of viral production only η=97% via GA fitting approach (**Table 1**). Empty circles, HCV RNA level lower than quantifiable limit (<6000 copies/mL).

Mouse#	Eclipse phase [hr] (Ω)	Infection rate (β)	Decay constant (ω)	Steepness of the production curve (γ)	Virus production at steady state (P_{st})	% of blocking infection (η)	% of blocking viral production (ε)	J-Score [Min-Max]	% of J<=0.70 (# of simulations)
M101	6-20 [5-28]	0.03 [0.006-0.03]	0.21 [0.1-0.78]	0.19 [0.11-0.58]	3 [1-6]	90 [80-98]	98 [91-98]	0.22-0.70	87% (6180)
M104	1-2 [1-10]	0.45 [0.16-0.47]	0.23 [0.1-0.68]	0.50 [0.5-4.97]	2 [1-2]	97 [69-99]	No drop	0.34-0.70	94% (6155)

Table 1: ABM parameter estimations for 2 representative mice using GA algorithm shown in Fig. 4. The cycle constant (δ) and mid-point (α) were assumed to be 6 and 10, respectively (**Fig. 3**). [min-max] for simulations with J score <= 0.7.

8 Conclusions

- The ABM provides novel insights into the HCV life cycle in vivo.
- The model suggests a partial block of virion production possibly due to an early stage of innate immune response.

9 Acknowledgements

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10 References

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