

Supplementary Information for

A dynamical motif comprising the interactions between antigens and CD8 T cells may underlie the outcomes of viral infections

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This PDF file includes:

- Supplementary Text S1 to S5
- Supplementary Figure S1
- Supplementary Table S1 and S2
- References for SI reference citations

Supporting Information Text

Supplementary Text S1. Predictions using an alternative model of CD8 T cell exhaustion. We examined the implications of CD8 T cell exhaustion triggered by cumulative rather than instantaneous antigenic stimulation. Following a previous formalism (1), we wrote:

$$\begin{aligned}\frac{dI}{dt} &= k_1 I \left(1 - \frac{I}{I_{max}}\right) - k_2 I E \\ \frac{dE}{dt} &= k_3 \frac{I E}{k_p + I} - k_4 \frac{Q E}{k_e + Q} \\ \frac{dQ}{dt} &= q_s \left(\frac{I}{\phi + I} - Q\right)\end{aligned}\quad [S1]$$

Here, Q represents the cumulative stimulation level, which increases with antigen load in a saturable manner with half-maximal constant ϕ and decays with the rate constant q_s . Q then determines the level of exhaustion, as opposed to the antigen load in Eq. 1 in the main text, and suppresses the effector response. The resulting motif is illustrated in Figure S1A. Solving the equations above yielded clearance with low viral inoculum sizes and/or high initial effector pool size, immunopathology with intermediate sizes, and persistence with high viral inoculum sizes and/or low initial effector pool sizes (Figure S1). The specific forms used to defining exhaustion thus did not alter our key conclusions.

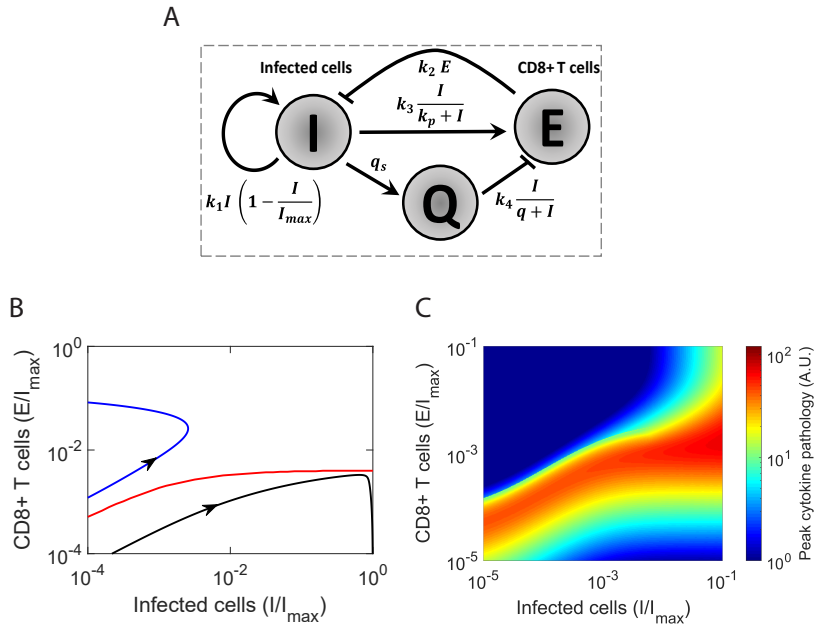


Figure S1: Dynamical motif with exhaustion induced by cumulative antigen stimulation. (A) A schematic of the motif described in Supplementary Text S1. (B) Phase portrait showing the basin boundary (red line) separating initial conditions that lead to clearance (above red line) and persistence (below red line). Blue and black lines show projections of trajectories leading to the two outcomes. (Note that the system is now high dimensional and the projections can thus cross the basin boundary.) (C) Cytokine pathology associated with a range of initial conditions illustrating maximum pathology near the basin boundary. Parameter values employed are as follows: $k_e = 0.8$; $q_s = 0.08/\text{day}$; and $\phi = 1000$ cells (1). The other parameters are the same as in Figure 1.

Supplementary Text S2. Linear stability analysis. The system in Eq. 1 in the main text with the exhaustion term away from saturation has 3 steady states. To determine the stability of these steady states, we performed linear stability analysis. The Jacobian matrix of the system is

$$A = \begin{bmatrix} k_1 - \frac{2k_1 I}{I_{max}} - k_2 E & -k_2 I \\ \frac{k_3 k_p E}{(I + k_p)^2} - k_4 E & \frac{k_3 I}{I + k_p} - k_4 I \end{bmatrix}\quad [S2]$$

For the steady state representing clearance ($I = 0$ and $E \geq 0$), the Jacobian becomes

$$A = \begin{bmatrix} k_1 - k_2 E & 0 \\ \frac{k_3 E}{k_p} - k_4 E & 0 \end{bmatrix}\quad [S3]$$

Thus, the $\text{trace}(A) = k_1 - k_2 E$ and $\text{det}(A) = 0$, which would yield a line of stable fixed points as long as $E \geq \frac{k_1}{k_2}$.

For the steady state representing persistence ($I = I_{max}$ and $E = 0$), the Jacobian becomes

$$A = \begin{bmatrix} -k_1 & -k_2 I_{max} \\ 0 & \frac{k_3 I_{max}}{I_{max} + k_p} - k_4 I_{max} \end{bmatrix}\quad [S4]$$

which has both eigenvalues real and negative if $\frac{k_3}{k_4} - k_p < I_{max}$. This steady state is thus stable as long as the latter inequality holds.

For the third steady state ($I = \frac{k_3}{k_4} - k_p$ and $E = \frac{k_1}{k_2}(1 - \frac{1}{I_{max}}(\frac{k_3}{k_4} - k_p))$), we can show that the signs of the elements of the Jacobian are

$$A = \begin{bmatrix} + & - \\ - & 0 \end{bmatrix} \quad [S5]$$

Thus, $\det(A) < 0$, so that the eigenvalues have opposite signs. The steady state is therefore a saddle point.

Supplementary Text S3: Mathematical model of the motif with NK cells. The following equations describe the behavior of the motif with NK cells (Figure 3):

$$\begin{aligned} \frac{dI}{dt} &= k_1 I \left(1 - \frac{I}{I_{max}}\right) - k_2 I E - \gamma I N \\ \frac{dE}{dt} &= k_3 \left(1 - \zeta \frac{N}{\phi_E + N}\right) \frac{I E}{k_p + I} - k_4 \frac{I E}{k_e + I} \\ \frac{dN}{dt} &= k_6 \left(\frac{I}{\phi_N + I} - N\right) \end{aligned} \quad [S6]$$

Here, we let the NK cell response, N , rise in proportion to the antigen load, I , in a saturable manner with the scaling constant ϕ_N and decay with the rate constant k_6 . Further, we let the NK cells eliminate infected cells at the rate γ and suppress the CD8 T cell response by the maximal extent ζ . The remaining terms are similar to those in Eq. 1 in the main text.

Supplementary Text S4: Mathematical model of the motif with the innate immune response. The following equations describe the behavior of the motif with the innate immune response (Figure 4):

$$\begin{aligned} \frac{dI}{dt} &= k_1 \left(1 - \epsilon \frac{X}{\phi_X + X}\right) I \left(1 - \frac{I}{I_{max}}\right) - k_2 I E \\ \frac{dE}{dt} &= k_3 \frac{I E}{k_p + I} - k_4 \frac{I E}{k_e + I} \\ \frac{dX}{dt} &= k_5 \left(\frac{I}{\phi_I + I} - X\right) \end{aligned} \quad [S7]$$

Here, X is a coarse-grained, normalized variable quantifying the innate immune response. X rises in proportion to the antigen load, I , in a saturable manner with the scaling constant ϕ_I and decays with the rate constant k_5 . We assumed that X restricts the spread of infection with the maximal efficacy ϵ and the scaling constant ϕ_X . ϕ_I sets the scale of the antigen load that triggers the innate immune response. Large values of ϕ_I imply weak immune responses. The remaining terms are similar to those in Eq. 1 in the main text.

Supplementary Text S5: Model of HCV dynamics with innate immune response. We constructed a model of HCV dynamics that included our framework above of the innate immune response (Figure 3A) in standard models of HCV kinetics (2, 3) (see Figure 4A). The model equations are as follows:

$$\begin{aligned} \frac{dT}{dt} &= s + r_T T \left(1 - \frac{T + I}{T_{max}}\right) - d_T T - \beta V T + f_2 m I E \\ \frac{dI}{dt} &= \beta V T + r_I I \left(1 - \frac{T + I}{T_{max}}\right) - \delta I - m(f_1 + f_2) I E \\ \frac{dV}{dt} &= p \left(1 - \epsilon \frac{X}{\phi_X + X}\right) - c V \\ \frac{dX}{dt} &= k_5 \left(\frac{I^n}{\phi_I^n + I^n} - X\right) \\ \frac{dE}{dt} &= \lambda \mathcal{H}(\tau_d) + k_3 \frac{I E}{k_p + I} - k_4 \frac{I E}{k_e + I} - \mu E \end{aligned} \quad [S8]$$

Here, T represents the population of target, uninfected hepatocytes; I , infected hepatocytes; V , virus; X , the innate immune response; and E , CD8 T cells. Target cells are produced at the rate s , proliferate at the per capita rate r_T , die at the per capita rate d_T , and are infected by virions at the rate $\beta V T$, to yield infected cells. The latter cells proliferate at the per capita rate r_I , and die at the per capita rate δ . Total cell proliferation is restricted by a logistic term with carrying capacity T_{max} . Virus is produced at the rate p per infected cell and cleared at the per capita rate c . These latter steps represent details of antigenic growth that we had subsumed into the proliferation of infected cells in our dynamical motif above (Figure 1A).

We let the innate immune response follow the form above (Eq. S7). Additionally, we allowed the sensitivity of the response to infected cells to be modulated by the Hill co-efficient n . The response suppresses viral production (2), which we assumed to occur with the maximal efficacy ϵ . For CD8 T cell dynamics, we followed earlier models of activation and exhaustion (1, 4) together with a delay in the induction of the response (5-7), characterized using τ_d (3). \mathcal{H} represents the Heaviside function such that $\mathcal{H}(x) = 0$ if $x < 0$ and $\mathcal{H}(x) = 1$ if $x \geq 0$. CD8 T cells are thus produced at the rate λ after a delay of τ_d following

the onset of infection and die at the per capita rate μ . Their effect on infected cells is both cytolytic and non-cytolytic (3). We represented the two effects using the terms f_1 and f_2 , respectively. Thus, infected cells are destroyed at the rate mf_1IE and recover and become target cells at the rate mf_2IE .

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Table S1. Parameter estimates. The parameter values employed in our model calculations are listed along with ranges available in the literature. Where no estimates were available, we have assumed parameters values to ensure that the key qualitative features of the system are maintained.

Parameter	Meaning	Value	Range or value from literature	Source
Figures 1 & 2				
k_1	Infection spread rate	1.3/day	3-4/day	(8, 9)
I_{max}	Maximum number of infected cells	10^6 cells	10^6 cells	(1)
k_2	Killing rate of infected cells by CD8 T cells	5×10^{-5} /cells/day	$\sim 10^{-6} - 10^{-4}$ /cells/day	(8, 9)
k_3	Antigen driven CD8 T cell proliferation rate	1/day	~ 1 /day	(1, 4, 10)
k_4	Antigen driven CD8 T cell suppression rate	3/day	2-4/day	(1, 4, 10)
k_p	Antigen driven proliferation threshold	10 cells	$10^{-1} - 10^3$ cells	(1, 4)
k_e	Antigen driven suppression threshold	2×10^5 cells	$5 - 2.7 \times 10^4$ cells	(4, 10)
α	Rate of growth of cytokine pathology	2×10^{-8} /cells ² /day		
d_c	Rate of loss of cytokine pathology	1/day		
Figure 3				
k_1	Infection spread rate	1.5/day	3-4/day	(8, 9)
I_{max}	Maximum number of infected cells	10^6 cells	10^6 cells	(1)
k_2	Killing rate of infected cells by CD8 T cells	1×10^{-4} /cells/day	$10^{-6} - 10^{-4}$	(8, 9)
k_3	Antigen driven CD8 T cell proliferation rate	1.55/day	~ 1 /day	(1, 4, 10)
k_4	Antigen driven CD8 T cell suppression rate	3/day	2-4/day	(1, 4, 10)
k_p	Antigen driven proliferation threshold	1000 cells	$10^{-1} - 10^3$ cells	(1, 4)
k_e	Antigen driven suppression threshold	1×10^5 cells	$5 - 2.7 \times 10^4$ cells	(4, 10)
k_6	NK cell activation rate	5/day		
	NK cell activation rate with NK cell depletion	0/day		
ϕ_N	NK cell efficacy threshold	100 cells		
ζ	Efficacy of NK cell suppression of CD8 T cell proliferation	0.3		
ϕ_E	NK cell activation threshold	0.5 cells		
γ	Rate of elimination of infected cells by NK cells	0.1 cells/day		
α	Rate of growth of cytokine pathology	2×10^{-8} /cells ² /day		
d_c	Rate of loss of cytokine pathology	1/day		
Figure 4				
k_1	Infection spread rate	1.5/day	3-4/day	(8, 9)
I_{max}	Maximum number of infected cells	10^6 cells	10^6 cells	(1)
k_2	Killing rate of infected cells by CD8 T cells	4×10^{-5} /cells/day	$10^{-6} - 10^{-4}$	(8, 9)
k_3	Antigen driven CD8 T cell proliferation rate	1.55/day	~ 1 /day	(1, 4, 10)
k_4	Antigen driven CD8 T cell suppression rate	3/day	2-4/day	(1, 4, 10)
k_p	Antigen driven proliferation threshold	1000 cells	$10^{-1} - 10^3$ cells	(1, 4)
k_e	Antigen driven suppression threshold	1×10^5 cells	$5 - 2.7 \times 10^4$ cells	(4, 10)
k_5	Innate immune response activation rate	10/day		
ϕ_I	Innate immune response activation threshold (strong response)	2000 cells		
	Innate immune response activation threshold (weak response)	4000 cells		
ζ	Efficacy of innate immune response suppression of viral replication	0.95		
ϕ_X	Efficacy threshold for innate immune response	0.8 cells		
α	Rate of growth of cytokine pathology	2×10^{-8} /cells ² /day		
d_c	Rate of loss of cytokine pathology	1/day		

Table S2. Parameter values used for our calculations of HCV dynamics (Figure 5).

Parameters	Meaning	Value	Source
s	Target cell production rate	61200 cells/mL/day	(3)
r_T	Target cell proliferation rate	0.53/day	(3)
T_{max}	Carrying capacity of liver	7×10^7 cells/mL	(3)
d_T	Target cell death rate	0.0034 /day	(3)
β	Infection rate constant	1×10^{-8} mL/cells/day	(3)
r_I	Infected cell proliferation rate	0.53/day	(3)
δ	Death rate of infected cells	$1.5 \times d_T$	(3)
m	Effector strength of CTL response	5 mL/cells/day	
f_1	Cytolytic fraction of CTL response	0.3	(3)
f_2	Non-cytolytic fraction of CTL response	0.7	(3)
p	Virus production rate	20 virions/cell/day	(3)
ϵ	Efficacy of innate immune response in blocking viral production	0.98	(3)
k_5	Innate immune response activation rate	5/day	
ϕ_I	Innate immune response activation threshold (strong response)	10^3 cells/ml	
	Innate immune response activation threshold (weak response)	5×10^4 cells/ml	
λ	CD8 ⁺ T cell recruitment rate	1 cells/mL/day	(4)
k_3	Antigen driven CD8 T cell proliferation rate	1/day	(4)
k_4	Antigen driven CD8 T cell suppression rate	2/day	(4)
k_p	Antigen driven CD8 T cell proliferation threshold	0.1 cells/mL	(4)
k_e	Antigen driven CD8 T cell suppression threshold	1000 cells/mL	
μ	Death rate of CD8 ⁺ T cells	2/day	(4)