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Research on the Nonlinear Dynamics and Biological Mechanism of CD8+ T Cell Response to Viral Infection with Time Delay and Reaction Diffusion

Yijia Chen*
Yuxi Normal University, Yuxi 65310, Yunnan, China

Author to whom correspondence should be addressed.

Abstract: To clarify the coupling mechanism of time delay and spatial diffusion during $CD8^+$ T cell immune response, this paper constructs a time-delay reaction-diffusion model. By means of stability analysis and bifurcation theory, the basic number of rebirths of viral infection and the conditions for the existence of various equilibrium points were clarified. The findings suggest that when the hysteresis exceeds the critical threshold, Hopf bifurcation is induced, causing the system to shift from a virus-cleared state to a periodic oscillation mode, and Turing instability prompts the formation of spatial patterns when the viral spread rate is significantly faster than that of T cells. The coupling effect between time delay and diffusion can give rise to more complex spatiotemporal dynamics. The findings illustrate the key regulatory role of immune delay and spatial heterogeneity in infection outcomes.

Keywords: $CD8^+$ T cells; Time lag; Reaction-diffusion; Hopf bifurcation; Turing instability; Viral dynamics

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1. Introduction

$CD8^+$ cytotoxic T lymphocytes (CTLS) are the core effector cells for clearing viral infections, but in persistent infections such as HIV and HBV, they often fail to clear completely due to functional decline. To deeply understand the regulatory mechanism of CTL antiviral response, two key points need to be focused on: First, there is a delay of several hours to several days between viral latency and CTL clone amplification. Experiments show that effective CTLS lag behind the viral peak to reach the infection site, and this delay, although it may exacerbate acute pathology, constitutes an evolutionary trade-off between clearance and damage. The spatio-temporal asynchronicity of viral spread and CTL migration leads to spatial heterogeneity, and the spatial "gaps" of CTL distribution may be the source of local viral reignition. Existing mathematical models have studied CTL immunodynamics from the perspectives of time-delay ordinary differential equations and reaction-diffusion equations, but there is still a lack of systematic research on the coupling of the two, and the theory of the synergistic regulation of viral infection by time delay and diffusion is still unclear [1]. For this purpose, this paper constructs a nonlinear dynamics model with time delay and reaction-diffusion to provide a verifiable theoretical basis for the optimization of therapeutic strategies.

2. Model establishment and main parameters

2.1. Model assumptions and systems of differential equations

Let the region $\Omega T, I, V, C$ represent the densities of uninfected target cells, infected cells, free virus, and $CD8^+$T effector $(D_T = D_I = 0)$ cells, respectively. Consider the free spread of the virus to T cells, while the spread of adherent target cells and infected cells is ignored. The model is:

$$\begin{cases} \dfrac{\partial T}{\partial t} = l - d_T T - bTV, \\ \dfrac{\partial I}{\partial t} = bT(t-t)V(t-t)e^{-d_I t} - d_I I - \dfrac{kCI}{l+aI}, \\ \dfrac{\partial V}{\partial t} = D_V \nabla^2 V + pI - d_V V, \\ \dfrac{\partial C}{\partial t} = D_C \nabla^2 C + \dfrac{rCI}{l+hC} - d_C C, \end{cases}$$

The ô boundary is homogeneous Neumann conditions, and the initial is non-negative. The time lag represents the intracellular latency of the virus and is the probability of survival during the latency. $e^{\hat{a}d_I}$ Both the killing term and the proliferation term take the Holling type II saturation function, which reflects the upper limit of efficacy and amplification caused by the competition of immune synaptic formation and growth factors.

2.2. Summary table of parameters

Table 1. Biological implications of model variables and parameters

Symbol	Biological implications	Dimension
T	Density of uninfected target cells	Cell · Volume
I	Density of infected cells	Cells · Volume
V	Free virus density	Virus particles · volume
C	$CD8^+$T effector cell density	Cells · Volume
λ	Target cell production rate	Cell · $Volume^{-1}$ · time
d_T,d_I,d_V,d_C	Natural mortality/clearance rate for each variable	Time
β	Virus infection rate	Volume · $Virus\ particle^{-1}$ · Time
P	Virus production rate	Virus particles · $cells^{-1}$ · time
K	CTL killing rate	Volume · $Cell^{-1}$ · time
a	CTL killing saturation coefficient	Volume · cell
r	CTL proliferation rate	Cells · $Volume^{-1}$ · time
η	CTL proliferation saturation coefficient	Volume · cells
τ	Viral intracellular latency (time-lag parameter)	Time
D_T,D_V,	Diffusion coefficient	$Length^2$ · Time

This model is constructed based on the following key biological assumptions: First, the rate of target cell generation is constant, and natural mortality is positively correlated with cell density, a widely accepted simplified assumption in viral dynamics modeling applicable to tissue cell populations with homeostasis renewal, such as $CD4^+$T cells and hepatocytes. Second, the cytotoxic effect of $CD8^+$T cells is based on the Holling II functional response function, as activated CTLS

need to form immune synapses with infected target cells to release cytotoxic molecules, and synaptic formation is limited by cell contact probability and maturation time, and the cytotoxic effect tends to saturate at high-density infection. Third, the proliferation of ôCD8$^+$T effector cells uses a nonlinear saturation function, reflecting the self-regulation of the immune system. Excessive proliferation consumes growth factors such as IL-2 and triggers activation-induced cell death (AICD), reducing proliferation efficiency. Fourth, the time lag parameter corresponds to the intracellular latency of the virus. The replication cycle of RNA viruses is 6–24 hours, and that of DNA viruses is longer. The length of the time lag determines the kinetics of infection. Fifth, the spatial diffusion term describes the tissue migration of the virus to CD8$^+$T cells, reflecting the spatial heterogeneity of the infection microenvironment and the CTL immune patrol behavior [2].

2.3. Classification of basic regeneration numbers and equilibrium points

Derived basic regeneration numbers using the next-generation matrix method:

$$R_0 = \frac{\beta\lambda p e^{-d_I t}}{d_T d_I d_V}.$$

The equilibrium points include:

(1) The infection-free equilibrium point $E_0{:}T_0=\lambda/d_T$,I=V=C=0,remains constant.

(2) Immune clearance/control of infection equilibrium $E_1{:}R_0>1$.occurs when immunity is adequate, corresponding to the low viral load control state.

(3) High infection-no-immune equilibrium: high viral homeostasis when CTL is not effectively activated. E_2

(4) Coexisting infection equilibrium point: A moderate homeostasis in a chronic tug-of-war between immunity and the virus. E_3

3. Stability and bifurcation analysis

3.1. Threshold stability without infection equilibrium points

Linearization yields characteristic equation analysis: At that time, local asymptotic stability, infection cannot be established. $E_0R_0<1E_0R_0>1$ indicates instability. R_0 The delay-dependent threshold reveals that prolonged latency can be reduced, providing a physiological antiviral window.

3.2. Time-delay-induced Hopf bifurcation and sustained oscillation

To investigate the stability of immune-controlled equilibrium points. E_1ôExponential terms appear in the characteristic equation due to a time lag. T Consider it as a bifurcation parameter, set pure imaginary roots $\pm i\omega$, and separate the real and imaginary parts to determine the critical delay and the corresponding frequency. $\tau_0\omega_0$ Verify that the cross-sectional condition holds and prove that it is stable τ when $<\tau_0$ (virus controlled). $E_1\tau\tau_0$ Hopf bifurcation occurs when >, creating a stable limit loop, with the viral load oscillating periodically with the number of CTLS. The analytical relationship between critical delay values and immune efficacy parameters such as killing rate and proliferation rate can explain the spontaneous “blips” phenomenon of viral load [3].

3.3. Diffusion-driven Turing instability

The first two steps are based on the assumption of spatial uniformity. $e^{\lambda t+iqx}$ Introduce spatial perturbations and derive characteristic equations with diffusion terms. Turing instability requirements: The uniform state is stable to zero wavenumber perturbations but q becomes unstable to some non-zero wavenumber. From this, we get the necessary conditions:

D_V Some critical ratio. D_C

When the virus spreads faster than T cells, the superimposition of local viral proliferation and delayed immune patrol can spontaneously form a spatial pattern of coexistence of high viral foci and low viral areas, providing a mechanism explanation for the spatial distribution of viral micro-reignition and latent repositories in tissues.

4. Discussion on numerical simulation and biological mechanisms

4.1. Numerical methods and parameter Settings

The Crank-Nicolson finite difference scheme is used to discretize the space, the second-order center difference discrete diffusion term is used, and the delay term is processed by linear interpolation and $\Omega=[0,L]$ solved over one-dimensional spatial intervals. $\Delta x=0.1$ The spatial step size is taken, the time step size is taken, and the convergence test meets the accuracy requirements. $\Delta t=0.01$ The reference parameters are taken as: and adjusted according to the requirements of each numerical experiment,

$$\lambda=10, d_T=0.1, \beta=0.001, d_I=0.5, p=100, d_V=3, k=0.5, a=0.01, r=0.3, h=0.01, d_C=0.1 \tau \text{and} D_V . D_C$$

4.2. Time-delay induced periodic oscillations of viral load

First examine the non-diffusion case, where the system degenerates into a system of time-delay ordinary differential equations. $(D_V=D_C=0)$ The critical delay values are obtained using the Hopf bifurcation criterion derived in Section 3.2. $\tau_0 \approx 2.3$ Take $\tau=1.5$ (subcritical) and $\tau=3.0$ (supercritical) for simulation, respectively.

When $\tau=1.5<\tau_0$, the infection equilibrium point gradually stabilizes: after the initial perturbation, the viral load shows damped oscillations and rapidly converges to a steady level, and the E_1 $CD8^+T$ effector cell density simultaneously tends to a steady state. This behavior mimics the clearance dynamics of acute self-limiting viral infections - CTL activation is delayed within an acceptable range, and the immune response is sufficient to contain the spread of the virus.

When =3.0>, $\tau\tau_0$ Hopf bifurcations occur and stable periodic solutions appear in the system. Viral load and CTL density oscillate in equal amplitude, with a period of approximately 18 time units. The oscillation phase relationship reveals that the virus peak is slightly ahead of the CTL peak, that is, the virus breaks out first, the CTL responds and suppresses the virus, the CTL decreases as the virus drops, the virus rises again when the CTL drops to a low point, and this cycle repeats. This pattern provides a class of mechanism explanations for the periodic “flash points” (blips) of viriemia observed in HIV-infected individuals: the prolonged delay in CTL activation leads to the fact that it is too late for the immune to follow, and the resulting lagging feedback loop is transformed into an intrinsic rhythmic outbreak of the system through Hopf bifurcations.

Amplitudes increase and cycles extend synchronously until oscillations tend to slack in large time-delay conditions - the virus remains at a low level for a long time and then suddenly erupts and is rapidly suppressed by a strong CTL response. τ The results suggest that it is possible to pull the system back to the stable zone and eliminate persistent oscillations by shortening the effective time delay (such as accelerating antigen presentation or vaccinating earlier).

4.3. Diffusion-driven spatial pattern formation

Introduce spatial diffusion and test the Turing instability conditions in Section 3.3. E_1 The uniform state is stable to the spatial perturbation at the reference parameters. When increased to 1.5 while maintaining =0.05, the initial uniform infection distribution spontaneously destabilizes after the ratio/exceeds the critical value. $D_V D_C D_V D_C$ The evolution is as follows: The initial random perturbation gradually increases, spatially differentiating into a regular pattern of alternating high-virus-density “hot zones” and low-density regions with wavelengths of approximately 1.2 spatial units. CTL density is enriched around the viral hot zone, forming an “encirclement” structure, while the hot zone remains highly infected due to local virus escape from the saturated killing of CTL.

The formation of the above spatial pattern is mainly based on the fact that when the viral diffusion coefficient is significantly higher than the T-cell diffusion coefficient, the rapid spatial spread of the virus will produce a positive feedback effect, while the slow response of CTL constitutes a long-term inhibitory effect - which is precisely the necessary prerequisite for the formation of the Turing pattern in the classical activator - inhibitory subsystem. From a biological perspective, this phenomenon can be used to explain the "immune cold region" in the tissue microenvironment: even if the systemic viral load is under control, the local tissue, due to insufficient infiltration of immune effector cells, becomes a sanctuary for low-level viral replication, a mechanism that precisely corresponds to the anatomical basis of the latent viral pool [4].

5. Conclusion

In this paper, by constructing an antiviral immune model of $CD8^+$T cells with time delay and reaction-diffusion, the intrinsic mechanism by which time delay and spatial diffusion are coupled to regulate viral infection dynamics was clarified. The main conclusions are as follows: First, the delay in $CD8^+$T cell activation has a dual effect. A moderate delay is beneficial for immune initiation, while an excessive delay provides a dynamic explanation for clinical phenomena such as HIV blips through the Hopf bifurcation-driven system. Second, the mismatch between viral diffusion ability and T cell migration rate $(\text{High} D_V / D_C \text{ratio})$ is a self-organizing mechanism for the formation of tissue-level "immune cold zones" - the appearance of spatial patterns does not require external lesion induction and is based solely on the Turing principle of local activation and long-range inhibition. Third, there is a coupling instability effect between time lag and diffusion, and the coexistence of the two can induce spatiotemporal chaotic behavior. Studies have shown that antiviral treatment requires both temporal and spatial strategies, and single-dimensional intervention is difficult to eliminate persistent infection.

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