Applied Mathematical Modelling 38 (2014) 6108–6121

Contents lists available at ScienceDirect

Applied Mathematical Modelling

journal homepage: www.elsevier.com/locate/apm

Global stability and periodic oscillations for an SIV infection model with immune response and intracellular delays

Haitao Song [a,*], Shengqiang Liu [b], Weihua Jiang [a], Jinliang Wang [c]

[a] Department of Mathematics, Harbin Institute of Technology, Harbin 150001, China
[b] The Academy of Fundamental and Interdisciplinary Science, Harbin Institute of Technology, 3041#, 2 Yi-Kuang Street, Harbin 150080, China
[c] School of Mathematical Science, Heilongjiang University, Harbin 150080, China

ARTICLE INFO

Article history:
Received 24 December 2012
Received in revised form 30 November 2013
Accepted 16 May 2014
Available online 29 May 2014

Keywords:
Simian immunodeficiency virus
CTL responses
Global stability
Hopf bifurcation
Lyapunov functional
Intracellular delays

ABSTRACT

In this paper, we consider the combined effects of cytotoxic T lymphocyte (CTL) responses on the competition dynamics of two Simian immunodeficiency virus (SIV) strains model. One of strains concerns a relatively slowly replicating and mildly cytopathic virus in the early infection (SIVMneCL8), the other is faster replicating and more cytopathic virus at later stages of the infection (SIVMne170). It is shown that the global dynamics of the ordinary differential equations can be determined by several threshold parameters, and we prove the global stability of the equilibria by rigorous mathematical analysis. To account for a series of infection mechanism leading to viral production, we incorporate time delays in the infection term. Using the methods of constructing suitable Lyapunov functionals and LaSalle's invariance principle, we obtain the sufficient conditions for the global attractiveness of infection-free equilibrium with both virus strains going extinct, single-infection equilibrium with one of two virus strains out-competing the other one and the two strains coexisting infection equilibrium. We establish that the intracellular delays can destabilize the single-infection equilibrium leading to Hopf bifurcation and periodic oscillations. We show that introduction of immune responses is responsible for the coexistence of two virus strains and the intracellular delays may alter the two-strain competition results. Numerical simulations are presented to illustrate the theoretical conclusions.

1. Introduction

Recently, clinical research combined with mathematical modeling has enhanced the understanding of Simian immunodeficiency virus (SIV) infection process, which is shown by a relatively slowly replicating and mildly cytopathic virus in the early infection and a faster replicating and more cytopathic virus at the later stage of infection [1]. In the process of infection, many common features are shared by SIV and HIV (Human Immunodeficiency Virus). They evolve and accommodate special selective pressures inside the host, resulting in the emergence of variants which may be different from the prior variants in the replication features. The fitness of the evolving variants is closely related to the conditions of viral replication [2]. During the initial infection, virus load rises to high levels in rapid, and the number of $CD4^+$ T helper cells which are the targets of the virus decreases to relatively low levels. The major site of $CD4^+$ T cell depletion and viral replication in SIV infection is gastrointestinal tract, especially the gut associated lymphoid tissue [3]. Afterwards, immune responses are stimulated and

* Corresponding author. Tel.: +86 451 86414209.
E-mail addresses: htsong@hit.edu.cn (H. Song), sqliu@hit.edu.cn (S. Liu), jiangwh@hit.edu.cn (W. Jiang), jinliangwang@hit.edu.cn (J. Wang).

http://dx.doi.org/10.1016/j.apm.2014.05.017
0307-904X/

virus load drop to lower levels, which is the symbol of the beginning for the asymptotic phase. As time goes on, virus load finally rises to high levels, which is the symbol of the onset for AIDS. However, the infection process from SIV to AIDS experiences a shorter time. In some experiments (see [4,5]), macaques were inoculated with a relatively slowly replicating and mildly cytopathic virus SIVMneCL8. At the later stage of the infection, a faster replicating and more cytopathic virus SIVMne170 appears.

Wodarz [1] formulated a two SIV strains model without immune responses as follows

$$\begin{cases} \frac{dx(t)}{dt} &= \lambda - dx(t) - x(t)(\beta_1 y_1(t) + \beta_2 y_2(t)), \\ \frac{dy_1(t)}{dt} &= \beta_1 x(t) y_1(t) - (d + a_1) y_1(t), \\ \frac{dy_2(t)}{dt} &= \beta_2 x(t) y_2(t) - (d + a_2) y_2(t), \end{cases} \tag{1}$$

where $x(t)$, $y_1(t)$, and $y_2(t)$ are the density of uninfected host cells, cells infected with virus strain 1 and cells infected with virus strain 2 at time t, respectively. Since the population of free viruses turns over with dramatically quicker rate than the population of infected cells, the model does not contain a variable of free viruses. The population of free viruses was assumed to be in a quasi-steady state. Furthermore, it was assumed in [1] that virus strain 1 is slowly replicating and mildly cytopathic, while virus 2 is faster replicating and more cytopathic, and that the variance of the two SIV strains in the cytopathic rate is higher than the variance in the replication rate. λ is the growth rate of uninfected host cells and d is the natural death rate of uninfected host cells. They become infected by virus strain 1 with a rate β_1 and by virus strain 2 with a rate β_2. $d + a_1$ and $d + a_2$ are the death rates of infected cells. By numerical simulations, Wodarz [1] showed that the basic reproductive ratio determines the outcome of the competition and the virus strain with the greater basic reproductive ratio out-competes the other virus strain, which are consistent with the arguments in [2].

Wodarz [1] added a CTL response into the model and by the methods of numerical simulations examined the effects of such a CTL response on the competition dynamics. The CTL responses were used in [6,7], which assumed that CTL proliferate in response to antigenic stimulation, and decay with a slow rate in the absence of antigenic stimulation. z denotes the population of CTL, c denotes the CTL proliferate rate and b is the decay rate of CTL. Then the system (1) is re-written as follows:

$$\begin{cases} \frac{dx(t)}{dt} &= \lambda - dx(t) - x(t)(\beta_1 y_1(t) + \beta_2 y_2(t)), \\ \frac{dy_1(t)}{dt} &= \beta_1 x(t) y_1(t) - (d + a_1) y_1(t) - p y_1(t) z(t), \\ \frac{dy_2(t)}{dt} &= \beta_2 x(t) y_2(t) - (d + a_2) y_2(t) - p y_2(t) z(t), \\ \frac{dz(t)}{dt} &= cz(t)(y_1(t) + y_2(t)) - bz(t). \end{cases} \tag{2}$$

For system (2), by numerical simulations, the author studied the competition dynamics about SIVMneCL8 and SIVMne170, and investigated the effect of CTL responses on the outcome of competition. The results revealed that the emergence of special CTL responses could not be the selection of more cytopathic strain SIVMne170 at the later stage of the infection. The relative value of R_0 determines the outcome of competition when CTL responses could kill virus effectively and control virus load, so the CTL response may be a very important factor determining the outcome of competition.

The virus life cycle plays a crucial role in the progress of SIV infection. In model (2), it was assumed that the target cell becoming infected and producing virus as soon as virus contacts a target cell. However, as showed in [8], there is a time delay between initial viral entry into a cell and subsequent viral production. As described in [8], we assume $\beta_3 = \beta_1 e^{-\alpha_1 \tau_1}$ and $\beta_4 = \beta_2 e^{-\alpha_2 \tau_2}$, where $\alpha_i (i = 1, 2)$ are the death rates of infected cells before viral production commences, τ_1 and τ_2 are the intracellular delays between viral entry and viral production. $e^{-\alpha_1 \tau_1}$ and $e^{-\alpha_2 \tau_2}$ are the probabilities that an infected cell survives the eclipse phase to produce virion. Here, we incorporate two intracellular delays τ_1 and τ_2 into the model (2). Then we obtain the following SIV model with immune response and intracellular delays:

$$\begin{cases} \frac{dx(t)}{dt} &= \lambda - dx(t) - x(t)(\beta_1 y_1(t) + \beta_2 y_2(t)), \\ \frac{dy_1(t)}{dt} &= \beta_3 x(t - \tau_1) y_1(t - \tau_1) - (d + a_1) y_1(t) - p y_1(t) z(t), \\ \frac{dy_2(t)}{dt} &= \beta_4 x(t - \tau_2) y_2(t - \tau_2) - (d + a_2) y_2(t) - p y_2(t) z(t), \\ \frac{dz(t)}{dt} &= cz(t)(y_1(t) + y_2(t)) - bz(t). \end{cases} \tag{3}$$

In a series of experiments, it was observed that the life span of cells influences viral fitness. Moreover, if the cell is naturally long lived, SIVMneCL8 is more fit than SIVMne170; if the cell is naturally short lived, SIVMne170 is more fit than SIVMneCL8 [2]. Then it is interesting for us to investigate the effect of the intracellular delays on the outcome of competition.

Our goal in this paper is to study the dynamics of systems (2) and (3). We will show that the global dynamics of systems are determined by several key threshold parameters, which are termed as the basic reproductive ratios for viral infection and second basic reproductive ratios for CTL responses, respectively. We prove that the equilibria are globally stable for a large range of parameter values. In [9], Li and Shu showed that whether intracellular delays can cause periodic oscillations is critically connected to the target cell dynamics. Therefore, we establish that the intracellular delays can destabilize the single-infection equilibrium leading to Hopf bifurcation and periodic oscillations. The proofs of our main results involve the methods of constructing Lyapunov functionals which has been successfully employed in [10–12,9,13–17]. In addition, there