Occurrence of periodic oscillations mediated by programmed proliferation of CTLs

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ABSTRACT

Dynamics of interaction between pathogen and immune system within a host is studied. Cytotoxic T Lymphocytes (CTLs) develop through an antigen-independent proliferation and differentiation program, which is referred as programmed CTL proliferation [3]. Mechanisms underlying the clearance of pathogen via CTLs expanded in programmed proliferation manner has not yet to be understood. In this paper, we investigate how programmed proliferation of CTLs would operate to eliminate pathogens. Periodic oscillations of CTLs can occur by programmed proliferation of CTLs provided that the proliferation of CTLs is strongly promoted by the stimulation of pathogens and programmed proliferation is not sufficient to eliminate pathogens completely.

Key words: immune system; cytotoxic T lymphocyte (CTL); chronic infection; programmed proliferation;

1   Introduction

Cytotoxic T lymphocyte (CTL) plays an important role in eliminating pathogens invaded in a host. Recent studies suggest that CTLs develop through an antigen-independent proliferation and differentiation program, which is referred as programmed proliferation [1], [3]. Mechanisms underlying the clearance of pathogen via CTLs expanded in programmed proliferation manner has not yet to be understood. In this paper, we investigate how the introduction of programmed proliferation would affect to the dynamics of pathogen-CTL interactions.

Let x and y denote the densities of pathogen and CTL, respectively. The programmed proliferation rate, denoted by $p(y)$, is normalized to ensure that the value of $p(y)$ is assigned between 0 and 1. We restrict ourselves to assume that $p(y) = \frac{my}{h+y}$. The model is given by

$$\begin{cases} x' = rx\left(1 - \dfrac{x}{K}\right) - \gamma xy, \\ y' = \alpha xy + m\dfrac{y}{h+y}y - (\mu + \delta y)y. \end{cases} \tag{1.1}$$

Initial condition is given by the points taken from the following nonnegative cone:

$$\Omega := \{(x,y) \in \mathbb{R}^2 | x \geq 0, y \geq 0\}. \tag{1.2}$$

Here r and K denote the rate of replication and the carrying capacity of pathogen, respectively. We assume that elimination of pathogen is achieved proportional to the density of both pathogens and CTLs with a constant rate γ. The proliferation of CTLs are initiated by two different ways. One way is a stimulation by pathogens. Proliferation of CTLs via stimulation is thereby a function of the density of pathogen. For simplicity, we assume that the degree of stimulation is proportional to the densities of pathogens and CTLs with a constant rate α. Another way is via programmed proliferation. Let m denote the maximum proliferation rate which is mediated by programmed proliferation. μ is the natural death rate of CTLs. Density dependent cell death can occur by inducing apoptosis and so on. Here we assume that density dependent cell death of CTLs is represented by $-\delta y^2$. Functional form of programmed proliferation can be derived from the quasi-steady state approximation for autocrine signalling mediated by self-secreting cytokines. A well known example for autocrine/paracrine proliferation is clonal expansion of CTL via self-secreting IL-2 activation. Let $c(t)$ denote the concentration of IL-2 secreted by CTLs themselves. The interaction between CTL and IL-2 is described by the following equations:

$$\begin{aligned} c'(t) &= ky(t) - dc(t), \\ y'(t) &= m\frac{c(t)}{h' + c(t)}y - (\mu + \delta y(t))y(t). \end{aligned} \tag{1.3}$$

Now we assume that the dynamics of IL-2 is very fast compared to the population dynamics of CTLs. Thus quasi-steady state approximation for the dynamics of IL-2 yields $c(t) = ky(t)/d$. Substituting approximated $c(t)$ into the second equation of (1.3) gives the second equation of (1.1) without the effect of activation from pathogen.

Parameter h is an important parameter to determine the shape of proliferation profile of CTLs. System (1.1) corresponds to the classical Lotka-Volterra prey-predator system if $h = 0$ and $m < \mu$. On the other hand, $p(y) \to 0$ as $h \to \infty$. These observations imply that the dynamics of system (1.1) is expected to behave like the classical Lotka-Volterra prey-predator system if h is either small or sufficiently large. Note that the positive equilibrium of the classical Lotka-Volterra prey-predator system is globally asymptotically stable whenever it exists. Chronic infection by pathogens is always established if no programmed proliferation of CTLs is considered. Hereafter we shall investigate how the programmed proliferation mediated by autocrine/paracrine proliferation affects to dynamics generated by pathogen-CTL interaction.

2   Numerical simulations

We shall perform numerical computations to investigate whether periodic oscillations can occur. The parameters for our numerical computations are given by

$$r = 1.0, K = 5.0, \gamma = 0.5, \alpha = 1.0, m = 4.5, \mu = 3.0, \delta = 0.5. \qquad (2.1)$$

With this parameter setting, $\mu < \alpha K$. This implies that stimulation by pathogen is sufficiently strong to activate CTL responses. By numerical computations we confirmed that there always exists a unique persistent equilibrium, denoted by E^p. Numerical continuation by MATCONT [2] is carried out to investigate the occurrence of Hopf bifurcation. Parameter h is used as a control parameter. System (1.1) undergoes Hopf bifurcations twice (see Figure 1). For h near 0.833, the real part of the first Lyapunov coefficient is $8.0 \times 10^{-3} > 0$, implying that the type of Hopf bifurcation is subcritical. On

the other hand, for h near 2.33, we found that the type of Hopf bifurcation is supercritical. Periodic oscillations are observed for h between these two critical values (see Figure 2).
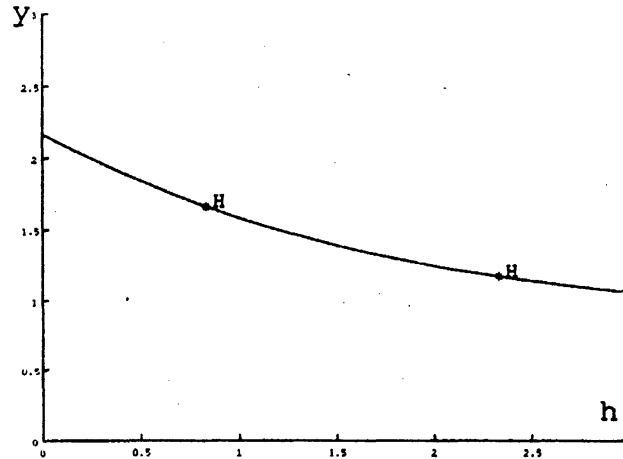

Figure 1: Stability diagram of (1.1). Equilibrium value of CTLs, y, is drawn with respect to the change of parameter h. System (1.1) undergoes Hopf bifurcations twice for particular values of h as indicated in red star marks.

3 Conclusions

We found that periodic oscillations can occur if programmed proliferation of CTLs is incorporated in the classical Lotka-Volterra prey-predator system. Note that $\mu < \alpha K$. Hence CTLs are stimulated by pathogens sufficiently strong to proliferate. If CTLs do not undergo programmed proliferation, the population density would decrease following the decline of the pathogen density, and subsequently the pathogen density increases because the population density of CTLs is not maintained by low density of pathogens without programmed proliferation. It is expected that with the default parameters, programmed proliferation of CTLs does exist but is not sufficiently effective. In this way, pathogens can persist within a host. Parameter h determines how fast the programmed proliferation reaches the maximum proliferation rate. If h is small, programmed proliferation would act as continuous input whereas
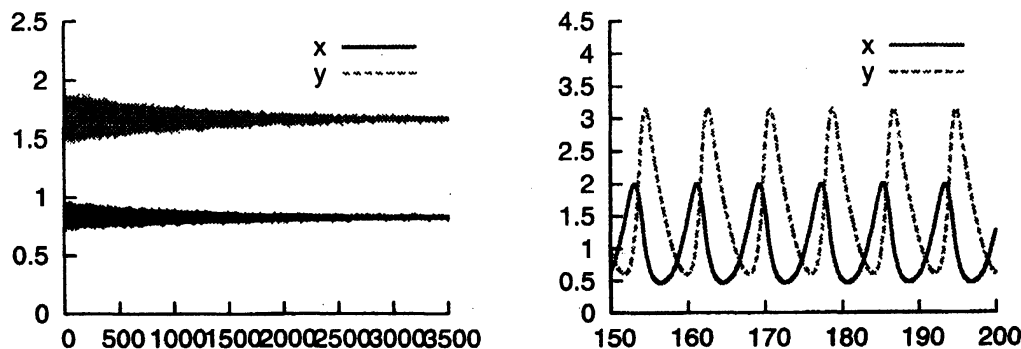
Figure 2: Numerical simulation results with the set of parameters (2.1). $h = 0.83 < 0.8333$, implying that the positive equilibrium is locally asymptotically stable. Periodic oscillations can be observed even if the positive equilibrium is stable by the occurrence of subcritical Hopf bifurcation. Left: Convergence to steady state (initial condition $x(0) = 0.8$ and $y(0) = 1.5$). Right: Periodic oscillations ($x(0) = 2.0$ and $y(0) = 1.5$).

the rate increases linearly if h is sufficiently large. Our numerical simulations suggest that periodic oscillations occur for intermediate h. Another aspects of pathogen-CTL interactions are studied as our future work.

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