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Global stability and periodic solution of a model for HTLV-I infection and ATL progression ☆

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Abstract

Human *T*-cell lymphotropic virus I (HTLV-I) infection is linked to the development of adult *T*-cell leukemia/lymphoma (ATL), among many illness. The healthy $CD4^+$ *T* cells infect HTLV-I through cell-to-cell contact with infected *T*-cells. The infected *T* cells can remain latent and harbor virus for several years before virus production occurs. Actively infected *T* cells can infect other *T* cells and can convert to ATL cells, whose growth is assumed to follow a classical logistic growth function. In this paper, we consider the classical mathematical model with saturation response of the infection rate. By stability analysis we obtained the condition for the infected *T* cells die out and the condition for HTLV-I infection becomes chronic. At the same time, we also obtained the condition for a unique endemic equilibrium is globally stable in the interior of the feasible region.

Keywords: Chronic HTLV-I infection; Adult *T*-cell leukemia; Basic reproduction number; Global stability

1. Introduction

Infection by HTLV-I is characterized by cell-to-cell infection [1–3] of $CD4^+$ *T* cells which HTLV-I preferentially infects [4,5]. Primary infection leads to a chronic infection that seems to last lifelong. Typically, a small fraction of infected individuals progress to disease and about 2–5% of HTLV-I carriers develop symptoms of ATL [6].

HTLV-I is a single-stranded RNA retrovirus with reverse transcriptase activity that leads to a DNA copy of the viral genome, The viral DNA copy is then integrated into the DNA of the host genome. After integration, the viral DNA can latently persist within a *T* cell for a long time. The latent infected *T* cells contain the viral DNA but are not producing it, and they cannot cause new infections of susceptible cells. Stimulation of

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the latent infected $CD4^+$ T cells by antigen can initiate activation of the infected cells. Actively infected T cells can produce virus and can cause new infections of susceptible T cells. Actively infected T cells may then convert to ATL cells through certain mechanisms which are not yet known.

HTLV-I infection in $CD4^+$ T cells takes place through cell-to-cell contact between actively infected cells and uninfected (susceptible) by the mass-action term kT_AT, where k is the infection rate which accounts for the overall effects of HTLV-I reproduction such as contact rate and infectivity. This type of term is sensible, since actively infected T cells must meet T cells in order to infect them and the probability of virus encountering a T cell at low concentrations (when actively infected T cells and T cells motion can be regarded as independent) can be assumed to be proportional to the product of their concentration, which is called linear infection rate. Thus, in what follows, the classical models assume that infected T cells at rate $-kT_AT$ and the generation of infected T cells at rate kT_AT.

In [7], Stilianakis and Seydel developed a mathematical model that describes the T-cell dynamics of the HTLV-I infection and the development of ATL. The model is formulated by the following system of non-linear differential equations:

$$\begin{cases} \dot{T} = \lambda - \mu_T T - kT_AT, \\ \dot{T}_L = kT_AT - (\mu_L + \alpha)T_L, \\ \dot{T}_A = \alpha T_L - (\mu_A + \rho)T_A, \\ \dot{T}_M = \rho T_A + \beta T_M\left(1 - \frac{T_M}{T_{M\max}}\right) - \mu_M T_M, \end{cases} \tag{1.1}$$

where T, T_L, and T_A denote the numbers of uninfected, latent infected, actively infected $CD4^+$ T cells, and T_M the number of leukemia cells, respectively. It is assumed that the body produces $CD4^+$ T cells at a constant rate λ and newly produced T cells are assumed to be susceptible. The parameter α is the transmission rate at which latent infected $CD4^+$ T cells become actively infected, and ρ is the transmission rate at which actively infected $CD4^+$ T cells convert to ATL cells; thus $1/\alpha$ and $1/\rho$ can be regarded as the mean latent and infectious periods, respectively. The death or removal rates for uninfected, latent infected, actively infected $CD4^+$ cells, and ATL cells are μ_T, μ_L, μ_A, and μ_M, respectively. ATL cells proliferate at rate β of a classical logistic growth function. $T_{M\max}$ is the maximal number that ATL cells can grow. All parameters in the model are assumed to be positive constants.

In principle, the rate of infection should saturate at high actively infected T cells concentration. For example, if the amounts of actively T cells exceeds T with a few magnitude of order, then a simple first order mass action is not reasonable, because increase in actively infected T cells in that case will not increase infection. Thus, it is reasonable for us to assume that the infection rate of modelling HTLV-I infection in saturated mass action, $kT_A^pT/(1 + \alpha_1 T_A^q)$, where p, q, $\alpha_1 > 0$ are constants.

(1.1) has been investigated by Wang et al. [8]. In this paper, we shall investigate the model with saturation response of the infection rate ($p = q = 1$). The model can be written as the following form:

$$\begin{cases} \dot{T} = \lambda - \mu_T T - \frac{kT_AT}{1+\alpha_1 T_A}, \\ \dot{T}_L = \frac{kT_AT}{1+\alpha_1 T_A} - (\mu_L + \alpha)T_L, \\ \dot{T}_A = \alpha T_L - (\mu_A + \rho)T_A, \\ \dot{T}_M = \rho T_A + \beta T_M\left(1 - \frac{T_M}{T_{M\max}}\right) - \mu_M T_M. \end{cases} \tag{1.2}$$

2. Model formulation and main results

Adding the first three equations in (1.2), we have

$$(T + T_L + T_A)' = \lambda - \mu_T T - \mu_L T_L - (\mu_A + \rho)T_A \leqslant \lambda - \gamma(T + T_L + T_A),$$

where $\gamma = \min\{\mu_T, \mu_L, \mu_A + \rho\}$. Hence $\lim_{t\to\infty}\sup(T + T_L + T_A) \leqslant \lambda/\gamma$. The last equation of (1.2) then leads to the logistic inequality, $\dot{T}_M \leqslant \rho\lambda/\gamma + \beta T_M(1 - T_M/T_{M\max}) - \mu_M T_M$, which in turn implies $\lim_{t\to\infty}\sup T_M \leqslant \widetilde{T}_M$,