Journal of Theoretical Biology 365 (2015) 337–346

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Dynamical analysis on a chronic hepatitis C virus infection model with immune response

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HIGHLIGHTS

- Our model for HCV infection includes the effect of dendritic cells and cytotoxic T lymphocytes.
- The basic reproduction numbers of chronic HCV infection and immune control are determined.
- Some complex dynamics including the occurrence of backward bifurcation and Hopf bifurcation are found.
- Our results show that the outcome of immune response may depend on the initial condition.
- The effect of dendritic cells and cytotoxic T lymphocytes on HCV infection is investigated.

ARTICLE INFO

Article history:
Received 19 May 2014
Received in revised form
23 August 2014
Accepted 29 October 2014
Available online 7 November 2014

Keywords:
Equilibrium
Backward bifurcation
Hopf bifurcation

ABSTRACT

A mathematical model for HCV infection is established, in which the effect of dendritic cells (DC) and cytotoxic T lymphocytes (CTL) on HCV infection is considered. The basic reproduction numbers of chronic HCV infection and immune control are found. The obtained results show that the infection dies out finally as the basic reproduction number of HCV infection is less than unity, and the infection becomes chronic as it is greater than unity. In the presence of chronic infection, the existence of immune control equilibrium is discussed completely, which illustrates that the backward bifurcation may occur under certain conditions, and that the two quantities, the sizes of the activated DC and the removed CTL during their average life-terms, play a critical role in controlling chronic HCV infection and immune response. The occurrence of backward bifurcation implies that there may be bistability for the model, i.e., the outcome of infection depends on the initial situation. By choosing the activated rate of non-activated DC or the cross-representation rate of activated DC as bifurcation number, Hopf bifurcation for certain condition shows the existence of periodic solution of the model. Again, numerical simulations suggest the dynamical complexity of the model including the instability of immune control equilibrium and the existence of stable periodic solution.

1. Introduction

Approximately 200 million people worldwide are infected with hepatitis C virus (HCV) (Shepard et al., 2005). The virus can be cleared spontaneously during acute infection. One of the main characteristics of HCV is its high propensity to establish chronic infection. By definition, hepatitis C is regarded to be chronic after persistence of more than six months (Liang et al., 2000; Alter, 2007). About 85% of infected patients established a chronic course. Once chronic infection is established, there is a very low rate of spontaneous clearance. This increases their risk for developing liver cirrhosis and hepatocellular carcinoma (Lavanchy, 2011).

In 1998, Neumann et al. (1998) first adapted a model of human immunodeficiency virus infection (Wei et al., 1995; Perelson et al., 1996) to research the dynamics of chronic HCV infection during treatment, in which it is assumed that the target cells (i.e. the hepatocytes) are produced in a constant rate. The model under the simplified assumption is not able to explain some observed dynamical features of HCV infection after the cessation of therapy (Dahari et al., 2007a). To model complex dynamics of HCV infection, the assumption of a constant inflow rate of target cells may be relaxed according to the fact that the liver is an organ with regenerative ability and that the loss of hepatocytes would be compensated for by the proliferation of existing hepatocytes (Fausto, 2004; Michalopoulos and DeFrances, 1997), thus the

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http://dx.doi.org/10.1016/j.jtbi.2014.10.039
0022-5193/

corresponding models would be more reasonable relative to realistic situations. Thereafter some researchers (see Reluga et al., 2009; Dahari et al., 2007b and references cited therein) incorporated the inflow rate of target cells, depending on the number of existing hepatocytes, into the original models to analyze the dynamics of HCV load during acute infection, under antiviral therapy, and after the cessation of therapy.

Recently, molecular techniques have provided fundamental insight into the molecular mechanisms of immune system for HCV infection (Zein, 2000; Puoti et al., 1992; Sharma, 2010; Plauzolles et al., 2013). But many biologically important questions are primarily concerned with the population dynamics of the immune response. Such questions usually cannot be answered by experimental methods alone but require the help of mathematical modeling and analysis. In 1996, Nowak and Bangham (1996) established a simple mathematical model to explore the relation between antiviral immune response and virus load. In 2003, Wodarz (2003) extended the model in Nowak and Bangham (1996) to investigate the role of cytotoxic T lymphocyte (CTL) and antibody response in HCV dynamics and pathology. In Nowak and Bangham (1996) and Wodarz (2003), they assumed that the inflow rate of target cells is constant. Zhou et al. (2009) considered a virus infection model with CTL immune response, where the growth of target cells is assumed to be dependent on existing target cells, and found that there are periodic orbits arising from Hopf bifurcation.

Though many important research results on HCV infection have been achieved by means of clinical trials and mathematical modeling, the mechanisms of HCV persistence are still not fully understood. This is largely related to inefficient clearance of the virus by the host immune system. Dendritic cells (DC) are the most important antigen-presenting cells for host immune responses. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system (see Zhou et al., 2012; Pachiadakis et al., 2005 and references cited therein). During the past decade, many research groups have focused on DC in order to unravel an HCV-specific DC signature or DC-dependent mechanisms of antiviral immunity which would lead to a successful HCV elimination strategy (Echeverria et al., 2011; Barth et al., 2005; Sehgal et al., 2013; Dolganiuc and Szabo, 2011; Matheoud et al., 2010). When HCV invade the liver, non-activated DC are loaded and activated due to the existence of infected hepatocytes, and activated DC are required for cross-presentation and CTL induction (Lechner et al., 2000). Up to now, it is rare to consider the effect of DC on CTL response and dynamics of chronic HCV infection.

Wodarz and Jansen (2003) suggested a mathematical model describing the mechanism of immune cell activation. They considered the phenomenon of cross-presentation in contrast to direct presentation, where cross-presentation means that antigen is recognized on the surface of professional antigen presenting cells (APCs) and then immune cells are induced, while direct representation means that antigen is seen on the surface of the target cells (i.e. infected cells) and immune cells directly act on antigen. The model in Wodarz and Jansen (2003) only described the effect of immune system on antigen, but does not include the viral infection.

In this paper, our motivation is to investigate the effect of immune system on chronic HCV infection. To this end, based on the framework of the model in Reluga et al. (2009), Dahari et al. (2007b), and Wodarz and Jansen (2003), we propose a simple model with immune response for chronic HCV infection, where it is assumed that CTL expand through cross-representation of DC, eliminate infected hepatocytes by direct action, and are removed due to direct presentation. Again, HCV infection is also considered in our model, in which we assume that the growth of healthy hepatocytes follows the logistic model depending on existing

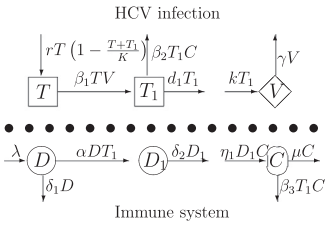

Fig. 1. Schematic representation of the mathematical model.

hepatocyte. By theoretical analysis and numerical simulations, we will show the dynamical complexity of the model, including the backward bifurcation and the existence of periodic solution, and demonstrate the relation between chronic HCV infection and immune response.

The organization of this paper is as follows. In Section 2 we construct a model of HCV infection with immune response including DC and CTL, and show the boundedness of solutions of the model. In Sections 3 and 4 we investigate existence and the stability of the boundary equilibria and positive equilibria, respectively. In Section 5 we make some numerical simulations for the case that the model has positive equilibrium. In Section 6 the effect of parameters related to immune response on HCV infection is analyzed, and Hopf bifurcation is illustrated for certain situation by choosing the activated rate of non-activated DC or the cross-representation rate of activated DC as bifurcation number. In Section 7 we briefly summarize our theoretical and numerical analysis.

2. Formulation of model and the boundedness

The model considered here consists of two parts: one based on the models in Dahari et al. (2007a,b) and Reluga et al. (2009) describes HCV infection, the other based on the model in Wodarz and Jansen (2003) formulates the effect of immune system including DC and CTL on HCV infection. The corresponding schematic diagram is shown in Fig. 1. The two parts of the model are connected by the infected hepatocytes and CTL response. The detailed explanations are described in the following two paragraphs.

For consideration of HCV infection, there are three variables: healthy hepatocytes (T), infected hepatocytes (T_1) and free virus (V). We assume that, in the absence of HCV infection, hepatocytes grow at a density-dependent rate $rT(1-T/K)$, where r is the intrinsic proliferation rate, and K is the carrying capacity of hepatocytes in the uninfected individual. After HCV invade the liver, only the healthy hepatocytes (T) have the ability to proliferate. Healthy hepatocytes (T) are infected at a rate β_1 per free virus per hepatocyte, infected hepatocytes (T_1) produce free virus (V) at a rate k per cell but also die with a rate d_1 per cell, free virus (V) is cleared at a rate γ. Again, infected hepatocytes are in addition lysed by CTL at a rate β_2 per cell per CTL as the CTL response sets up.

When considering the effect of immune system on HCV infection, there are also three variables: non-activated DC (D) which do not present antigen, loaded and activated DC (D_1) which have taken up antigen and display it, and CTL (C). We assume that non-activated DC (D) are produced at a constant rate λ and die at a rate δ_1 per non-activated DC. They take up antigen and become activated at a rate α per infected hepatocyte per non-activated DC. Activated DC (D_1) are lost at a rate δ_2 per activated DC. It is assumed that upon cross-presentation CTL (C) expand at a rate η per infected hepatocyte per activated DC, and direct presentation results in removal of CTL at a rate β_3 per infected hepatocyte per CTL, and CTL (C) die at a rate μ per CTL.