Commun Nonlinear Sci Numer Simulat 59 (2018) 488–514

Contents lists available at ScienceDirect

Commun Nonlinear Sci Numer Simulat

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

Research paper

Block effect on HCV infection by HMGB1 released from virus-infected cells: An insight from mathematical modeling

Wei Wang, Wanbiao Ma*

Department of Applied Mathematics, School of Mathematics and Physics, University of Science and Technology Beijing, Beijing 100083, China

ARTICLE INFO

Article history:
Received 29 November 2016
Revised 20 July 2017
Accepted 23 November 2017
Available online 5 December 2017

Keywords:
HCV
Block effect
HMGB1
Basic reproduction number
Spreading speed
Travelling wave solutions

ABSTRACT

The nuclear protein high-mobility group box 1 (HMGB1) can have an active role in deoxyribonucleic acid (DNA) organization and the regulation of transcription. Based on the new findings from a recent experimental study, the blocking effect on HCV infection by HMGB1 released from virus-infected cells is investigated using a diffusive model for viral infection dynamics. In the model, the diffusion of the virus depends not only on its concentration gradient, but also on the concentration of HMGB1. The basic reproduction number, threshold dynamics, stability properties of the steady states, travelling wave solutions, and spreading speed for the proposed model are studied. We show that the HMGB1-induced blocking of HCV infection slows the spread of virus compared with random diffusion only. Numerically, it is shown that a high concentration of HMGB1 can block the spread of virus and this confirms, not only qualitatively but also quantitatively, the experimental result.

1. Introduction

Hepatitis C virus (HCV) has spread quickly to most regions around the world since its discovery. HCV is regarded as one of the major causative agents of hepatitis, linear cirrhosis, and hepatocellular carcinoma (HCC) [1,2]. It is estimated that more than 170 million people worldwide are infected with HCV [1]. Chronic and persistent infection is a characteristic feature of HCV pathogenesis [2]. A great number of treatment strategies have been frequently applied to try to cure the aforementioned disease [3–5]. However, there is currently no effective vaccination method or approved therapy for HCV. In recent years, the study of viral dynamics using mathematical models has had a substantial impact on understanding the within-host dynamics of HCV [10–12,18].

The highly conserved nuclear protein high-mobility group box 1 (HMGB1) plays an active role in DNA organization and the regulation of transcription. HMGB1 also plays a significant role as a cytokine, mediating the responses to infection and inflammation [6–8,14]. A great deal of research has shown that extracellular HMGB1 can function not only by itself but also in association with other molecules, such as CpG DNA, lipopolysaccharide (LPS), and interleukin-1 (IL-1) [9]. All kinds of cellular responses that can contribute to innate immunity, tissue repair, and cell migration can be induced by HMGB1 protein. It is widely known that viruses are usually thought to spread in infected hosts through an iterative process that involves entry of virus into the cell, reverse transcription of viral RNA to DNA, and integration of viral DNA into the host-cell genome. In view of such a mechanism, the spreading speed of a virus can be limited by the reproduction of the virus

* Corresponding author.
E-mail addresses: weiw10437@gmail.com (W. Wang), wanbiao_ma@ustb.edu.cn (W. Ma).

https://doi.org/10.1016/j.cnsns.2017.11.024
1007-5704/

in infected cells. A recent study by Jung et al. [13] revealed that HCV infection can be blocked by HMGB1 released from virus-infected cells. In their experiment, Jung et al. selected purified wild-type HMGB1 (30 or 300 ng/ml) proteins to treat Huh7.5.1 cells for 18 h and then infected these cells with JFH/5aRluc virus for 3 days. The authors then used luciferase assays to monitor the proliferation of HCV. After the treatment of purified wild-type HMGB1 proteins, the relative virus infectivity is decreased from 100% to 75% (54%) when the concentration of purified wild-type HMGB1 proteins is 30 (300) ng/ml [13].

To explain this phenomenon, a new molecular mechanism was discovered, that is, the blocking effect on HCV infection by HMGB1 released from virus-infected cells. In [7,13], HMGB1 protein can be translocated from the nucleus to cytoplasm. Then it can be released into the extracellular milieu from infected cells by HCV infection [7,13,15]. Secreted HMGB1 can trigger an antiviral response and block the spread of HCV [7,13,15]. Indeed, Toll-like receptor (TLR4), similarly to other potential receptors (RAGE, TLR2, and TLR9), can not only trigger proinflammatory responses through nuclear factor kappa B (NF-κB) activation but also mediate antiviral responses through the activation propagation of HCV infection [13]. Hence, the anti-HCV activity of HMGB1 can be mediated by TLR4, which is the receptor candidate [7,13,15]. By monitoring the effects of TLR4 knockdown and over-expression on HCV infection, Jung et al. [13] showed that secreted HMGB1 can trigger the production of antiviral proteins through TLR4-mediated interferon responses, which can prevent the generation of new viruses [13,15,16].

The anti-HCV effect of HMGB1 can also contribute to limiting the propagation of HCV. TLR4, which is the major component of the LPS, can engage in downstream signaling through myeloid differentiation primary response gene 88 (MyD88) and the Toll-like adapter protein TRIF to produce proinflammatory cytokines and type I interferons (IFNS), which participate in blocking the propagation of HCV [13,16]. IFNS can induce the dsRNA-activated serine, which is now known as PKR. Viral-specific RNAs can activate PKR and this inhibits the propagation of the virus and the production of virion progeny [13,16,17].

Mathematical models have been confirmed to be an effective approach to understand the dynamical behavior of viral infection. The dynamical properties of a variety of viruses such as human immunodeficiency virus (HIV-1), hepatitis B virus (HBV), HCV, and human T-cell leukemia type-1 (HTLV-1) infections have been studied by considerable mathematical models [37,38,43,50]. Most of these works assume that cells (both uninfected and infected) and virus are well mixed. Indeed, spatial structure plays an important role in understanding the dynamical behavior of viral dynamics. Wang and Wang [34] developed a diffusive mathematical model to describe the infection of HBV under the assumption of well-mixed susceptible host cells and infected cells. However, they assumed that the virus can move from a high-concentration region to a low-concentration region. For this model, a minimal wave speed was estimated. In subsequent papers, diffusive HBV infection models with time delay were investigated [35,37,38]. In these models, the global stabilities of the steady states and the existence of travelling wave solutions were investigated. Lai and Zou [39] constructed a general virus infection model to investigate the influence of the repulsion effect of superinfecting virion by infected cells (see also [40]). Wang et al. [41] developed a diffusive chemotaxis mathematical model to study the repellant activity of infected cells on virus.

The Beddington–DeAngelis functional response, which was first introduced by Beddington [58] and DeAngelis et al. [59] in the predator–prey model, has the following form

$$p(U,V)=\frac{aU}{1+bU+cV}.$$

Here U and V are the densities of the prey and predator populations, b determines how fast the per-capita feeding rate approaches its saturation value a, and c measures the magnitude of the mutual interference between individuals of the predators. The Beddington–DeAngelis functional response has similar characteristics to the saturation response $\beta UV/(1+nV)$ and this can lead to less infection than a linear response due to saturation at high virus concentration. However, the Beddington–DeAngelis functional response has an extra term mU in the denominator modeling mutual interference among healthy cells. Thus, this kind of functional response is affected by the concentration of both healthy cells and free virus. The high concentration of both healthy cells and free virus can inhibit the increase of infected cells [42]. In recent years, some further research studying viral infection models by using the Beddington–DeAngelis functional response have received wide attention [38,42]. Hence, we further consider an HCV infection dynamic model by adding the Beddington–DeAngelis functional response as the incidence rate that is defined by

$$\frac{\beta(x)U(x,t)V(x,t)}{1+m(x)U(x,t)+n(x)V(x,t)}.$$

Here $m(x)$ determines how fast the infection rate approaches its saturation value and $n(x)$ is a measure of virus interference during infection, which depends on the location x, under the assumptions of spatially heterogeneous infection.

From the biological perspective, in this paper we consider the blocking effect on HCV infection by HMGB1 released from virus-infected cells in the within-host environment. Let $U(x,t)$, $I(x,t)$, $H(x,t)$, and $V(x,t)$ represent the concentration of target cells, infected cells, HMGB1, and virus at time t and location x, respectively. Thus, we consider the following HCV infection