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Modelling of the Immune Response to Viral Infection †

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Abstract: The spreading of the respiratory viral infections is currently being widely investigated, and the influence of the immune response on these infection spreading is of particular interest. In this work, the set of hierarchical models for the infection spreading with respect to the immune response is formulated and analysed. The models are based on the one-dimensional reaction-diffusion equations, and they are investigated both numerically and analytically. For these models the speed of the wave propagation and the total viral load are evaluated, and their dependencies on the parameters characterizing the intensity of the innate and adaptive immune response are defined. These results show that more intense immune response leads to the small infectivity and severity of the decease. Different parts of the immune response influence the infectivity and severity of the decease in different ways. These dependencies can help in planning of the treatment strategy.

Keywords: immune response; adaptive immune response; innate immune response; interferon; CTL; antibodies; reaction-diffusion equations

1. Introduction

Investigations of respiratory viral infections have always attract much attention as socially significant deceases. The respiratory virus can be characterized by its infectivity, showing how easily it transmits between individuals, and by its virulence, which correlates to the severity of virus induced decease. The organism reacts to the viral infection by immune response. At the first stage of infection the innate immune response is activated. It contains the interferon (IFN) system, which down-regulates the virus replication at every stage [1–3]. The innate immune response activates the adaptive immune response through different mediators. The adaptive immune response is divided into the cellular immune response, which is induced by type 1 population of helper T cells (Th1), and the humoral immune response induced by type 2 population of helper T cells (Th2). The Th1 branch of the adaptive immune response leads to the production of cytotoxic T lymphocytes (CTL) which eliminate infected cells, and the Th2 branch leads to the production of antibodies which neutralise viral particles.

In [4], we proposed a model of virus spreading in the cell culture taking into account diffusion, and showed, that in this case the infection spreads as a reaction-diffusion wave. In this work, we include the innate (IFN) and adaptive (CTL and antibodies) parts of the immune response and investigate how the parameters of the immune response influence the wave propagation speed and the total viral load, which are interpreted as the virus virulence and virus infectivity respectively.

2. Materials and Methods

In this work, a set of hierarchical models of immune response to the viral infection are formulated and investigated both analytically and numerically. All these models are

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based on the one-dimensional reaction-diffusion equations. The first model considers the influence of locally distributed IFN on the infection spreading:

$$\frac{\partial U}{\partial t} = -aUV, \ \frac{\partial I}{\partial t} = aUV - \beta I, \tag{1}$$

$$\frac{\partial V}{\partial t} = D_1 \frac{\partial^2 V}{\partial x^2} + \frac{b_1}{1 + k_1 C} I_{\tau_1} - \sigma_1 V, \ \frac{\partial C}{\partial t} = D_2 \frac{\partial^2 C}{\partial x^2} + \frac{b_2}{1 + k_2 V} I_{\tau_2} - \sigma_2 C \tag{2}$$

Here, U is the concentration of uninfected cells, I is the concentration of infected cells, V is the concentration of viral particles, C is the concentration of IFN. Virus penetrates into the uninfected cell (the right-hand side of the first equation) and thus the last becomes infected (the first term in the right-hand side of the second equation). The infected cells produce both new viral particles and IFN with time delays τ_1 and τ_2 respectively (second terms in right-hand sides of Equation (2)). The virus down-regulates the production of IFN, and IFN in turn down-regulates the virus replication. Virus and IFN are located in the extracellular space and they randomly move in this space. This behaviour is described by the diffusion terms in (2). The death of infected cells and degradation of virus and IFN are taken into account in last terms in right-hand sides of the second equation in (1) and in (2).

The next model takes into account the global circulating IFN in the following way:

$$\frac{\partial U}{\partial t} = -aUV, \ \frac{\partial I}{\partial t} = aUV - \beta I, \ \frac{\partial V}{\partial t} = D_1 \frac{\partial^2 V}{\partial x^2} + \frac{b_1}{1 + k_1 Z} I_{\tau_1} - \sigma_1 V, \tag{3}$$

$$\frac{dZ}{dt} = b_2 J(I) e^{-k_2 J(V)} - \sigma_2 Z, \tag{4}$$

where

$$J(I) = \int_{-\infty}^{\infty} I(x,t)dx, \quad J(V) = \int_{-\infty}^{\infty} V(x,t)dx.$$

We assume here that IFN is rapidly distributed by blood all over the infection site, and thus the IFN concentration ($Z(t)$) in every space point depends only on time.

In the last model, CTL (T) and antibodies (A) are taken into account by their integral distributions, as they also are distributed by blood in the infection site:

$$\frac{\partial U}{\partial t} = -aUV, \ \frac{\partial I}{\partial t} = aUV - (\beta_0 + \beta_1 T) I, \tag{5}$$

$$\frac{\partial V}{\partial t} = D_1 \frac{\partial^2 V}{\partial x^2} + \frac{b_1}{1 + k_1 Z} I_{\tau_1} - (\sigma_{10} + \sigma_{11} A) V, \ \frac{dZ}{dt} = b_2 J(I) e^{-k_2 J(V)} - \sigma_2 Z, \tag{6}$$

$$\frac{dT}{dt} = b_3 J(V) - \sigma_3 T J(I), \ \frac{dA}{dt} = b_4 J(V) - \sigma_4 A J(V). \tag{7}$$

Here, we include the elimination of infected cells by CTL and the neutralisation of virus by antibodies in last terms of the second equation in (5) and of the first equation in (6) respectively. The equations for CTL dynamics and for antibody dynamics (7) take into account their production induced by total amount of virus in the infection site in the first terms of equations. The last terms in right-hand sides of these equations represent consumption of CTL and antibodies in the processes of virus neutralisation and infected cell elimination.

3. Results

The following proposition have been proved for these models [5].

Proposition 1. *If there exists a travelling wave solution of system (1) and (2), then the minimal speed c_0 satisfies the inequality $c_0 \geq c$, where c is given by equality*

$$c^2 = \min_{\mu > \mu_0} \frac{D_1 \mu^2 (\mu + \beta)}{(\mu + \sigma_1)(\mu + \beta) - a u_0 g_1(0) e^{-\mu \tau_1}}, \tag{8}$$

where $\mu_0 > 0$ is the value for which the denominator vanishes.

Here and below, under the travelling wave solution we understand the monotone limited solution depending on the combination of variables $x - ct$ considered on the whole real axis.

Proposition 2. *If there exists a travelling wave solution of system (3) and (4), then the wave speed and total viral load satisfy equality*

$$J(v) = \frac{c u_0}{\beta \sigma_1} \left(b_1 - \alpha J(v) e^{-k_2 J(v)} \right).$$

The minimal wave speed c_0 satisfies the inequality $c_0 \geq c$, where c is given by equality

$$c^2 = \min_{\mu > \mu_0} \frac{D \mu^2 (\mu + \beta)}{(\mu + \beta)(\mu + \sigma_1) - a b(J) u_0 e^{-\tau \mu}},$$

where $\mu_0 > 0$ is the value for which the denominator vanishes.

Proposition 3. *If there exists a travelling wave solution of system (5)–(7), then the wave speed and total viral load satisfy equality*

$$J(v) = \frac{c u_0}{\beta(\theta) \sigma_1(y)} b(J) = \frac{c u_0}{\beta(\theta) \sigma_1(y)} \left(b_1 - \alpha(y) J(v) e^{-k_2 J(v)} \right),$$

The minimal wave speed c_0 satisfies the inequality $c_0 \geq c$, where c is given by equality

$$c^2 = \min_{\mu > \mu_0} \frac{D \mu^2 (\mu + \beta(\theta))}{(\mu + \beta(\theta))(\mu + \sigma_1(y)) - a b(J) u_0 e^{-\tau \mu}},$$

where

$$\beta(\theta) = \beta_0 + \beta_1 \theta, \ \theta = \frac{b_3 J(v)}{\sigma_3 J(w)}, \ \sigma_1(y) = \sigma_{10} + \sigma_{11} y, \ y = \frac{b_4}{\sigma_4}.$$

Using these propositions and numerical analysis, the dependence of the total viral load and wave speed on the parameters of immune response is obtained [5]. In particular, comparing formula (8) with similar formula for the system without IFN from [4] we conclude that the IFN in this model does not influence the wave speed. The total viral load decreases when the IFN presence. In model (3) and (4), both the total viral load and the wave speed decrease under IFN influence. In model (5)–(7), increased production of antibodies and production of CTL decrease both the total viral load and the wave speed, but the first correlates with increased level of IFN while the second correlates with decreased level of IFN.

4. Discussion

In these models, the total viral load correlates with the infectivity of the decease, induced by virus, and the wave speed correlates with the severity of this decease. The results of model (1) and (2) analysis show that the local production of IFN can not reduce the severity of the disease, but it can reduce the infectivity. This model considers only the aspect of IFN reducing the replication of virus in infected cells. From the modeling results we conclude that this mechanism does not influence the severity of the disease. However,

IFN counteracts virus in different ways, for example, it is known, that IFN influences not only infected cells but also uninfected ones which as a result develop "antiviral" state [1] and they become hardly infected by virus, i.e. the rate of virus penetrating the cell reduces. This aspect can be taken into account in the future work.

The second model shows that the global distribution of the IFN by blood reduces both severity and infectivity of the decease, i.e., if the IFN is effectively and rapidly distributed in the infection site then the recovery would be faster. In this relation, it is interesting to investigate the nature of swelling of the infected tissue due to concomitant inflammation: whether it increases (because of vasodilation of blood capillary) or decreases (because of constriction of blood capillaries) the rate of cytokine, namely, IFN, distribution in the infection region. Modeling results lead to the hypothesis that the antiviral therapy can be more efficient with vasodilation drugs. The rate of the cytokine distribution in the infection site can be influenced not only by mechanic reasons but also by osmotic pressure gradients. The possibility of using this in increasing the effectivity of anti-viral therapy is also to be investigated and discussed.

The third model (5)–(7) evaluates correlation between the adaptive immune response (CTL and antibodies) and the innate immune response (IFN). Interestingly, the production of antibodies and the CTL production do not depend on the IFN production and vise versa from the physiology of these processes, but as they have indirect connections through the virus and infected cells they correlate to each other in this model. These results can represent further motivation for investigation of such highly indirect interactions between the innate and adaptive immune response. The antibodies are included in the humoral adaptive immune response headed by the Th2 sub-population, and CTL are included in the cellular immune response which is induced by Th1 sub-population. These two branches of adaptive immune response directly influence each other in complex manner [6]. This model shows that there is mutual indirect dependencies of these two parts of the adaptive immune response with the innate immune response. Such correlations can be investigated and potentially they can open some new perspectives for the drug design and treatment paradigms.

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Abbreviations

The following abbreviations are used in this manuscript:

IFN	Interferon
CTL	Cytotoxic T-lymphocytes
Th1	Type 1 helper T cells
Th2	Type 2 helper T cells

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