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A mathematical design of vector vaccine against autoimmune disease

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ABSTRACT

Viruses have been implicated in the initiation, progression, and exacerbation of several human autoimmune diseases. Evidence also exists that viruses can protect against autoimmune disease. Several proposed mechanisms explain the viral effects. One mechanism is "molecular mimicry" which represents a shared immunologic epitope with a microbe and the host. We consider, using a simple mathematical model, whether and how a viral infection with molecular mimicry can be beneficial or detrimental for autoimmune disease. Furthermore, we consider the possibility of development of a vector therapeutic vaccine that can relieve autoimmune disease symptoms. Our findings demonstrate that vaccine therapy success necessitates (i) appropriate immune response function, (ii) appropriate affinities with self and non-self antigen, and (iii) a replicative vector vaccine. Moreover, the model shows that the viral infection can cause autoimmune relapses.

1. Introduction

The concept of autoimmunity was first predicted by Nobel Laureate Paul Ehrlich at the start of the twentieth century: he described it as "horror autotoxicus" (Janewa et al., 2004). His experiments led him to conclude that the immune system is normally focused on responding to foreign materials; it has an inherent tendency to avoid attacking self tissues. Nevertheless, when this process goes wrong, the immune system can attack self tissues, resulting in autoimmune disease (Bell and Bird, 2005). Autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis (MS), can create life-long disability and increased mortality.

Even in 2008, we do not completely understand the primary initiators or causes of many of these autoimmune diseases. No single theory or mechanism can adequately explain all features or pathogeneses of autoimmune diseases. The clinically wide spectrum of autoimmune diseases is best considered as the mosaic of autoimmunity. The many factors involved are genetic, hormonal, immunological, and environmental (Deodhar, 1992). In particular, virus infections have long been associated with autoimmune diseases, whether MS, diabetes, or myocarditis (Fujinami, 2004; Fujinami et al., 2006; Horwitz and Sarvetnick, 1999; von Herrath and Oldstone, 1996). Several mechanisms have been proposed to explain virus triggers of autoimmune diseases. One mechanism is "molecular mimicry" (Fujinami, 2001; Fujinami et al., 2006; Libbey and Fujinami, 2002), which represents a shared immunologic epitope with a microbe and the host. For example, molecular mimicry has been assigned a presumptive role in the pathogenesis of several human diseases, including insulin-dependent diabetes mellitus type-1 (IDDM), ankylosing spondylitis, Guillain-Barre syndrome, primary biliary cirrhosis, and MS (Fujinami, 2001; Horwitz and Sarvetnick, 1999; Janewa et al., 2004). The immune response to the virus cross-reacts with self because of molecular mimicry, which engenders autoimmunity as follows (Fujinami et al., 2006); virus-infected-antigen presenting cells (APCs) present viral peptides in the contexts of MHC class I and II, respectively, to naive $CD8^+$ T cells and $CD4^+$ T cells. Activation of T cells engenders IFN-γ production, which further activates APCs, leading to production of IL-12, a potent T-cell-differentiating cytokine. Effector $CD4^+$ T cells release proinflammatory cytokines such as IFN-γ and IL-2, thereby stimulating T cells to differentiate into effector T cells. Activated T cells can also secrete IFN-γ and TNF, which can engender macrophage activation. The activated macrophages in turn release TNF, nitric oxide, and reactive oxygen intermediates, which can kill infected cells and uninfected cells. Dead and dying cells are then phagocytosed by macrophages and dendritic cells (DCs), which

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can present self antigens to autoreactive $CD4^+$ T cells. Similarly, effector $CD8^+$ T cells can kill infected cells via perforin and granzyme granules. Cell debris is taken up by APCs, which can present self antigens to autoreactive $CD8^+$ T cells. The generation of such cells can engender autoimmune responses with enhanced inflammation if not modulated by regulatory T cells releasing IL-10 and/or TGF-γ. Consequently, patients can develop autoimmune disease through virus-induced autoimmunity.

Although some viruses can modulate the development of autoimmune disease as discussed above, interestingly, some experimental evidence exists for experimental allergic encephalomyelitis (EAE) (Barnett et al., 1996; Fujinami et al., 2006), which is an experimental model of MS, that viruses can protect against autoimmune disease. Possible mechanisms of protecting against autoimmune disease are considered as "altered peptide ligand", which activates regulatory cells that modulate the disease (Barnett et al., 1996; Fujinami et al., 2006), and "activation-induced cell death" (AICD) which engenders anergy or unresponsiveness of T cells (Fujinami, 2001). These imply that viruses having molecular mimicry with self proteins are useful to vaccinate against autoimmune disease. Using molecular biology and DNA manipulation methods, it has also been possible to express mimic proteins in adequate live vectors (Arnon and Ben-Yedidia, 2003) and thereby design transgenic vector vaccines (Janewa et al., 2004; Roitt et al., 1998) against autoimmune disease. The development of vaccines has been an important contribution of autoimmune disease therapy and public health.

Herein, we construct a simple mathematical model based on the autoimmune disease model proposed in Iwami et al. (2007a) and Iwami (2007). We consider a viral infection that can induce cross-reactive immune responses with self antigen caused by molecular mimicry. Our model suggests that the viral infection can induce various symptoms of autoimmune disease such as relapse. Furthermore, we propose that a form of immune response function determines whether a viral infection can be beneficial or detrimental. Using the model, we consider the possibility of development of a vector vaccine that can relieve autoimmune disease symptoms.

2. Mathematical model

The breaking of tolerance or unresponsiveness to self antigens, involving the activation of autoreactive lymphocytes, is a critical event in the pathogenesis of autoimmune disease (von Herrath and Oldstone, 1996). The molecular mimicry theory has become an important paradigm to explain the triggering of autoaggressive T lymphocytes (Anderton, 2006). Viruses and microbial agents might possess protein structures or shapes that mimic normal host self proteins. An immune response elicited against the pathogen will eliminate it and will cross-react with one or more self antigens that share determinants with the agent (von Herrath and Oldstone, 1996). The cross-reactive immune response can break a tolerance for self antigens and might engender autoimmune disease. We consider a viral infection that can induce cross-reactive immune responses with a self antigen caused by molecular mimicry (see Fig. 1). To explore effects of the viral infection and dynamical behavior of the vicious cycle of autoimmunity, we propose the following mathematical model based on the autoimmune disease model proposed in Iwami et al. (2007a) and Iwami (2007);

$$
\begin{aligned}
T' &= g(T) - \hat{\beta}_1 TI,\\
D' &= \hat{\beta}_1 TI - \alpha D,\\
I' &= f(D,V) - \gamma I,\\
V' &= (k - u - \beta_2 I)V.
\end{aligned}
$$

Variables T, D, I, and V, respectively, signify the number of target (uninfected) cells, damaged cells (which implies a concentration of self antigen), cross-reactive immune cells, and viral agents with molecular mimicry. The immune responses eliminate target cells and viral agents at a rate of $\hat{\beta}_1$ and β_2, respectively. We assume a "Malthusian growth rate" k in viral agents, which decay at a rate u as considered in Nowak et al. (1991). The parameters α and γ represent the decay rate of damaged and cross-reactive immune cells, respectively. The function $g(T)$ is the "target cell growth function". In Iwami et al. (2007a), we consider two target cell growth functions

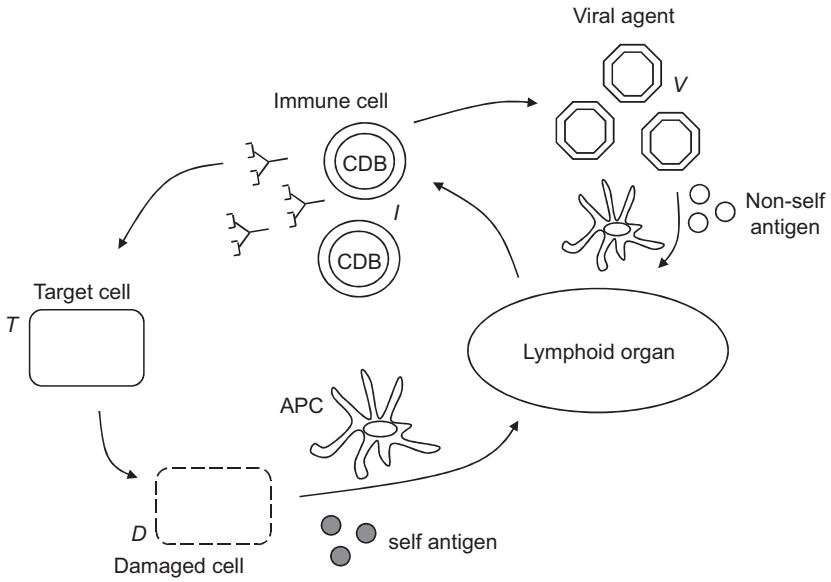

Fig. 1. Vicious cycle of autoimmunity induced by a viral infection with molecular mimicry: (virus-infected) APCs present a viral antigen (non-self antigen) to naive T cells at a lymphoid organ. Subsequently, these T cells are activated and secrete further activation signals to T cells or B cells. These activated immune cells (CTL and antibodies produced by plasma cells: I) attack infected cells (virus with molecular mimicry, V) and uninfected cells (target cells, T) because of the molecular mimicry. Dead and dying cells (damaged cells: D) are then phagocytosed by APCs, which can present a self antigen to autoreactive T cells. Subsequently, further cross-reactive immune responses are similarly enhanced and attack infected cells and uninfected cells.

$g_1(T)=\lambda-\mu T$, which means a constant growth and $g_2(T)=\lambda-\mu T+pT(1-T/L)$ which means a logistic growth. A form of this function considerably affects the dynamics of autoimmune disease (Iwami et al., 2007a; Iwami, 2007). However, to examine the effect of viral infection with molecular mimicry specifically, we consider that target cells are always constant $T=T^*$ (we omit target cell dynamics). This assumption is justified by some homeostatic ability of organs, which exactly balances the growth of target cells with the damage. A modeling approach of this kind is used in Nowak and May (1994). On the other hand, the assumption is not biologically unnatural if the target cells are abundant in the organ. We leave the inclusion of target cell dynamics as a subject for future work. We can model the vicious cycle in the following form:

$$\begin{aligned} D' &= \beta_1 I-\alpha D,\\ I' &= f(D,V)-\gamma I,\\ V' &= (k-u-\beta_2 I)V, \end{aligned} \tag{1}$$

where $\beta_1=\hat{\beta}_1 T^*$. Therein, β_1 and β_2, respectively, represent a degree of affinity to self and viral antigens (non-self antigen). A property of molecular mimicry can be described using these parameters. The function $f(D,V)$ is the "immune response function" (see Iwami et al., 2007a). In general, the proliferation ability is saturated for a sufficiently large amount of antigens (Borghans and de Boer, 1995; Borghans et al., 1998; De Boer and Perelson, 1995). We consider that the proliferation of immune response is dependent on the total number of self and viral antigens as

$$f_1(D,V)=\frac{m(D+V)}{h+D+V},\quad f_2(D,V)=\frac{m(D+V)^2}{h^2+(D+V)^2}.$$

The forms of f_1 and f_2 can be regarded, respectively, as functional responses of Holling types II and III. Parameters m and h, respectively, signify the maximum proliferation rate and the efficiency of the proliferation.

3. Results

The mechanism of immune proliferation remains unclear. However, using mathematical and experimental models, many theoretical immunologists study the proliferation function to obtain better knowledge related to immune response (Borghans et al., 1999; Wodarz and Jansen, 2001; Wodarz and Thomsen, 2005). The function might depend on the immune cell type, genetic and physiological factors, and so on. As described herein, we investigate two immune response functions f_1 and f_2 which are not biologically unnatural. The difference of the immune response function strongly affects dynamic behaviors of model (1), as discussed below.

3.1. Convex immune response function

We consider in the context that immune response function is convex form f_1. Therefore, our mathematical model is the following:

$$\begin{aligned} D' &= \beta_1 I-\alpha D,\\ I' &= \frac{m(D+V)}{h+D+V}-\gamma I,\\ V' &= (k-u-\beta_2 I)V. \end{aligned} \tag{2}$$

We must consider two different situations for model (2): (i) $k-u<0$ and (ii) $k-u>0$. If (i) holds, then $\lim_{t\to\infty}V(t)=0$, which implies that the virus cannot maintain its replication in the host. Then the system has two possible equilibria:

$$E_h=(0,0,0),\quad E_a=(D_a,I_a,0).$$

Equilibria E_h and E_a, respectively, represent the "healthy state" and the "autoimmune disease state". If (ii) holds, then the virus can persist in the host and we have one more equilibrium,

$$E_c=(D_c,I_c,V_c),$$

which represents the "complication state" (i.e., the patient develops autoimmune disease with the viral infection). Furthermore, the number of viral agents can explode ($\lim_{t\to\infty}V(t)=\infty$) under (ii) and the dynamics of model (2) converges to some steady state

$$E_\infty=(D_\infty,I_\infty,\infty),$$

which represents the "infection state" (see Appendix C). The exact expressions for equilibria are referred to Appendix A. Fig. 2 portrays the existence and stability conditions of these equilibria in model (2). For detailed mathematical analysis of the equilibria, see Appendix A.

3.1.1. Symptoms of autoimmune disease in model (2)

We consider that the number of damaged cells, such as D_a or D_c, represents the level of autoimmune disease progression. A strong immune affinity with self antigen (large β_1) engenders the development of autoimmune disease E_a (see Fig. 2(c)) when the virus cannot establish the persistence infection ($k-u<0$). Because $\mathrm{d}D_a/\mathrm{d}\beta_1>0$, an increase of the affinity with self antigen deteriorates autoimmune disease (which means that autoimmune disease is worsening; so is the patient's condition). In other words, if we can appropriately reduce the immune affinity with self antigen using some drugs or therapies, we can delay autoimmune disease progression (a marked decrease of the affinity with self antigen ($\beta_1<\alpha h\gamma/m$) can engender immune tolerance E_h).

On the other hand, when the virus can maintain its replications ($k-u>0$), strong immune affinities with self and viral antigen (large β_1 and β_2) also engender the development of autoimmune disease without viral replication (see Fig. 2(d)). However, if the immune affinity with self antigen is weak, the patient develops autoimmune disease with viral infection E_c. Because $\mathrm{d}D_a/\mathrm{d}\beta_1>0$ and $\mathrm{d}D_c/\mathrm{d}\beta_1>0$, a decrease of the affinity with self antigen also reduces autoimmune disease progression. The immune tolerance cannot occur under viral persistence (the viral infection initiates autoimmune disease) even if we can reduce the immune affinity with the self antigen. A decrease of the affinity with viral antigen engenders deterioration of autoimmune disease progression because $\mathrm{d}D_c/\mathrm{d}\beta_2<0$ whenever the patient is in a complication state. Furthermore, a decrease of the affinity with viral antigen engenders unlimited replications of viral agents and a deterioration E_∞ (note that $D_\infty>D_a$).

3.2. Sigmoid immune response function

We consider in the context that immune response function is sigmoid form f_2. Therefore, our mathematical model is the following:

$$\begin{aligned} D' &= \beta_1 I-\alpha D,\\ I' &= \frac{m(D+V)^2}{h^2+(D+V)^2}-\gamma I,\\ V' &= (k-u-\beta_2 I)V. \end{aligned} \tag{3}$$

We must also consider two different situations for model (3): (i) $k-u<0$ and (ii) $k-u>0$. The virus cannot maintain its replication in the host under (i). Then the system has three

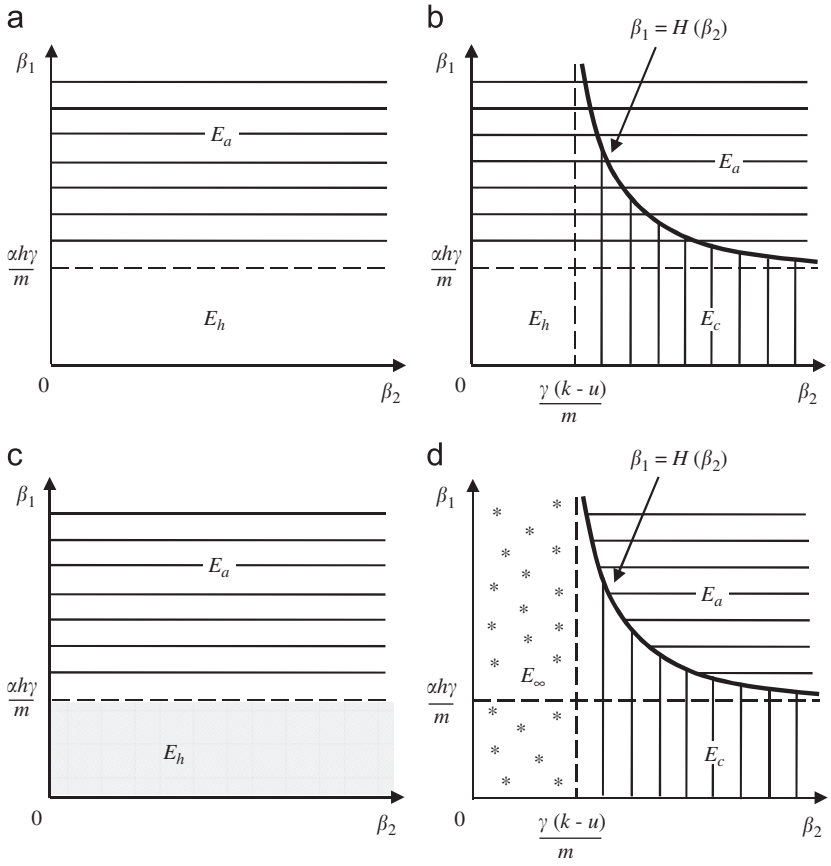

Fig. 2. Existence and stability conditions of the equilibria in model (2): panels (a) and (b), respectively, present the existence conditions of the equilibria with $k-u<0$ and $k-u>0$. Horizontal and vertical stripes, respectively, signify the existence regions for E_a and E_c. Equilibrium E_h always exists. Panels (c) and (d), respectively, present the stability conditions of the equilibria with $k-u<0$ and $k-u>0$. The horizontal and vertical stripes, respectively, signify the stability regions for E_a and E_c. Shadows and asterisks, respectively, denote the stability and attractive regions for E_h (or E_∞). Function $H(\beta_2)$ is referred from Appendix A.

possible equilibria:

$$E_h=(0,0,0),\quad E_a^+=(D_a^+,I_a^+,0),\quad E_a^-=(D_a^-,I_a^-,0),$$

but E_a^- is not biologically appropriate because the equilibrium is always unstable even if it exists (see Appendix B). The equilibria E_h and E_a^+ also, respectively, represent the "healthy state" and the "autoimmune disease state". On the other hand, if the virus can persist in the host ((ii)), then we have one more equilibrium,

$$E_c^*=(D_c^*,I_c^*,V_c^*),$$

which also represents the "complication state". Furthermore, the number of viral agents can explode under (ii). The dynamics of model (3) converges to the infection state E_∞. The exact expressions for the equilibria are referred from Appendix B. Fig. 3 depicts the existence and stability conditions of these equilibria in model (3).

If $k-u>0$, then model (3) represents various dynamical behaviors (see Fig. 4, which corresponds to Fig. 3(d)). The parameter region (I) represents that E_a^+ is stable; the region (V) represents that E_c^* is stable. In addition, E_a^+ and E_c^* are stable simultaneously (bistability) in region (III). Therefore, the orbit converges to E_a^+ or E_c^* according to its initial values. In parameter region (IV), we can observe periodic behavior by Hopf bifurcation of E_c^* (all orbits except E_c^* converge to the limit cycle). Furthermore, the limit cycle and E_a^+ are stable simultaneously in region (II); the orbit also converges to the limit cycle or E_a^+ according to its initial values (see Fig. 5). However, if we choose a parameter set near $G(\beta_2)$ in (II), we can numerically confirm that almost all orbits converge to E_a^+ because the amplitude of the periodic orbit increases as a parameter set approaches $G(\beta_2)$, the orbit crosses the stable manifold of E_a^+, the periodic orbit vanishes and the orbit converges to E_a^+. This phenomenon is also observed and particularly explained in Iwami (2007). Therefore, we can classify the dynamical behavior of model (3) under $k-u>0$. For detailed mathematical analysis of the equilibria, see Appendix B.

3.2.1. *Symptoms of autoimmune disease in model (3)*

We also consider that the number of damaged cells, such as D_a^+ or D_c^*, represents a level of autoimmune disease progression. A strong immune affinity with self antigen (β_1) tends to develop into autoimmune disease E_a^+ according to initial values (see Fig. 3(c)) when the virus cannot establish persistent infection ($k-u<0$). The healthy state E_h is always stable, which implies that the immune tolerance can occur after development of autoimmune disease if we can remove the damaged cells and the immune responses (simulations not shown). Furthermore, because $dD_a^+/d\beta_1>0$, an appropriate decrease of the immune affinity with self antigen can delay autoimmune disease progression (a considerable decrease of the affinity with self antigen ($\beta_1<2\alpha h\gamma/m$) can engender the immune tolerance E_h).

On the other hand, when the virus can maintain its replications ($k-u>0$), strong immune affinities with self and viral antigen (large β_1 and β_2) also engender the development of autoimmune disease without viral infection (Fig. 4(I)). However, if the immune affinity with self antigen is weak, the patient develops autoimmune disease with a viral infection (Fig. 4(V)). Because $dD_a^+/d\beta_1>0$ and $dD_c^*/d\beta_1>0$, a decrease of the affinity with self antigen also reduces autoimmune disease progression in regions (I) and (V). A decrease of the affinity with viral antigen engenders

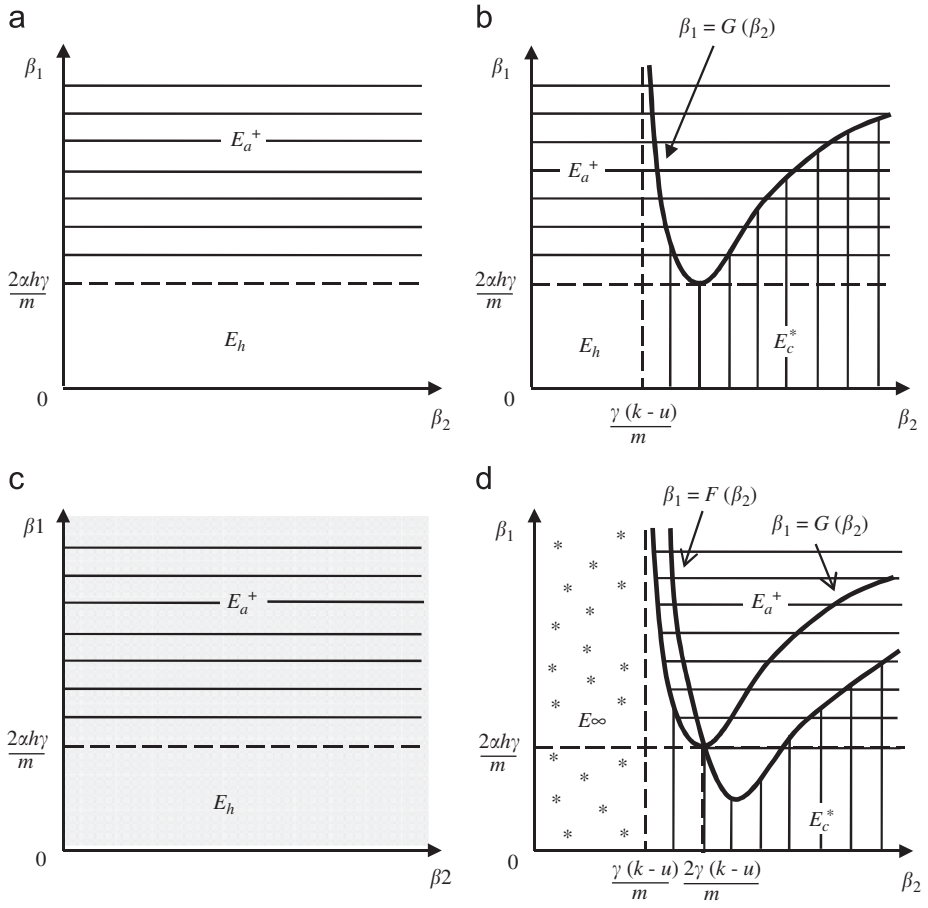

Fig. 3. Existence and stability conditions of the equilibria in model (3). Panels (a) and (b), respectively, represent the existence conditions of equilibria with $k-u<0$ and $k-u>0$. The horizontal and vertical stripes, respectively, mark the existence regions for E_a^+ and E_c^*. Equilibrium E_h always exists. Panels (c) and (d), respectively, represent the stability conditions of equilibria with $k-u<0$ and $k-u>0$. Horizontal and vertical stripes, respectively, signify the stability regions for E_a^+ and E_c^*. Shadows and asterisks, respectively, denote the stability and attractive regions for E_h (or E_∞). Functions $F(\beta_2)$ and $G(\beta_2)$ are referred from Appendix B.

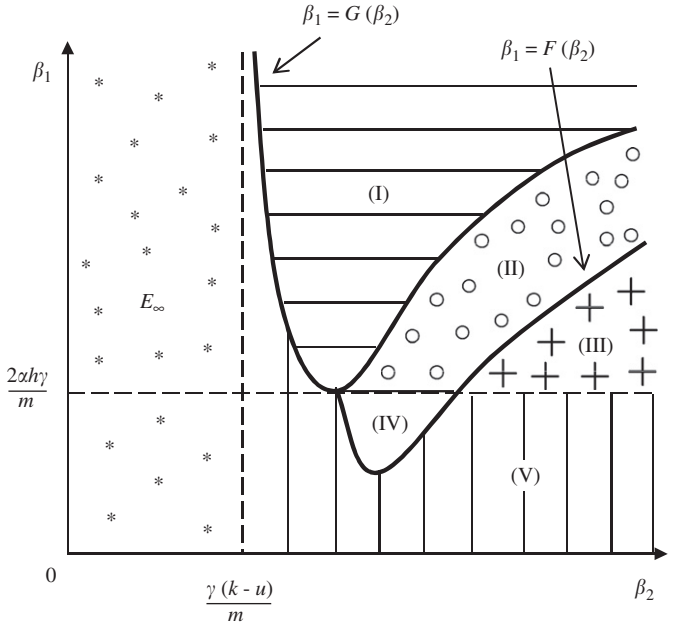

Fig. 4. Classification of the dynamical behavior of model (3) under $k-u>0$. The parameter regions are represented as (I) E_a^+ is stable, (II) E_a^+ and the limit cycle are stable, (III) E_a^+ and E_c^* are stable, (IV) the limit cycle is stable, and (V) E_c^* is stable.

deterioration of autoimmune disease progression because $dD_c^*/d\beta_2<0$ in region (V) (a marked decrease of affinity with viral antigen engenders unlimited viral replications). Interestingly, because E_a^+ and E_c^* are stable simultaneously in region (III), the symptoms of autoimmune disease depend on the patients' states. Furthermore, in regions (II) and (IV), the relapse of autoimmune disease, which is a common symptom of autoimmune disease, can occur. Actually, the symptoms of autoimmune disease also depend on the patients' states in (II) (patients with affinities near $G(\beta_2)$ in (II) tend not to represent relapse symptoms, as discussed above). Consequently, the viral infection prevents immune tolerance and engenders the relapse pattern of autoimmune disease.

4. Vector vaccine against autoimmune disease

Virus infection can initiate or accelerate autoimmune disease via epitope spreading (Libbey and Fujinami, 2002; Miller et al., 1995) and molecular mimicry, thereby engendering the development of an inflammatory region with activated APCs and possible presentation of a self antigen (Fujinami et al., 2006; von Herrath and Oldstone, 1996; von Herrath et al., 2003). However, several interesting experimental examples exist for prevention of autoimmune disease caused by viral infections. Possible mechanisms of prevention caused by viral infections are immunosuppression, chemokine gradients, apoptosis of autoaggressive lymphocytes,

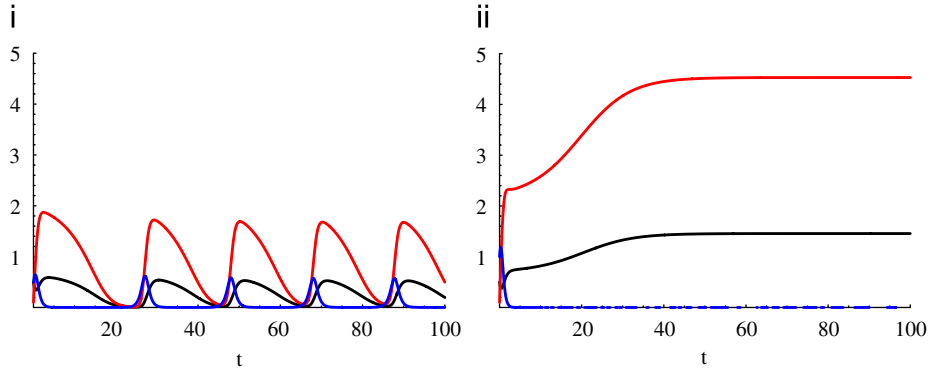

Fig. 5. Dynamical behavior of model (3) in region (II): (i) the orbit converges to the limit cycle, and (ii) the orbit converges to E_a^+. The parameters are fixed at $\beta_1 = 0.45$, $\beta_2 = 1.5$, $\alpha = 1.4$, $m = 4$, $h = 1$, $\gamma = 0.6$, $k = 2.5$, and $u = 1.2$. The initial values are the following: (i) $D(0) = 0.5$, $I(0) = 0.1$, $V(0) = 0.5$; and (ii) $D(0) = 0.5$, $I(0) = 0.1$, $V(0) = 1.0$. The black, red and blue lines, respectively, represent D, I and V.

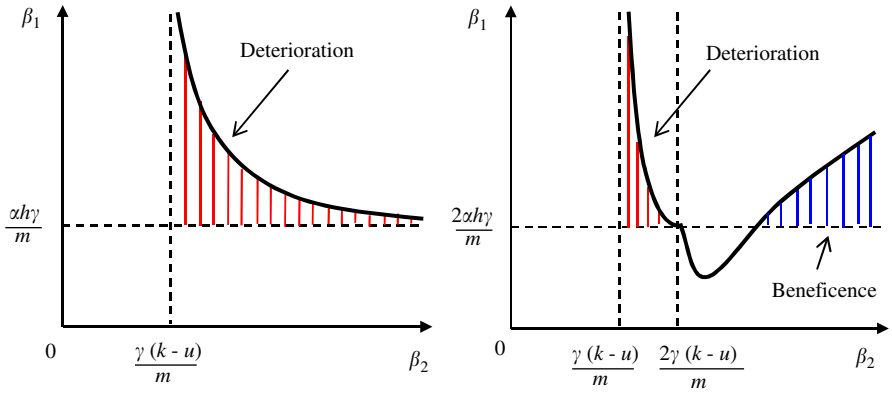

Fig. 6. Deteriorative vs. beneficial viral infection: we consider the viral infection with molecular mimicry ($k-u>0$) to autoimmune disease patients (E_a or E_a^+ with $V(0)=0$). The left and right panels, respectively, present a prognosis of autoimmune disease for patients with immune response function f_1 and f_2. "Deterioration" means that the viral infection increases damaged cells ($D_a<D_c$ or $D_a^+<D_c^*$) and cross-reactive immune responses ($I_a<I_c$ or $I_a^+<I_c^*$). "Beneficence" means that the infection decreases damaged cells ($D_a^+>D_c^*$) and cross-reactive immune responses ($I_a^+>I_c^*$). Existence of the beneficial region implies the possible use of the vector vaccine against autoimmune disease.

and so on (Fujinami et al., 2006). Furthermore, experimental evidence indicates that a viral infection with molecular mimicry can provide protection from EAE (Fujinami, 2001; Fujinami et al., 2006). Reasons for the protection are said to be altered peptide ligand, AICD, and so on, which implies that viruses having molecular mimicry with self proteins are useful for vaccination against autoimmune disease.

4.1. Detrimental or beneficial viral infection

We consider whether infection by a virus having molecular mimicry with a self antigen that can replicate itself ($k-u>0$) is beneficial or detrimental for autoimmune disease. First we assume that autoimmune disease has already developed before the patient is infected with the virus having molecular mimicry with self proteins ($V(0)=0$). In model (2), we assume that E_a is stable ($\beta_1>\alpha\gamma h/m$) with $V(0)=0$, which corresponds to Fig. 2(c), irrespective of the sign of $k-u$ (we remark that the infection with $k-u>0$ persists and initiates autoimmune disease even if $\beta_1<\alpha\gamma h/m$). Furthermore, to avoid the obvious result, we assume that the immune affinity with viral antigen is high ($\beta_2>\gamma(k-u)/m$). Actually, if the affinity with viral antigen is low ($\beta_2<\gamma(k-u)/m$), then the viral population explodes (see Appendix C) and the number of damaged cells (D_∞) represents its maximum value, which implies that the viral infection detrimental affects the patients. We also exclude the high affinity with self antigen ($\beta_1>H(\beta_2)$) because the viral infection cannot affect the disease progression. Consequently, we assume the following conditions:

$$k-u>0, \quad \frac{\alpha\gamma h}{m}<\beta_1<H(\beta_2), \quad \beta_2>\frac{\gamma(k-u)}{m}.$$

We evaluate the effect of viral infection as follows. Let $V(0)>0$; then the stable equilibrium changes from E_a to E_c (the patients get the viral infection). We then have the following relations:

$$\beta_1<H(\beta_2)\Rightarrow D_a<D_c, \quad I_a<I_c.$$

They imply that the viral infection always imparts a detrimental effect on patients and accelerates autoimmune disease on the region because the viral infection increases damaged cells ($D_a<D_c$) and cross-reactive immune responses ($I_a<I_c$) (see Fig. 6).

On the other hand, in model (3), we assume that E_a^+ is stable ($\beta_1>2\alpha\gamma h/m$) with $V(0)=0$, which fundamentally corresponds to Fig. 3(c), irrespective of a sign of $k-u$. Furthermore, let the immune affinity with viral antigen be high ($\beta_2>\gamma(k-u)/m$). We also exclude high affinity with self antigen ($\beta_1>G(\beta_2)$) because of a neutral effect of the infection. To avoid a bad prognosis such as a relapse of autoimmune disease, we also exclude the possibility of the relapse caused by viral infection ($\beta_2>2\gamma(k-u)/m$ and $F(\beta_2)<\beta_1<G(\beta_2)$; (II)(IV) in Fig. 4). Consequently, we assume the

following conditions:

$$k-u>0,\quad \frac{2\alpha\gamma h}{m}<\beta_1<\min\{F(\beta_2),G(\beta_2)\},\quad \beta_2>\frac{\gamma(k-u)}{m}.$$

Let $V(0)>0$ and then the convergence equilibrium changes from E_a^+ to E_c^* (the patients get the viral infection) or it does not change because the region (III) in Fig. 4 represents bistability of E_a^+ and E_c^*. When the viral infection changes the convergence equilibrium, we evaluate the effect of viral infection as shown below.

$$\begin{cases}\beta_2>\dfrac{2\gamma(k-u)}{m}\Rightarrow D_a^+>D_c^*,\quad I_a^+>I_c^*,\\ \beta_2<\dfrac{2\gamma(k-u)}{m},\quad \beta_1<G(\beta_2)\Rightarrow D_a^+<D_c^*I_a^+<I_c^*.\end{cases}$$

The expressions presented above imply that the viral infection can give patients a beneficial effect and relieve autoimmune disease symptoms for the former case because the viral infection engenders a decrease of damaged cells and cross-reactive immune responses (Fig. 6).

4.2. Mathematical design of the vector vaccine

Vaccines are, by definition, prophylactic, but in recent years we saw an interest in developing therapeutic vaccines, in infectious diseases (for diseases such as AIDS, tuberculosis, and peptic ulcer), in cancer (a variety of approaches to combat different kinds of cancer), and in autoimmune diseases (a definite success in developing a drug/vaccine against MS and hopes for myasthenia gravis, lupus and diabetes) (Arnon and Ben-Yedidia, 2003). Using molecular biology and DNA manipulation methods, it is possible to produce a therapeutic vaccine against autoimmune disease.

We consider the possibility of development of a vector vaccine having molecular mimicry with self proteins. After emergence of autoimmunity, the vector vaccine can reproduce itself, induce a cross-reactive immune response, and be removed by the immune response in patients as a similar mechanism for viral infection with molecular mimicry (see Fig. 7). Therefore, we can consider that the vaccine can be described similarly as the viral infection in terms of the mathematical model. Fujinami (2001) and Fujinami et al. (2006), explained that a possible mechanism of protection from EAE by the viral infection might be suppression of autoreactive immune cells caused by regulatory cells, AICD, and so on. However, our results demonstrate that a viral infection in model (3) can be effective for autoimmune disease without involving these suppressive effects. This shows that, when the immune response function is f_2, the vector vaccine can reduce the cross-reactive immune response ($I_a^+>I_c^*$) and relieve symptoms of autoimmune disease ($D_a^+>D_c^*$), which implies that the vector vaccine can be effective by itself even if we consider no additional suppressive abilities in our immune system.

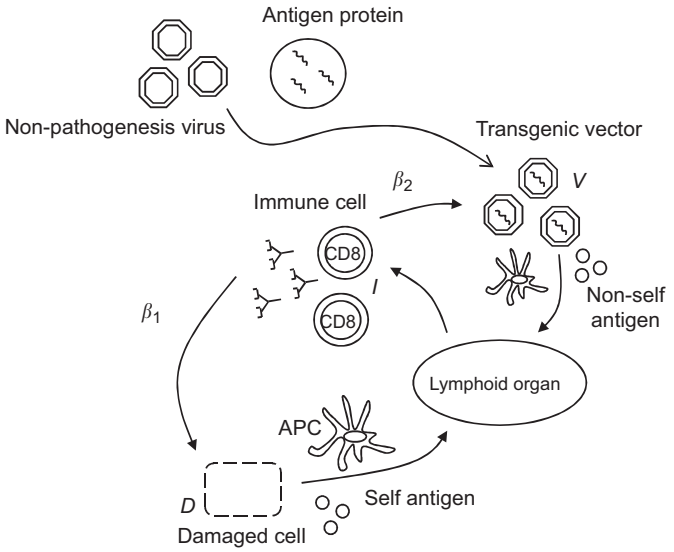

Fig. 7. A transgenic vector vaccine having molecular mimicry with self proteins; after emergence of autoimmunity, the vaccine can induce a cross-reactive immune response as a similar mechanism for viral infection with molecular mimicry.

Therefore, to make the vector vaccine effective, we at least require that the immune proliferation be a sigmoid function such as f_2 (we explain the immune response function in Discussion). The affinities with self and non-self antigen are in the beneficial region, as shown in Fig. 6. Actually, our immune system has high affinity with non-self antigen and low affinity with self antigen because, in the process of differentiation thymic, lymphocytes undergo positive and negative selection. Positive selection generates a functional T cell repertoire restricted to self MHC expressed on the epithelial cells of the thymic cortex. Negative selection eliminates T cells that are aggressively reactive to self antigen (Goldrath and Bevan, 1999; Janewa et al., 2004). Consequently, the beneficial region, which has high affinity with non-self antigen and low affinity with self antigen, is biologically realistic. Furthermore, the vector vaccine must replicate effectively in autoimmune disease patients, which means that the orbit converges to E_c^*. We remark that the vaccine might be unable to replicate (the orbit converges to E_a^+) according to patients' states because of bistability. Therefore, the vector vaccine might have to be used with other immunosuppressive drugs to switch the patient state from E_a^+ to E_c^*. Although many restrictions discussed above exist for the success of therapeutic vaccine, we can theoretically design the transgenic vector vaccine (because of these stringent restrictions, it is also true that the transgenic vector vaccine might only be effective to certain specific patient states). Moreover, if we consider the additional effects for suppression of autoreactive immune cells, these restrictions can be relaxed. However, we leave the inclusion of additional effects as a subject for future work.

5. Discussion

Increasing evidence exists that infectious agents play an important role in autoimmune disease (Janewa et al., 2004; Roitt et al., 1998). Viruses are an important factor that can precipitate autoimmune disease by various mechanisms (Fujinami, 2004; Pender, 2004; von Herrath et al., 2003). For example, viruses that stimulate the production of IL-12, such as herpes simplex virus, human herpesvirus, influenza virus, and coronavirus, have been isolated from or have been associated with exacerbation of MS (Fujinami, 2001; Libbey and Fujinami, 2002; Monteiro et al., 1998; Whitton and Fujinami, 1999). On the other hand, viruses can abrogate an ongoing autoimmune reaction by inducing apoptosis of autoreactive cells, by secreting various cytokines, or by immune suppression (Fujinami, 2001). Nevertheless, it is difficult to obtain direct evidence for virus-induced initiation of autoimmune disease or protection from autoimmune disease because we are all infected by multiple viruses (Fujinami et al., 2006).

Using the simple mathematical model, we analyzed whether and how a viral infection having molecular mimicry with self proteins can impart a detrimental or beneficial effect to autoimmune disease patients (see Fig. 6). Furthermore, we consider the possibility of development of a therapeutic vaccine against autoimmune disease. Our findings suggest that the success of therapeutic vaccine necessitates the following: (i) patients have an appropriate immune response function, such as f_2; (ii) affinities with self and non-self antigen are in

the beneficial region shown in Fig. 6; (iii) the vector vaccine replicates in vivo. Although these restrictions can be relaxed if we consider additional immunological effects such as immune suppression, memory response, and exhaustion of effector cells, we found the distinct possibility of designing a therapeutic vaccine.

In Iwami et al. (2007a) and Iwami (2007), we investigated the influence of functional form of immune proliferation on autoimmune disease symptoms. We demonstrated that sigmoid function such as f_2 can induce a bistable structure and periodic behavior. As described in this paper, we omit the target cell dynamics and add the viral replication cycle compared with the model considered in Iwami et al. (2007a). The difference of immune response functions also strongly affects the autoimmune disease symptoms. If the virus cannot establish a persistent infection ($k-u<0$), then f_2 induces bistability (Fig. 3(c)) but f_1 does not, then (Fig. 2(c)). On the other hand, if the virus can replicate itself ($k-u>0$), then f_2 induces bistability and a periodic orbit (Fig. 3(d)), but f_1 does not, then (Fig. 2(d)). Consequently, the sigmoid function f_2, which is biologically more reasonable (because APCs only slightly induce immune cells when only a few antigens exist, Iwami et al., 2007a) than the convex function f_1 represents various symptoms such as relapse in autoimmune disease. That slight inducement implies that the various symptoms of autoimmune disease might be related with the function. However, the results might not be sufficiently robust to the form of immune proliferation function. We need to know an appropriate proliferation function that has biological relevance. For example, APCs are known to induce immune cells only slightly when many antigens exist (high zone tolerance) (Janewa et al., 2004). For that reason, we might have to use a bell-shaped proliferation function to consider high zone tolerance instead of the proliferation as an increasing function of antigen load (De Boer et al., 1993, 1996). Consequently, a more complete understanding of immune proliferation must be the foundation for the development of a therapeutic vaccine.

Viruses trigger autoimmune disease, but they are also likely to be important for reactivation of autoimmunity (viruses can behave as reactivators of autoimmune disease) (Horwitz and Sarvetnick, 1999). Some clinical data show that viral infections trigger MS relapse (Andersen et al., 1993). It has been suggested that a determinant spreading (self-antigen diversification) is a relapse mechanism (Lehmann et al., 1993). Furthermore, in Borghans et al. (1998), they showed that T cell regulatory circuitry induces autoimmune relapse using a simple mathematical model. Another possible mechanism of the relapse is considered as cross-reactive immune responses through a process of molecular mimicry. In our model, relapses can also occur under the viral infection with molecular mimicry (in the absence of determinant spreading). The immune response function f_2 can induce a limit cycle that corresponds to relapse of autoimmune disease only when the virus can replicate itself (see Fig. 4). This implies that the viral infection engenders the relapse. Therefore, our model supports that the cross-reactive immune response is also a relapse mechanism.

This study highlights the immune response functions and molecular mimicry with the self antigen to investigate the possibility of vector vaccine development. Although our model might over-simplify complex interactions in autoimmune disease, its simplicity illustrates the general and qualitative properties of viral infection with molecular mimicry. This prediction should be verified using actual experiments. Our model is a starting point, but must include more immunological factors such as immunosuppression and apoptosis to merit further theoretical and mathematical investigation.

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Appendix A

We analyze the existence and stability conditions of the equilibria in (2). The model has three possible equilibria:

$$E_h=(0,0,0),$$
$$E_a=(D_a,I_a,0),\quad D_a=\frac{m\beta_1}{\alpha\gamma}-h,\quad I_a=\frac{\alpha}{\beta_1}D_a,$$
$$E_c=(D_c,I_c,V_c),\quad D_c=\frac{\beta_1 k-u}{\beta_2\ \alpha},\quad I_c=\frac{k-u}{\beta_2},$$
$$V_c=\frac{\gamma h(k-u)}{m\beta_2-\gamma(k-u)}-\frac{\beta_1 k-u}{\beta_2\ \alpha}.$$

It might be readily apparent that E_h always exists. The existence conditions of E_a and E_c are as follows:

$$E_a\in\mathbb{R}^3_+\ \Leftrightarrow\ \beta_1>\frac{\alpha\gamma h}{m},$$
$$E_c\in\mathbb{R}^3_+\ \Leftrightarrow\ k-u>0,\quad \beta_2>\frac{\gamma(k-u)}{m},$$
$$\beta_1<\frac{\alpha\gamma h}{m}\frac{\beta_2}{\beta_2-\gamma(k-u)/m}.$$

It is noteworthy that E_c cannot exist in $\mathbb{R}^3_+$ if $k-u<0$. In Fig. 2(a) and (b), we summarize these conditions in the $\beta_1-\beta_2$ plane.

Hereinafter we explain the stability of these equilibria in detail. The Jacobian matrix of (2) at E_h is

$$J(E_h)=\begin{bmatrix}-\alpha & \beta_1 & 0\\ \frac{m}{h} & -\gamma & \frac{m}{h}\\ 0 & 0 & k-u\end{bmatrix}.$$

The characteristic equation of $J(E_h)$ is

$$(p-k+u)\left\{p^2+(\alpha+\gamma)p+\alpha\gamma-\frac{m\beta_1}{h}\right\}=0.$$

Therein, p denotes the indeterminate of the polynomial. Therefore, from the Routh–Hurwitz criterion, all eigenvalues of $J(E_h)$ have negative real parts if and only if

$$k-u<0,\quad \beta_1<\frac{\alpha\gamma h}{m}.$$

That is, if the above conditions hold, then E_h is *locally asymptotically stable* (LAS); otherwise E_h is unstable. We can show that E_h is *globally asymptotically stable* (GAS) using similar methods to those described in Iwami et al. (2007b).

The Jacobian matrix of (2) at E_a is

$$J(E_a)=\begin{bmatrix}-\alpha & \beta_1 & 0\\ \frac{mh}{(h+D_a)^2} & -\gamma & \frac{mh}{(h+D_a)^2}\\ 0 & 0 & k-u-\beta_2 I_a\end{bmatrix}.$$

The characteristic equation of $J(E_a)$ is

$$(p-k+u+\beta_2 I_a)\left\{p^2+(\alpha+\gamma)p+\alpha\gamma-\frac{mh\beta_1}{(h+D_a)^2}\right\}=0.$$

Therefore, all eigenvalues of $J(E_a)$ have negative real parts if and only if

$$\beta_1 > \frac{\alpha\gamma h}{m}, \quad \beta_1 > \frac{\alpha\gamma h}{m}\frac{\beta_2}{\beta_2 - (k-u)\gamma/m}.$$

We remark that the above second condition holds with $k-u<0$ if the first is satisfied, which implies that E_a is always LAS if it exists. Let

$$H(\beta_2) = \frac{\alpha\gamma h}{m}\frac{\beta_2}{\beta_2 - (k-u)\gamma/m}.$$

It is clear that $H(\beta_2) > \alpha\gamma h/m$ when $k-u>0$. Consequently, E_a is LAS if $\beta_1 > H(\beta_2)$. We can show that E_a is GAS under $k-u<0$ using similar methods to those explained in Iwami et al. (2007b).

The Jacobian matrix of (2) at E_c is

$$J(E_c) = \begin{bmatrix} -\alpha & \beta_1 & 0 \\ \dfrac{mh}{(h+D_c+V_c)^2} & -\gamma & \dfrac{mh}{(h+D_c+V_c)^2} \\ 0 & -\beta_2 V_c & 0 \end{bmatrix}.$$

The characteristic equation of $J(E_c)$ is

$$p^3 + a_1 p^2 + a_2 p + a_3 = 0,$$

where

$$a_1 = \alpha + \gamma, \quad a_2 = \frac{mh(\beta_2 V_c - \beta_1)}{(h+D_c+V_c)^2} + \alpha\gamma,$$
$$a_3 = \frac{\alpha\beta_2 mhV_c}{(h+D_c+V_c)^2}.$$

Therefore, from the Routh–Hurwitz criterion, the stability of E_c is determined by the sign of $a_1a_2 - a_3$. Because the following relation holds:

$$D_c + V_c = \frac{\gamma h(k-u)}{m\beta_2 - \gamma(k-u)}, \quad D_c + V_c + h = \frac{\beta_2 mh}{m\beta_2 - \gamma(k-u)},$$

we can obtain

$$\begin{aligned} a_1a_2 - a_3 &= \frac{mh\{\gamma\beta_2 V_c - (\alpha+\gamma)\beta_1\}}{(h+D_c+V_c)^2} + (\alpha+\gamma)\alpha\gamma \\ &= \frac{\gamma^2(k-u)m\beta_2 - \gamma(k-u)}{m}\frac{\beta_2}{} - \frac{\beta_1}{mh}\left\{\frac{m\beta_2 - \gamma(k-u)}{\beta_2}\right\}^2 \\ &\quad \times \left\{\frac{\gamma(k-u)}{\alpha} + \alpha + \gamma\right\} + (\alpha+\gamma)\alpha\gamma. \end{aligned}$$

Direct but tedious calculations yield

$$\begin{aligned} &a_1a_2 - a_3 > 0 \\ &\Leftrightarrow \beta_1 < \frac{\dfrac{\gamma^2(k-u)m\beta_2 - \gamma(k-u)}{m}\dfrac{\beta_2}{} + (\alpha+\gamma)\alpha\gamma}{\dfrac{1}{mh}\left\{\dfrac{m\beta_2 - \gamma(k-u)}{\beta_2}\right\}^2\left\{\dfrac{\gamma(k-u)}{\alpha} + \alpha + \gamma\right\}} \\ &\Leftrightarrow \beta_1 < \frac{\alpha\gamma h}{m}\left\{\frac{\beta_2}{\beta_2 - \gamma(k-u)/m}\right\}^2\left\{1 - \frac{1}{}\frac{\gamma^2(k-u)^2}{m\beta_2\gamma(k-u) + \alpha(\alpha+\gamma)}\right\} \\ &\Leftrightarrow \beta_1 < \frac{\alpha\gamma h}{m}\frac{\beta_2}{\beta_2 - \gamma(k-u)/m} \\ &\quad \times \left\{\frac{\gamma(k-u)}{\gamma(k-u) + \alpha(\alpha+\gamma)} + \frac{\beta_2}{}\frac{\alpha(\alpha+\gamma)}{\beta_2 - \gamma(k-u)/m\gamma(k-u) + \alpha(\alpha+\gamma)}\right\}. \end{aligned}$$

It is noteworthy that

$$\frac{\gamma(k-u)}{\gamma(k-u) + \alpha(\alpha+\gamma)} + \frac{\beta_2}{}\frac{\alpha(\alpha+\gamma)}{\beta_2 - \gamma(k-u)/m\gamma(k-u) + \alpha(\alpha+\gamma)} > 1.$$

That relation implies that

$$a_1a_2 - a_3 > 0 \Leftarrow \beta_1 < \frac{\alpha\gamma h}{m}\frac{\beta_2}{\beta_2 - \gamma(k-u)/m}.$$

Therefore, we can conclude that E_c is always LAS whenever it exists. In Fig. 2(c) and (d), we present these conditions in the $\beta_1-\beta_2$ plane.

Appendix B

We also analyze the existence and stability conditions of the equilibria in (3). The model has four possible equilibria as follows:

$$E_h = (0,0,0),$$
$$E_a^{\pm} = (D_a^{\pm}, I_a^{\pm}, 0), \quad D_a^{\pm} = \frac{m\beta_1 \pm \sqrt{m^2\beta_1^2 - 4\alpha^2\gamma^2h^2}}{2\alpha\gamma},$$
$$I_a^{\pm} = \frac{\alpha}{\beta_1}D_a^{\pm},$$
$$E_c^* = (D_c^*, I_c^*, V_c^*), \quad D_c^* = \frac{\beta_1 k - u}{\beta_2}\frac{}{\alpha},$$
$$I_c^* = \frac{k-u}{\beta_2}, \quad V_c^* = \sqrt{\frac{\gamma(k-u)h^2}{m\beta_2 - \gamma(k-u)}} - \frac{\beta_1 k - u}{\beta_2}\frac{}{\alpha}.$$

Clearly, E_h always exists. The existence condition of $E_a^{\pm}$ and E_c^* are as follows:

$$E_a^{\pm} \in \mathbb{R}^3_+ \Leftrightarrow \beta_1 > \frac{2\alpha\gamma h}{m},$$
$$E_c^* \in \mathbb{R}^3_+ \Leftrightarrow k-u>0, \quad \beta_2 > \frac{\gamma(k-u)}{m},$$
$$\beta_1 < \sqrt{\frac{\gamma}{m(k-u)}}\frac{\alpha\beta_2 h}{\sqrt{\beta_2 - \gamma(k-u)/m}}.$$

It might be readily apparent that E_c^* cannot exist in $\mathbb{R}^3_+$ if $k-u<0$. In Fig. 3(a) and (b), we present these conditions in the $\beta_1-\beta_2$ plane.

Hereinafter, we explain the stability of these equilibria in detail. From a direct calculation, the eigenvalues of $J(E_h)$ are $-\alpha$, $-\gamma$, and $k-u$, where J is the Jacobian matrix of (3). Those results imply that if $k-u<0$, then E_h is always LAS; otherwise, E_h is unstable.

The Jacobian matrix of (2) at $E_a^{\pm}$ is

$$J(E_a^{\pm}) = \begin{bmatrix} -\alpha & \beta_1 & 0 \\ \dfrac{2mh^2D_a^{\pm}}{(h^2 + D_a^{\pm 2})^2} & -\gamma & \dfrac{2mh^2D_a^{\pm}}{(h^2 + D_a^{\pm 2})^2} \\ 0 & 0 & k - u - \beta_2 I_a^{\pm} \end{bmatrix}.$$

The characteristic equation of $J(E_a^{\pm})$ is

$$(p - k + u + \beta_2 I_a^{\pm})\left\{p^2 + (\alpha+\gamma)p + \alpha\gamma - \frac{2m\beta_1 h^2 D_a^{\pm}}{(h^2 + D_a^{\pm 2})^2}\right\} = 0.$$

As a result of tedious but straightforward calculations, we can show that $\alpha\gamma - 2m\beta_1 h^2 D_a^- /(h^2 + D_a^-)^2 < 0$ and $\alpha\gamma - 2m\beta_1 h^2 D_a^+ / (h^2 + D_a^+)^2 > 0$. That relation implies that E_a^- is always unstable if it exists. Consequently, the stability of E_a^+ is determined by a sign of $k - u - \beta_2 I_a^+$, which is an eigenvalue of $J(E_a^+)$. If $k-u<0$, then E_a^+ is LAS. On the other hand, if $k-u>0$, then we have

$$k - u - \beta_2 I_a^+ < 0 \Leftrightarrow \frac{k-u}{\beta_2} - \frac{m}{2\gamma} < \frac{\sqrt{m^2\beta_1^2 - 4\alpha^2\gamma^2h^2}}{2\gamma\beta_1}.$$

Therefore, if $(k-u)/\beta_2 - m/2\gamma < 0$, then E_a^+ is LAS. Although, if $(k-u)/\beta_2 - m/2\gamma > 0$, then the following relations hold:

$$\frac{k-u}{\beta_2} - \frac{m}{2\gamma} < \frac{\sqrt{m^2\beta_1^2 - 4\alpha^2\gamma^2h^2}}{2\gamma\beta_1} \tag{4}$$
$$\Leftrightarrow \frac{\gamma\alpha^2\beta_2^2h^2}{m} < \beta_1^2\,(k-u)\left\{\beta_2 - \frac{\gamma(k-u)}{m}\right\}. \tag{5}$$

Here we assume that $\beta_2>\gamma(k-u)/m$; otherwise the above condition does not hold. Therefore, if the following conditions hold,

$$\beta_1>\sqrt{\frac{\gamma}{m(k-u)}}\frac{\alpha\beta_2 h}{\sqrt{\beta_2-\gamma(k-u)/m}},$$
$$\frac{\gamma(k-u)}{m}<\beta_2<\frac{2\gamma(k-u)}{m},$$

then E_a^+ is LAS. Consequently, we can infer the stability conditions of E_a^+ as

$$\begin{cases} k-u<0 & \text{or} \\ k-u>0, & \beta_2>\dfrac{2\gamma(k-u)}{m} \quad \text{or} \\ k-u>0, & \beta_1>\sqrt{\dfrac{\gamma}{m(k-u)}}\dfrac{\alpha\beta_2 h}{\sqrt{\beta_2-\gamma(k-u)/m}}, \\ & \dfrac{\gamma(k-u)}{m}<\beta_2<\dfrac{2\gamma(k-u)}{m}. \end{cases}$$

The Jacobian matrix of (2) at E_c^* is

$$J(E_c^*)=\begin{bmatrix} -\alpha & \beta_1 & 0 \\ \dfrac{2mh^2(D_c^*+V_c^*)}{\{h^2+(D_c^*+V_c^*)^2\}^2} & -\gamma & \dfrac{2mh^2(D_c^*+V_c^*)}{\{h^2+(D_c^*+V_c^*)^2\}^2} \\ 0 & -\beta_2 V_c^* & 0 \end{bmatrix}.$$

The characteristic equation of $J(E_c^*)$ is

$$p^3+a_1p^2+a_2p+a_3=0,$$

where

$$a_1=\alpha+\gamma,$$
$$a_2=\alpha\gamma+\frac{2\beta_2 mh^2(D_c^*+V_c^*)V_c^*}{\{h^2+(D_c^*+V_c^*)^2\}^2}-\frac{2\beta_1 mh^2(D_c^*+V_c^*)}{\{h^2+(D_c^*+V_c^*)^2\}^2},$$
$$a_3=\frac{2\alpha\beta_2 mh^2(D_c^*+V_c^*)V_c^*}{\{h^2+(D_c^*+V_c^*)^2\}^2}.$$

Therefore, from the Routh–Hurwitz criterion, the stability of E_c^* is determined by the sign of $a_1a_2-a_3$. Because the following relation holds:

$$\frac{2mh^2(D_c^*+V_c^*)}{\{h^2+(D_c^*+V_c^*)^2\}^2}=\frac{2(m-\gamma I_c^*)\sqrt{\gamma I_c^*}\sqrt{m-\gamma I_c^*}}{mh},$$

we can obtain

$$\begin{aligned} a_1a_2-a_3 &= \alpha\gamma(\alpha+\gamma)+\frac{2\gamma^2\{m\beta_2-\gamma(k-u)\}(k-u)}{m\beta_2} \\ &\quad -\frac{\gamma(k-u)+\alpha(\alpha+\gamma)2\beta_1\{m\beta_2-\gamma(k-u)\}\sqrt{\gamma(k-u)}\sqrt{m\beta_2-\gamma(k-u)}}{\alpha\qquad\qquad mh\beta_2^2}. \end{aligned}$$

Therefore, if the following conditions hold,

$$\beta_1<\frac{\alpha\beta_2\gamma h[m\alpha\beta_2(\alpha+\gamma)+2\gamma(k-u)\{m\beta_2-\gamma(k-u)\}]}{2\{\alpha(\alpha+\gamma)+\gamma(k-u)\}\sqrt{\gamma(k-u)}\{m\beta_2-\gamma(k-u)\}^{3/2}},$$

then E_c^* is LAS. We define the following functions.

$$F(\beta_2)=\frac{\alpha\beta_2\gamma h[m\alpha\beta_2(\alpha+\gamma)+2\gamma(k-u)\{m\beta_2-\gamma(k-u)\}]}{2\{\alpha(\alpha+\gamma)+\gamma(k-u)\}\sqrt{\gamma(k-u)}\{m\beta_2-\gamma(k-u)\}^{3/2}},$$
$$G(\beta_2)=\sqrt{\frac{\gamma}{m(k-u)}}\frac{\alpha\beta_2 h}{\sqrt{\beta_2-\gamma(k-u)/m}}.$$

Because we have

$$G(\beta_2)-F(\beta_2)=\frac{\alpha\beta_2 h}{2\{m\beta_2-\gamma(k-u)\}^{3/2}}\sqrt{\frac{\gamma}{k-u}}\frac{\alpha(\alpha+\gamma)\{m\beta_2-2\gamma(k-u)\}}{\alpha(\alpha+\gamma)+\gamma(k-u)},$$

the stability conditions of E_c^* are

$$\begin{cases} k-u>0, & \beta_1<G(\beta_2), \quad \dfrac{\gamma(k-u)}{m}<\beta_2<\dfrac{2\gamma(k-u)}{m} \quad \text{or} \\ k-u>0, & \beta_1<F(\beta_2), \quad \beta_2>\dfrac{2\gamma(k-u)}{m}. \end{cases}$$

In Fig. 3(c) and (d), we present these conditions in the $\beta_1-\beta_2$ plane.

Appendix C

We show that $V(t)$ in (1) blows up for sufficiently large t if $\beta_2<\gamma(k-u)/m$ and $k-u>0$. Because $\max\{f_1,f_2\}\leqslant m$, we have the following inequality:

$$I'=f(D,V)-\gamma I\leqslant m-\gamma I.$$

Using a comparison theorem for ordinary differential equations, we can obtain

$$I(t)\leqslant\left(I(0)-\frac{m}{\gamma}\right)e^{-\gamma t}+\frac{m}{\gamma}.$$

Therefore, we can evaluate

$$V'=(k-u-\beta_2 I)V\geqslant\left\{k-u-\beta_2\left(I(0)-\frac{m}{\gamma}\right)e^{-\gamma t}-\frac{m\beta_2}{\gamma}\right\}V.$$

Because $\beta_2<\gamma(k-u)/m$ and $k-u>0$, there exist some T such as $k-u-\beta_2(I(0)-m/\gamma)e^{-\gamma t}-m\beta_2/\gamma>0$ for any $t>T$, which implies that $\lim_{t\to\infty}V(t)=\infty$. Consequently, we can show that $\lim_{t\to\infty}I(t)=m/\gamma$ and $\lim_{t\to\infty}D(t)=m\beta_1/\alpha\gamma$. All orbits in (1) converge to E_∞ if $\beta_2<\gamma(k-u)/m$ and $k-u>0$.

References

Andersen, O., Lygner, P.E., Bergstrom, T., Andersson, M., Vahlne, A., 1993. Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. J. Neurol. 240, 417–422.

Anderton, S.M., 2006. Avoiding autoimmune disease-T cells know their limits. Tre. Immunol. 27, 208–214.

Arnon, R., Ben-Yedidia, T., 2003. Old and new vaccine approaches. Inter. Immunopharmacol. 3, 1204–1995.

Barnett, L.A., Whitton, J.L., Wang, L.Y., Fujinami, R.S., 1996. Virus encoding an encephalitogenic peptide protects mice from experimental allergic encephalomyelitis. J. Neuroimmunol. 64, 163–173.

Bell, E., Bird, L., 2005. Autoimmunity. Nature 435, 583.

Borghans, J.A.M., de Boer, R.J., 1995. A minimal model for T-cell vaccination. P. Roy. Soc. Lond. B 259, 173–178.

Borghans, J.A.M., de Boer, R.J., Sercarz, E., Kumar, V., 1998. T cell vaccination in experimental autoimmune encephalomyelitis: a mathematical model. J. Immunol. 161, 1087–1093.

Borghans, J.A.M., Taams, L.S., Wauben, M.H.M., de Boer, R.J., 1999. Competition for antigen site during T cell proliferation: a mathematical interpretation of in vivo data. Proc. Natl. Acad. Sci. USA 96, 10782–10787.

De Boer, R.J., Perelson, A.S., 1995. Towards a general function describing T cell proliferation. J. Theor. Biol. 175, 567–576.

De Boer, R.J., Perelson, A.S., Kevrekidis, I.G., 1993. Immune network behavior-I. From stationary state to limit cycle oscillations. Bull. Math. Biol. 55, 745–780.

De Boer, R.J., Boerlijst, M.C., Sulzer, B., Perelson, A.S., 1996. A new bell-shaped function for idiotypic interactions based on cross-linking. Bull. Math. Biol. 58, 285–312.

Deodhar, S.D., 1992. Autoimmune diseases: overview and current concepts of pathogenesis. Clin. Biochem. 25, 181–185.

Fujinami, R.S., 2001. Viruses and autoimmune disease-two sides of the same coin? Tre. Microbiol. 9, 377–381.

Fujinami, R.S., 2004. Autoimmunity. Encyclopedia Virol., 108–112.

Fujinami, R.S., von Herrath, M.G., Christen, U., Whitton, J.L., 2006. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clin. Microbiol. Rev. 19, 80–94.

Goldrath, A.W., Bevan, M.J., 1999. Selecting and maintaining a diverse T-cell repertoire. Nature 402, 255–262.

Horwitz, M.S., Sarvetnick, N., 1999. Viruses, host responses, and autoimmunity. Immunol. Rev. 169, 241–253.

Iwami, S., 2007. Potential mechanisms of relapse in autoimmune disease. RIMS Kokyuroku Bessatsu B3, 177–192.

Iwami, S., Takeuchi, Y., Miura, Y., Sasaki, T., Kajiwara, T., 2007a. Dynamical properties of autoimmune disease models: tolerance, flare-up, dormancy. J. Theor. Biol. 246, 646–659.
Iwami, S., Takeuchi, Y., Liu, X., 2007b. Avian-human influenza epidemic model. Math. Biosci. 207, 1–25.
Janewa, C., Travers, P., Walport, M., Shlomchik, M.J. 2004. Immunobiology: The Immune System in Health and Disease, Garland Pub.
Lehmann, P.V., Sercarz, E.E., Forsthuber, T., Dayan, C.M., Gammon, G., 1993. Determinant spreading and the dynamics of the autoimmune T-cell repertoire. Immunol. Today 14, 203.
Libbey, J.E., Fujinami, R.S., 2002. Are virus infections triggers for autoimmune disease? Clin. Microbiol. Newslett. 24, 73–76.
Miller, S.D., Vanderlugt, C.L., Lenschow, D.J., Pope, J.G., Karandikar, N.J., Dal Canto, M.C., Bluestone, J.A., 1995. Blockade of CD28/B7-1 interaction prevents epitope spreading and clinical relapses of murine EAE. Immunity 3, 739.
Monteiro, J.M., Harvey, C., Trinchieri, G., 1998. Role of interleukin-12 in primary influenza virus infection. J. Virol. 72, 4825–4831.
Nowak, M.A., May, R.M., 1994. Superinfection and the evolution of parasite virulence. P. Roy. Soc. Lond. B 255, 81–89.
Nowak, M.A., Anderson, R.M., McLean, A.R., Wolfs, T., Goudsmit, J., May, R.M., 1991. Antigenic diversity thresholds and the development of AIDS. Science 254, 963–969.
Pender, M.P., 2003. Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases. Tre. Immunol. 24, 584–588.
Roitt, I., Male, D., Brostoff, J. 1998. Immunology, Mosby.
von Herrath, M.G., Oldstone, M.B.A., 1996. Virus-induced autoimmune disease. Curr. Opt. Immunol. 8, 878–885.
von Herrath, M.G., Fujinami, R.S., Whitton, J.L., 2003. Microorganisms and autoimmunity: making the barren field fertile? Nat. Rev. Microbiol. 1, 151–157.
Whitton, J.L., Fujinami, R.S., 1999. Viruses as triggers of autoimmunity: facts and fantasies. Curr. Opin. Microbiol. 2, 392–397.
Wodarz, D., Jansen, V.A.A., 2001. The role of T cell help for anti-viral CTL responses. J. Theor. Biol. 211, 419–432.
Wodarz, D., Thomsen, A.R., 2005. Does programmed CTL proliferation optimize virus control? Tre. Immunol. 26, 305–310.