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Understanding virus–host dynamics following EIAV infection in SCID horses

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HIGHLIGHTS

- We develop mathematical models of competition between two EIAV virus strains in SCID horses.
- We examine the effect of infused antibody on viral dynamics.
- We determine the conditions for virus elimination, one virus escape and coexistence.
- We determine the differences in dynamics when the antibody levels are constant and decaying over time.

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ABSTRACT

We develop a mathematical model for the interaction between two competing equine infectious anemia virus strains and neutralizing antibodies. We predict that elimination of one or both virus strains depends on the initial antibody levels, the strength of antibody mediated neutralization, and the persistence of antibody over time. We further show that the ability of a subdominant, neutralization resistant virus to dominate the infection transiently or permanently is dependent on the antibody-mediated neutralization effect. Finally, we determine conditions for persistence of both virus strains. We fit our models to virus titers from horses (foals) with severe combined immunodeficiency to estimate virus–host parameters and to validate analytical results.

1. Introduction

Equine infectious anemia virus (EIAV) is a macrophage-tropic lentivirus that establishes persistent infection in horses and ponies (Leroux et al., 2004). Infection with EIAV results in a clinical course characterized by acute, chronic, and asymptomatic stages (Hammond et al., 1997, 2000; Leroux et al., 2001). During the acute stage animals experience fever, high viral titer, and a decrease in the number of platelets. Upon resolution of acute infection, animals enter the chronic stage, where they display a series of recurring disease episodes at irregular intervals, associated with oscillations in the viral load. These typically subside with time, resulting in persistent, low-level infection without disease manifestation in the asymptomatic stage. At this stage, the infection is well-controlled by the adaptive immune system through cytotoxic T lymphocytes (CTL) and neutralizing antibodies (Perryman et al., 1988; Mealey et al., 2001).

EIAV is in the lentivirus subgroup, Retroviridae. This is the same subgroup that contains human immunodeficiency virus (HIV), and the two viruses are structurally similar. Unlike HIV infection, which leads to CD4 T-cell decline and progression to AIDS, however, EIAV infection is controlled by antibody and T-cell mediated immune responses (Maury and Oaks, 2010; Mealey et al., 2003, 2005). Therefore the study of immune control of EIAV is potentially important for the understanding of HIV pathogenesis. Furthermore this may provide crucial insights into HIV vaccine design and treatment.

It would be worthwhile to establish the individual contributions of different arms of the immune system to EIAV control. Horses with severe combined immunodeficiency (SCID) provide an opportunity to study EIAV in the absence of adaptive immune responses (Perryman et al., 1988). Moreover, the effects of the antibody response can be isolated by studying EIAV infection in SCID horses that have received infusions of EIAV-specific antibodies.

Recent studies by Taylor et al. (2010, 2011) investigated EIAV infection in SCID foals after infusion with plasma from immunocompetent horses. In some foals, the establishment of viral

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infection was blocked due to the transferred antibodies, while in other foals, viral escape was observed. The escaping virus, which was present in low doses in the challenge inoculum (Taylor et al., 2010), was found to contain a mutation in the antibody binding region. Followup studies showed that infusion of sufficient purified plasma immunoglobulin (PPIg) prior to viral challenge led to complete protection against infection, but low-dose PPIg allowed viral escape (Taylor et al., 2011).

Mathematical models have been used in the past to examine strain competition in lentiviral infection (Ball et al., 2007; Ciupe et al., 2011; Weinberger and Perelson, 2011; Wodarz, 2008). In this study we develop, analyze and compare to data a mathematical model of antibody pressure following EIAV infection. The available data allow us to examine the effect of antibodies in isolation from the other branches of the adaptive immune response. Understanding the role of antibodies in EIAV pathogenesis can provide insight into immune control of other viral infections. Such knowledge is useful for the development of vaccines that stimulate the antibody response.

The following issues are addressed: (1) we determine the conditions that give rise to virus elimination, strain co-existence, and wild-type dominance vs. mutant escape; (2) we estimate model parameters (including infected cells death rates and antibody neutralization rates) given the data on a neutralization-resistant virus strain; (3) we examine conditions for virus escape (and existence of single or multiple coexisting strains) due to low and high dose of antibody; and (4) we determine the effects on viral outcomes of constant antibody levels vs. decreasing antibody levels. Analytical results are illustrated with numerical simulations.

2. Mathematical model

We develop a mathematical model for virus–host dynamics in SCID foals that were challenged with EIAV after receiving either normal, immune or purified plasma immunoglobulin (PPIg) infusions (Taylor et al., 2010, 2011). Our model describes the interaction between target monocyte/macrophage cells, T, two virus strains (a wild-type virus and a neutralization-resistant virus), V_i, $i\in\{1,2\}$, monocytes/macrophages infected with the i-th variant, I_i, and EIAV-specific antibodies from infused plasma, A. We assume that target cells are produced at rate s and die at per capita rate d. In the presence of virus i they get infected at rate β_i. Cells infected with strain i die at per capita rates $\delta_i \geq d$, due to virus induced cytotoxicity (Cook et al., 1998; Li et al., 2000; Leroux et al., 2004). Infected cells produce virus at rates p_i per infected cell per day and viruses are cleared at per capita rates c_i. We assume that the infused antibody reduces the infection rate β_i by a factor $1+\eta_i A$, for $i=\{1,2\}$ (we will refer to η_i as the antibody neutralization effect on virus i). Here, $\eta_i=0$ represents a lack of antibody-mediated neutralization (Tomaras et al., 2008). The passively administered antibody decays over time at per capita rate d_A.

A model diagram is given in Fig. 1 and the system describing these interactions is

$$\begin{aligned}
\frac{dT}{dt} &= s - dT - \sum_{i=1}^{2} \frac{\beta_i}{1+\eta_i A} T V_i,\\
\frac{dI_i}{dt} &= \frac{\beta_i}{1+\eta_i A} T V_i - \delta_i I_i,\\
\frac{dV_i}{dt} &= p_i I_i - c_i V_i,\\
\frac{dA}{dt} &= -d_A A,
\end{aligned} \tag{1}$$

with initial conditions $T_0=s/d$, $I_i(0)=0$, $V_i(0)=V_{i,0}$, $A(0)=A_0$, $i=\{1,2\}$.

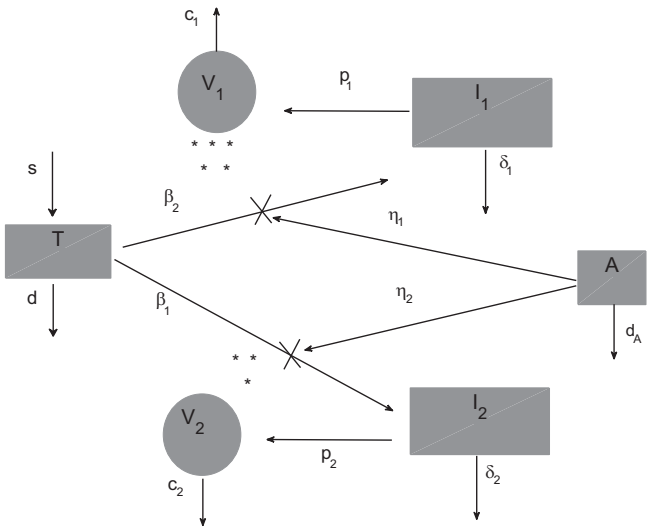

Fig. 1. Schematic diagram for model (1).

We assume that, in the absence of antibody, *i.e.* $A=0$, virus grows and establishes viremia as shown experimentally (Taylor et al., 2010). This occurs for parameter values satisfying $R_{0i}=\beta_i p_i s/c_i d\delta_i>1$, for at least one $i=\{1,2\}$ (Bonhoeffer et al., 1997). In this study, we are interested in determining the effects of neutralizing antibody on viral dynamics. We analyze system (1) following immune plasma infusion and we examine conditions for virus clearance and for persistence of one or both variants.

3. Results

3.1. Analytical results

Constant antibody levels: When continual immunization (through repeated infusion) leads to constant antibody levels both viruses are eliminated if their modified basic reproductive numbers are less than one, *i.e.*,

$$R_{0i}^A = \frac{R_{0i}}{1+\eta_i A_0} < 1, \tag{2}$$

where $A=A_0=$ constant and $i=\{1,2\}$.

Strain i persists while strain j is cleared ($i\neq j\in\{1,2\}$) when

$$R_{0i}^A = \frac{R_{0i}}{1+\eta_i A_0} > 1 \quad \text{and} \quad R_{0j}^A = \frac{R_{0j}}{1+\eta_j A_0} < 1. \tag{3}$$

The model predicts co-existence of the two viral strains when: $R_{01}^A = R_{02}^A > 1$ (see Appendix A).

Decaying antibody: In the more likely event that the antibody effect wanes, model (1) cannot predict complete virus elimination when at least one $R_{0i}>1$, for $i=\{1,2\}$. Both viruses will decay, however, for all t such that

$$\frac{R_{0i}}{1+\eta_i A(t)} < 1, \tag{4}$$

for $i=\{1,2\}$. Since $A(t)=A_0\exp\{-d_A t\}$, virus i decays for all $t<\theta_i$ where

$$\theta_i = -\frac{1}{d_A}\ln\left(\frac{R_{0i}-1}{\eta_i A_0}\right). \tag{5}$$

We define $V_e=3\times10^{-4}$ per mL (corresponding to less than one virus in the body) to be the theoretical elimination threshold. If at any point t_i, $V_i(t_i)<V_e$ for $i=\{1,2\}$, then we assume that both viruses have been eliminated.