



Dynamics of lentiviral infection in vivo in the absence of adaptive immune responses



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ABSTRACT

Understanding the dynamics of acute viral infection is crucial for developing strategies to prevent and control infection. In this study, lentiviral dynamics in a host without adaptive immunity were examined in order to determine kinetic parameters of infection and quantify the effect of neutralizing antibodies in preventing infection, using mathematical modeling of data from equine infectious anemia virus (EIAV) infection of horses with severe combined immunodeficiency (SCID). Estimated parameters were used to calculate the basic reproductive number and virus doubling time and found that the rate that antibodies neutralized virus was ~18 times greater than the virus clearance rate. These results establish EIAV replication kinetics in SCID horses and the minimal efficacy of antibodies that blocked infection. Furthermore, they indicate that EIAV is at most mildly cytopathic. This study advances our understanding of EIAV infection and may have important implications for the control of other viral infections, including HIV.

1. Introduction

The dynamics of acute lentivirus infection have not been fully understood. In particular, viral kinetics independent of adaptive immune responses have not been elucidated but can inform effective vaccine development. Here we determine estimates of kinetic parameters of acute lentivirus infection in a host without adaptive immunity and quantify the effects of antibody infusions that prevented viral infection. Equine infectious anemia virus (EIAV) is a macrophage-tropic lentivirus that establishes a persistent infection in horses and ponies (Issel et al., 2014; Maury and Oaks, 2010). While EIAV infection typically induces an effective adaptive immune response including cytotoxic T lymphocytes (CTL) and antibodies (Cook et al., 2013; Mealey et al., 2005, 2003), horses with severe combined immunodeficiency (SCID) lack functional B and T lymphocytes and therefore completely lack the ability to mount these responses to infection (Taylor et al., 2010, 2011). Thus, kinetic analysis of EIAV dynamics in SCID horses provides a unique opportunity to study the dynamics of viral infection and to estimate infection kinetics in the absence of CTL and antibody

involvement. Using these results, we are able to quantify the efficacy of neutralizing antibody infusions that can block infection.

Our previous studies document the time course of early EIAV infection in SCID horses and demonstrate the protection from infection of a SCID horse by passive transfer of broadly neutralizing antibodies (Taylor et al., 2010; Mealey et al., 2008). In the present study, EIAV infection dynamics in these SCID horses were examined using mathematical modeling in order to investigate viral growth kinetics in the absence of adaptive immunity and to estimate the effect of the antibodies that inhibited infection. The kinetic estimates were used to calculate the basic reproductive number, virus doubling time, and steady state values for viral load, uninfected target cells, and infected cells. Due to the availability of this rare data set of viral loads in the complete absence of T and B cell-mediated immune responses, this study provides estimates of key parameters of lentivirus dynamics in vivo without the interference of adaptive immunity. Such estimates may have considerable implications for understanding the dynamics of other lentiviral infections, including human immunodeficiency virus (HIV-1) (Cook et al., 2013; Sponseller et al., 2007). Moreover, our

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estimate of the efficacy of infused antibodies that can prevent infection may be useful in vaccine development.

2. Methods

To mathematically model the viral load data, the following basic model of viral infection was considered (Perelson and Ribeiro, 2013; Neumann et al., 1998; Nowak and Bangham, 1996; Perelson et al., 1996):

$$\frac{dM}{dt} = \lambda - \rho M - \beta MV$$

$$\frac{dI}{dt} = \beta MV - (\delta + \sigma)I$$

$$\frac{dV}{dt} = bI - (\gamma + \alpha)V$$

The target cells of EIAV infection are primarily tissue macrophages (Harrold et al., 2000; Oaks et al., 1998; Sellon et al., 1992). Uninfected target cells are represented by M . The model assumes that these cells become infected cells (I) at rate β following contact with EIAV (V). Infected cells produce virus at rate b ; the model accommodates the possibility that viral particles either bud or burst. Uninfected target cells arise at rate λ and die at rate ρ . Infected cells die at rate δ , and virus is cleared at rate γ . We introduce σ and α to represent the effects of infected cell killing by CTLs and virus cleared by neutralizing antibodies, respectively.

To determine the values of the model parameters, we fit the model to plasma viral load data from seven Arabian SCID horses experimentally infected with EIAV (see [Supplementary Material](#)) (Taylor et al., 2010; Mealey et al., 2008). For each horse, the model was fit to data on plasma viral load using nonlinear least squares data fitting, as described previously (Vaidya et al., 2010). Viral load measurements were taken beginning the initial day of infection through 4–6 weeks post-infection with sampling every few days. As part of previous studies, horses A2245 and A2247 received infusions of irrelevant control antibodies from an uninfected immunocompetent horse (Taylor et al., 2010), and horses A2193, A2199, A2202, A2205, and A2217 received infusions of EIAV-specific CTL clones that did not engraft (Mealey et al., 2008). Thus all of these SCID horses were completely devoid of all EIAV-specific adaptive immunity. Therefore, we take the infected cell killing by CTLs and the virus clearance by neutralizing antibodies equal to zero (i.e., $\sigma = \alpha = 0$) for these seven horses. An eighth horse (horse A2241) was infused with plasma containing EIAV-specific neutralizing antibodies from a long-term EIAV-infected immunocompetent horse, which protected horse A2241 from EIAV challenge (see [Supplementary Material](#)) (Taylor et al., 2010). As this horse showed protection from infection due to EIAV-specific antibodies, we used $\sigma = 0$ and $\alpha > 0$ to model viral dynamics in this horse. All experiments involving animals in these previously published studies were approved by the Washington State University Institutional Animal Care and Use Committee.

We carried out an analysis to determine whether the model parameters we expect to estimate are uniquely identifiable for the available EIAV viral load data. Based upon estimates derived from previous experimental studies (see [Table 1](#) footnote 2), we fixed the values of two model parameters, λ (the uninfected target cell recruitment rate) and ρ (the uninfected target cell death rate). Using the techniques of Wu et al. (2008), we found that with λ fixed and at least eight viral load (V) data points, five parameters (β , ρ , δ , γ , b) of our model can be uniquely estimated. Since we fixed ρ using previously available data, and as we have greater than eight viral load data points (average number of data points per horse = 11), identifying four parameters, δ (the death rate of infected cells), β (the infection rate), b (the virus production rate), and γ (the virus clearance rate), in this study is feasible and does not violate the conditions required for unique parameter identifiability.

3. Results

Parameter estimates for infection rate (β), death rate of infected cells (δ), virus production rate (b), and viral clearance rate (γ) were determined for each unprotected horse. These parameter estimates, along with 95% confidence intervals and the median values across all horses, are given in [Table 1](#). Of note, these values were calculated with the benefit of frequent sampling during early infection (median number of data points before viral peak = 12). To our knowledge, no similar study has included this many data points before peak viremia in acute infection. Furthermore, these parameter estimates are independent of the contributions of adaptive immune mechanisms such as CTL killing, neutralization by antibodies, and inhibition by CD8-derived soluble factors (Cocchi et al., 1995; Klatt et al., 2010; Levy, 2015; Mosoian et al., 2010; Saksena et al., 2008). Previously, an appropriate data set that could be utilized to yield quantitative estimates of infection kinetics in the absence of adaptive immunity was unavailable.

Fits of the model (lines) to the data (points) are shown in [Fig. 1](#). There is excellent agreement between the model and the data. The model fits identified a trend in the dynamics in which the viral load increased exponentially and then saturated, reaching a plateau (or steady state) at the peak virus load, around 10^6 or 10^7 vRNA copies/ml. Notably, it is a valid question why virus replication does not continue to increase in the absence of adaptive immune responses. These trends indicate that adaptive immunity is not essential to limit the exponential viral growth during acute EIAV infection in SCID horses. The leveling off of the growth could be due to target cell limitation or innate immune responses.

The median estimate for the infected cell death rate, δ , was 0.057/day, which indicates that infected cells turned over in about 18 days, implying only a slight reduction in cell lifespan due to infection, since uninfected cells turn over in 21 days ($\rho = 0.048/\text{day}$ (Valli, 2007), [Table 1](#)). Because the confidence interval for δ includes 0.048 in six of the seven horses, we also report parameter estimates obtained assuming equal infected and uninfected cell death rates (i.e., $\delta = \rho = 0.048/\text{day}$) ([Table 1](#)). There was little evidence against this constrained model in any of the horses (F-test p-value > 0.05 for each horse). Therefore, all subsequent results are shown for the model assuming equal death rates $\delta = \rho = 0.048/\text{day}$. Model simulations using these median values from [Table 1](#) are shown in [Fig. 1](#) (bottom right panel). Together, these results imply that EIAV infection in SCID horses is at most mildly cytopathic, certainly less cytopathic than other lentiviruses studied in immunocompetent hosts (Stafford et al., 2000). A modest cytopathicity is plausible because the evidence for macrophage cytopathicity caused by EIAV in vivo is not definitive, and SCID horses lack CTLs to kill infected cells. In vitro, EIAV can kill some of the cell types it infects but not others (Maury et al., 2003; Rasty et al., 1990). In vivo, the extent of EIAV-induced infected cell lysis in either SCID or immunocompetent hosts needs further study.

The basic reproductive number, R_0 , which indicates the average number of cells infected by a single infected cell when uninfected cells are not limiting (Stafford et al., 2000; Bonhoeffer et al., 1997), was calculated to be

$$R_0 = \frac{\lambda \beta b}{(\delta + \sigma)(\gamma + \alpha)\rho}$$

Values for R_0 for each unprotected horse ($\sigma = \alpha = 0$; i.e., no infected cell killing by CTLs (σ) nor virus clearance by neutralizing antibodies (α)) are shown in [Table 2](#); the median value was 18.8. According to mathematical theory (Ribeiro et al., 2010), a value of $R_0 > 1$ indicates that the infection establishes, consistent with the data. Another SCID horse A2241 (see [Supplementary Material](#)), which was infused with broadly neutralizing antibodies from a long-term EIAV-infected immunocompetent horse (Taylor et al., 2010), however, showed no viral load and was protected from infection. The data from this horse clearly indicate that the infection was prevented, implying $R_0 < 1$. Note

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