doi 10.18699/bgrs2024-12.2-12

A role for CD4 helper cells in HIV control and progression

Rouzine I.M.*

Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, Saint Petersburg, Russia

** igor.rouzine@iephb.ru*

Key words: mathematical modeling; post-treatment control

Motivation and Aim: Untreated HIV infection is characterized by persistent viremia and a gradual loss of CD4 T cells eventually causing AIDS [1, 2]. However, a small fraction of individuals is capable of controlling HIV replication at low levels in the absence of antiretroviral treatment (ART) [3, 4]. The other individuals, termed "post-treatment controllers", can achieve control after an early antiviral therapy [5] or antibody treatment [6]. Controllers progress to AIDS very slowly or not at all [3, 4]. Substantial evidence demonstrates that controllers suppress HIV replication due to an active immune response including cytotoxic CD8 T cells and CD4 T cells [7, 8]. The range of the functional avidity of HIV-specific CD8 T cells does not differ between a progressive and non-progressive infection [9]. A striking feature setting the two cohorts apart, which remains unexplained, is that an active CD4 T cell response with IL-2 secretion capacity and proliferative responses is observed in controllers but not in progressors [10]. The CD4 T cell avidity distribution for progressors is much narrower than for controllers and centered at much lower values (a higher threshold in antigen) (Fig. 1) [11].

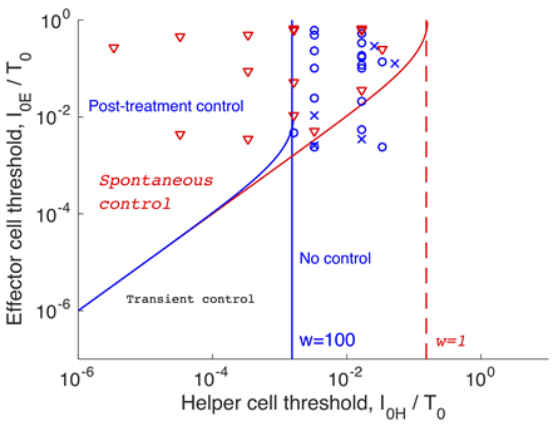

Fig. 1. The difference in CD4 cell avidity between controllers and progressors based on [11]. X-axis: Rescaled inverse functional avidity of CD4 T cells, denoted I_{H0}, measured in three different cohorts of patients [11]. Y-axis: simulated points of the inverse avidity of CD8 T cells, denoted I_{E0}, distributed in a way similar to data from patients in another study [9]. Red symbols (o) correspond to spontaneous controllers, and blue symbols (o, *) correspond to untreated patients with high viremia and patients on long-term ART, respectively. Blue and red lines show the phase diagrams predicted in this work at two different values of infectivity ratio between activated and resting CD4 T cells, $w = 100$ and $w = 1$. The other parameters are given in [12] The methods of measurement and the units are different between the CD8 and CD4 avidity, so that X-axis and Y-axis use two separate scaling factors found from fitting [12]

The present work offers a model that helps to understand this puzzle, as well as explains the differences in viral dynamics between controllers and progressors, with potential clinical applications.

Methods and Algorithms: The key idea is that the survival strategy of HIV may be to infect and suppress CD4 T cells and thus impair the immune system by making it much less sensitive to the presence of the virus. The model (Fig. 2) comprises five cell compartments. To elucidate the systems dynamics, two parallel methods are used: mathematical analysis and numeric computer simulation. It is formalized by a system of differential equations

$$\frac{dT}{dt} = b - pIT - d_T T,\ \frac{dI}{dt} = [1 - p_L(E)]pIT - d_I\left(1 + \frac{E}{E_0}\right)I + r(E)L$$

$$\frac{dL}{dt} = p_L(E)pIT - r(E)L,\ \frac{dH}{dt} = cH\alpha\left(\frac{I}{I_{0H}}\right)\beta\left(\frac{H}{H_m}\right) - pwIH - d_H H$$

$$\frac{dE}{dt} = cE\alpha\left[\frac{I}{I_{0E}} + \frac{H}{H_0}\alpha\left(\frac{I}{I_{0H}}\right)\right]\beta\left(\frac{E}{E_m}\right) - d_E E,\ r(E) = r_0 + r_{max}\frac{E}{E+E_{0L}},\ p_L(E) = p_{L0}\frac{E_{0L}}{E+E_{0L}}$$

$$\alpha(x) \equiv 1 - e^{-x}, \beta(y) \equiv (1-y)^{\frac{1}{3}}, p = 0 \text{ if } I < \frac{I_{in}}{2}$$

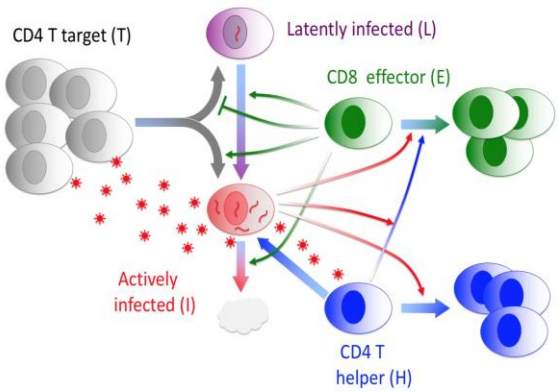

Fig. 2. The model of the immune response and virus dynamics. Included are five cell compartments, as follows: uninfected but susceptible target cells of CD4 T CCR5 phenotype, which number is denoted T, actively infected cells, I, latently-infected cell subset, L [16, 17], virus-specific helper CD4 T cells, H, and cytotoxic effector CD8 T cells, E. Broad arrows show cell flow and proliferation, thin arrows show control signals. Little red stars are free virions. Based on [12]

The general ranges of parameters are taken from [13, 14]. The specific (default) values of parameters are adjusted to fit data in Fig. 1, to obtain oscillation-free dynamics, and to match the representative levels of various cell types (see experimental references in [15]).

Results: Numeric simulation and analysis of the model above demonstrates that the system has two possible stable steady states. The helper-dependent steady state has a very low virus load corresponding to a spontaneous or post-treatment controller. The helper-independent state has no helper cells and a high virus load. If the ratio of infectivity of virus in activated HIV-specific to resting non-HIV specific cells w is on the order of 1, and the avidity of helper cells is sufficiently high, a controller state is established spontaneously, consistent with the clinical observation [11].

If parameter w is much larger than 1, helper cells are completely depleted during the acute phase of infection before they have a chance to reach their stable steady-state level (Fig. 3A). As a result, the high-viremia state ensues indefinitely (until AIDS not considered here). The low viremia state can be rescued with the help of early external intervention, such as anti-retroviral therapy [5] or broadly neutralizing antibodies [6]. The model explains this effect: by blocking infection of helper cells, ART started early rescues helper cells (Fig. 3B). ART must start in a narrow window depending on patient's parameters: basic reproduction ratio R_0, the initial level of naive T cells, and cell lifespans. Data for CD4 T cell avidity obtained for different patient cohorts [11] agree with the phase diagrams predicted by the model for two different values of the infectivity asymmetry parameter (Fig. 1). Because w is typically quite high [13, 14], post-treatment control is predicted to be much more likely than the spontaneous control, which agrees with observations (10–15 and 0.5% of patients, respectively).

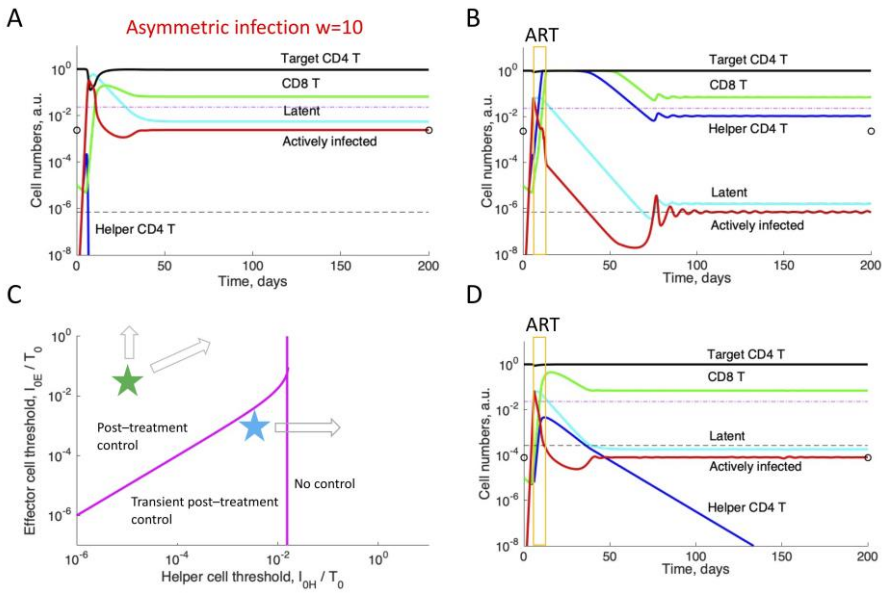

Fig. 3. A much higher infectivity of activated HIV-specific than resting non-specific CD4 T cells predicts a post-treatment controller. Infectivity of virus-specific (and hence activated) CD4 T cells is assumed to be 10 times higher than for non-specific (and hence resting) CD4 T cells, $w = 10$. (A) Early infection and killing of CD4 T cells leads to a high-viremia helper-free state. (B) ART between days 6 and 12 with the efficacy of 97% leads to the rescue of helper cells and establishment of a low-viremia state. (D) If avidity of helper cells is lower than the avidity of killer cells, helper cells decay gradually and control is only transient. (C) Phase diagram predicting the three outcomes of infection. The asterisks show parameters used in simulation: (A,B) $I_{0E} = 0.03, I_{0H} = 9 \cdot 10^{-6}$, (D) $I_{0E} = 0.001, I_{0H} = 0.003$. Relevant parameters in (D) are $w = 10, T_0/[R_0 d_I \int I(t)dt] = 0.2$. Based on [12]

The model does not include the "exhaustion" of CD8 T cells previously proposed to explain the divergent outcome in controllers and progressors [18]. In fact, CD8 T cell anergy is associated with long-term chronic infections [19, 20], while the outcome of HIV infection is decided during the first weeks. Anergy is usually modeled using either a time integral of virus load [21] or a third-party cell type [22]. More likely, exhaustion is not the cause but a consequence of persistence, which occurs for an unrelated reason. Also, the exhaustion model does not use any virological details specific for HIV and does not explain why all viruses do not persist like HIV. The phase diagram in Fig. 3C differs substantially from the diagram predicted by "exhaustion" model [18]. In particular, it does not depend on the killing efficacy of CTLs.

Conclusion: The study [12] offers a model that predicts a testable connection between HIV control, T cell avidity, and the dependence of HIV infectivity on cell activation status that agrees with data better than the previous "exhaustion" model. It can be used to more exactly time the time of ART to achieve post treatment control. The rather strict timing requirement raises the possibility that the currently-observed post-treatment controllers may be only a small fraction of their potential number.

Funding: The study was carried out within the framework of the governmental assignment to the IEPhB RAS (No. 075-00264-24-00).

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