
Freda Wasserstein-Robbins

Department of Mathematics, New Jersey City University, 2039 Kennedy Blvd., Jersey City, NJ 07305-1597, USA

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Abstract A mathematical model of the host’s immune response to HIV infection is proposed. The model represents the dynamics of 13 subsets of T cells (HIV-specific and nonspecific, healthy and infected, T4 and T8 cells), infected macrophages, neutralizing antibodies, and virus. The results of simulation are in agreement with published data regarding T4 cell concentration and viral load, and exhibit the typical features of HIV infection, i.e. double viral peaks in the acute stage, sero conversion, inverted T cell ratio, establishment of set points, steady state, and decline into AIDS. This result is achieved by taking into account thymic aging, viral and infected cell stimulation of specific immune cells, background nonspecific antigens, infected cell proliferation, viral production by infected macrophages and T cells, tropism, viral, and immune adaptation. Starting from this paradigm, changes in the parameter values simulate observed differences in individual outcomes, and predict different scenarios, which can suggest new directions in therapy. In particular, large parameter changes highlight the potentially critical role of both very vigorous and extremely damped specific immune response, and of the elimination of virus release by macrophages. Finally, the time courses of virus, antibody and T cells production and removal are systematically investigated, and a comparison of T4 and T8 cell dynamics in a healthy and in a HIV infected host is offered.

Keywords HIV T cell subset dynamics · Infected macrophage dynamics with tropism and mutation

1. Introduction and biological background

1.1. Introduction

HIV infection and disease progression have been carefully studied and well documented. Many successful models investigating fundamental HIV-immune dynamics have been
developed, among which we may mention the works by Perelson et al. (1993, 1996), Ho et al. (1995), Kirschner and Webb (1996), Perelson and Nelson (1999), Hellerstein et al. (1999), Stafford et al. (2000), and Jones and Perelson (2005) to cite only a few. The mathematical models, in concert with the wealth of experimental data, produced deep understanding of disease dynamics and gave help in devising significant interventions.

This paper presents a multifaceted model of the progression of HIV infection by describing the dynamics of different T cell subpopulations and of infected macrophages, and taking into account immune recognition of infected cells, production of neutralizing specific antibodies, viral adaptation and change in virus tropism, and thymic aging. In particular, the T cell population is subdivided in the model into T4 and T8 cells and into HIV-specific and non-HIV-specific cells and into healthy and infected cells.

The results of model simulation are in agreement with published experimental data regarding virus, T cell subsets, and antibody concentrations and dynamics (Stafford et al., 2000; Pilcher et al., 2004; Scamurra et al., 2000). The results conform to established features peculiar to HIV progression: initial double viral peaks, initial high T cell concentration, seroconversion, inverted T8/T4 ratio, establishment of a long quasi-steady state, with declining T cell concentrations coupled to rising viral concentration, and eventual descent into AIDS. Simulations predict that slight adjustments of single parameter values may account for commonly reported variations of individual responses. An investigation of the model response with large changes in the parameter values has been also performed, revealing unexpected dynamics and suggesting novel possible interventions.

1.2. Biological background

Human immunodeficiency virus infects cells that present the membrane antigen CD4 (CD4+ cells, mainly macrophages and CD4+ lymphocytes), and as any RNA-virus, mutates extensively during its replication. These characteristics are the major factors affecting the success of the immune system and of drug intervention in combating the disease. The immune efforts of host are thought to be indeed critical in disease control, progression, and long-term survival (Greenberg et al., 1997; Walker and Scadden, 2000; Fauci, 2003; Tripathi and Agrawal, 2007).

The HIV inoculate produces extensive infection of host macrophages (Hatzakis et al., 2000), some infection of CD4+ lymphocytes (T4 cells), and rapid exponential viral growth. Pools of infected cells have been documented as early as 10 days after inoculation (Chun et al., 1998; Dimitrov et al., 1998). The viral concentration reaches two peaks, once after several weeks to about $10^6$ viral RNA molecules/mL and again, after several months, to about $10^4$ viral RNA molecules/mL (Rouzioux, 2001). These extremely high early viral (and infected cells) concentrations stimulate the innate and the specific immune systems, as revealed by seroconversion. Stimulated by the virus, HIV-specific T4 cells proliferate and differentiate into effector helper cells that stimulate specific B cells proliferation and subsequent antibody production (Brander et al., 2005; Tran, 1999). Specific antibodies bind to the virions and neutralize them or target them for removal. Neutralizing antibodies are a promising component of an effective HIV vaccine (Stiegler et al., 2001; Nishimura et al., 2002). Specific CD8+ lymphocytes (T8 cells), stimulated by infected cells, proliferate