Journal of Theoretical Biology 335 (2013) 57–78

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Modeling interleukin-2-based immunotherapy in AIDS pathogenesis

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HIGHLIGHTS

- Comprehensive mathematical modeling for AIDS pathogenesis is developed.
- Mechanisms underlying the immunological effects of IL-2 therapy are investigated.
- Sustained CD4 T-cell expansion is not justified by increased CD4 T-cell survival.
- Instead, changed dynamics of Fas-dependent apoptotic pathways can play a critical role.
- IL-2+HAART has a greater effect on immunocompetence restoration than does HAART alone.

ARTICLE INFO

Article history:
Received 12 September 2012
Received in revised form
16 April 2013
Accepted 13 June 2013
Available online 25 June 2013

Keywords:
HIV
IL-2
Immunotherapy
T-lymphocyte
Immune system

ABSTRACT

In this paper, we sought to identify the $CD4^+$ T-cell dynamics in the course of HIV infection in response to continuous and intermittent intravenous courses of interleukin-2 (IL-2), the principal cytokine responsible for progression of $CD4^+$ T-lymphocytes from the G1 to the S phase of the cell cycle. Based on multivariate regression models, previous literature has concluded that the increase in survival of $CD4^+$ T-cell appears to be the critical mechanism leading to sustained $CD4^+$ T-cell levels in HIV-infected patients receiving intermittent IL-2 therapy. Underscored by comprehensive mathematical modeling, a major finding of the present work is related to the fact that, rather than due to any increase in survival of $CD4^+$ T-cells, the expressive, selective and sustained $CD4^+$ T-cell expansions following IL-2 administration may be related to the role of IL-2 in modulating the dynamics of Fas-dependent apoptotic pathways, such as activation-induced cell death (AICD) or HIV-specific apoptotic routes triggered by viral proteins.

1. Introduction

Restoration and preservation of the $CD4^+$ T-cell count remain crucial in the successful clinical management of the human immunodeficiency virus (HIV) infection (Kovacs et al., 1995). In this regard, attempts to improve immunological functions have considered a variety of immune-based therapies (Kovacs et al., 1995; Dybul et al., 2003), including interleukin-2 (IL-2), a T-cell-derived lymphokine with several immunomodulating effects including the progression of $CD4^+$ T-cells from the G1 to the S phase of the cell cycle.

IL-2 is a 14–17 kDa glycoprotein encoded by a single gene on chromosome 4 and has been considered a valid anti-HIV therapeutic option in the clinical arena, since several clinical phase I/II studies have demonstrated that intermittent subcutaneous or continuous intravenous administration of IL-2 in asymptomatic HIV-infected patients may induce a substantial, selective and sustained expansion of $CD4^+$ T-lymphocytes, the major HIV target (Kovacs et al., 1995, 1996; Dybul et al., 2003; De Paoli, 2001; Levy et al., 2003; Sereti et al., 2007; Read et al., 2008; INSIGHT-ESPIRIT, 2009).

However, the mechanisms leading to these increases remain unknown (Markowitz et al., 2012). The complexity of the *in vivo* cytokine network renders the interpretation of the role of individual cytokines in HIV pathogenesis quite difficult, since the role of

Abbreviations: AICD, activation-induced cell death; AIDS, acquired immunodeficiency syndrome; APC, antigen presenting cells; CCF, cell–cell fusion; CNS, central nervous system compartment; DAE, differential-algebraic equations; ENV, *Env*-CD4 cross-linking mediated apoptosis; FDC, follicular dendritic cells; HAART, highly active antiretroviral therapy; HEV, high endothelial venules; HIV, human immunodeficiency virus; IFN-γ, interferon γ; IL-2, interleukin-2; IL-12, interleukin-12; IU, International Unit; IVST, intracellular viral stock transference; LT, lymphoid tissue compartment; MHC, major histocompatibility complex; MIU, million International Units; PB, peripheral blood compartment; PCD, passive cell death; PCR, polymerase chain reaction; PSVE, polarized secretion of viral envelopes; TAT, *Tat*-induced apoptosis; VTC, virus-to-cell.

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0022-5193/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jtbi.2013.06.019

HIV-induced dysregulation of cytokine networks in disease pathogenesis is likely multifactorial; many of the dysfunction in cytokine production, such as the increases in proinflammatory cytokines, favor viral replication whereas others, such as the decrease in IL-2 production, have effects that are less clear (Dybul et al., 2003). Since a major concern with the use of IL-2 was the theoretical risk that this cytokine could stimulate HIV replication (Levy et al., 2003), the mechanisms underlying the immunological effects of IL-2 therapy have been widely investigated in the last decade. Findings based on experimental work suggest that IL-2 acts through several, sometimes conflicting, mechanisms that are deeply influenced by (De Paoli, 2001): (a) the host immunological status, (b) the concomitant highly-active antiretroviral therapy (HAART) scheme adopted, and (c) the nature of target cells.

To better understand the association between the $CD4^+$ T-cell increases seen verified following IL-2 therapy and key biological mechanisms thought to be affected by such therapy, we extend our previous work on comprehensive mathematical modeling of HIV disease to help us provide further phenomenological interpretation of the impact of IL-2 on its vertiginous dynamics. In particular, the goal of the current study was to determine whether there was a theoretical association between any of the proposed biological mechanisms in the past, such as preferential expansion and survival of naïve ($CD27^+CD45RO^-$) and central memory ($CD27^+CD45RO^+$) subpopulations of IL-2 receptor chain-expressing (CD25) $CD4^+$ T-cells (Read et al., 2008), and the magnitude of change in $CD4^+$ T-cell numbers following a cycle of IL-2.

2. Model development

When developing a mathematical model for any complex biological system, the trade-off between complexity and utility must be considered. Although conclusive kinetic data on HIV-1 dynamics have been first derived on the basis of nonlinear fitting of simple ODE systems by Ho et al. (1995) and Wei et al. (1995), the most cited scientific medical research published in 1995, since then important conclusions about the dynamics of HIV infection *in vivo* have continuously been produced based on more sophisticated models in which distinct types of immune cells are represented separately (e.g., Perelson and Nelson, 1999). In order to study the impact of IL-2 therapy on HIV infection, our motivation to adopt a modeling approach that considers a set of immune cells phenotypically well characterized relied on the following major aspects:

- The cytokine network that regulates the immune system dynamics is differentially impacted by the CD4 T-cell phenotype (see Section 2.4);
- HIV infection of a CD4 T-cell is a process highly dependent on the cell phenotype (Joly and Pinto 2005), and
- Lymphocyte homing and recirculation among anatomic compartments is dependent on the cell phenotype.

In this regard, we have, as others (Perelson and Nelson, 1999; Essunger and Perelson, 1994; Wendelsdorf et al., 2011), modeled the CD4 T-cell population dynamics as composed by three major subpopulations: naïve, effector and memory CD4 T-cells. By focusing on the effector CD4+ T-cell pool resident in the lymphoid tissues, the model formulation and rationale are presented in the following seven subsections. The full model structure is summarized in Appendix A, whereas Appendix B lists the model nomenclature, their explanation and reference to experimental data.

2.1. Transportation, recirculation and homing models

Although high-profile studies have continuously been published considering the human body as a single anatomic compartment (Ho et al., 1995; Wei et al., 1995; Perelson and Nelson 1999; Wendelsdorf et al., 2011; Perelson et al., 1993; Hadjiandreou et al., 2009), a more realistic representation of the dynamics of HIV infection in the bloodstream, the usual site for host clinical monitoring, may be (highly) dependent on endogenous and exogenous factors acting differentially on each host tissue. In fact, early events in HIV infection may be intimately related to lymphocyte recirculation and homing among anatomic compartments of the host (Abbas et al., 2000). More importantly, "*measuring the viral load in blood after initiation of antiretroviral treatment does not provide sufficient information to identify the biological processes underlying the second phase of viral decline*", as concluded by Perelson and Nelson (1999).

Aiming at considering some aspects thought to be relevant in delineating the real-world dynamics of HIV infection in the peripheral blood (e.g., lymphocyte recirculation and homing, and differentiated distribution of therapeutic agents among host tissues), the human body is here represented by three interconnected anatomic compartments well characterized in the context of HIV disease: the peripheral blood (PB) for clinical evaluation, the lymphoid tissue (LT), where most HIV replication occurs (Dybul et al., 2003), and the central nervous system (CNS), which is also referred as an "HIV sanctuary" or "immunologically privileged" site due to the poor penetration of therapeutic agents or limited traffic of immune cells through the blood–brain barrier (BBB) (Dybul et al., 2003; Cohen, 1998). In doing this, we attempt to consider the impact of the mass transfer associated to the transportation of immune cells, viral particles and cytokines on the infection dynamics throughout the human body. The proposed anatomic model is schematically illustrated in Fig. 1, in which the arrival of HIV trapped by antigen-presenting cells from the peripheral tissues into the LT compartment is also taken into account. This may be the case of sexually transmitted infection, the major AIDS contagious route (Dybul et al., 2003).

As a result, two types of viral reservoirs are considered. The first one is site-dependent and is modeled by considering that the mass transfer throughout the BBB is limited by either "mechanical" restrictions or selective (active) transportation. The second one, which may arise in any anatomic compartment, is represented by long-lived immune cells, such as memory T-cells and cells of the monocyte–macrophage lineage. As in other HIV models, we hypothesize that long-lived cells, even when infected by HIV, have an extended period of life.

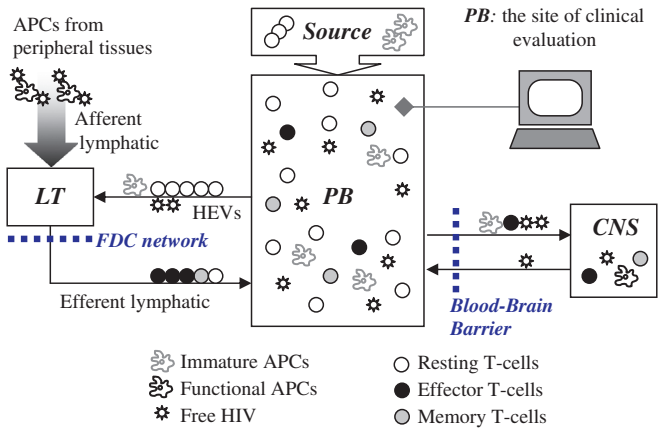

Fig. 1. The host anatomic model.