Modelling the influence of activation-induced apoptosis of CD4\(^+\) and CD8\(^+\) T-cells on the immune system response of a HIV infected patient

Guy-Bart Stan\(^*\), Florence Belmudes\(^\#\), Raphael Fonteneau\(^\#\), Frederic Zeggwagh\(^\#\), Marie-Anne Lefebvre\(^\#\), Christian Michelet\(^\#\) and Damien Ernst\(^\#\)

\(^*\)University of Cambridge (United Kingdom), \(^\#\)University of Liège (Belgium), \(^\#\)Ecole Supérieure d’Electricité (France), \(^\#\)Hôpital Pontchaillou, Rennes (France)

Abstract

Based on the HIV infection dynamics model proposed by Adams et al. in [1], we propose an extended model represented by a set of nonlinear Ordinary Differential Equations (ODEs) that aims at incorporating the influence of activation-induced apoptosis of CD4\(^+\) and CD8\(^+\) T-cells on the immune system response of HIV infected patients. Through this model we study the influence of this phenomenon on the time evolution of specific cell populations such as plasma concentrations of HIV copies, or blood concentrations of CD4\(^+\) and CD8\(^+\) T-cells. In particular, this study shows that depending on its intensity, the apoptosis phenomenon can either favor or mitigate the long-term evolution of the HIV infection.

Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that may lead to the lethal Acquired Immune Deficiency Syndrome (AIDS). Progression from HIV infection to AIDS is primarily due to an extensive depletion of CD4\(^+\) T-cells. T-cell loss may be due to direct destruction by the virus (direct virus-induced cytolysis) or to defective T-cell generation. In 1991, apoptosis, also called programmed cell death, has been suggested as another mechanism responsible for T-cell depletion during the evolution of HIV-1 infection and an extensive body of recent literature is supporting this hypothesis. To the best of our knowledge, no mathematical model has yet tried to explain the influence of the activation-induced apoptosis phenomenon on the HIV infection dynamics.

We propose here a modification of the model proposed by Adams et al. in [1]. This modification aims at modelling the activation-induced apoptosis phenomenon and at analyzing its influence on the HIV infection dynamics.

The Model of Adams et al.

\[
\begin{align*}
T_1 &= \lambda_1 - d_1 T_1 - k_1 V T_2 \\
T_2 &= \lambda_2 - d_2 T_2 - k_2 V T_2 \\
T_1' &= k_1 V T_1 - \delta T_1' - m_1 E T_1' \\
T_2' &= k_2 V T_2 - \delta T_2' - m_2 E T_2' \\
V &= N \delta (T_1' + T_2') - c V \\
E &= k_0 + \left( \frac{T_1' + T_2'}{T_1' + T_2'} + k_v \right) V \\
\dot{E} &= k_0 + \frac{T_1' + T_2'}{T_1' + T_2'} V - \delta E V \\
\end{align*}
\]

\(T_1\) and \(T_2\) : number of non-infected (infected) CD4\(^+\) T-lymphocytes (in cells/ml);
\(T_1'\) and \(T_2'\) : number of non-infected (infected) macrophages (in cells/ml);
\(V\) : number of free HIVs (in virions/ml);
\(E\) : number of HIV-specific cytotoxic CD8\(^+\) T-cells (in cells/ml).

Analysis of the apoptosis-compliant model

\[
T_1 = \lambda_1 - d_1 T_1 - k_1 V T_2 - \Delta T_1 T_2' E \\
T_2 = \lambda_2 - d_2 T_2 - k_2 V T_2 \\
T_1' = k_1 V T_1 - \delta T_1' - m_1 E T_1' \\
T_2' = k_2 V T_2 - \delta T_2' - m_2 E T_2' \\
V = N \delta (T_1' + T_2') - c V \\
E = k_0 + \frac{T_1' + T_2'}{T_1' + T_2'} V - \Delta T_1 T_2' E \\
\dot{E} = k_0 + \frac{T_1' + T_2'}{T_1' + T_2'} V - \delta E V - \Delta T_1 T_2' E
\]

\(\Delta T_1\) and \(\Delta T_2\) are expressed in \(\text{ml/(cells x day)}\).

Discussion

Using a combination of numerical simulations and bifurcation analysis, we found that for some ranges of values of theapoptosis parameters, these activation-induced apoptosis phenomena had non-linear effects that could be beneficial to the immune system during the HIV infection. On the other hand, when the magnitude of the apoptosis parameters becomes too large, this potential beneficial effect disappears and activation-induced apoptosis mechanisms were then found to aggravate the HIV infection. Furthermore, since the HIV infection worsens when these activation-induced apoptosis rates become too large, one could also relate the progression of the HIV infection to AIDS to a change in magnitude in these rates. These findings need to be taken with caution since they are dependent on several modelling assumptions that would certainly require careful experimental validation.

These results could potentially help in designing new anti-HIV therapies based on a drug-mediated regulation of the activation-induced apoptosis factors (such as galectin 120) in HIV infected patients. These therapies could be based on the injection of some specific interleukins to HIV positive patients, such as for example IL-2, IL-7 and IL-15 [2, 3, 5], although the role of interleukins on the immune system of HIV-infected patients/macrophages is still a controversial issue since other studies (see e.g. [4]) have shown that they could have a detrimental effect.

References