Mathematical Biosciences 236 (2012) 36–43

Contents lists available at SciVerse ScienceDirect

Mathematical Biosciences

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

Kinetic model of HIV infection including hematopoietic progenitor cells

Vladimir P. Zhdanov *

Department of Applied Physics, Chalmers University of Technology, S-412 96 Göteborg, Sweden
Boreskov Institute of Catalysis, Russian Academy of Sciences, Novosibirsk 630090, Russia

ARTICLE INFO

Article history:
Received 20 August 2010
Received in revised form 10 January 2012
Accepted 13 January 2012
Available online 28 January 2012

Keywords:
HIV kinetics
Antiretroviral therapy
Hematopoietic progenitor cells
Lymphocytes
Immune-response cells
Mean-field kinetic equations

ABSTRACT

Recent experiments indicate that one of the likely reasons of the failure of eradication of HIV is in infection of hematopoietic progenitor cells. Such cells are nurtured in stem-cell niches residing in the bone marrow. Our generic four-variable kinetic model focused on this ingredient of HIV infection describes (i) a rapid increase of the population of infected $CD4^+$ T cells at the beginning of verimia, (ii) a sharp decline of this population due to immunological control, (iii) a long period of latency followed by a collapse of the immune system, and (iv) predicts that in the case of the therapy fully eradicating infected $CD4^+$ T cells the infection starts rapidly again after the therapy.

1. Introduction

Modelling of reaction of the immune system on viral infection has long attracted attention of mathematicians and biochemical and biophysical communities. Many decades, the corresponding studies were focused on the global temporal interplay of the cell and virion populations [1–4]. Recently, the spatio-temporal kinetics have also been analyzed [5–7]. With the accumulation of detailed experimental data about the mechanisms of interaction of viruses and cells, the global coarse-grained models have been complemented by the models focused on intracellular viral kinetics (see Refs. [8–14] and references therein). The kinetic models of HIV (human immunodeficiency virus) infection are primarily of the former category (see, e.g., recent review [15], articles [16–40] and references therein; for the models aimed at some aspects of the intracellular HIV kinetics, see Refs. [41–44]). Compared to other infections, modelling of HIV viremia is especially challenging, because with its resistance to therapy this infection incorporates various physicochemical and biological processes occurring on very different length and time scales (see, e.g., recent reviews [45–54]). The interplay of many factors behind this infection and their relative importance are still open to debate [53].

For a brief general introduction into the HIV pathogenesis, we recall that the immune homeostasis is achieved via export of newly generated cells from primary lymphoid organs, such as the bone marrow (BM) and thymus, and proliferation and death of these cells in the periphery, including the spleen, lymph nodes and gut [55–60] (the thymic activity is high in early life and continues later on albeit at lower level [59–61]; at adulthood, the peripheral activity may occur in the absence of thymus at least for a while [62,63]). The whole process is highly dynamic and tightly regulated by internal stimuli, including mainly cytokines [55–57]. On the bottom level, the cell-mediated immunity is related to white blood cells known as lymphocytes. HIV results in latent infection of T lymphocytes (or, more specifically, resting memory $CD4^+$ T cells) [64,65]. The latent infection of other cells of the immune-defence system cannot be excluded either [53,54]. With appropriate stimulus, the latently infected cells can be reactivated to produce infectious virions. This factor is widely considered [15,53,54,66] to be a key reason why HIV cannot be completely eradicated by the available antiretroviral drug therapy (there are now 17 drugs in common use [67]). The HIV treatment is, however, heavily complicated also by other factors including, e.g., HIV mutation [68] and HIV-related erosion of the ingredients of the immune system, e.g., lymph nodes [46,47].

On the top level, the hematopoiesis in humans is related to the BM-hosted hematopoietic progenitor cells (HPCs) representing a heterogeneous population of cells that includes the hematopoietic stem cells, which are the most primitive HPCs. The HIV infection of BM HPCs and their role in trafficking and viral dissemination is comprehensively reviewed by Alexaki and Wigdahl [69]. One of their key messages supported by many references is as follows:

"Patients with HIV-1 often present with a wide range of hematopoietic abnormalities, some of which may be due to the presence of opportunistic infections and to therapeutic drug treatments.

* Address: Boreskov Institute of Catalysis, Russian Academy of Sciences, Novosibirsk 630090, Russia.
E-mail address: zhdanov@catalysis.ru

0025-5564/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.mbs.2012.01.003

However, many of these abnormalities are directly related to HIV-1 replication in BM. Although the most primitive HPCs are resistant to HIV-1 infection, once these cells begin to differentiate and become committed HPCs they become increasingly susceptible to HIV-1 infection and permissive to viral gene expression and infectious virus production. ... The central role of BM in the pathogenesis of HIV-1 is highlighted by the wide spectrum of hematopoietic abnormalities observed in patients with HIV-1. It is has been questioned whether any of these abnormalities are due to direct HIV-1 infection of HPCs; however, collectively the data suggest that the presence and replication of HIV-1 in the BM impact either directly or indirectly the normal proliferation and differentiation of HPCs, resulting in changes in the cell populations of the blood."

The difficulty and controversy in detecting HIV-infected HPCs *in vivo* may be due to many factors including, e.g., the limited time frame during which these cells express progenitor cell markers following their infection [69].

More recently (compared to the bulk of references compiled in review [69]), the evidence that the HIV effect on hematopoiesis *in vivo* and *in vitro* is at least partially caused by viral infection of the HPC population was presented by Redd et al. [70].

In the most recent studies, Carter et al. [71] (see also Ref. [72]) have demonstrated (for highlights, see Refs. [73,74]) that HIV can infect HPCs *in vivo* and *in vitro* to cause an active and latent infection. To assess the susceptibility of HPCs to HIV *in vitro*, they examined intracellular expression of the HIV capsid protein in purified bone marrow $CD34^+$ cells treated with a HIV molecular clone. The evidence that the cells of this type are infected *in vivo* was obtained by using samples from HIV-infected people with high viral loads. The important point is that latently infected HPCs (in such cells, the virus was integrated into the chromosomes and did not reproduce) may be long lived (compared to $CD4^+$ T lymphocytes) and could carry latent HIV for extended periods of time [71], because the asymmetrical division of latently infected HPCs may result in the formation of infected blood cells.

The marked HIV-related impairment of $CD34^+$ HPCs has recently been observed by Sauce et al. [75].

The understanding of the whole immune-defence pathway (from hematopoietic stem/progenitor cells to T lymphocytes) is crucial for the development of anti-HIV therapies. The currently used antiretroviral drug therapy is primarily aimed at the downstream part of this pathway [67]. This therapy radically improves the treatment of HIV patients but does not solve the ultimate goal of eradicating HIV infection. The most promising novel therapeutic strategies are focused on the upstream part of the immune-defence system or, more specifically, on HPCs [76]. Two major approaches here are aimed at the protection of cells from productive infection with HIV and targeting immune cells to directly combat HIV infection.

The finding that the long-lived HPCs may mediate HIV, play a role of latently infected cells, and be responsible for resistance to therapy shed new light on the reasons of the difficulties of eradication of HIV [71,72]. The relative importance of HPSs and resting memory $CD4^+$ T cells in the maintenance of latent HIV infection is now one of the central items in the list of what one wants to know and should dare to ask about HIV (see Table 1 in Ref. [53]).

The available kinetic models successfully describe many aspects of HIV kinetics including the latency related to infected $CD4^+$ T cells [15]. The likely role of infection of HPCs has, however, not been scrutinized mathematically. Complementing the earlier studies, we propose here the first generic kinetic model describing the HIV-infection scenario including BM HPCs. The key ingredients of the model are described in Section 2. The HIV kinetics predicted in the absence of therapy are shown in Section 3. The kinetics after the conventional therapy (without complete eradication of HIV infection) are illustrated in Section 4. The outcome of our study is summarized in Section 5.

2. Model

As already noted in the Introduction, the pathogenesis of HIV infection occurs on very different length and time scales, and in this field there are many unresolved issues. The corresponding models are numerous and range from those containing a few variables to those including a multitude of variables and parameters, related, e.g., to HIV mutation (see, for example, Refs. [19,40]). In our study, we have no ambition to describe mechanistically in detail many aspects of HIV (this is hardly possible at present). Our goal is to focus the presentation on BM HPCs. Under such conditions, a reasonable strategy is to choose one of the already available models and to complement it by the ingredients related to HPCs. In principle, the terms corresponding to HPCs can be introduced in one or another form into almost any available model including those containing many variables. To not obscure the main message, it makes sense to choose for modification one of generic models containing only a few variables.

Following the strategy outlined above and taking into account that HIV causes a chronic infection characterized by depletion of $CD4^+$ T lymphocytes, we operate with the fraction of healthy BM HPCs, f (the fraction of latently infected HPCs is $1-f$), populations of healthy and infected $CD4^+$ T cells, x and y, and population of immune-response cells, z. The free virus is considered to be short-lived relative to infected cells, its concentration is assumed to be proportional to y, and the corresponding variable is explicitly not introduced. The equations we use for x, y and z are the same (except the terms related to HPCs) as those in the three-variable model analyzed by Culshaw et al. [16]. The latter model is in turn a reduced version of the four-variable model proposed by Wodarz and Nowak [77] (the kinetics predicted by these models are very similar). Taking into account that the models [16,77] have already been validated, we do not discuss the corresponding terms in detail. To validate our model, we focus on the terms related to HPCs.

HPCs are considered to be long lived and their death is neglected. The rate of infection of HPCs is assumed to be proportional to y,

$$df/dt = -\rho f y, \tag{1}$$

where ρ is the corresponding rate constant.

Compared to the conventional equations used to model immune reaction on viral infection, Eq. (1) does not contain a source term. At first sight, this might appear to be unusual because HPCs are well known to be able to proliferate both in *in vivo* and *in vitro*. One should, however, take into account that *in vivo* the proliferation and differentiation of stem cells in general (see reviews [80–89] and kinetic models [86,87]) and BM HPCs in particular [80,82,83,88,89] occur in stem-cell niches representing microscopic compartments formed of environmental cells that nurture stem cells and enable them to maintain tissue homeostasis. For this reason, the amount of stem cells is limited by the capacity of stem-cell niches. The cells located in a stem-cell niche are in close contact, and accordingly after infection of one of the stem cells located there the others (or at least part of them) are expected to be rapidly infected. If the infected stem cells are long lived (this is assumed in our model), the niche remains infected. For this reason, globally, the population of healthy stem cells is reduced and cannot be restored. Thus, the peculiarity of Eq. (1) is related to the specifics of the function of HPCs in stem-cell niches.

The stem-cell niches nurturing HPCs reside in BM on the inner surface of the trabecular bones. In analogy with other stem cells, HPCs are sometimes assumed to be immortal. Whether HPCs can rejuvenate infinitely is, however, still under debate [88,90]. Anyway, the life span of HPCs is expected to be longer than that of the naive T cells operating in the thymus. The life span of the latter