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Human immunomodulation and initial HIV spread

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ABSTRACT

We use published data in order to build up a networked mathematical framework aiming at providing: (a) a predictive understanding on how distinct stressors and immunosenescence may potentially affect the natural inflammatory response mechanisms and (b) new insights to developing early interventions that seek to exploit natural immune processes. Relying on fifty fundamental assumptions on HIV immunopathogenesis, the model simulations suggested that: (a) from a translational perspective, forthcoming physiological transitions in the systemic inflammation process do exist with conditions for bifurcation between the uninfected and the infected state being seriously impacted by immunomodulation and (b) the required therapy efficacy for pre-exposure prophylaxis may be decisively affected by immunomodulation and by the drug class used. Whereas unsuitable to make quantitative predictions due to limited experimental data and the complexity in vivo, this modeling effort paves the way for assessing the impact of personalized medicine for global epidemics within complex systems thinking.

1. Introduction

Seemingly out of nowhere, mathematical modeling devoted to describing the dynamics of early immune responses to human immunodeficiency virus (HIV) infection triggered at mucosal sites has become a new, insightful focus of research in theoretical biology (Hogue et al., 2008; Wendelsdorf et al., 2011). A fine look at this question reveals, however, that such modeling efforts emerged in concert with the fact that the picture of acquired immunodeficiency syndrome (AIDS) has changed worldwide over the past decade.

And this change was clear. Whereas the scale-up of highly active antiretroviral therapy mainly in developing countries has provided a dramatic reduction in morbidity and mortality in HIV patients, the number of new HIV-infected individuals, mostly of which are now infected with highly resistant viruses, shows a continuous and perturbing increase globally. This fact allied with paradigm-breaking findings that AIDS arises and propagates in scale-free networks (Liljeros et al., 2001) reinforces the need for increased attention to the development of preventive interventions. If considered that scale-free networks are resilient to random failure, but are highly susceptible to destruction of the best connected nodes (Albert et al., 2000), effective measures to contain or stop the propagation of AIDS must be radically different from those adopted in the past. The pharmaceutical intervention, while impacting mortality, may have a smaller effect on the forecasted trajectory of challenging epidemics such as HIV or Ebola (Rivers et al., 2014).

However, the major challenge to the development of a successful HIV preventive vaccine is an incomplete understanding of the correlates of protective immunity to early events in HIV infection (Liu et al., 2011). Whereas pioneers models provided initial, yet valuable insights for identifying new biological mechanisms which are crucial to early HIV infection outcomes, they did not investigate the differences in host physiological and psychological states that could potentially be associated with aging and nutritional imbalance or the exposition to other stressors. The impetus for further research aiming at analyzing the role of endogenous and exogenous factors on the initial HIV spread is at least threefold. Firstly, no two

Abbreviations: Ab, antibody; AHI, acute HIV infection; AIDS, acquired immunodeficiency syndrome; APC, antigen-presenting cell; CTE, critical therapy efficiency; DC, dendritic cell; FDC, follicular dendritic cell; Fe, iron; GLN, genital lymph node; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IL-2, interkeukin-2; IL-10, interkeukin-10; IL-12, interkeukin-12; IFN-γ, interferon-γ; LP, lamina propria; LT, lymphoid tissues; RTI, reverse transcriptase inhibitor; NK, natural killer (cell); O.E., old elderly; PB, peripheral blood; PI, protease inhibitor; PVL, peak viral load; PVT, peak viremia time; RNA, ribonucleic acid; Se, selenium; SPT, set-point time; SPVL, set-point viral load, T4, helper CD4+ T-cell; T4SP, set point CD4+ T-cell count; T_8, CD8+ T-cell; T_r, regulatory CD4+ T-cell; V_A, vitamin A; Zn, zinc; Y.E., young elderly.

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individuals respond to infection (and treatment) in quite the same way. Genome, age, gender, history of infections and vaccinations, and lifestyle factors such as diet, smoking, sleep, psychological stress and physical activity, may contribute to this myriad variation in susceptibility to infection and disease progression (Hamer et al., 2004; Harper et al., 2006; Tomkins, 2002). Secondly, theoretical biology becomes key if considered that experimental data concerning the early dynamics of the immune response to HIV in humans is difficult to obtain as it requires invasive tissue biopsies within a very short time period post-infection (Wendelsdorf et al., 2011). Therefore, the use of a virtual experimental model may be instrumental to test hypotheses and to yield biological insights through repeated model simulations and analysis of the simulation data. Thirdly, HIV pathogenesis and immunology form a complex system (Ottino, 2003) characterized by many puzzling quantitative features (Joly and Pinto, 2006) with straightforward therapeutic implications on a patient-specific basis (Joly and Odloak, 2013a). In light of this, forecasting and simulation of preventive interventions may subsidize biomedical research and, hence, optimize public health efforts.

In this paper, we extend recent literature (Joly and Pinto, 2012; Joly and Odloak, 2013b; Wendelsdorf et al., 2011) and present a unique study that proposes a predictive understanding about how stressors (nutritional imbalance, psychological and physical exercise stress, and sleep deprivation) and immunosenescence may potentially affect the dynamics of HIV immunopathogenesis right after host exposure to the virus via sexual intercourse. The mathematical framework is based on a multi-compartment model and relies on biological assumptions beyond the traditional HIV modeling aiming at deterministically represent the complex relation between HIV and the human immune system. With the objective of addressing current high-profile questions in public health, such as malnourishment and prophylactics, the assumptions consider specific biological mechanisms thought to impact the early viral dynamics, such as the regulatory pathway and HIV trapping in the lymphoid tissues (LT), and more realistic physiological conditions in vivo, such as immune system activation by natural antigens. Similarly to other comprehensive models of human immunology (e.g., Friedman et al., 2008; Joly and Pinto, 2012; Sud et al., 2006; Wendelsdorf et al., 2011), the model presented also involves mechanisms that are still speculative and for which parameter and validating data sets are not yet available. This difficulty has been masterly discussed in Wendelsdorf et al. (2011) by emphasizing that there is a balance between model complexity and utility in the developing a model for any complex biological system. Here, utility refers to the capability of the model to polarize thoughts and aid in posing fundamental questions concerning what one does and does not know for certain about the real-world system (Wendelsdorf et al., 2011). Having this in mind, we have extended past literature aiming at capturing new salient features of the system and for which lacking parameters can, however, be plausibly estimated based on the sparse data available or indirectly (or iteratively) determined regarding (Joly and Pinto, 2006, 2012):

- either the order of magnitude of the parameter or qualitative information from the literature, and/or
- the order of magnitude of the variable with which the parameter is correlated, and/or
- the steady-state behavior of the immune system for the uninfected state.

The model considers a highly networked biological regulatory system in which the early dynamics of HIV infection is analyzed in terms of an expanded set of immune cells and biological mechanisms (Joly and Pinto, 2006), and under distinct scenarios for prophylactic interventions based on conventional drug chemotherapy. Since immunotherapy is increasingly being considered to stimulate or to inhibit inflammation, immunity and hematopoiesis in vivo (Joly and Odloak, 2013b), cytokines are explicitly modeled here aiming at representing their pleiotropic and overlapping actions on acute HIV infection (AHI). In particular, the regulatory role of interleukin-10 (IL-10) is focused on, since under pathologic conditions, anti-inflammatory mediators may either provide insufficient control over pro-inflammatory activities or overcompensate and inhibit the immune response, exposing the host to the risk of systemic infection (Opal and DePalo, 2000). This article is structured as follows. Section 2 is devoted to present the biological and the mathematical models. Results are reported in Section 3 and discussed in Section 4. Section 5 concludes the paper.

2. Methods

2.1. The biological model

Mechanisms underlying the natural history of HIV disease are intricately intertwined with normal immune processes at the cellular and molecular immunology levels (Abbas et al., 2012). These include cell production in the generative organs, cell homing and recirculation, cytokine secretion and cell signaling, cell activation, proliferation and differentiation, cell deactivation and cell death.

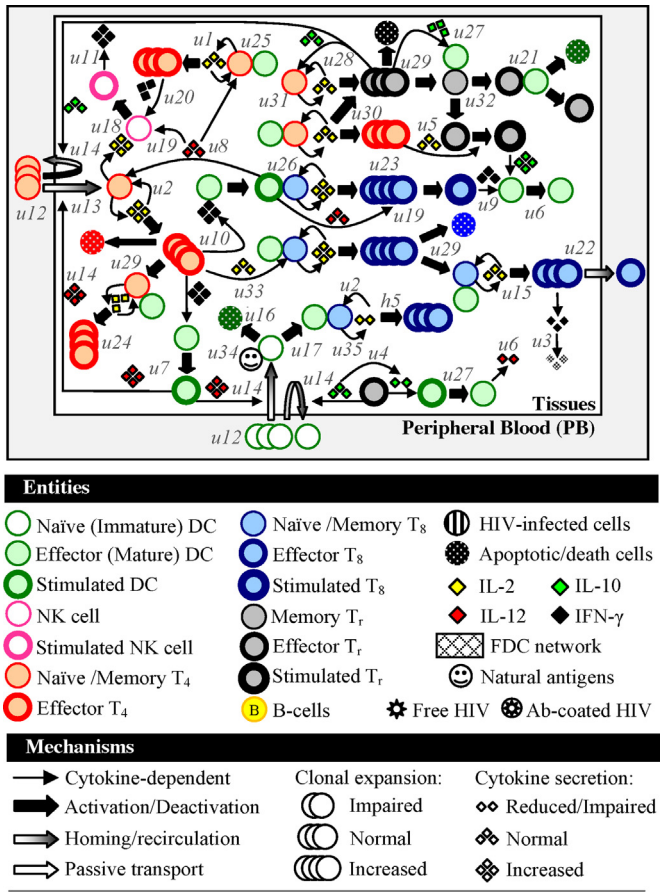

Fig. 1. The immune system model (uninfected state). Naïve/immature immune cells produced in the generative organs (assumption *u12*, see Table 1) migrate to peripheral blood (PB) from which they are selectively recruited to distinct tissues (*u13*, *u14*, *u17*, *u22*). Once there, these cells are stimulated (*u15*, *u33*, *u34*) becoming activated cells able to secrete cytokines (*u1–u3*, *u35*), proliferate (*u23*, *u32*) and differentiate (*u24*, *u28*, *u30*, *u31*) into distinct phenotypes, each specialized on performing specific immunological functions. Cell signaling plays a key role on the structuration (*u7–u11*, *u18–u20*, *u25*, *u26*) and regulation (*u4–u6*, *u21*, *u27*, *u33*) of the immune response. Lastly, immune cells may deactivate into a resting phenotype or die (*u16*, *u29*). Assumptions *u1–u35* are stated in Table 1. Abbreviation: PB, peripheral blood.