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Short communication

Effector cytotoxic T lymphocyte numbers induced by vaccination should exceed levels in chronic infection for protection from HIV

Hester Korthals Altes [a,*], David A. Price [b], Vincent A.A. Jansen [c]

[a] *WTCEID, University of Oxford, South Parks Road, Oxford OX1 3PS, UK*
[b] *MRC Human Immunology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, UK*
[c] *School of Biological Sciences, Royal Holloway, University of London, Egham, London TW20 0EX, Surrey, UK*

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Abstract

Recent technological advances have revolutionised our capacity to induce cytotoxic T lymphocyte (CTL) responses with a variety of vaccine formulations and delivery systems. However, the conditions required for a CTL-inducing vaccine to provide protection from infection or disease are poorly understood, and the results of challenge experiments have not been consistent. Here we use a mathematical model to examine the requirements necessary for successful vaccination against human immunodeficiency virus (HIV) through cellular immunity. We describe the interaction between cytotoxic T cells and infected lymphocytes, capturing the essence of a persistent infection of immune cells. We conclude that to protect from infection, the cellular immune response should be boosted to levels exceeding those in chronic infection. This requires either that effector CTL exceed this threshold before infection, or that a memory CTL population is established that can yield this level of effector CTL very quickly upon infection.

Keywords: Persistent infection; Cellular immunity; Prophylactic vaccine

1. Introduction

Cytotoxic T lymphocytes (CTL) are key effectors in mediating protective immunity against immunodeficiency viruses [1–5]. CTL responses can be readily induced [6–9], but the inconsistent results of challenge experiments [7,10–22] raise questions concerning the correlates of protective immunity. Here we use a mathematical model to clarify the requirements necessary for successful prophylactic vaccination against human immunodeficiency virus (HIV) through cellular immunity. To this end, we describe the interaction between cytotoxic T cells, uninfected and infected lymphocytes, capturing the essence of a persistent infection of immune cells.

The model used to describe the infection process is the basic tool for the study of in vivo HIV dynamics [23–26]. A schematic representation is given in Fig. 1.

This system can be described with the following differential equations:

$$\frac{dT}{dt} = \lambda - \delta_T T - \beta IT, \qquad \frac{dI}{dt} = \beta IT - \delta_I I - kEI,$$
$$\frac{dE}{dt} = aEI - \delta_E E \tag{1}$$

2. CTL threshold for protection

A prophylactic vaccine should prevent primary infection by controlling viral growth, thereby avoiding a rise in viremia after exposure to HIV. In other words, a small number of cells might become infected upon exposure, but if the virus-specific CTL elicited by the vaccine suppress the growth of the virus population, the number of infected cells subsequently will not increase. For a vaccine to be successful, it must induce a specific immune response exceeding a certain threshold [27]. We used the above model to predict the number of virus-specific CTL required to prevent infection with HIV.

* Corresponding author. Present address: Laboratoire d'Immunologie Cellulaire et Tissulaire, Faculté de Médecine Pitié-Salpêtrière, 91, bd de l'Hôpital, 75013 Paris, France.
E-mail address: korthals@ccr.jussieu.fr (H.Korthals Altes).

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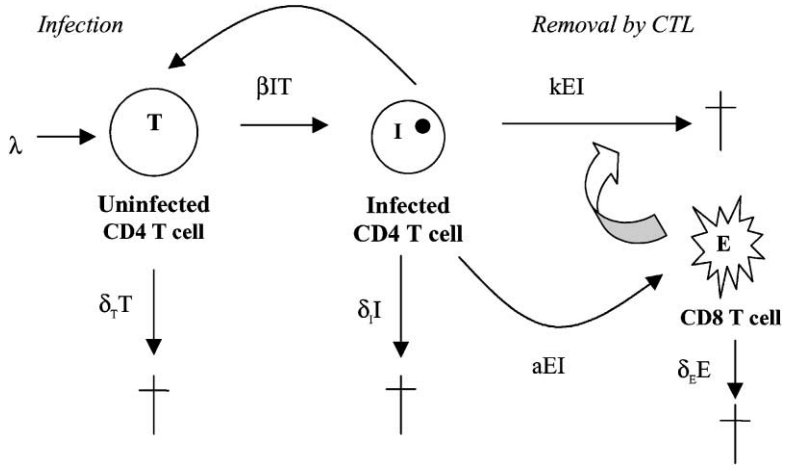

Fig. 1. Schematic representation of the model of HIV infection used. CD4+ T cells are produced at rate λ and die at a rate $\delta_T T$. Hence, their average lifetime is $1/\delta_T$. CD4+ T cells can be infected by free virus. The rate of infection is proportional to the number of uninfected CD4+ T cells and the number of infected cells I, so CD4+ T cells are infected at rate βIT. Infected cells have an average lifetime of $1/\delta_I$, so die at rate $\delta_I I$. Cytotoxic T lymphocytes (CTL, represented by variable E) lyse infected cells at rate k, leading to a death rate of infected cells by CTL lysis kEI. CTL can proliferate after activation by the infected cells: the CTL population grows at rate aEI. CTL have an average life span of $1/\delta_E$, so they die at a rate $\delta_E E$. The assumptions made all favour the possibility that a CTL-inducing vaccine is a biologically feasible approach. We assumed that the CTL response successfully targets the infection virus, that HIV-infected cells are uniformly susceptible to killing by CTL, and that CTL are qualitatively uniform and unaffected by antigen encounter.

To calculate this threshold we used the notion of basic reproductive number (R_0) [28], the number of cells infected by a single cell in a susceptible cell population (see Appendix A). If R_0 of the infecting virus is smaller than 1, the infection cannot spread within an individual [29]. In the chronic phase of HIV infection, the immune response just manages to keep the viral population at bay. Each infected cell then yields by definition on average one infected cell during its lifetime. To prevent the virus population from growing in a newly infected individual, a vaccine should reduce the average number of newly infected cells per infected cell below 1. Increasing the number of CTL reduces the virus basic reproductive number. In a healthy individual, the number of target cells is higher than in a chronically infected patient, raising the basic reproductive number of an infecting virus. To keep the virus basic reproductive number below 1, the number of CTL effectors should be higher than in post-acute infection (see Appendix A). This result is robust: whatever the mechanism of activation and proliferation of effector T cells in response to antigen, the threshold of CTL as formulated above remains the same. It is an important observation: a successful vaccine should boost CTL to levels exceeding those in chronic infection. If the immune system is incapable of clearing the infection under normal circumstances, it is unlikely that a single vaccination will cause lasting protection.

Achieving these levels of CTL at infection is not a full guarantee for protection. An additional requirement is that CTL exceed this level as long as virus can potentially replicate. If upon infection, CTL are above the threshold, virus will not grow and cannot stimulate the CTL to proliferate. As antigenic stimulation declines, CTL numbers will drop over time, until they reach the threshold level. If at that stage virus is still present at significant levels, the viral population can grow and infection may follow. The exact number of CTL needed to guarantee clearance will depend on what virus titre is associated with viral clearance, on the number of CTL present at the moment of infection, and on the rates of decline of CTL and infected cells.

3. Implications

Vaccination should lead to a level of CTL effectors above the threshold at the moment of infection, or to the establishment of a CTL precursor population that would allow the anamnestic response to rapidly reach this threshold number on subsequent exposure to virus. In the first scenario, it is improbable that such CTL levels could be maintained without a vaccine delivery system that provides a constant source of antigenic stimulation. In the second scenario, experimental data describing the speed with which the threshold must be reached to prevent the establishment of persistent infection is needed. The magnitude of the peak of the CTL response after challenge, in terms of percentage CD8 cells specific for SIV Gag p11C, can be greatly increased by vaccination, reaching 40% [10]. However, the timing of the peak is the same in vaccinated and control animals, and virus is not cleared. In two other experiments, vaccination leads to a higher and earlier post-challenge peak of CTL effectors but does not protect the animals from infection, probably because the response does not peak early enough [30,31]. It is likely that a narrow kinetic window, which will depend on a variety of biological factors, applies. For example, if persistent infection ensues at a certain virus threshold, then

the speed with which the effector threshold must be reached will increase with inoculation dose.

Stimulating the CD4 T helper response is a possible way to increase the efficiency of the primary and secondary CTL response. However, enhancing the CD4 T helper response may present a problem in the context of HIV infection as this provides more target cells for infection — this is discussed separately [32]. We have not taken into account possible differences in CTL efficiency in our model because it is presently unclear how CTL exactly they differ. Homing properties are likely determinants of efficiency, as CTL that reach antigen probably expand preferentially. Mucosally delivered vaccines may be more effective at inducing these CTL populations, suggesting such vaccines may be better candidates [33,34].

Vaccination-challenge experiments should attempt to identify the factors that govern the kinetics of the CTL response to challenge, in order to determine more consistent predictors of biological outcome. Our observations indicate that alternative vaccination strategies would potentially be more promising, either alone or combined with approaches enhancing other effector arms of the immune response.

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Appendix A

R_0 can be expressed as the average life span of an infected cell, multiplied by the number of target cells infected during its lifetime:

$$R_0 = \frac{\beta T_{\text{uninf}}}{\delta_I + kE_{\text{uninf}}} \tag{A.1}$$

where T_{uninf} and E_{uninf} are target cell and CTL numbers in an uninfected individual. If the number of effector cells E_{uninf} is sufficiently high, the basic reproductive number will be lower than 1. The threshold number of CTL can be found by solving $R_0 = 1$, to find:

$$E_{\text{threshold}} = \frac{\beta T_{\text{uninf}} - \delta_I}{k} \tag{A.2}$$

where $E_{\text{threshold}}$ is the threshold level of CTL above which control of virus growth is possible.

In the chronic phase of infection, the viremia stabilises at a set point until the patient develops AIDS. As the viral population does not grow in size, we may assume that $R_0 \approx 1$. Consequently, target cell numbers stabilise at the following level:

$$T_{\text{chronic}} = \frac{\delta_I + kE_{\text{chronic}}}{\beta} \tag{A.3}$$

where E_{chronic} is the number of CTL during chronic infection. Using expressions (A.2) and (A.3), we can now rewrite the CTL threshold as

$$E_{\text{threshold}} = \left(\frac{T_{\text{uninf}}}{T_{\text{chronic}}}\right) E_{\text{chronic}} + \frac{\delta_I}{k}\left(\frac{T_{\text{uninf}}}{T_{\text{chronic}}} - 1\right) \tag{A.4}$$

where δ_I, k and β are constant from primary infection to chronic infection.

This threshold depends on the ratio of target cells in a healthy individual to target cells in chronic infection ($T_{\text{uninf}}/T_{\text{chronic}}$). This ratio normally exceeds 1: in any given individual, target cell numbers are reduced in chronic HIV infection compared to the healthy state.

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