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Generals die in friendly fire, or modeling immune response to HIV

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Abstract

We develop a kinetic model for CD8 T lymphocytes (CTL) whose purpose is to kill cells infected with viruses and intracellular parasites. Using a set of first-order nonlinear differential equations, the model predicts how numbers of different cell types involved in CTL response depend on time. The model postulates that CTL response requires continuous presence of professional antigen-presenting cells (APC) comprised of macrophages and dendritic cells. It assumes that any virus present in excess of a threshold level activates APC that, in turn, activate CTL that expand in number and become armed "effector" cells. In the end, APC are deactivated after virus is cleared. The lack of signal from APC causes effector cells to differentiate, by default, into "transitory cells" that either die, or, in a small part, become long-lived memory cells. Viruses capable of infecting APC will cause premature retirement of effector CTL. If transitory cells encounter virus, which takes place after the premature depletion, CTL become anergic (unresponsive to external stimuli). The model is designed to fit recent experiments on primary CTL response to simian immunodeficiency virus closely related to HIV and lymphocytic choriomeningitis virus. The two viruses are known to infect APC and make them targets for CTL they are supposed to control. Both viruses cause premature depletion and anergy of CTL and persist in the host for life.

Keywords: Immune; CD8 T; Virus

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1. Introduction

Cytotoxic CD8 T lymphocytes (CTL) represent the main immune mechanism used by animals to defend themselves against viruses and intracellular parasites. Although wealth of information on molecular mechanisms of CTL response is available, its organization at the level of organism remains unknown. It is also unknown why some notorious viruses, such as HIV, hepatitis B and hepatitis C viruses are not cleared from the body but persist at high levels, eventually resulting in premature death of the infected individuals.

A major reason for the uncertainty in these, truly vital issues is the lack of well-established and carefully tested mathematical theory. Until recently, accurate experiments that make the foundation of any theory were absent. In an early experiment that stimulated a number of theoretical studies, Moskophidis et al. [13] measured CTL kinetics in mice infected with lymphocytic choriomeningitis virus (LCMV, strain Docile). At low infecting doses of the virus, CTL expand, clear virus, and then die out leaving behind a small sentinel of long-lived "memory" cells. At high doses, functional CTL disappear soon after the initial expansion, and virus remains in the body. A mathematical model by Wodarz et al. [20] explained the dose-dependent CTL response on a qualitative level, as follows. It postulated that expansion of CTL depends on (unspecified) helper cells that can be infected and depleted by LCMV Docile. A high initial dose of virus may change the outcome of its race against CTL. Bocharov [2] proposed a more complex model that did not include infectable helper cells but featured activation-induced apoptosis and anergy of CTL exposed continuously to high amounts of virus. His model fit the quoted data set on LCMV Docile quite accurately. De Boer et al. [6] addressed kinetics of CTL response to another LCMV strain Armstrong that does not persist even at high infecting doses [14]. These authors postulated the existence of a threshold that the virus load has to cross to initiate the CTL response. The model did not include any mechanisms by which virus could impair CTL response and was not designed to explain the response to persisting viruses.

Recent invention of accurate techniques of quantitation of antigen-specific CD8 T cells gave a powerful boost to the field [1,10,14–16,21]. The aim of the present work is to develop a model of primary CTL response that agrees, on the quantitative level, with two new, accurate data sets obtained for persisting and nonpersisting virus infections. The first experiment was carried out in monkeys infected with simian immunodeficiency virus (SIV) closely related to HIV [10]. The second experiment involved mice infected with 4 strains of LCMV, some of which persist at high doses [16]. Our model is based on the idea that successful primary CD8 T cell response requires continuous presence of controlling cells, identified as professional antigen-presenting cells (APC), macrophages and dendritic cells. HIV/SIV and LCMV can infect APC making them legitimate targets for the same CTL they are supposed to control. Most cell types and processes featuring in our models are well-known in the literature. However, the exact chart of CTL response we propose differs from the previous theories. The model also includes some elements that have not been discussed before.

The full model of host–virus interaction is expected to be rather complex. It has to include virus interaction with its prey, target cells and the mechanisms of target cell death and replenishment [7,12,18,19]. It also must specify how CTL control virus replication; there are several possible mechanisms that are being disputed. The full model also must describe both the primary (acute) response and the steady state (persistence) phase. CTL properties are known to differ between the two phases of the response [4,8,9,11]. Even if we consider only biologically meaningful models by using the existing knowledge about possible interaction mechanisms, the number of variants grows rather fast with the number of cell