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Paradoxical suppression of poly-specific broadly neutralizing antibodies in the presence of strain-specific neutralizing antibodies following HIV infection

Stanca M. Ciupe [a,*], Patrick De Leenheer [b], Thomas B. Kepler [c]

[a] Department of Mathematics, University of Louisiana at Lafayette, 433 Maxim Doucet, Lafayette, LA 70504, United States
[b] Department of Mathematics, University of Florida, 411 Little Hall, P.O. Box 118105, Gainesville, FL 32611-8105, United States
[c] Center for Computational Immunology, Department of Biostatistics and Bioinformatics, Duke University Medical Center, 2424 Erwin Road, Suite 1102, Durham, NC 27710, United States

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ABSTRACT

One of the first immunologic responses against HIV infection is the presence of neutralizing antibodies that seem able to inactivate several HIV strains. Moreover, *in vitro* studies have shown the existence of monoclonal antibodies that exhibit broad crossclade neutralizing potential. Yet their number is low and slow to develop *in vivo*. In this paper, we investigate the potential benefits of inducing poly-specific neutralizing antibodies *in vivo* throughout immunization. We develop a mathematical model that considers the activation of families of B lymphocytes producing poly-specific and strain-specific antibodies and use it to demonstrate that, even if such families are successful in producing neutralizing antibodies, the competition between them may limit the poly-specific response allowing the virus to escape. We modify this model to account for viral evolution under the pressure of antibody responses in natural HIV infection. The model can reproduce viral escape under certain conditions of B lymphocyte competition. Using these models we provide explanations for the observed antibody failure in controlling natural infection and predict quantitative measures that need to be satisfied for long-term control of HIV infection.

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1. Introduction

The ability of human immunodeficiency virus (HIV) to persist in an infected individual and eventually cause AIDS is dependent on its ability to avoid immune responses. Many factors facilitate virus persistence, from high genetic diversity and evolution (Walker and Korber, 2001) to the ability to stay latent in the body (Blankson et al., 2002), to the infection of immune cells, whose activation by vaccine candidates leads to an increase in the target cell population (Stebbing et al., 2004). The large-scale vaccine clinical trials (AIDSVax (Gilbert et al., 2005), STEP (Priddy et al., 2008) and RV144 (Rerks-Ngarm et al., 2009) that were aimed at stimulating both arms of the adaptive immune system: the antibody-mediated, the cell-mediated and combined antibody and cell-mediated immunity showed limited clinical efficacy (Fauci et al., 2008).

We study the roles of antibodies in limiting virus replication during HIV infection. Antibodies directed against HIV structural proteins are detected in the body within a few weeks following a natural infection (Aasa-Chapman et al., 2004; Richman et al., 2003). Only a small fraction of them, however, neutralize the virus, which escapes recognition by ensuing reduced accessibility to antibody-binding sites, heavy glycosylation of the envelope proteins and rapid mutation (Douek et al., 2006; Parren et al., 1999; Richman et al., 2003; Wyatt and Sodroski, 1998). Despite the hurdles the immune system has to overcome, neutralizing antibodies do develop during natural infection (Burton et al., 2005; Haynes and Montefiori, 2006; Pantophlet and Burton, 2006). Most of them are strain-specific and preferentially recognize and inhibit preceding but not current viral strains (Burton et al., 2004; Richman et al., 2003; Wei et al., 2003). To completely control infection, the immune system has to find ways to elicit potent, high affinity antibody responses capable of broad neutralization, viral inactivation and protection against current infection and/or disease (Hone et al., 2002). A limited number of known broadly neutralizing human monoclonal antibodies (2F5, 4E10, b12, 2G12, PG9, PG16 and VRC01) have been identified (Burton et al., 2004; Zhou et al., 2010). They neutralize primary isolates of HIV from different genetic subtypes *in vitro* (Buchacher et al., 1994; Burton et al., 2004; Li et al., 2007), but are very rarely produced *in vivo* (Dhillon et al., 2007), and are, therefore, difficult

* Corresponding author. Tel.: +1 337 482 5287.
E-mail address: msc6503@louisiana.edu (S.M. Ciupe).

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to induce through vaccination. The failure may be due to host regulatory constraints (Haynes et al., 2005), incorrect epitope conformation (Moore et al., 2006), HIV induction of polyclonal B cell activation and terminal differentiation (Levesque et al., 2009), and/or B cell competition (Deem and Lee, 2003; Heyman, 2003).

While many different B cells clones can recognize a given HIV virus strain, only those of high affinity (strain-specific) respond in large numbers to produce neutralizing antibodies. For a series of discrete random infections over time (continuous immunization), competition among B cell clones may lead to the phenomenon of original antigenic sin, where B cells produced in response to a first viral infection can suppress the creation of new immune cells in response to a second infection with a related strain (Deem and Lee, 2003). For a chronic infection with a mutating virus, the original antigenic sin may be limited, since there is enough time for the immune system to create B cells against the new strain. However, there is a time delay in the production of each strain-specific neutralizing antibody that may cause that virus strain to expand at high levels before the antibody can control it (Burton et al., 2004; Richman et al., 2003). Most importantly, the continuous presence of strain-specific antibodies may lead to suppression of the less fit poly-specific B cell clones capable of producing broad neutralizing antibodies. The limitation in number of broadly neutralizing antibodies may represent the greatest weakness of the immune system.

Antibody-mediated immune suppression has been observed during passive administration of antibodies as well. In this situation, B cells are prevented from stimulation through a reduction of available antigenic determinants (Heyman, 2003). Finally, studies of Hepatitis C chronic infections have shown that strain-specific antibodies may inhibit the development of poly-specific antibodies by preventing them from recognizing antigen (Zhang et al., 2004).

To investigate the competition among strain-specific and poly-specific antibodies, we developed mathematical models of virus–antibody interactions during both immunization and natural infection with HIV. We start with the assumption that the immune system produces both strain-specific and poly-specific, cross reactive, neutralizing antibodies. The strain-specific and poly-specific neutralizing antibodies target variable (unique to each variant) or conserved (shared among variants) epitopes, respectively, on the virus envelope. The governing hypothesis is that while B cells producing both (strain-specific and poly-specific) neutralizing antibodies are activated during the infection, those producing poly-specific broadly neutralizing antibodies are made inefficient and consequently kept at undetectable levels. This process is mediated by their competition with the B cells that produce more fit strain-specific antibodies with which they share antigenic stimulation, kinetic prolongation, space in the lymph nodes and T cell conjugates.

We use information from previous modeling studies of HIV viral infection (Ho et al., 1995; Nowak and May, 2000; Perelson et al., 1996, 1997), cellular immune responses (Ciupe et al., 2006; Stafford et al., 2000), antibody formation (Oprea and Perelson, 1996; Tomaras et al., 2008) and competition (Antia et al., 1998; Boer et al., 2001; Borghans et al., 1999; Leenheer and Pilyugin, 2008) to derive and analyze models of the interaction between virus and neutralizing antibodies. Our aim is to determine the parameter regimes that lead to antibody failure and viral persistence, and to predict ways to reverse these phenomena.

The paper is structured as follows. In Section 2 we develop and analyze the mathematical model describing the interaction between families of B lymphocytes producing poly-specific and strain-specific neutralizing antibodies following continuous immunization with several HIV variants. In Section 3 we expand the model to account for natural infection and viral evolution; their analysis is presented in two appendices. In Section 4 we present numerical results of the two models. We conclude with a discussion.

2. Model of antibody responses following continuous immunization

Let $V=(V_1,V_2,\ldots,V_n)^T$ be viruses of specificity $1\le i\le n$, $A=(A_1,A_2,\ldots,A_n)^T$ be strain-specific neutralizing antibodies of specificity $1\le i\le n$, and A_0 be the poly-specific broadly neutralizing antibody. Viruses are introduced into the body at times t_i, $V_i(t_i)=V_{i,0}$, and do not mutate. We coarse-grain the viral life-cycle, aggregating the processes of infection, integration and host–cell viral production into a simple replication model in which viruses replicate with different viral fitness per-capita rates r_i. We treat the dynamics of antibody production similarly, assuming that antibody concentration is in quasi-equilibrium with the B cell population that produces them, and without representing the component subprocesses such as activation, differentiation and antibody secretion. The concentration of antibody specific to viral strain i is denoted A_i, and that of poly-specific antibody A_0. We only consider the fraction of the produced antibodies that has neutralizing function. In the presence of neutralizing antibodies viruses are removed at rates K and K_0 by the strain-specific and poly-specific neutralizing antibodies, respectively. We assume that the removal rates are independent of strain and that $K>K_0$.

Strain-specific neutralizing antibodies are elicited at rate λ by the viral strain to which they are specific. Poly-specific neutralizing antibodies are elicited at rate λ_0 by all viral strains. We denote by a the differences between B cells proliferation and death rates, effectively treating the antibody at quasi-equilibrium with these cells as surviving at that rate. Finally, all B cells compete with each other (within and between clones) for antigen, space in the lymph nodes, and conjugate T-cell help. The strength of this competition is governed by parameter β.

The dynamics of the system is described by the following equations:

$$\frac{dV_i}{dt}=(r_i-KA_i-K_0A_0)V_i,$$

$$\frac{dA_i}{dt}=\lambda V_i+A_i(a-\beta A_T),$$

$$\frac{dA_0}{dt}=\lambda_0 T+A_0(a-\beta A_T), \tag{1}$$

with $V_i(t_i)=V_{i,0}$, $A_i(t_i)=0$, $A_0(t_1)=0$, $T=1^TV$ and $A_T=A_0+1^TA$.

In Section 2.1 we investigate the system dynamics for the case where strain-specific B cells are absent. In Section 2.2 we explore the dynamics when both poly-specific and strain-specific antibodies are produced in response to infection.

2.1. Virus dynamics during poly-specific antibody responses

Let us consider the case where viruses $V=(V_1,V_2,\ldots,V_n)^T$ are introduced into the body at times $t=(t_1,t_2,\ldots,t_n)^T$, independent of each other. The immune system reacts by producing poly-specific antibodies, A_0, at rate λ_0, which neutralize all virus strains at rate K_0. For simplicity, we assume that all viral strains are equally adapted to the host and they replicate at the same rate $r_i=r$ independent of the strain i. System (1) becomes

$$\frac{dV}{dt}=(r-K_0A_0)V,$$

$$\frac{dA_0}{dt}=\lambda_0 T+A_0(a-\beta A_0), \tag{2}$$

with $V_i(t_i)=V_{i,0}$ and $A_0(t_1)=0$.

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