

ADVANCED REVIEW

Towards multiscale modeling of the CD8⁺ T cell response to viral infections

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The CD8⁺ T cell response is critical to the control of viral infections. Yet, defining the CD8⁺ T cell response to viral infections quantitatively has been a challenge. Following antigen recognition, which triggers an intracellular signaling cascade, CD8⁺ T cells can differentiate into effector cells, which proliferate rapidly and destroy infected cells. When the infection is cleared, they leave behind memory cells for quick recall following a second challenge. If the infection persists, the cells may become exhausted, retaining minimal control of the infection while preventing severe immunopathology. These activation, proliferation and differentiation processes as well as the mounting of the effector response are intrinsically multiscale and collective phenomena. Remarkable experimental advances in the recent years, especially at the single cell level, have enabled a quantitative characterization of several underlying processes. Simultaneously, sophisticated mathematical models have begun to be constructed that describe these multiscale phenomena, bringing us closer to a comprehensive description of the CD8⁺ T cell response to viral infections. Here, we review the advances made and summarize the challenges and opportunities ahead.

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KEYWORDS

cell fate, effector function, exhaustion, mathematical models

1 | INTRODUCTION

CD8⁺ T cells play a central role in defining the outcomes of viral infections (Masopust, Vezys, Wherry, & Ahmed, 2007; Zhang & Bevan, 2011). Naïve CD8⁺ T cells become activated upon recognizing antigen presented on infected cells and can proliferate rapidly. In the process, they differentiate into effector cytotoxic T lymphocytes, which can kill infected cells and control the infection. A strong effector response is argued to be essential for the clearance of viral infection (Zhang & Bevan, 2011). Once the infection is cleared, the size of the effector population diminishes, leaving behind memory CD8⁺ T cells, which can be recruited rapidly following a subsequent challenge with the same pathogen (Ahmed & Gray, 1996). If an infection spreads substantially before or as the cytotoxic T lymphocyte (CTL) response is mounted, the tissue damage due to the ensuing widespread CTL-mediated killing of infected cells may lead to immunopathology and possibly host mortality (Nathanson & Ahmed, 2007). If the CTL response is unable to curtail the infection, sustained antigen stimulation may alter

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the differentiation program of CD8⁺ T cells and render them exhausted (Hashimoto et al., 2018; Wherry, 2011). These exhausted cells have limited functionality, which allows them to control but not clear the infection while limiting tissue damage. Exhausted CD8⁺ T cells are predominant in chronic infections (Kahan, Wherry, & Zajac, 2015).

A key pursuit in CD8⁺ T cell biology has been to unravel the determinants of the fates of CD8⁺ T cells and devise ways of engineering them to orchestrate the outcomes of viral infections. The ability to manipulate the CD8⁺ T cell response has major implications. For instance, it may help eliminate chronic viral infections, minimize tissue damage when acute viral infections are cleared, and design vaccines that prime specific CD8⁺ T cells to prevent the transmission of infection. Understanding the dynamics of the CD8⁺ T cell response to infections would help define manipulations that would be optimal. Recent years have seen enormous progress in our understanding of the CD8⁺ T cell response, due both to the advent of novel experimental techniques, especially at the single cell level, and to the development of increasingly sophisticated mathematical models. Key insights into the signaling events that drive CD8⁺ T cell activation and differentiation at the single cell level have been gained (Courtney, Lo, & Weiss, 2018). Molecular mechanisms of the proliferation program following activation have been unraveled (Heinzel et al., 2017; Heinzel, Marchingo, Horton, & Hodgkin, 2018). Interactions between infected cells and CD8⁺ T cells that lead to CD8⁺ T cell exhaustion have been identified and drugs that can block these interactions developed (Hashimoto et al., 2018; Wherry & Kurachi, 2015; Wykes & Lewin, 2018). Intervention strategies are also being developed that can ensure CD8⁺ T cell stimulation and lead to the lasting control if not cure of otherwise progressive chronic infections (Fuller et al., 2013; Nishimura et al., 2017). Simultaneously, mathematical models of several of these phenomena have been constructed that not only solidify our understanding of the underlying biology but also present novel avenues of intervention. Models of CD8⁺ T cell population dynamics have been combined with within-host viral dynamics to unravel systems-level properties that characterize the outcomes of infection and treatment (Baral, Roy, & Dixit, 2018; Conway & Perelson, 2015). Models have also been constructed to analyze experiments of CD8⁺ T cell dynamics to elucidate their proliferation and differentiation programs and estimate the strength of their effector function and memory (Antia, Ganusov, & Ahmed, 2005; de Boer & Perelson, 2013). At the single cell level, both mechanistic and phenomenological models of activation and differentiation have been constructed (Chakraborty & Weiss, 2014; Courtney et al., 2018; Francois, Voisinne, Siggia, Altan-Bonnet, & Vergassola, 2013). The challenge now is to integrate the models at the single cell and cell population levels and develop a comprehensive framework of the CD8⁺ T cell response to viral infections. More recent advances that have unraveled mechanisms with which collections of CD8⁺ T cells influence the behavior of individual cells (Butler, Kardar, & Chakraborty, 2013; Voisinne et al., 2015) present promising avenues for such multiscale modeling and integration.

Here, we present an overview of the advances in the modeling of CD8⁺ T cell dynamics both at the single cell and at the population level and highlight outstanding issues. We begin in Section 2 with models of CD8⁺ T cell population dynamics with a focus on their proliferation and differentiation programs. In Section 3, we examine models that integrate the latter descriptions with formalisms of viral dynamics. In Section 4, we describe models at the single cell level that examine signaling events underlying cell fates. In Section 5, we consider multiscale models that integrate single cell and population level models. We present concluding remarks in Section 6.

2 | PROLIFERATION AND DIFFERENTIATION

Following stimulation by peptides presented on major histocompatibility complex class I molecules expressed on the surfaces of infected cells, naïve CD8⁺ T cells get activated and proliferate (Murphy & Weaver, 2016). In the process, they also differentiate into short-lived effector cells and long-lived memory cells (Homann, Teyton, & Oldstone, 2001; Murali-Krishna et al., 1998). Efforts to understand how activated cells proliferate and differentiate have triggered longstanding debates in the literature, enriched by mathematical models.

2.1 | Population-based models

2.1.1 | Proliferation

Until the advent of single cell techniques some years ago, the understanding of the CD8⁺ T cell response to infections was predominantly from cell population-based studies. The CD8⁺ T cell population rises sharply following infection and contracts once the infection is cleared (Althaus, Ganusov, & de Boer, 2007; Homann et al., 2001; Murali-Krishna et al., 1998). Analysis of the population dynamics in the expansion and the contraction phases has yielded estimates of cell division and death rates (de Boer et al., 2001; de Boer, Homann, & Perelson, 2003). The rates have also been estimated using labeling techniques involving 5-bromo-2'-deoxyuridine (BrdU), deuterium, or carboxy-fluorescein diacetate succinimidyl ester (CFSE), with models developed to analyze the resulting data. Recent reviews have described the data and the models extensively (Borghans, Tesselaar, & de Boer, 2018; de Boer & Perelson, 2013). It is now accepted that following activation, cells enter a proliferation program that does not require antigen, although antigen and other stimulatory and co-stimulatory signals can modify the program (Allan, Callard, Stark, & Yates, 2004; Antia, Bergstrom,

Pilyugin, Kaech, & Ahmed, 2003; Chao, Davenport, Forrest, & Perelson, 2004; Kaech & Ahmed, 2001; van Stipdonk, Lemmens, & Schoenberger, 2001; Wodarz & Thomsen, 2005a, 2005b). Thus, following de Boer and Perelson (2013), denoting the subpopulation of proliferating cells that have completed n divisions at time t as $P_n(t)$, one writes

$$\begin{aligned} \frac{dP_0}{dt} &= -(p + d)P_0, \\ \frac{dP_n}{dt} &= 2pP_{n-1} - (p + d)P_n, \quad n = 1, 2, \dots, \infty. \end{aligned} \quad (1)$$

Here, p and d are the proliferation and death rates, respectively, of the dividing cells. The above equations have been shown to capture data of cellular immune responses to lymphocytic choriomeningitis virus (LCMV) infection in mice (de Boer et al., 2003; de Boer & Perelson, 2013). Variations of this formalism that allow for antigen-dependent recruitment into proliferation have been proposed (Jones & Perelson, 2005). Further, more sophisticated partial differential equation (PDE) models that allow for the proliferation and death rates to be functions of the time after recruitment have been developed (Antia et al., 2003; Antia et al., 2005; de Boer, 2006; Pilyugin, Ganusov, Murali-Krishna, Ahmed, & Antia, 2003). A limitation of the models is the lack of a description of the precursor population that is recruited into proliferation (de Boer & Perelson, 2013). In other words, what determines $P_0(0)$ is unknown. The size of the precursor pool is usually estimated from fits to data (Blattman et al., 2002; de Boer & Perelson, 2013). A second limitation is the poor understanding of the number of proliferation events each recruited cell experiences. As a simplification, the model above admits an unlimited number of such events. In practice, the number appears to have an upper bound. A remarkable series of recent experiments that probe events at the single cell level have addressed some of these limitations (Heinzel et al., 2018), which we return to later.

2.1.2 | Differentiation

A second question that population-based studies have addressed is of the differentiation pathway of naïve $CD8^+$ T cells following their activation (Figure 1). Naïve cells could differentiate into memory cells, some of which could eventually become terminally differentiated as effectors (Figure 1a) (Wodarz, May, & Nowak, 2000). Alternatively, naïve cells could become effectors first, and then leave behind a small fraction that become the memory pool (Figure 1b) (de Boer et al., 2001). Evidence in support of both hypotheses exists (see below). Models have attempted to distinguish between the two. If the former pathway were to hold, one would write, following Antia et al. (2005),

$$\begin{aligned} \frac{dM}{dt} &= f(t)(p - r)M, \\ \frac{dE}{dt} &= f(t)rM - (1 - f(t))dE. \end{aligned} \quad (2)$$

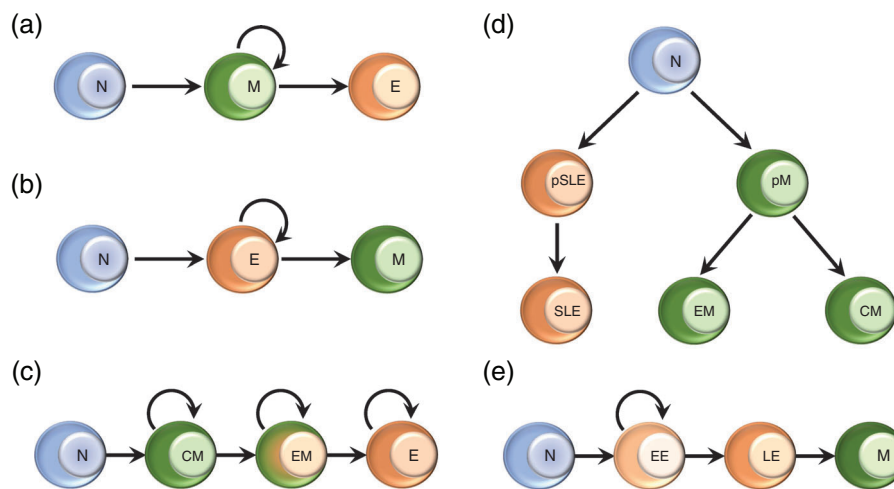


FIGURE 1 Schematics of proposed differentiation pathways. (a) Naïve cells (N) differentiate into memory cells (M) and then to terminally differentiated effectors (E). Memory cells proliferate. (b) Naïve cells differentiate into effectors, which can proliferate and differentiate into memory cells. (c) The pathway in (a) is expanded by separating memory cells into central (CM) and effector memory (EM) classes. Memory cells and effectors can proliferate. (d) A branched pathway with naïve cells differentiating into precursors of short-lived effectors (pSLE) and memory (pM) cells. The former differentiate into effectors (SLE) and the latter branch into central memory and effector memory cells. (e) The pathway in (b) is expanded by separating effectors into early (EE) and late (LE) effector stages. The early effectors proliferate

Here, memory cells, M , proliferate at the rate p and differentiate into effectors, E , at the rate r . The effectors die at the rate d . Memory cells are assumed to be long-lived and so their death rate is negligible. The function $f(t) = 1$ when $T_{ON} \leq t < T_{OFF}$ and $f(t) = 0$ otherwise, so that proliferation starts at time T_{ON} following precursor recruitment and ends at time T_{OFF} . Note that here no distinction is made between cells that have undergone different numbers of proliferation events. For the latter pathway, the corresponding equations would be (Antia et al., 2005)

$$\begin{aligned}\frac{dE}{dt} &= f(t)pE - (1-f(t))(d+r)E, \\ \frac{dM}{dt} &= (1-f(t))rE.\end{aligned}\tag{3}$$

When the models were applied to the analysis of CD8⁺ T cell population dynamics in response to LCMV infection in mice, fits with realistic parameter estimates were obtained with the latter model, thus favoring a differentiation pathway where naïve cells yield effector cells which eventually could become memory cells (Figure 1b) (Antia et al., 2005). A third pathway, where naïve cells could differentiate either into effector or into memory cells based on the strength of stimulation was also inconsistent with data (Ganusov, 2007).

While such analyses help distinguish between alternative hypotheses, they do not present conclusive evidence of the underlying differentiation pathways. Burnet's clonal selection theory argues that a single CD8⁺ T cell should be able to trigger an effector response as well as develop lasting memory (Burnet, 1960). Do all cells thus behave identically, with each cell dividing asymmetrically into effector and memory daughter cells, or is there partitioning of the precursor population, with some cells preferentially differentiating into effectors and others into memory cells? Population-based models capture average behavior, which does not allow the resolution of the above possibilities. Yet, answering this question is important, particularly to vaccine design, which aims to establish memory without a full-blown effector response. Recent single cell studies have made significant advances in answering this question.

2.2 | Insights from single cell studies

2.2.1 | Stochastic variability in differentiation

In two elegant studies, Gerlach et al. (2013) and Buchholz et al. (2013) traced lineages of individual CD8⁺ T cells using adoptive transfer of barcoded cells or of cells bearing congenic markers that were responsive to the same antigenic peptide. Remarkably, both studies found that a small percentage of cells yielded $\sim 10^5$ progeny cells whereas the rest yielded $\sim 10^3$ progeny cells. Further, the former lineages were effector-like in their cytokine and gene expression profiles, whereas the latter lineages were memory cell-like. Interestingly, the specific naïve cells that differentiated into effectors were different following a second, identical challenge, although the percentages of cells differentiating into effector and memory phenotypes were similar. Thus, although the CD8⁺ T cell response at the population level was similar, the fates of individual cells were subject to strong stochastic variations. Reproducible CD8⁺ T cell responses were thus a consequence of averaging the stochastic variations across a large number of cells (Rohr, Gerlach, Kok, & Schumacher, 2014).

2.2.2 | Differentiation pathways

To determine the differentiation pathway, Buchholz et al. (2013) constructed models that considered naïve, effector, central memory and effector memory cells, following a previously defined classification (Sallusto, Lenig, Forster, Lipp, & Lanzavecchia, 1999). A model for every possible differentiation pathway involving these cell types was constructed, amounting to a total of 304 different possibilities. The events in the models occurred stochastically. When they compared predictions of the models to their data, a linear pathway where naïve cells differentiated to central memory cells, which differentiated into effector memory cells and finally into effectors, was found to yield the best fit (Figure 1c). Ten percent of the time, naïve cells could differentiate directly to effector memory and then to effectors. The proliferation rate increased along the pathway. Thus, most naïve cells differentiated into central and peripheral memory cells, which proliferated slowly. A few differentiated stochastically into effectors, which then proliferated rapidly, explaining the disparity in lineage sizes observed (Buchholz et al., 2013; Gerlach et al., 2013).

Paralleling the debates in the cell population-based studies, however, the differentiation pathway proposed by Buchholz et al. (2013) has been contested. To determine the genetic origins of the various differentiation states, Arsenio et al. (2014) measured temporal gene expression profiles in individual activated CD8⁺ T cells and employed machine learning techniques to compartmentalize cells. They found, in contrast to the above linear pathway, that a branched differentiation pathway best described their data (Figure 1d). A naïve cell could differentiate into either a precursor of effectors or a precursor of memory cells. The precursor of effectors eventually differentiated into an effector. The memory precursor could again differentiate into either a central memory or an effector memory cell. Further, whether a naïve cell differentiates into an effector or a memory cell is argued to be determined by the asymmetry in the earliest division stages. In particular, the preferred pathway depended

strongly on the expression level of IL-2R, the receptor for IL-2; the higher the IL-2R expression, the more likely the cell became effector-like. Interestingly, this finding is consistent with previous reports of sustained IL-2 stimulation triggering effector-like properties (Kalia et al., 2010). In a subsequent study, asymmetric division has been argued to be sustained in subsequent divisions, with cells differentiating into effectors retaining memory like properties as long as the expression of a key regulator of T cell memory, T cell factor 1 (TCF-1), is high (Lin et al., 2016). The loss of memory-like properties has been argued to be cell division dependent (Lin et al., 2016) and may be subject to epigenetic control (Pace et al., 2018).

More recently, Crauste et al. (2017) employed unsupervised clustering of transcriptomics data to argue that the effector phenotype comprises two distinct differentiation states, an early and a late effector state. Further, they identified two cell surface markers, Mki67 and Bcl2, that distinguished the different states, along with the activation marker CD44. Naïve cells were thus CD44⁻ Mki67⁻ Bcl2⁺. Antigen priming rendered them CD44⁺. Of the latter cells, Mki67 expression increased and Bcl2 decreased on cell populations in response to either an infection or a tumor in mice. Early effectors, Mki67⁺ Bcl2⁻, dominated the response till day 10 of challenge; late effectors, Mki67⁻ Bcl2⁻, were predominant around day 15; and memory cells, Mki67⁻ Bcl2⁺, alone remained day 30 onwards. To unravel the differentiation pathway, they adopted an approach similar to Buchholz et al. (2013). They advanced their earlier models of T cell population dynamics (Crauste et al., 2015; Terry, Marvel, Arpin, Gandrillon, & Crauste, 2012) to incorporate the two effector states and constructed a number of models, each for a different potential differentiation pathway. Comparing model predictions to data of the time course of the various cell populations, they found that the model that best described their data corresponded to a linear differentiation pathway with naïve cells differentiating into early effectors, and then into late effectors, and eventually memory cells (Figure 1e). Using early time data to estimate parameters, the model also faithfully reproduced the eventual memory pool size. Importantly, the model captured both the expansion and the contraction phases of the primary immune response, whereas the alternative linear differentiation pathway in Buchholz et al. (2013) was restricted to the expansion phase.

Evidence that memory cells formed from effectors comes from a recent study on the methylation patterns of promoters of genes expressed differentially in naïve, effector, and memory states (Youngblood et al., 2017). Many genes are expressed in naïve cells, turned off in effectors, and expressed again in memory cells. Youngblood et al. (2017) used the cell surface markers Klrp1 and CD127 to distinguish between effector cells that are terminally differentiated and those that are memory precursors, which eventually yield long-lived memory cells. They found, remarkably, that memory precursors had methylation patterns closely resembling terminally differentiated effectors and that the patterns reversed in memory cells, suggesting that effector cells dedifferentiated into memory cells. A similar differentiation pattern was also found in CD8⁺ T cells in humans after vaccination (Akondy et al., 2017). While this does not rule out fate determination into effector and memory cells early in the differentiation process, it presents strong evidence of memory cells arising from effector cells, supporting the pathway proposed by Crauste et al. (2017).

Despite the growing evidence in support of the naïve → (early→late) effector → memory differentiation pathway, how to reconcile it with the alternative pathways inferred from lineage tracing and other gene expression studies above remains an open question. Confounding matters is an earlier study, which used mass spectrometric analysis to estimate the expression of nine different markers and found that CD8⁺ T cells could exist in over 200 different functional phenotypes (Newell, Sigal, Bendall, Nolan, & Davis, 2012). These phenotypes, however, may not all represent differentiation states (Rohr et al., 2014). Further, tissue-resident memory cells, a recently discovered lymphocyte lineage, occupy niche tissue locations without recirculating and have been found to have differentiation patterns more strongly dependent on their environments than circulating cells (Schenkel & Masopust, 2014). Finally, how the resulting descriptions yield the observed population-level dynamics of the CD8⁺ T cell response remains to be established.

2.2.3 | The proliferation program

In a parallel series of studies, Hodgkin and colleagues have devised novel ways to elucidate the processing of the various stimulatory and costimulatory signals, such as antigen dose and cytokines, that drive the proliferation program in activated CD8⁺ T cells (and B cells) (Heinzel et al., 2017; Heinzel et al., 2018; Marchingo et al., 2014; Marchingo et al., 2016). They found that individual activated cells integrated the various signals they received and based on the sum upregulated the expression of a key cell cycle regulator, Myc (Figure 2a). When the Myc level rose above a threshold in a cell, the cell commenced proliferation (Figure 2b). Gradually, the Myc level declined. When the level dropped below the threshold, proliferation ceased. The level of Myc, interestingly, was heritable and its decline was independent of the number of proliferation events a cell had experienced. Thus, the number of proliferation events was determined simply by the level of Myc at the start of proliferation and the cell doubling time. Myc thus acted as a “timer,” defining the duration for which a cell continued to proliferate following stimulation. Importantly, Myc overexpression did not allow proliferation to proceed indefinitely; an independent, heritable mechanism, set the “time-to-die” after stimulation, at which point cell death occurred. Using a stochastic model that combined variations in the time to first division, Myc-driven duration of proliferation, and the time-to-die, they showed that small

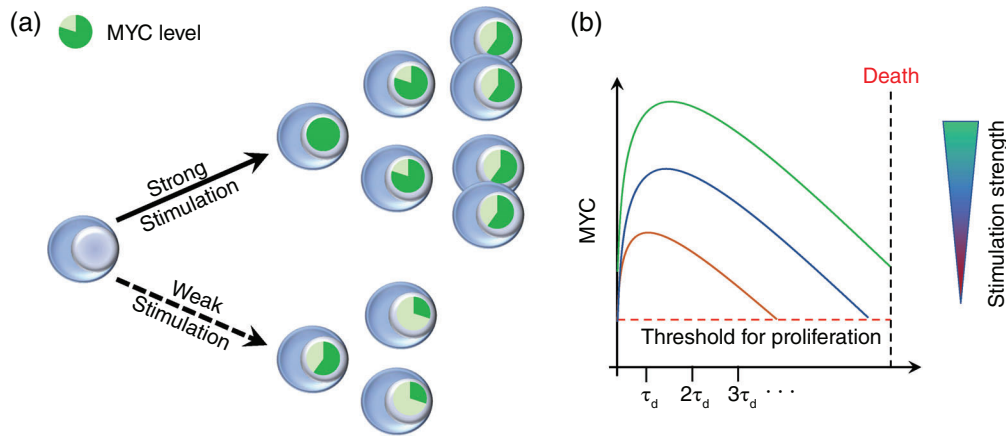


FIGURE 2 The proliferation program. (a) Strong stimulation leads to high Myc levels and more proliferation events than weak stimulation. (b) the Myc level in cells rises following stimulation and declines at a constant rate. Proliferation stops when the Myc level drops below a threshold or if the time-to-die is reached. τ_d is the time for one proliferation cycle

changes in these processes could lead to large changes in progeny numbers, explaining at least in part the heterogeneity in lineage sizes observed above (Buchholz et al., 2013; Gerlach et al., 2013).

It would be of interest to examine whether lineages that had large progeny numbers in the above *in vivo* studies (Buchholz et al., 2013; Gerlach et al., 2013) also had high Myc levels in their activated precursors following stimulation. An important question that follows is the mechanism with which properties are inherited across lineages (Asquith & de Boer, 2017). How is the Myc level maintained in proliferating cells? Similarly, how were all the cells in the large progeny lineages strongly biased towards the effector phenotype? Future studies may address these questions. At the same time, the link between the proliferation program and the predominant differentiation pathways remains to be established. The above studies have all focused on short periods following infection, where the exhaustion phenotype may not be predominant. How exhaustion fits into the proliferation and differentiation program remains another key open question. Finally, the studies have mostly been done using mice models of infection. How well they translate to larger animals and humans remains to be ascertained.

3 | EFFECTOR FUNCTION

Effector CD8⁺ T cells can exert both cytolytic and noncytolytic effects on infected cells. Following successful contact with an infected cell, which leads to the formation of an immunological synapse, CD8⁺ T cells deliver perforin and granzymes which destroys the infected cell (Murphy & Weaver, 2016). The effectors may also secrete soluble factors and cytokines such as interferon γ and macrophage inflammatory protein 1 α (MIP-1 α) and MIP-1 β , which control viral production without causing cell death (DeVico & Gallo, 2004; Saunders et al., 2011; Sperandio et al., 2015). The magnitude of these effects appears to determine whether an infection is eventually cleared, turns chronic, or leads to severe immunopathology and host mortality (Elemans et al., 2011; Moskophidis, Lechner, Pircher, & Zinkernagel, 1993). Quantifying the effects *in vivo* is important, therefore, to the design of T cell-based vaccines (Johnson et al., 2011; Schmidt et al., 2018; van Drunen Littel-van den Hurk, Mapletoft, Arsic, & Kovacs-Nolan, 2007). Akin to the CD8⁺ T cell differentiation pathways discussed above, efforts to quantify the effector functions too have been the subject of rich ongoing debates in the literature.

3.1 | Viral dynamics and the CD8⁺ T cell response

The effector function has been the most studied *in vivo* in the context of HIV infection. Following the onset of HIV infection, the plasma viral load rises sharply, reaches a peak, and declines to a set point, where it stays for many years in untreated individuals (Simon, Ho, & Abdool Karim, 2006). Efforts have been made to estimate the extent to which CD8⁺ T cells are responsible for establishing and maintaining the viral load at the set point. The approaches used have been drawn from an understanding of the underlying viral dynamics gained using mathematical models (Nowak & Bangham, 1996; Nowak & May, 2000; Perelson, 2002). Broadly, the models have the following architecture:

$$\begin{aligned}
 \frac{dT}{dt} &= \lambda - d_T T - T \sum_i k_i V_i, \\
 \frac{dI_j}{dt} &= T \sum_i Q_{ji} k_i V_i - d_I I_j - f(I_j, E_k) I_j, \\
 \frac{dV_i}{dt} &= \frac{p_i I_i}{h(I_i, E_k)} - c V_i, \\
 \frac{dE_k}{dt} &= g(I_j, E_k) - d_E E_k.
 \end{aligned}
 \tag{4}$$

The viral population within an infected individual comprises virions containing closely related but not identical viral genomes (Andino & Domingo, 2015; Padmanabhan & Dixit, 2016). V_i denotes the viral subpopulation containing genomes of type i . (For an alphabet of size 4 and a genome of $\sim 10^4$ nucleotides, i ranges from 1 to $\sim 4^{10^4}$. Here, the focus is on regions of the genome targeted by CD8⁺ T cells, which drastically reduces the range and renders the formalism tractable.) The virions V_i infect target cells, T , with an infection rate constant k_i . Following the infection, random mutations during reverse transcription yield a provirus of type j with the probability Q_{ji} , thus giving rise to an infected cell I_j , capable of producing virions V_j . Target cells are produced at the rate λ and die at the per capita rate d_T . Infected cells die naturally and due to virus-induced cytopathicity at the per capita rate d_I . They are killed by effectors at the per capita rate f , which is a function of the infected cells, I_j , and the various effector clones E_k . Whether effectors of a particular clonotype E_k kill cells I_j depends on whether the genome j contains the antigenic epitope recognized by E_k . Each I_j can express many epitopes and thus be a target of many effector clonotypes. $f(I_j, E_k)$ is thus the net loss rate of I_j from all the relevant E_k . Virions V_i are produced from infected cells I_i at the per capita rate p_i and are cleared at the per capita rate c . Noncytolytic effects of the effectors reduce the production rate by the factor $h(I_i, E_k) \geq 1$. Effectors E_k grow at the rate g , which is a function of I_j and E_k and includes activation of naïve cells and antigen-dependent and independent proliferation of activated cells. The function g thus incorporates the proliferation program discussed above. k_i and p_i together define the intrinsic fitness of virions V_i .

The above Equations (4) can be solved for steady state, where the production of each species is balanced by its loss, thus marking the set point in the chronic phase of infection. Variants of the model have captured the changes in viral load when this balance is perturbed using antiretroviral therapy (ART) and yielded estimates of the half-lives of virions and infected cells in vivo (Ho et al., 1995; Nowak & May, 2000; Perelson, 2002; Perelson, Neumann, Markowitz, Leonard, & Ho, 1996; Wei et al., 1995). The models have also been extended to other viruses (Best et al., 2017; Dixit, Layden-Almer, Layden, & Perelson, 2004; Neumann et al., 1998; Nowak et al., 1996; Padmanabhan & Dixit, 2016; Padmanabhan, Garaigorta, & Dixit, 2014). It has been of interest to estimate the contribution of effector CD8⁺ T cells in the observed loss of infected cells (Gadhamsetty, Beltman, & de Boer, 2015). More specifically, what are the relative magnitudes of d_I and f ? How do they compare to the effect of h on viral control?

3.2 | CD8⁺ T cell killing rates

Several studies have argued that CD8⁺ T cell killing contributes negligibly to infected cell loss during HIV-1 infection (Asquith, Edwards, Lipsitch, & McLean, 2006; Elemans et al., 2011; Klatt et al., 2010; Seich Al Basatena et al., 2013; Wong et al., 2010). One approach employed in these studies is to examine the response to perturbations of the balance in the chronic infection set point using ART, CD8⁺ T cell depletion or adoptive transfer of CD8⁺ T cells (Gadhamsetty et al., 2015). Soon after the start of ART, the viral load declines rapidly (Perelson, 2002). Because new infections can be blocked nearly completely with ART (Conway & Perelson, 2016) and because viral clearance and production are fast compared to infected cell half-lives (Ramratnam et al., 1999), the slope of this decline yields an estimate of the loss rate of productively infected cells (Perelson, 2002). The slope, $d_I + f$, has been estimated to be $\sim 1/\text{day}$ (Markowitz et al., 2003). The set point viral load varies over nearly four orders of magnitude across infected individuals (Fraser et al., 2014). If CD8⁺ T cell killing varied across individuals and was responsible for this variation in the set point viral load, the decline following ART should exhibit a significant variation across individuals and be correlated with the set point viral load. Surprisingly, the slope showed hardly any dependence on the set point viral load or on the baseline (target) CD4⁺ T cell counts (Bonhoeffer, Funk, Gunthard, Fischer, & Muller, 2003). Further, in macaques chronically infected with simian immunodeficiency virus (SIV), the slope of the decline following the initiation of ART was similar whether the macaques had their CD8⁺ T cells depleted or not (Klatt et al., 2010; Wong et al., 2010). The loss of infected cells thus seemed to have a negligible contribution from CD8⁺ T cell killing.

A second line of argument to suggest low CD8⁺ T cell killing rates comes from analysis of CD8⁺ T cell escape mutant dynamics. If a mutation or a set of mutations occurs that eliminates CD8⁺ T cell recognition and control of infected cells, the frequency of virions harboring the escape mutation(s) would rise. The greater the control originally exerted, the greater would

be the rate of the rise observed following escape. Surprisingly, the escape rates observed were slow and were slower in the chronic phase of infection than in the acute phase (Asquith et al., 2006; Ganusov et al., 2011; Roberts et al., 2015). These data argued against a strong role for CD8⁺ T cell killing of infected cells. That CD8⁺ T cells become exhausted during chronic infections (Kahan et al., 2015) further strengthens this argument.

Recent work from de Boer and colleagues has challenged the above arguments (Althaus & de Boer, 2011; Gadhamsetty, Coorens, & de Boer, 2016). They recognized that infected cells must pass through an eclipse phase, which lasts ~1 day, before producing virions (Dixit, Markowitz, Ho, & Perelson, 2004; Herz, Bonhoeffer, Anderson, May, & Nowak, 1996). Accordingly, they constructed multistage models, where target cells first became infected but not yet productive, and following the eclipse phase, transitioned to virus producing cells (Althaus & de Boer, 2011; Gadhamsetty, Coorens, et al., 2016). Because cells in the eclipse phase expressed viral peptides, CD8⁺ T cells could recognize and kill them (Sacha et al., 2010). The production phase could be short because of massive viral production, which could drive cell death. They showed that the decline of viral load following ART was a reflection of the latter loss of viral production and was independent of CD8⁺ T cell killing because a majority of the killing happened of cells in the eclipse phase, not producing virus. Using a model with a stage dependent CD8⁺ T cell killing rate, and a reanalysis of data from a number of studies, they showed that viral decay slopes during ART as well as the temporary rise of viremia following CD8⁺ T cell depletion and the slow immune escape rates were consistent with CTL killing rates >1/day (Gadhamsetty, Coorens, et al., 2016). They argued further that such high killing rates were essential for balancing the rapid viral replication rates of 0.5–1/day in the chronic phase (Gadhamsetty, Coorens, et al., 2016).

Several factors unrelated to CD8⁺ T cell killing may lead to the slow immune escape rates observed. Immune escape mutations often carry severe fitness costs (Ganusov, Goonetilleke, et al., 2011). Compensatory mutations can recover these costs at least partially (Kelleher et al., 2001). But the accumulation of such mutations is prevented by clonal interference, where competition between strains carrying either the escape or the compensatory mutation drives the less fit strain extinct (Garcia & Regoes, 2014). Recombination and stochastic effects can slow the accumulation down further depending on the underlying fitness landscape (Nagaraja, Alexander, Bonhoeffer, & Dixit, 2016; Read, Tovo-Dwyer, & Chakraborty, 2012). When multiple CD8⁺ T cell clones can target the virus, escape from all the strains typically happens sequentially, which renders clonal interference even more significant (Pandit & de Boer, 2014). With time, the number of CD8⁺ T cell clones tends to increase, making escape harder, which may underlie the slower escape rates seen in the chronic phase than in the acute phase (Ganusov, Goonetilleke, et al., 2011; Garcia, Feldman, & Regoes, 2016). Longitudinal data of whole genome sequences are providing crucial insights into this process of immune escape (Goonetilleke et al., 2009; Henn et al., 2012; Zanini et al., 2015). Future studies that integrate descriptions of viral evolution with CD8⁺ T cell killing may help estimate the role of CD8⁺ T cells from immune escape data.

Evidence thus exists for and against a strong role of CD8⁺ T cell killing during HIV infection. A more recent analysis of viral load resurgence data following CD8⁺ T cell depletion during ART in macaques using a model that includes CD8⁺ T cell exhaustion presents a more nuanced explanation of the conflicting observations above (Cao, Cartwright, Silvestri, & Perelson, 2018). We discuss this explanation in a subsequent section. Further, more concrete evidence of the role of CD8⁺ T cells in establishing viral control comes from recent studies on elite controllers and long-term controllers of viremia induced by ART as well as passive immunization with broadly neutralizing antibodies, which also we discuss in a subsequent section. We turn next to studies that define the dependence of CD8⁺ T cell killing rates on the abundance of effectors and infected cells.

3.3 | Killing regimes

Individual infected cells have been observed to form simultaneous contacts with multiple CD8⁺ T cells (Caramalho, Faroudi, Padovan, Muller, & Valitutti, 2009). Individual CD8⁺ T cells too have been found to be able to kill multiple target cells simultaneously (Wiedemann, Depoil, Faroudi, & Valitutti, 2006). Recent single cell studies have observed dynamic contacts, termed “kinapses,” where the contact between a CD8⁺ T cell and an infected cell is highly dynamic and is associated with the movement of the CD8⁺ T cell on the infected cell (Halle et al., 2016). While the overall CD8⁺ T cell mediated killing rate was estimated above, it is of interest to understand how this overall killing rate depends on the abundance of CD8⁺ T cells and infected cells given the nature of cell–cell interactions. In other words, how do we define the function $f(I_j, E_k)$ in Equation (4)?

The simplest formalisms assume the function to be mass action driven; that is, $f(I_j, E_k) = k_{CTL} \sum_k \alpha_{jk} E_k$, where k_{CTL} is the killing rate constant and α_{jk} is an indicator of recognition; $\alpha_{jk} = 1$ if E_k recognizes I_j and $\alpha_{jk} = 0$ otherwise (Conway & Perelson, 2015; Ganusov, Barber, & de Boer, 2011; Nagaraja et al., 2016). Other studies have found the function to depart from mass action kinetics and saturate with either infected cell densities (Merrill, 1982) or effector densities (Graw & Regoes, 2009). In a series of elegant studies, Gadhamsetty et al. have simulated an immune environment, such as a lymph node, using

the cellular Potts model and found that a double saturation function best describes the overall killing rate (Gadhamsetty, Maree, Beltman, & de Boer, 2014; Gadhamsetty, Maree, Beltman, & de Boer, 2017; Gadhamsetty, Maree, de Boer, & Beltman, 2016). Thus, using I and E as the total population of infected cells and effectors, the overall killing rate, $\sum_j f(I_j, E_k) I_j = k_{CTL} I E / (1 + I/p + E/q)$, where p and q are constants. This expression reduces to mass action kinetics when p and q are large relative to I and E , respectively, and to the other saturating dependencies observed above when only one of the latter conditions holds, thus reconciling the above observations. Interestingly, the double saturation function was found to hold, with different magnitudes of the constants p and q , under all possible regimes, namely, (a) monogamous killing, where one effector can only kill one target cell at a time; (b) simultaneous killing, where one effector can kill multiple target cells; (c) joint killing, where multiple effectors kill a single target; or (d) mixed killing, where multiple effectors can kill multiple targets simultaneously. A general description of the dependence of CD8⁺ T cell killing rates of infected cells on cell densities thus emerges.

Two key questions remain. First, the ability of the general description to capture data quantitatively remains to be ascertained. Second, with high target cell densities, it is likely that CD8⁺ T cells get exhausted (Mueller & Ahmed, 2009; Tay et al., 2014; Wherry, 2011), diminishing their killing ability (see below). The double saturation function may then have to be replaced with a function displaying a maximum with varying infected cell sizes. Future studies may integrate the inhibitory and stimulatory effects of infected cells on effectors to arrive at such a description of CD8⁺ T cell killing. That these competing effects are at play is evident in studies of long-term control of infection. They present the most direct evidence of the influence of CD8⁺ T cells on viral control. We consider them next.

3.4 | CD8⁺ T cell-based control of viral infections: Activation versus exhaustion

Growing evidence points to the crucial role of CD8⁺ T cells in the control and elimination of viral infections. In mice, the LCMV Armstrong strain typically leads to spontaneous clearance after acute infection. In CD8⁺ T cell deficient mice, this control is lost (Matloubian, Concepcion, & Ahmed, 1994). In chimpanzees, antibody-mediated depletion of virus-specific CD8⁺ T cells impaired control of hepatitis C virus (HCV) infection until the CD8⁺ T cells recovered (Shoukry et al., 2003). With HIV, three independent lines of evidence, together with corresponding mathematical models, point to the role of CD8⁺ T cells in viral control.

3.4.1 | Elite controllers

The first line of evidence comes from a rare group of individuals called elite controllers, in whom the infection remains spontaneously suppressed and does not progress to AIDS (Deeks & Walker, 2007). Specific human leukocyte antigen (HLA) molecules have been found to be correlated with this control (Migueles et al., 2000). Kosmrlj et al. (2010) present an ingenious explanation of this observation. They argue that elite controllers possess CD8⁺ T cells that are more cross reactive than others. The CD8⁺ T cells in elite controllers would thus target a wider spectrum of viral mutants, rendering immune escape difficult and establishing lasting control. To test this, they developed an *in silico* simulation model of thymic selection that determines the T cell repertoire in individuals (Kosmrlj, Jha, Huseby, Kardar, & Chakraborty, 2008). Each T cell expresses a single kind of T cell receptor (TCR). In the thymus, the T cells undergo selection based on the interaction of their TCRs with self-peptides presented on MHC molecules (Murphy & Weaver, 2016). They are positively selected if the TCRs bind to at least one peptide–MHC complex (pMHC) with an affinity larger than the positive selection threshold. They are negatively selected if they bind to any pMHC with an affinity higher than the negative selection threshold. Some HLA molecules, such as HLA-B*57, bind to and present fewer self-peptides in the thymus than others. Thymic selection then yields TCRs that bind to a few loci on the peptides with relatively high affinities. Other HLA molecules, such as HLA-B*8, present many more self peptides. To prevent negative selection, TCRs that bind to a larger number of loci on peptides but with relatively low affinities get preferred. Thus, in the periphery, TCRs restricted by HLA-B*57 can recognize viral variants with mutations at many more loci, because mutations at the non-binding loci do not affect this recognition, and thus are more cross-reactive than TCRs restricted by HLA-B*8. Based on this argument, extending the above framework of viral dynamics (Equation (4)) to include effector and memory CD8⁺ T cell responses, they showed that individuals with more cross-reactive CD8⁺ T cells were better viral controllers (Kosmrlj et al., 2010).

3.4.2 | Post-treatment controllers

The second line of evidence comes from post-treatment controllers, who, unlike elite controllers, do not exert spontaneous control of viremia, but can sustain the control established by ART even after the cessation of treatment (Saez-Cirion et al., 2013). Post-treatment controllers, too, form a small percentage (5–15%) of individuals treated (Cockerham, Hatano, & Deeks, 2016). To explain post-treatment control, Conway and Perelson (2015) constructed a description of viral dynamics that built

on the framework above and included latently infected cells and CD8⁺ T cell exhaustion (Figure 3). Latently infected cells, which contain integrated HIV proviruses but are not virus producing, survive ART and hide from the immune system, presenting the major obstacle to HIV cure (Finzi et al., 1999). For lasting control, they must be prevented from reigniting full-blown infection. The equations became:

$$\begin{aligned} \frac{dT}{dt} &= \lambda - d_T T - (1 - \varepsilon)kTV, \\ \frac{dL}{dt} &= f_L(1 - \varepsilon)kTV + \rho L - d_L L - rL, \\ \frac{dI}{dt} &= (1 - f_L)(1 - \varepsilon)kTV + rL - d_I I - k_{CTL}IE, \\ \frac{dV}{dt} &= \rho I - cV, \\ \frac{dE}{dt} &= \lambda_E + \frac{b_E IE}{k_B + I} - \frac{d_E IE}{k_D + I} - \mu_E E. \end{aligned} \quad (5)$$

Here, as a simplification, the distinction between viral variants is ignored. A fraction f_L of the infection events results in latently infected cells, L , which proliferate and die at the per capita rates ρ and d_L , respectively, and can be reactivated into productively infected cells, I , at the per capita rate r . The remaining fraction leads to productive infection. ART blocks infection with the efficacy ε . Latent cells do not express viral proteins and thus are not targets of CD8⁺ T cell killing. λ_E is the recruitment rate of naïve CD8⁺ T cells into the virus-specific effector pool and μ_E the per capita loss rate. Following an earlier approach (Bonhoeffer, Remiszewski, Ortiz, & Nixon, 2000), antigen-dependent proliferation and exhaustion of CD8⁺ T cells are modeled as Hill functions with maximal per capita rates b_E and d_E and half-maximal antigen levels of k_B and k_D , respectively. Exhaustion is thought to result from sustained and/or heightened stimulation with antigen, which typically occurs when the antigen load is large (Mueller & Ahmed, 2009; Tay et al., 2014; Wherry, 2011). Thus, $b_E < d_E$ and $k_B < k_D$, so that proliferation is dominant when antigen levels are low and exhaustion when antigen levels are high. More sophisticated models where the level of exhaustion is determined by the gradual accumulation of stimulation by antigen have been proposed (Johnson et al., 2011), but do not lead to qualitatively different results (Conway & Perelson, 2015).

Conway and Perelson (2015) showed that the model admitted two non-trivial steady states, one with high viremia and the other with low viremia. When the CD8⁺ T cell response was strong—that is, when k_{CTL} was high—the low viremic state alone was admitted, representing elite controllers. When k_{CTL} was low, the high viremic state alone was admitted, representing most other infected individuals, with high set point viremia. At intermediate k_{CTL} , both steady states became accessible. The steady state reached then depended on the initial conditions. With treatment, viremia is driven to undetectable levels with little active replication (Conway & Perelson, 2016). Exhaustion of CD8⁺ T cells can then be reversed partially (He et al., 2016; Im et al., 2016; Tay et al., 2014; Utzschneider et al., 2016). The state reached following the cessation of treatment depends on the size of the latent cell pool. If the pool is large, reactivation of latent cells (Hill, Rosenbloom, Fu, Nowak, & Siliciano, 2014;

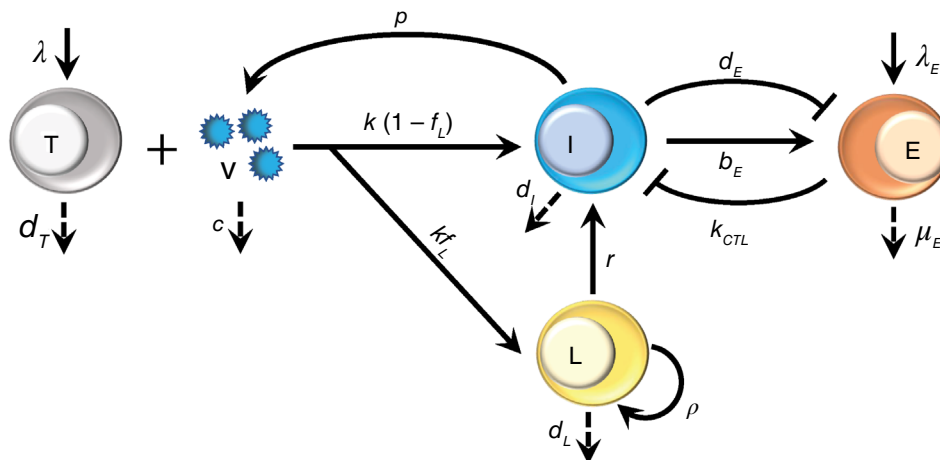


FIGURE 3 Schematic of the model of post-treatment control. Target cells (T) are infected by free virions (V) yielding productively infected cells (I) or latently infected cells (L). The former stimulate effectors (E), activating them at low antigen loads and triggering exhaustion at high antigen loads. Productively infected cells produce free virions. Effectors kill productively infected cells. Latently infected cells can proliferate and get reactivated into productive infected cells. The rates of the various processes are described in the text

Pinkevych et al., 2015) can lead to high enough viral loads that drive the infection to the high viremic state. If the pool is small, however, any reactivation does not result in sufficiently high viremia to reinduce CD8⁺ T cell exhaustion. The reinvigorated CD8⁺ T cells can then control the infection, explaining the observed post treatment control (Conway & Perelson, 2015). Because the latent pool size increases with the duration of infection, early treatment is more likely to lead to post-treatment control, although treating too early may prevent immune responses from building up (Conway & Perelson, 2015).

A promising recent development in hepatitis C treatment may represent a parallel to the post-treatment control of HIV, suggesting a wider role for CD8⁺ T cell control of infection. Patients with detectable viremia at the end of treatment with direct acting antiretroviral drugs (DAAs) can get cured spontaneously (Kohli et al., 2015; Malespin et al., 2017). The treatment duration may thus be reduced from the current guidelines (Lau et al., 2016). Baral et al. constructed a model similar to the one above (Equation (5)), which exhibited bistability and was consistent with patient data, and predicted that treatment with DAAs lowered CD8⁺ T cell exhaustion, leading to viral control (Baral et al., 2018). Alternative hypotheses, where the DAAs are argued to render virions produced noninfectious and which also capture patient data, have been proposed (Goyal et al., 2017; Nguyen et al., 2017). Future studies may construct ways to distinguish between these possibilities and attribute a clearer role to CD8⁺ T cell control.

3.4.3 | Control with passive immunization

The third line of evidence comes from a more recent study wherein a short course of passive immunization with a combination of HIV broadly neutralizing antibodies (bNAbs) was administered to monkeys infected with SHIV and a far greater percentage of monkeys than following ART was found to achieve long-term post-treatment control (Nishimura et al., 2017). The increased percentage may be partly because the immunization was commenced on day 3 following challenge when the latent pool size may be restricted. At the same time, the effects bNAbs have on the infection may be fundamentally different from that of ART. Importantly, depletion of CD8⁺ T cells long after the control was established led to temporary but rapid viral resurgence, which was eventually controlled when the CD8⁺ T cells were replenished. The control established thus was attributed at least in part to CD8⁺ T cells (Nishimura et al., 2017). The strategy is now being explored with humans (Bar-On et al., 2018; Mendoza et al., 2018). How short term bNAb treatment can sustain long term CD8⁺ T cell activity remains unknown. Nonetheless, the evidence above argues for an important role for CD8⁺ T cells in establishing HIV control.

3.4.4 | Pleiotropic effects

In chronically infected individuals who do not control HIV, the role of CD8⁺ T cells may be compromised. Cao et al. (2018) analyzed data (Cartwright et al., 2016) of viral resurgence following CD8⁺ T cell depletion in macaques infected with SIV after the initiation of ART using a model similar to that in Equation (5). They found that the effect of CD8⁺ T cells varied with time. The effect was small before ART, when the viremia was high and CD8⁺ T cells were exhausted. With the onset of ART, viremia dropped and the level of exhaustion decreased. The effect of CD8⁺ T cell killing was then significant, going beyond the 1/day estimated from viral decay dynamics above and was much larger than virus-induced cytopathy (i.e., $f > d_I$). Further, they found that both cytolytic and noncytolytic effects of CD8⁺ T cells were necessary to describe the data accurately. This study thus presents an explanation of the earlier data where no change in the viral load decay rates were observed with or without CD8⁺ T depletion (Klatt et al., 2010; Wong et al., 2010). The depletion was done before ART, where the effect of CD8⁺ T cells is expected to be small. It further reinforces the pleiotropic effects, both cytolytic and non-cytolytic, exerted by CD8⁺ T cells, as well as the nonmonotonic dependence of the effects on antigen load, determined by the levels of activation and exhaustion. We mention here that the discussion above has focused on HIV infection because it has been the most actively studied; how well these effects translate to the other infections remains to be established. Regardless of whether cytolytic or noncytolytic effects dominate, CD8⁺ T cells remain critical to the clearance of viral infections. It is important, therefore, to understand the mechanistic origins of the fates assumed by CD8⁺ T cells and ways to manipulate them so that these effects can be engineered and the clearance of viral infections optimized. In the following sections, we consider recent studies that unravel at least in part these mechanistic underpinnings.

4 | SIGNALING, ACTIVATION AND EXHAUSTION

The models of the proliferation, differentiation and effector function of CD8⁺ T cells described above assume that the behavior of individual CD8⁺ T cells is independent of others. Increasingly, it is being recognized that CD8⁺ T cells display collective behavior where the fate of a cell is coupled to the fates of its neighbors (Butler et al., 2013; Voisinne et al., 2015). The coupling is typically mediated via signaling molecules that trigger cascades of downstream events which not only drive fate decisions but also modulate the secretion of the same signaling molecules, in turn influencing the fate decisions of neighboring cells. Here, we briefly examine the signaling networks and models constructed to describe the behavior of individual CD8⁺ T

cells. These models set the stage for describing their collective behavior, which we return to in the next section. They also identify key molecular players and motifs that may be potential targets of intervention.

4.1 | Proximal TCR signaling and CD8⁺ T cell activation

Following the successful engagement of the TCR with its cognate peptide complexed to an MHC molecule (pMHC) expressed on an infected cell, a series of signaling events is triggered that culminates in the activation of the CD8⁺ T cell (Courtney et al., 2018). The molecular players involved in this cascade and their predominant interactions are now well established (Courtney et al., 2018). Briefly, TCR engagement triggers the recruitment of the kinase Lck by the colocalization of CD8 molecules to the TCR-pMHC complex. Recent evidence suggests that the TCR-pMHC complex responds to a mechanical force exerted by the interacting cells (Brazin et al., 2015; D. K. Das et al., 2015; Feng et al., 2017; Kim et al., 2009; Lee et al., 2015; Liu, Chen, Evavold, & Zhu, 2014; Ma, Janmey, & Finkel, 2008). Lck phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMs) on the cytoplasmic domains of the TCR. Phosphorylated ITAMs recruit and phosphorylate a key signaling molecule, Zap70, which is otherwise in its inactive form. Phosphorylated, activated Zap70 phosphorylates the linker for activation of T cells (LAT), which acts as a signaling hub, triggering a further series of downstream events leading ultimately to the activation of the MAP kinase ERK. ERK activates transcriptional regulators in response to several signaling inputs, resulting in T cell activation.

This signaling machinery exhibits the remarkable properties of speed, specificity, and sensitivity (Altan-Bonnet & Germain, 2005; Feinerman, Germain, & Altan-Bonnet, 2008; Francois et al., 2013): TCRs scan a large number of pMHC complexes on antigen presenting cells to detect foreign antigen. Thus, speed is of the essence. The response is highly sensitive. Trace amounts of foreign antigen elicit a response. The response is also selective. Even large amounts of self-peptides do not trigger a response. The other key property is a conversion of an analog input into a digital response (J. Das et al., 2009; Feinerman, Veiga, Dorfman, Germain, & Altan-Bonnet, 2008). Whereas the ligand concentrations and binding affinities may vary continuously, the signaling must end in a “yes/no” decision on activation. Mathematical models of TCR signaling have attempted to unravel the origins of these properties. Sophisticated models that consider explicitly the large number of molecular players involved and their interactions have been constructed (Altan-Bonnet & Germain, 2005; J. Das et al., 2009; Lipniacki, Hat, Faeder, & Hlavacek, 2008; Stefanova et al., 2003). At the same time, phenotypic models that recapitulate the essential observations above have been proposed (Feinerman, Germain, et al., 2008; Francois et al., 2013; Lever, Maini, van der Merwe, & Dushek, 2014). Here, we highlight the key features of the models.

The idea of kinetic proofreading (McKeithan, 1995) is at the heart of many models of proximal TCR signaling (Figure 4). Here, pMHC binding to the TCR triggers a “sequence” of downstream events, typically phosphorylation events (of ITAMs, Zap70, etc.), which culminates in a critical event, say LAT activation. If the pMHC dissociates from the TCR, the sequence is aborted. Thus, pMHC-TCR interactions that are strong enough for the complex to stay associated longer than a threshold duration required for the occurrence of the critical event lead to activation. Francois et al. (2013) showed that such a kinetic proofreading mechanism coupled with a negative feedback attributed to Src homology 2 domain phosphatase-1 (SHP-1) recapitulates the key observations of TCR signaling qualitatively. Models have made advances to this kinetic proofreading mechanism by describing the kinetically sensitive steps in greater detail, for instance, by incorporating serial TCR-pMHC

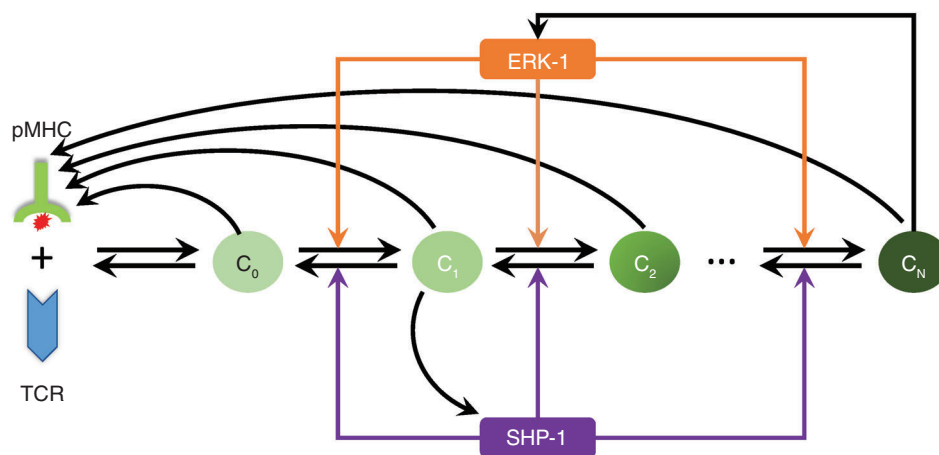


FIGURE 4 Phenotypic model of proximal TCR signaling. Schematic of the kinetic proofreading model where TCR-pMHC contact triggers the sequence of events from C_0 to C_N . Unbinding of the TCR-pMHC complex resets the system. Following C_1 , a negative feedback via SHP-1 suppresses the cascade. Following C_N , a positive feedback via ERK-1 amplifies the cascade

engagement (Valitutti, Muller, Cella, Padovan, & Lanzavecchia, 1995) or rebinding of pMHC to TCR after dissociation (Aleksic et al., 2010; Govern, Paczosa, Chakraborty, & Huseby, 2010), and CD8 coreceptor scanning of TCR-pMHC complexes for Lck recruitment (Stepanek et al., 2014). Models that account explicitly for the signaling events involved have considered both negative and positive feedback loops to elucidate the mechanistic origins of the observed TCR signaling properties (Altan-Bonnet & Germain, 2005; J. Das et al., 2009).

While the models thus provide key insights into CD8⁺ T cell activation, they are restricted to proximal TCR signaling and do not address gene regulation and the resulting proliferation and differentiation programs. In addition to transcriptional regulation (Kaech & Cui, 2012), cellular metabolism is also altered following activation and differentiation to effector and memory phenotypes (C. H. Chang et al., 2013; Chi, 2012). Establishing links between proximal TCR signaling and the ensuing transcriptional and metabolic regulation leading to the proliferation and differentiation programs described above remains an outstanding challenge. Secondly, the models do not consider CD8⁺ T cell exhaustion, which too results from the same signaling cascade. Much less is known of the fate decisions that lead to CD8⁺ T cell exhaustion. Yet, they form important drug targets (Wherry & Kurachi, 2015; Wykes & Lewin, 2018). Recent studies have developed novel characterizations of exhausted cells and contrasted them with activated and memory cells (Doering et al., 2012; Singer et al., 2016), which could potentially aid in the construction of models of TCR signaling leading to exhaustion. We briefly describe these characterizations next.

4.2 | CD8⁺ T cell exhaustion

CD8⁺ T cell exhaustion, also termed dysfunction, which results from sustained stimulation of the TCR, when antigen is present in large abundance or over extended durations (Moskophidis et al., 1993; Mueller & Ahmed, 2009; Tay et al., 2014; Wherry, Blattman, Murali-Krishna, van der Most, & Ahmed, 2003; Zajac et al., 1998), is a predominant feature of chronic infections and cancers (Kahan et al., 2015; Wherry, 2011). It has been proposed as an altered differentiation program designed to exert restricted control during chronic infections while preventing massive immunopathology (Cornberg et al., 2013). It is associated with the upregulation of a host of inhibitory molecules such as PD-1 and Lag-3, blocking which can reverse exhaustion at least in part (Wherry & Kurachi, 2015). Understanding the origins of exhaustion and devising ways of preventing or reversing it form areas of intense focus today, as they bring promise of identifying novel avenues of intervention for diseases that may otherwise be incurable (Pardoll, 2012; Wykes & Lewin, 2018). Indeed, remarkable progress has been made in the recent years in characterizing the exhausted state and its implications for disease progression (Kahan et al., 2015; Wang, Singer, & Anderson, 2017; Wherry, 2011; Wherry & Kurachi, 2015).

CD8⁺ T cell exhaustion occurs in a progressive manner, with effector functions lost gradually (Kahan et al., 2015; Wang et al., 2017). The capacity to produce the proinflammatory cytokine IL-2 is the first that is compromised. Subsequently, the production of other proinflammatory cytokines, TNF and IFN- γ , is suppressed. Simultaneously, the production of the immunosuppressive cytokine IL-10 increases. Together with this, the expression of inhibitory receptors increases. The last effector function to be lost is the cytotoxic potential. The cells eventually lose their proliferative capacity and become apoptotic.

Attempts have been made to characterize cells in the various exhausted states. The level of expression of the inhibitory receptors, including PD-1, CTLA-4, Lag-3, and Tim-3, was found to correlate with the severity of dysfunction (Wherry & Kurachi, 2015). Indeed, drugs that interfere with PD-1 or CTLA-4 or their interactions with their ligands, PD-L1 and CD80/CD86, respectively, have been approved for the treatment of some cancers (Pardoll, 2012; Ribas & Wolchok, 2018). However, the inhibitory receptors are also expressed on activated cells (Duraismamy et al., 2011), or may not be expressed on dysfunctional cells (Singer et al., 2016), compromising their utility as unequivocal markers of exhaustion. More recently, dysregulation of intracellular zinc has been argued to be a major driver of CD8⁺ T cell dysfunction (Singer et al., 2016). In the same study, using unsupervised clustering of gene expression data at the single cell level during chronic LCMV infection in virus-specific CD8⁺ T cells with normal zinc regulation and those with engineered zinc dysregulation, the module of genes preferentially upregulated in exhausted cells was identified. The transcription factors Gata3 and Helios were found to be the most upregulated. When CRISPR/Cas-9 was used to delete Gata3 in tumor-specific CD8⁺ T cells, better tumor control resulted. Similarly, the module associated with activation was identified (Singer et al., 2016). Earlier studies have contrasted the gene expression profiles in the exhausted state against the memory phenotype (Doering et al., 2012). Whereas how effector cells may dedifferentiate into memory cells has recently been unraveled (Akondy et al., 2017; Youngblood et al., 2017), the origins of the transition from activation to exhaustion as well as the gradation within the exhausted pool associated with the progressive loss of effector function remain to be unraveled. In other studies, other factors, including NFAT, Maf, Batf, Blimp-1 and Eomes, with the latter inversely correlated with T-bet, have been implicated in CD8⁺ T cell dysfunction (Buggert et al., 2014; Giordano et al., 2015; Intlekofer et al., 2005; Martinez et al., 2015; Paley et al., 2012; Quigley et al., 2010; Shin et al., 2009). Epigenetic changes associated with exhaustion have also been identified, including some that cannot be reversed with PD-1 blockade (Pauken et al., 2016; Sen et al., 2016; Youngblood et al., 2011). Importantly, the CD8⁺ T cell population that expresses CXCR5, Tcf7 and Bcl6 was identified recently as the subpopulation of exhausted cells with a higher

proliferative capacity and the potential to be restored to effectors with PD-1 blockade (He et al., 2016; Im et al., 2016; Utzschneider et al., 2016), defining limits on the extent to which exhaustion can be reversed by PD-1-based immunotherapy.

It would be of interest to construct mathematical models of cell signaling and gene and metabolic regulation that describe the exhausted state and integrate the models into those of viral dynamics. Such models would inform strategies to optimize drugs and vaccines. Mechanistic models of CD8⁺ T cell dysfunction have yet to be constructed. Mechanistic models of CD8⁺ T cell activation and phenotypic models of exhaustion, however, have been integrated into models of cell and viral population dynamics to describe the CD8⁺ T cell response. We describe these models next.

5 | MULTISCALE MODELS

The CD8⁺ T cell response to viral infections is an intrinsically multiscale phenomenon. It is also a collective phenomenon. At the individual cell level, signaling and gene regulation determine fate decisions. The signaling inputs are derived from antigen, via TCR-pMHC contacts, as well as costimulatory cytokines, such as IL-2. IL-2 is produced by activated CD8⁺ T cells, so that its level is determined by the fates of other cells. Activated CD8⁺ T cells also suppress antigen levels. Lower antigen levels prevent CD8⁺ T cell exhaustion, resulting in a positive feedback loop. At the cell population level, the interactions of the activated and exhausted CD8⁺ T cells with infected cells determine the overall outcome of infection. The dynamics has both temporal and spatial aspects, which introduces additional complexities. The dynamics is also modulated by other factors, such as regulatory T cells, which compete for IL-2, and IFN- α , which can also influence fate decisions. Integrating all of these aspects into a unified framework remains a grand challenge. Yet, the sophisticated understanding of the phenomena at each of the scales involved gained from studies described in the preceding sections has set the stage for constructing such a unified framework. Elements of the framework have been constructed and represent interesting advances. Here, we present an overview of these multiscale models.

5.1 | Models integrating local and global cues

Voisinne et al. (2015) showed how CD8⁺ T cells that are strongly activated can influence weakly stimulated ones into proliferation (Figure 5). They considered two signals, which could both influence cell fate decisions: antigen, via pMHC-TCR interactions, and, IL-2, through the IL-2 receptor, IL-2R. Strong TCR signaling drove a cell into proliferation regardless of IL-2. If antigen stimulation was weak, the cell could still enter the proliferation program if the stimulation by IL-2 was strong. IL-2 triggered the PI3K-AKT pathway leading to proliferation. IL-2 signaling, however, involves a positive feedback loop. Phosphorylated STAT5 (pSTAT5), which is downstream of the IL-2R, triggers the expression of IL-2R. Further, IL-2R, via PI3K, triggers the expression of IL-2, which is secreted out of the cell. This positive feedback yielded bistability. In one state, IL-2R levels were high and proliferation resulted. In the other, they remained low and the cell ceased to enter the proliferation program. IL-2 is also expressed by TCR signaling. Thus, cells that were strongly stimulated by antigen could produce IL-2, which enhanced the IL-2/IL-2R signaling in neighboring cells that may not be stimulated strongly enough by antigen and drove them

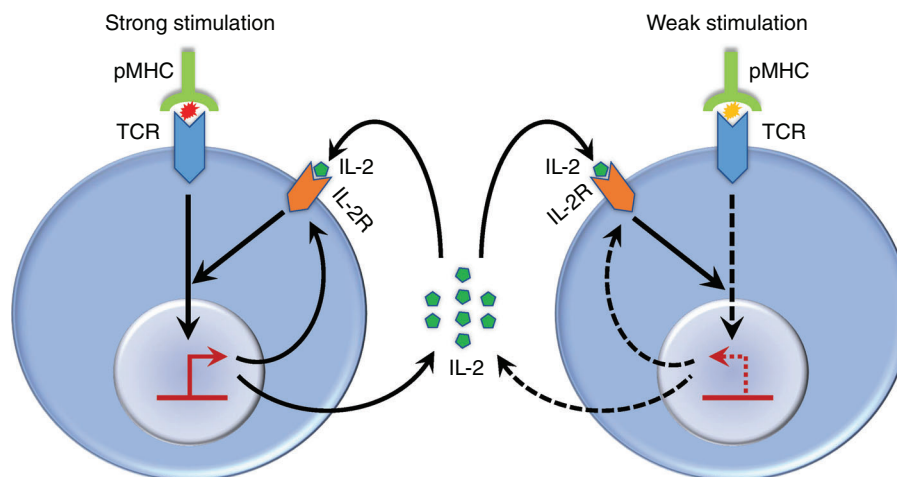


FIGURE 5 Multiscale model of collective decision making. TCR-pMHC stimulation can either be strong (left) or weak (right). Strong signaling leads to proliferation, which triggers IL-2 secretion and IL-2R expression, amplifying the proliferation signal. The enhanced extracellular IL-2 can trigger signaling via IL-2R in the weakly stimulated cell and drive it into proliferation

into the proliferation program. Thus, the overall CD8⁺ T cell response was determined by the distribution of basal IL-2R levels in the cell population and the strength of TCR signaling.

Voisinne et al. (2015) constructed a hybrid stochastic/deterministic model, where the signaling events were recognized to be fast and described deterministically and the gene regulatory events were slow and described stochastically. The difference in the timescales of signaling and gene expression events has been recognized in earlier models (Tiwari, Balazsi, Gennaro, & Igoshin, 2010). They then integrated this description into a model of cell and infection dynamics, where the antigen level was dependent inversely on the activated CD8⁺ T cell population. Finally, the incorporated regulatory T cells, which are known to compete for IL-2 and lower its availability for CD8⁺ T cell stimulation. In vitro experiments validated their model predictions, showing how CD8⁺ T cells integrate local and global cues and arrive at fate decisions in a collective manner.

In an earlier study, CD8⁺ T cells were argued to employ collective decision making as a design to prevent autoimmune responses (Butler et al., 2013). Thymic selection is necessarily imperfect. Cells that are strongly activated by self pMHC complexes presented in the thymus are negatively selected, but not all self pMHC complexes are sampled by any CD8⁺ T cell in the thymus. Thus, cells that are likely to be autoreactive are expected to be produced from the thymus. Yet, autoimmune responses are rare. At the same time, responses to foreign peptides are robust. Butler et al. (2013) argued that this was possible if for a CD8⁺ T cell to get activated, a sufficient number of other CD8⁺ T cells in the neighborhood had also to be activated. The reinforcement could occur through IL-2 levels, as suggested above, and parallel quorum sensing in bacteria (Miller & Bassler, 2001). In such a scenario, if a cell were to bind a self pMHC complex tightly, it is unlikely that a sufficient number of other CD8⁺ T cells would do so too, as they would not all be likely to miss the pMHC in the thymus. On the other hand, a foreign pMHC is likely to evoke a strong response from many different CD8⁺ T cell clones. A model built on these ideas was consistent qualitatively with experiments, reinforcing the multiscale and collective nature of the CD8⁺ T cell response.

5.2 | Spatial models

On the above single cell and cell population level descriptions, models have superimposed spatial structure, recognizing that the interactions between cells require proximity if not direct contact. Prokopiou et al. (2014) have thus integrated a model of intracellular signaling and differentiation with the cellular Potts model of cell movement and interactions. Signaling via the TCR, IL-2R as well as Fas, which leads to apoptosis, were considered. Cytokine concentrations were obtained by solving reaction–diffusion equations. Ordinary differential equations were solved to capture intracellular signaling events. Antigen presenting (infected) cells and CD8⁺ T cells in various differentiation states—naïve, preactivated, activated, and effector—were considered and the movement of the cells was determined based on the energetics of inter-cellular interactions, following the framework in cellular Potts models. The model was designed to mimic a lymph node. Model predictions qualitatively reproduced the CD8⁺ T cell counts observed in mice lymph nodes early in infection. Bouchnita, Bocharov, Meyerhans, and Volpert (2017) have constructed a more detailed model incorporating, additionally, signaling via the interferon receptors, as well as help from CD4⁺ T cells. Further, cell division was assumed to be asymmetric (J. T. Chang et al., 2011; J. T. Chang et al., 2007). They found that spatial segregation of the signals from antigen, IL-2 and interferon could lead to early terminal differentiation of cells and an exhausted CD8⁺ T cell response. More comprehensive models that mimic the architecture of the lymph node have also been constructed (Baldazzi, Paci, Bernaschi, & Castiglione, 2009; Gong et al., 2013). A natural extension would be to integrate these models with those incorporating tissue resident memory cells and recall responses, with the overall response compartmentalized between circulating and tissue specific cells (Schiffer, Swan, Prlic, & Lund, 2018; Zarnitsyna et al., 2016). Future studies may test the predictions made by these models against experiments.

5.3 | Age-structured models

The above models have focused on early infection and the ensuing CD8⁺ T cell activation and effector function. Persistent infections and the associated CD8⁺ T cell exhaustion may require a different approach. Unlike activation, exhaustion results typically from an accumulation of stimulation over an extended duration. Stromberg and Antia (2012) recognized that with thymic output continuously introducing new non-exhausted cells, at any time following infection, a distribution of the age of CD8⁺ T cells is expected and thus a distribution of the level of exhaustion. To describe the resulting infection dynamics, they built an age-structured model, where the level of exhaustion of each cell increased with time based on the accrued stimulation, dependent in turn on the antigen level (or pathogen load). The antigen level was suppressed by effector cells, whose function depended inversely on the level of exhaustion. The resulting PDE was solved to examine whether thymic influx of non-exhausted cells could control the infection. They found that while a certain level of CD8⁺ T cell responses can be maintained by the continuous thymic influx, it may be inadequate to clear the infection (Stromberg & Antia, 2012).

In summary, models that explicitly recognize the multiscale and collective nature of the CD8⁺ T cell response are being constructed. The models have focused on specific aspects of the response, namely, the development of the response after

infection and its sustenance and exhaustion during chronic infection. The descriptions have been largely qualitative. Future studies may integrate the different aspects into a more comprehensive framework and draw upon new experimental data of the kind discussed above to establish parameter settings that would allow quantitative comparisons with experiments. The resulting frameworks may have the potential to optimize interventions with drugs or vaccines targeting CD8⁺ T cells.

6 | CONCLUDING REMARKS

Quantitative characterization of the CD8⁺ T cell response to viral infections has proven a rich challenge. The underlying phenomena are diverse and span multiple length and time scales. Remarkable progress has been made over the years in unraveling these phenomena. Recent single cell studies have drastically improved our understanding of these processes. How cells process stimulatory signals to become activated and enter a proliferation program has been understood. How the effector response depends on the abundance of infected cells and effectors have been characterized. Descriptions of how CD8⁺ T cells may interact to influence their collective fate decisions are being developed. The cytolytic and noncytolytic aspects of the effector response are being quantified. The influence of CD8⁺ T cell exhaustion on the effector response and the resulting outcomes of infection and treatment has been characterized. Studies of viral dynamics are being coupled with models of the effector response of CD8⁺ T cells to develop frameworks for optimizing drug and vaccine interventions.

Several questions remain to be answered. The differentiation pathways that lead from naïve to effector and memory cells need to be established. Links between proximal TCR signaling and gene and metabolic regulation that drive these fate decisions remain to be identified. Signaling networks that lead to exhaustion need to be constructed and quantified. The signaling programs that recruit memory CD8⁺ T cells and mount secondary responses are yet to be comprehensively characterized. Long-term dynamics of persistent viral infections, where fate decisions including those of entering progressive exhaustion states by individual cells are coupled to the pathogen load and vice versa, need to be constructed. These descriptions must be integrated with models of viral evolution and CD8⁺ T cell immunodominance to yield a comprehensive framework of the CD8⁺ T cell response that is amenable to engineering using drugs and vaccines. Such a framework brings with it the promise of establishing new, more robust principles of the design of vaccines for rapidly evolving pathogens.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

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