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Dynamics of CD8$^+$ T Cell Responses during Acute and Chronic Lymphocytic Choriomeningitis Virus Infection$^1$

Christian L. Althaus, Vitaly V. Ganusov, and Rob J. De Boer

Infection of mice with lymphocytic choriomeningitis virus (LCMV) is frequently used to study the underlying principles of viral infections and immune responses. We fit a mathematical model to recently published data characterizing Ag-specific CD8$^+$ T cell responses during acute (Armstrong) and chronic (clone 13) LCMV infection. This allows us to analyze the differences in the dynamics of CD8$^+$ T cell responses against different types of LCMV infections. For the four CD8$^+$ T cell responses studied, we find that, compared with the responses against acute infection, responses against chronic infection are generally characterized by an earlier peak and a faster contraction phase thereafter. Furthermore, the model allows us to give a new interpretation of the effect of thymectomy on the dynamics of CD8$^+$ T cell responses during chronic LCMV infection: a smaller number of naive precursor cells is sufficient to account for the observed differences in the responses in thymectomized mice. Finally, we compare data characterizing LCMV-specific CD8$^+$ T cell responses from different laboratories. Although the data were derived from the same experimental model, we find quantitative differences that can be solved by introducing a scaling factor. Also, we find kinetic differences that are at least partly due to the infrequent measurements of CD8$^+$ T cells in the different laboratories. The Journal of Immunology, 2007, 179: 2944–2951.

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$^3$ Abbreviations used in this paper: LCMV, lymphocytic choriomeningitis virus; p.i., postinfection; SThx, sham-thymectomized; Thx, thymectomized; CI, confidence interval.

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Materials and Methods

The data used in our analysis have been published recently (4, 14). In the study by Wherry et al. (4), 4- to 6-wk-old female C57BL/6 mice were infected with LCMV Armstrong (2 × 10^6 PFU, i.p.) or LCMV clone 13 (2 × 10^6 PFU, i.v.) causing acute and chronic infection, respectively. The numbers of Ag-specific CD8+ T cells/spleen were determined by MHC tetramer staining at several time points after infection against the following epitopes: NP396, GP33, GP34, and GP276. Mice infected with LCMV Armstrong were able to control the virus effectively in serum and tissues, whereas in mice infected with LCMV clone 13, virus persisted at high levels in the brain and kidneys (4). The study by Miller et al. (14) used Thx and SThx C57BL/6 mice. Surgeries were performed when the mice were ~6 wk old. Two to 3 wk after surgery, mice were infected with 2 × 10^6 PFU of LCMV clone 13 i.v. Specific CD8+ T cells against the epitopes NP396, GP33, and GP276 were measured as cells per spleen by MHC tetramer staining. At day 80 p.i., virus was cleared in the liver but persisted in the lung. For a more detailed description of how data were obtained, we refer to the original studies (4, 14). The data were provided to us by the authors of these papers.

Different models have been proposed to describe the dynamics of CD8+ T cells after viral infections (8, 9, 12, 15). De Boer et al. (12) published a mathematical model that was fitted to CD8+ T cell responses following LCMV Armstrong infection. In this study, we used the same model to estimate the dynamics of CD8+ T cell responses during acute and chronic LCMV infection. The model considers clones of activated (A) and effector/memory (M) cells. Because the proliferation of T cells after antigenic stimulation seems to be programmed (16–19), the dynamics are split into two distinct phases. Before the peak of the response at time Toff, there is rapid proliferation. After the peak, activated cells die or turn into effector/memory cells.

The dynamics can be described by a set of ordinary differential equations. During the expansion phase, when t < Toff, we assume that there are no effector/memory cells and activated T cells A proliferate according to the following:

\[
\frac{dA}{dt} = \rho A, 
\]

where \(\rho\) is the net expansion rate, and \(A_0\) is the initial number of cells at \(t = 0\). More realistically, naive precursor cells should start proliferating after they have been recruited through antigenic stimulation. For simplicity, we lump these precursor numbers and the recruitment time together, and consider a proliferation that starts at \(t = 0\). Therefore, our estimates of \(A_0\) are lower than the precursor frequency of naive cells that has been estimated by Blattman et al. (20). After the peak at time Toff, activated cells A die with a net death rate of \(\delta\) (representing activation-induced cell death and normal death) and turn into effector/memory cells M at a rate \(r\). Therefore, the dynamics of activated and effector/memory cells for \(t > T_{\text{off}}\) can be described as follows:

\[
\frac{dA}{dt} = -(r + \delta)A, 
\]

\[
\frac{dM}{dt} = rA - \delta M, 
\]

where \(\delta\) represents the net death rate of effector/memory cells, consisting of a balance between cell renewal and death. This balance is maintained through ongoing cell division, which has been shown with BrdU labeling for cells that persist after acute and chronic LCMV infection (5, 14).

Using the number of activated cells at the peak of the response, A(Toff), as an initial condition for Equation 2, the solution of Equations 1–3 gives a continuous function for the total cell number \(N = A + M\). Parameter estimates of the differential equations were obtained by fitting the prediction of the total cell number, \(N\), to the data (taking the natural logarithm) based on the Levenberg-Marquardt algorithm (21) for solving nonlinear least-squares problems. The 95% confidence intervals (CIs) for the inferred parameters were determined using a bootstrap method (22), where the residual to the optimal fit were resampled 500 times. When we compared a smaller model with restricted parameters to a bigger model with a higher number of free parameters, we perform the F test to compare the two nested models by the difference between their residual sum of squares per additional parameter, divided by the residual mean square of the larger of the two models (23). Given this value, the F distribution contains two parameters. The one in the numerator is the difference in the number of parameters between the two models. The one in the denominator is the number of degrees of freedom of the larger model (i.e., the number of data points minus the number of parameters). Throughout the paper, we accepted the hypothesis that the model with the larger number of parameters provides the best fit with a significance level of \(p < 0.05\).

To compare data sets of CD8+ T cell responses from different laboratories, we introduced a scaling factor, s. First, the mathematical model was fitted to a specific CD8+ T cell response from laboratory 1. Then, the estimated total cell numbers, \(N_i\), were scaled and used as a prediction for the specific CD8+ T cell response from laboratory 2 (\(N_2 = sN_1\)). Regression analysis and Student’s t test were performed using Gnumeric (version 1.0.12) and the R statistical software package (24). Significance was defined as \(p < 0.05\).

Results

CD8+ T cell responses during acute and chronic LCMV infection

We fit the data of Wherry et al. (4) with a simple mathematical model described in Materials and Methods to detect differences between the dynamics of CD8+ T cell responses during acute and chronic LCMV infection (Fig. 1, Tables I and II). Due to the limited number of data points before the peak of the response, one cannot estimate the expansion rate, the time of the peak, and the initial cell number from these data. We therefore used previous estimates of the net expansion rate that were obtained by fitting the same mathematical model to CD8+ T cell responses against LCMV Armstrong in the same mouse strain (13). The data used in this study had several measurements before the peak of the response and therefore allowed to estimate the expansion rates (25).

Because clone 13 differs from LCMV Armstrong by 2 aa not affecting the relevant CD8+ T cell epitopes (26, 27), we consider the initial expansion rate of the corresponding CD8+ T cell responses to be similar for both acute and chronic LCMV infection (see also Discussion). We also force the number of naive precursor cells for each epitope to be the same for acute and chronic responses. Because there are no data points during the expansion phase for the GP34-specific CD8+ T cell response during acute infection, we only fit the contraction phase of this response.

Fitting the model to all data sets of CD8+ T cell responses during acute and chronic infection gave reasonable fits (Fig. 1). As observed in De Boer et al. (13), allowing the net death rate of effector/memory cells, \(\delta_{\text{E/M}}\), to be a free parameter failed to improve the quality of the fits and converged to a value close to zero for both acute and chronic infection. Therefore, we set \(\delta_{\text{E/M}}\) to be zero. The time of the peak, \(T_{\text{off}}\), appeared to be different between responses during acute and chronic infection but similar for the epitope-specific responses for one type of infection. Based on an F test, we could indeed restrict the model to a single \(T_{\text{off}}\) for the responses during acute infection, and another single \(T_{\text{off}}\) for the responses during chronic infection. Furthermore, the responses during acute infection could be fitted with the same effector/memory formation rate, \(r\). In combination, this means that we restricted the model having eight \(T_{\text{off}}\) parameters and eight \(r\) parameters for the four responses against both types of infection to a smaller model having five \(r\) parameters and two \(T_{\text{off}}\) parameters (i.e., reducing the number of parameters by nine, which gives \(F_{(5,225)} = 1.6\) and \(p = 0.13\)).

CD8+ T cell numbers specific for GP33 measured by intracellular cytokine staining for IFN-γ roughly correspond to the sum of GP33- and GP34-specific CD8+ T cells obtained by MHC tetramer staining (25). To compare the dominance ranking for the four responses to the results in De Boer et al. (13), which were obtained by fitting the model to CD8+ T cell numbers measured by intracellular cytokine staining, we use the sum of GP33- and GP34-specific CD8+ T cells. The results are in agreement with that study. For responses during acute LCMV infection, the data shows the same dominance ranking for the epitopes at the peak and in the memory phase, given as GP33 + GP34 > NP396 > GP276.
We find the same hierarchy at the peak of the response during chronic LCMV infection, but the hierarchy is changed after the peak because the GP276 response becomes the largest, i.e., \(GP276 > GP33 > GP34 > NP396\). The change in immunodominance can be explained by different apoptosis rates and different effector/memory formation rates between the responses during chronic infection (Fig. 2 and Table II). Apoptosis rates also differ between responses during acute infection, which is in contrast to the study by De Boer et al. (13); however, the differences are minor (Fig. 2A and Table I). Comparing the obtained parameters between acute and chronic responses shows two major differences. The studied responses during chronic infection generally show an earlier peak (at day 6.5, compared with 7.3 for the responses during acute LCMV infection) and a faster contraction phase thereafter.

**Table I.** Parameter estimates obtained by fitting the model to the data on CD8\(^+\) T cell responses to four different epitopes during acute LCMV infection (Armstrong).

<table>
<thead>
<tr>
<th>Name</th>
<th>Units</th>
<th>NP396 Value (95% CI)</th>
<th>GP33 Value (95% CI)</th>
<th>GP34 Value (95% CI)</th>
<th>GP276 Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\delta_1)</td>
<td>day(^{-1})</td>
<td>0.13 (0.10–0.17)</td>
<td>0.23 (0.18–0.31)</td>
<td>0.08 (0.06–0.11)</td>
<td>0.13 (0.10–0.17)</td>
</tr>
<tr>
<td>(r)</td>
<td>day(^{-1})</td>
<td>0.004 (0.003–0.006)</td>
<td>0.004 (0.003–0.006)</td>
<td>0.004 (0.003–0.006)</td>
<td>0.004 (0.003–0.006)</td>
</tr>
<tr>
<td>(T_{off})</td>
<td>days</td>
<td>7.3</td>
<td>7.2–7.5</td>
<td>7.3</td>
<td>7.2–7.5</td>
</tr>
<tr>
<td>(A_0)</td>
<td>Cells</td>
<td>4.9</td>
<td>3.8–6.2</td>
<td>8.6</td>
<td>6.9–11.1</td>
</tr>
</tbody>
</table>

\(^*\) Previous estimates of proliferation rates were used: 1.92 day\(^{-1}\) for NP396, 1.89 day\(^{-1}\) for GP33 and GP34, and 1.87 day\(^{-1}\) for GP276 (13). The death rate of effector/memory cells is \(\delta_1 = 0\).
after the peak. During the contraction phase of responses during chronic LCMV infection, both the death rate of activated cells, and the effector/memory formation rate are faster (Fig. 2, A and B).

**Dynamics of CD8\(^+\) T cell responses in Thx mice**

Miller et al. (14) investigated the role of thymic output in the dynamics of Ag-specific CD8\(^+\) T cell responses during chronic LCMV infection (Fig. 3). The authors argue that there is a transient CD8\(^+\) T cell defect in Thx mice compared with SThx mice. The argument is based on the observation that there is a significantly lower CD8\(^+\) T cell response in Thx mice at day 30 p.i. compared with SThx mice for all measured epitopes. Because there is no significant difference in the responses at later time points after day 30 p.i., Miller et al. (14) conclude that cells in Thx mice later rebound to levels similar to those in SThx mice, which suggests that there is an increase of the responses in Thx mice between days 30 and 80 p.i. BrdU labeling between days 15 and 25 p.i., and between days 30 and 40 p.i. with subsequent flow cytometry at the end of each pulse showed no difference in the proliferation rates between Thx and SThx mice, however. Another explanation for the reduced number of T cells in day 30 p.i. for Thx mice is that T cells are more sequestered to peripheral tissues because of higher viral load at these sites, compared with SThx mice (14).

To test the hypothesis of a transient CD8\(^+\) T cell deficit in Thx mice, we performed a Student t test to check whether the CD8\(^+\) T cell numbers at days 30, 45, and 80 p.i. are significantly different from each other but found no evidence (\(p > 0.05\)). Furthermore, we performed a linear regression across all data points at days 30, 45, and 80 p.i., and found no evidence for a slope significantly different from zero (\(p > 0.05\)). Both these analyses argue against the increase in T cell responses in Thx mice from day 30 p.i.

This statistical analysis is in agreement with the results of our dynamical model: the stable phase of effector/memory cells given the reduced number of T cells in day 30 p.i. for Thx mice is that there is no CD8\(^+\) T cell rebound after day 30 p.i. Therefore, we fit our model to the data describing CD8\(^+\) T cell responses against three epitopes for SThx and Thx mice concurrently. Again, there is only one time point of measurements before the expected peak of the response (at day 5 p.i.). Hence, we set the proliferation rates to previously estimated parameters (13), and assume the time of the peak, \(T_{\text{off}}\), to be equal for Thx and SThx mice because both of them are infected with the same type of virus. The only parameters that can vary between Thx and SThx mice are the initial number of naive cells that become activated, \(A_0\), the rate of effector/memory cell formation, \(r\), and the net death rate of activated cells, \(\delta_4\). Because young Thx mice are expected to have markedly lower naive T cell numbers (~50% compared with control mice) (I. den Barber, manuscript in preparation), a basic hypothesis to test is whether we can account for the difference between the responses by assuming a difference in the initial number of T cells \(A_0\) only. Indeed, the quality of the fit is not reduced when we restrict \(r\) and \(\delta_4\) to be the same in Thx and SThx mice (\(F_{2,185} = 0.75; p = 0.48\)), which is not the case for restricting identical \(A_0\) with a free \(r\). Furthermore, we are able to estimate a constant fraction of 62% for the initial number of specific T cells in Thx mice compared with SThx mice (Table III). Given this result, we are able to explain the differences in T cell responses for SThx only by a lower precursor frequency of naive T cells.

**Comparing data of CD8\(^+\) T cell responses between laboratories**

The availability of data characterizing CD8\(^+\) T cell responses against LCMV infections from different laboratories allows us to examine whether the published data are consistent with each other. We can compare the dynamics of T cell responses during acute LCMV infection between the study of Homann et al. (25) and Wherry et al. (4). Additionally, we have two studies that quantify T cell responses against chronic LCMV infection (4, 14). It is important to note that these studies measure CD8\(^+\) T cell responses after the same challenge with virus in the same mouse strain (see Materials and Methods). The only difference is that, compared with normal C57BL/6 mice in Wherry et al. (4), Miller et al. (14) use SThx mice. However, it is typically assumed that CD8\(^+\) T cell dynamics do not show a different behavior due to surgery without thymus removal.

First, we compared the data on CD8\(^+\) T cell responses against NP396 and GP276 during acute LCMV infection from Wherry et al. (4) to previously estimated parameters by De Boer et al. (13). Those parameters were obtained by fitting the model to

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### Table II. Parameter estimates obtained by fitting the model to the data on CD8\(^+\) T cell responses to four different epitopes during chronic LCMV infection (clone 13)^

<table>
<thead>
<tr>
<th>Name</th>
<th>Units</th>
<th>Value 95% CI</th>
<th>Value 95% CI</th>
<th>Value 95% CI</th>
<th>Value 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\delta_4)</td>
<td>day(^{-1})</td>
<td>1.52</td>
<td>1.16–1.86</td>
<td>0.31</td>
<td>0.22–0.42</td>
</tr>
<tr>
<td>(r)</td>
<td>day(^{-1})</td>
<td>0.032</td>
<td>0.024–0.041</td>
<td>0.017</td>
<td>0.011–0.026</td>
</tr>
<tr>
<td>(T_{\text{off}})</td>
<td>days</td>
<td>6.5</td>
<td>6.4–6.6</td>
<td>6.5</td>
<td>6.4–6.6</td>
</tr>
</tbody>
</table>

*Previous estimates of proliferation rates were used: 1.92 day\(^{-1}\) for NP396, 1.89 day\(^{-1}\) for GP33 and GP34, and 1.87 day\(^{-1}\) for GP276 (13). The death rate of effector/memory cells is \(\delta_0 = 0\). The initial numbers of activated cells, \(A_0\), are the same as for acute LCMV infection and given in Table I.

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**FIGURE 2.** A and B. Estimated death rates of activated cells, \(\delta_4\) (A), and estimates of the rate, \(r\), at which effector/memory cells are formed for CD8\(^+\) T cell responses during acute and chronic LCMV infection (B). Error bars represent 95% CI of parameter estimates. The rates are largely increased for responses during chronic infection except for the specific response against GP33.
data from Homann et al. (25), which resulted in very accurate fits. In Fig. 4, A and B, the data are shown together with the previously estimated dynamics depicted by the solid line. For both responses, the data are described well around the peak, whereas it drops below the previous estimate after 30 days p.i. We also compared responses during chronic infection. NP396- and GP276-specific CD8\(^+\)/H11001 T cell responses as measured in Miller et al. (14) are shown together with the prediction of the model fitted to data by Wherry et al. (4) (Fig. 4, C and D). In this study, the estimated dynamics are far below the data of CD8\(^+\)/H11001 T cell responses from the other laboratory. This comparison raises the question why T cell measurements using the same experimental protocol lead to different results. On the one hand, it is important to note that the T cell measurements in Homann et al. (25) were done using intracellular cytokine staining, whereas the other studies used MHC tetramer technology. However, a previous study using both techniques to count Ag-specific CD8\(^+\) T cells shows more consistent measurements (3). In contrast, it is likely that the total numbers of T cells that are measured depend on certain experimental procedures. For example, the preparation of a single-cell suspension of splenocytes is done by squeezing the spleen through a mesh. In this study, some laboratories use stainless steel, whereas others use meshes made of plastic. To account for problems with eliminating total cell numbers, we introduce a scaling factor where the prediction of cell numbers from one laboratory are given relative to the estimated cell numbers from another laboratory.

FIGURE 3. A–F, Comparison of CD8\(^+\) T cell responses during chronic LCMV infection (clone 13) in SThx (A–C) and Thx (D–F) mice. Each data point represents one mouse as measured by Miller et al. (14). Statistical analysis using Student’s t test and linear regression (dashed line) showed no significant change in T cell numbers after day 30 p.i. for Thx mice and therefore no evidence for a rebound. The solid lines represent the best fit of the model to the data for each epitope. \(r\) and \(\delta_A\) are restricted to be the same in SThx and Thx mice, \(\delta_A = 0\) and \(T_{off} = 5.6\) days. The difference in Thx mice can be explained by a reduced number of naive precursor cells (62%) compared with SThx mice. Other parameters are given in Table III.

Table III. Parameter estimates obtained by fitting the model to the data on CD8\(^+\) T cell responses against three epitopes in SThx mice and Thx mice during chronic LCMV infection (clone 13)

<table>
<thead>
<tr>
<th>Name</th>
<th>Units</th>
<th>Value</th>
<th>95% CI</th>
<th>Value</th>
<th>95% CI</th>
<th>Value</th>
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<tr>
<td>(\delta_A)</td>
<td>day(^{-1})</td>
<td>0.23</td>
<td>0.15–0.35</td>
<td>0.19</td>
<td>0.11–0.31</td>
<td>0.072</td>
<td>0.026–0.215</td>
</tr>
<tr>
<td>(r)</td>
<td>day(^{-1})</td>
<td>0.017</td>
<td>0.012–0.026</td>
<td>0.024</td>
<td>0.015–0.035</td>
<td>0.035</td>
<td>0.010–0.080</td>
</tr>
<tr>
<td>(T_{off})</td>
<td>days</td>
<td>5.6</td>
<td>5.4–5.8</td>
<td>5.6</td>
<td>5.4–5.8</td>
<td>5.6</td>
<td>5.4–5.8</td>
</tr>
<tr>
<td>(A_0) in SThx</td>
<td>Cells</td>
<td>42.8</td>
<td>28.4–58.9</td>
<td>95.5</td>
<td>62.3–136.9</td>
<td>46.0</td>
<td>30.0–65.0</td>
</tr>
<tr>
<td>(\alpha)</td>
<td></td>
<td>0.62</td>
<td>0.54–0.72</td>
<td>0.62</td>
<td>0.54–0.72</td>
<td>0.62</td>
<td>0.54–0.72</td>
</tr>
</tbody>
</table>

*The death rate of effector/memory cells, \(\delta_A\), is zero. The number of naive precursor cells in Thx mice are 62% of that in SThx mice. The fraction is given as \(\alpha\).*
there are still kinetic differences in the data between laboratories as can be seen at 15 days p.i. in Fig. 4, E and F, and at days 15 and 80 p.i. in Fig. 4H. Together, this comparison shows distinct differences between measurements of CD8⁺ T cell responses from different laboratories.

**Discussion**

Our analysis of CD8⁺ T cell responses allowed us to get new insights into their dynamics. The parameter that differs between Ag-specific responses is the apoptosis rate $\delta_A$. For responses during chronic infection, also the effector/memory formation rate, $r$, varies. Comparing acute to chronic infection, we observed that the time of the peak of the response, $T_{\text{off}}$, is different. All other parameters are the same. Zajac et al. (5) already observed that immunodominance changes during chronic LCMV infection. We can now further discriminate the CD8⁺ T cell responses between acute and chronic LCMV infection. The four studied responses during chronic infection generally show an earlier peak and a faster contraction of the response. In our model, at the time of the peak of the response, cells stop to proliferate. Virus replication and dynamics could affect this process. Although LCMV Armstrong and clone 13 differ by only 2 aa (26, 27), virus replication differs dramatically for chronic infection compared with acute infection. Between days 5 and 8 p.i., acute LCMV infection shows a decrease in serum viral load compared with chronic LCMV infection where virus load is increasing (Fig. 5) (data from Wherry et al. (4)). Ongoing expansion of CD8⁺ T cells may cause immunopathology when the virus is not cleared. Therefore, the CD8⁺ T cell proliferation might be stopped to reduce acute symptoms (28).

In Results, we assumed the expansion rates to be the same for an epitope-specific CD8⁺ T cell response during acute and chronic LCMV infection. We also wanted to test two alternative hypotheses for the different dynamics during proliferation. First, we fitted the model to the data with a free expansion rate for CD8⁺ T cell responses during chronic infection but a restricted $T_{\text{off}}$ and $A_0$ for responses during acute and chronic infection. Second, CD8⁺ T cells might start to proliferate earlier in one type of infection, i.e., the recruitment time could be different. As mentioned in Materials and Methods, in our model, the recruitment time is at $t = 0$ and lumped together with the precursor frequency $A_0$. We can also
be influenced by the levels of secreted IL-10. Another recent study recently shown that the cytokine IL-10 is involved in the immune responses to all epitopes during acute infection is in line with our findings that naive T cell numbers in Thx young mice are reduced by ~50% (I. den Barber, manuscript in preparation). To test our prediction, one could also perform experiments infecting Thx mice with LCMV Armstrong to see whether cell numbers around the peak of the CD8^+ T cell response are lower compared with SThx mice. An alternative explanation for the difference in the CD8^+ T cell responses is the lack of continued thymic output of naive T cells in Thx mice. It has indeed been shown that there is continuous recruitment of naive T cells during persistent polyoma virus infection (32). Our model can also allow for the lower cell numbers in Thx mice by a difference in the net death rate of activated cells, δα (results not shown). A decrease in a net death rate can be interpreted as missing recruitment of naive cells into the activated T cell pool of Thx mice.

Because the analyzed data are derived by infecting mice of the same strain with LCMV, it is interesting to compare the different studies. We show that the data sets from different laboratories are kinetically and quantitatively different. Comparing the T cell measurements of a recent study by Grayson et al. (31) by digitizing their published data also shows large differences to the data sets we used for our analysis (results not shown). Upon introducing a scaling factor between laboratories to account for differences in the total number of cells, the data sets become more consistent. However, there are still kinetic differences. Indeed, several factors could influence the CD8^+ T cell responses in these experiments. For example, the environment where the mice are kept in laboratories might be different, and cause a distinct state of the mice immune systems. Especially SThx mice could have a more inflammatory environment due to surgery that might change the dynamics of CD8^+ T cell responses. Furthermore, the mouse age at the time of infection differs between the study by Wherry et al. (4) and that by Miller et al. (14), which might affect the number of CD8^+ T cells in the spleen. Even within a laboratory, data fluctuations are expected due to the intrinsic stochasticity of the immune response, the so-called process noise (33). Alternatively, the estimated kinetic differences could derive from the number of measurements over time. Again, several measurements around the peak of the response (i.e., between days 5 and 15 p.i.) appear to be important to precisely model the contraction phase of the response. However, some kinetic differences remain that seem to suggest different biological differences in different laboratories, e.g., different apoptosis rates (Tables I and II). Nevertheless, we would like to highlight the importance for multiple measurements around the peak to provide a better understanding of CD8^+ T cell dynamics.

Our analysis proved to be useful in discriminating the dynamics between CD8^+ T cell responses during acute and chronic LCMV infection. However, it remains to be established whether our results can be generalized for other LCMV-specific CD8^+ T cell responses not studied here. Although the analysis was done for responses that are dominant during acute or chronic infection, several other epitope-specific responses are likely to be important in clearance or control of viral replication. Indeed, a recent study by Kotturi et al. (34) identified 19 novel epitopes in LCMV that have not been investigated so far. Additional insight into the dynamics of CD8^+ T cell responses could be provided by knockout experiments of mice. The recent study by Grayson et al. (31) looks promising to get a more detailed knowledge on the influence of apoptosis during the contraction phase of the response. Further analysis in this direction can shed more light on the nature of acute and chronic infections and their accompanying cellular immune responses.

**FIGURE 5.** Serum viral load during acute and chronic LCMV infection as given in Wherry et al. (4). The dashed lines represent the estimated time of the peak of the CD8^+ T cell responses, \( T_{\text{off}} \), during chronic and acute infection, respectively. It can be seen that virus load increases between days 5 and 8 during chronic infection (X) but decreases during acute infection (O).
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Disclosures
The authors have no financial conflict of interest.

References