ELECTRONIC APPENDIX

This is the Electronic Appendix to the article

Pathology during acute infections: contributions of intracellular pathogens and the CTL response

by

Vitaly V. Ganusov and Rustom Antia

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Appendix

Efficacy of the immune response

The observation that pathology during acute infection depends on the product hZ_0 can be shown in the following way. We replace the variable $Z(t)$ with a new variable $Z_1(t) = hZ(t)$. We note that now the immune response affects directly the dynamics of the infected and uninfected cells only through the variable $Z_1(t)$. The equation for the dynamics of the immune response in turn remains the same, $\frac{dZ_1}{dt} = \frac{sZ_1I}{k+I}$ with the changed initial condition $Z_1(0) = hZ_0$. Therefore, the dynamics of infected and uninfected cells involved in defining pathology during acute infection (see eqn. (5) in the main text) will be determined by the immune response through parameters s, k, and the product hZ_0.

Changing properties of the pathogen and host cells

In Figure 3 we plot how pathology depends on the properties of the pathogen and target cells. These include the infection rate, β, the pathogen-induced death rate of infected cells, α, and the rate of target cell turnover, d. We find that:

1. Pathology increases with the increasing infectivity, β. This is because a higher infectivity increases the number of target cells infected and subsequently killed.

2. Pathology decreases with the increasing pathogen-induced death rate, α. This seemingly counterintuitive result occurs because while high rates of pathogen-induced death α lead to faster death of infected cells, high α also causes a decrease in the rate of spread of the infection and consequently fewer cells becoming infected and being killed. Importantly, however, this prediction may be reversed if there is a correlation between the pathogen production rate p and lysis rate α (Figure 3D). Also note that changes in pathology with increasing lysis rate α depend critically on the correlation between the production rate p and α. For example, pathology always increases for a linear correlation, decreases if there is no correlation or reaches a maximum at intermediate α for a saturating correlation.

3. Pathology decreases with the increasing rate of target cell turnover, d. This is because higher rates of cell turnover will lead to a faster replacement of killed cells and thus to lower pathology.

Pathology during an acute infection with a programmed CTL response

Recent studies suggest that the CTL response may be "programmed" early during the infection (Kaech et al., 2002). In this model, naive CD8 T cells (CTL precursors), $N(t)$, are recruited into the response depending on the pathogen density early during the infection, while CTLs, $Z(t)$, expand exponentially in a pathogen-independent manner. After a fixed time T_{off} being set independently of proliferating CTLs, proliferation is ceased and the contraction phase takes place (Antia et al., 2003). The mathematical model describing the dynamics of the pathogen is identical to eqns. (1)–(3) given in the main text, while the expansion of the CTL response is described by

$$\text{(naive cells)} \quad \frac{dN}{dt} = -\frac{\lambda_r I N}{k+I}. \tag{6}$$

$$\text{(CTL response)} \quad \frac{dZ}{dt} = \frac{\lambda_r I N}{k+I} + s(t) Z \left(1 - \frac{Z}{Z_{max}}\right), \tag{7}$$

where λ_r is the recruitment rate of naive cells into the response, $s(t) = s$ if $t < T_{off}$ and 0 otherwise, T_{off} is the time when the CTL response stops proliferating, and Z_{max} is the maximum density of CTLs allowed during the response. As shown in Figure 4, similarly to the model considered in the main text increasing the killing or activation efficacy of the CTL response generally leads to lower pathology.

References

Antia, R., Bergstrom, C. T., Pilyugin, S. S., Kaech, S. M., and Ahmed, R. 2003. Models of CD8+ responses: 1. What is the antigen-independent proliferation program. *J Theor Biol* 221:585–98.

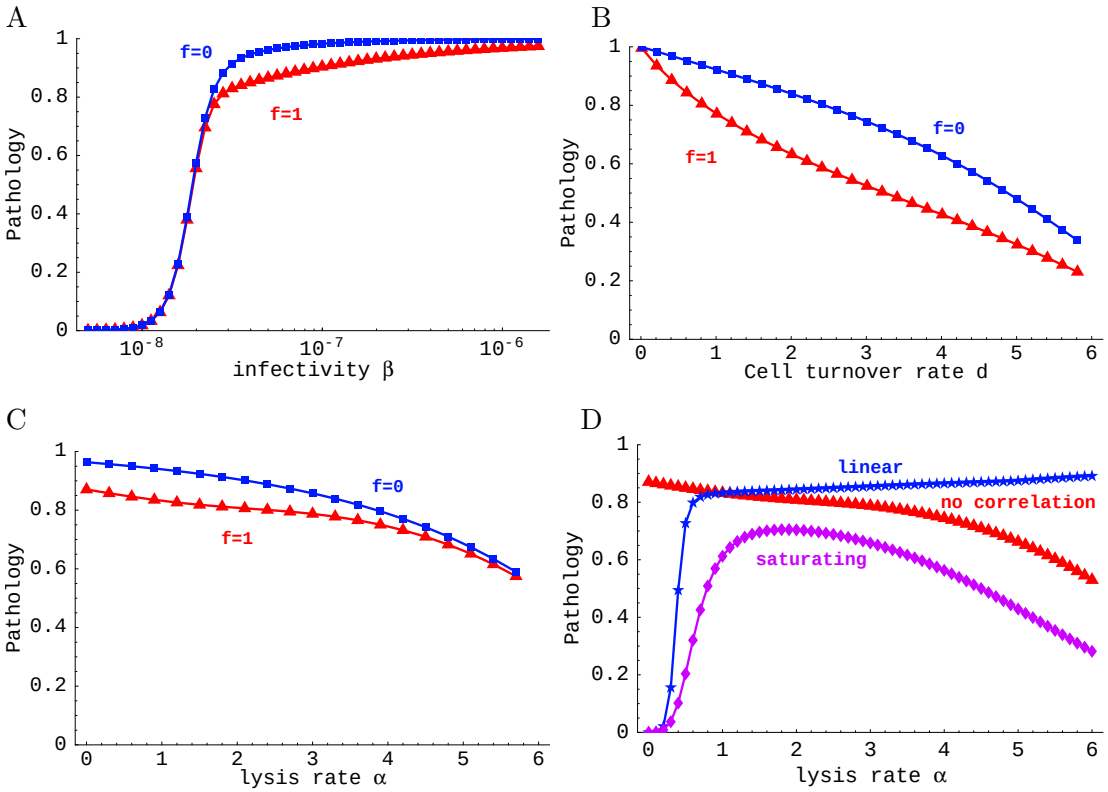

Figure 3: Pathology during acute infection at different infectivity rates β (panel A), the target cell turnover rates d (panel B) and lysis rates α (panel C and D). Pathology is shown for $f = 1$ (▲) and $f = 0$ (■). In panel D we let $f = 1$ and assume a positive correlation between the pathogen production rate p and lysis rate α including no correlation (▲, $p = 10^3$), a linear correlation (★, $p = 10^3\alpha$), and a saturating correlation (♦, $p = 10^3\alpha/(1+\alpha)$) with $f = 1$. Other parameters are $T(0) = T_0 = 10^6$, $I(0) = 0$, $V(0) = 10^3$, $Z(0) = 1$, $d = 0.5$, $\beta = 5 \cdot 10^{-8}$, $\alpha = 0.1$, $p = 10^3$, $c = 3$, $k = 10^2$, $s = 2.5$, $h = 10^{-3}$.

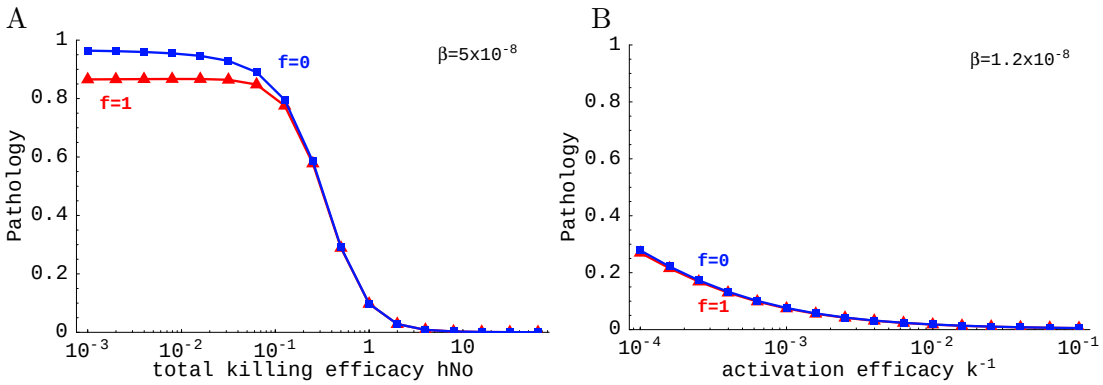

Figure 4: Pathology during acute infections when the total killing efficacy hN_0 (panel A) or activation efficacy k^{-1} (panel B) of the "programmed" CTL response is changed. Parameters are the same as in Figure 3 and $Z(0) = 0$, $N(0) = N_0 = 1$, $\beta = 5 \cdot 10^{-8}$ (panel A), $\beta = 1.2 \cdot 10^{-8}$ (panel B, for $\beta = 5 \cdot 10^{-8}$ there is almost no change in pathology with the efficacy k^{-1}), $r = 1$, $T_{off} = 10$, and $Z_{max} = 10^7$.

Kaech, S. M., Wherry, E. J., and Ahmed, R. 2002. Effector and memory T-cell differentiation: implications for vaccine development. *Nat Review Immunol* 2:251–262.