IMMUNE EVASION

Slowly does it…

A new study published in the *Journal of Virology* shows that viruses that replicate slowly invoke a weak adaptive immune response, specifically a weak cytotoxic T-lymphocyte response, which could contribute to virus persistence and chronic disease.

Two facets of the CTL response can affect virus clearance. Specific CTL clones are amplified in response to antigen stimulation — the magnitude of amplification of CTLs increases with increasing antigen concentrations. Viruses that replicate rapidly produce large amounts of antigen, which can overwhelm the specific CTL response. This physical deletion of CTLs — known as exhaustion — results in virus persistence.

Using lymphocytic choriomeningitis virus (LCMV) infection of mice as a model, the amplification of CTLs in response to LCMV strains that have different replication rates was assessed. A bell-shaped response was found: both slow and fast replicating virus strains produced weaker $CD8^+$ T-cell responses compared with a strain that had an intermediate replication rate.

What about hepatitis C virus, which replicates more slowly than LCMV? Available data sets were analysed, and slower virus replication correlated with virus persistence. For hepatitis B virus, one well-documented study of virus kinetics and CTL response has been analysed. A predator–prey model was constructed by Bocharov *et al.* — with the CTLs as predators, and the virus as prey — and calibrated using this available HBV data set.

The model was used to predict the effect of changes in virus replication kinetics on the CTL response. Reducing the virus replication rate led to a weaker CTL response, which could result in virus persistence. Certain individuals — 'high-responders' — have a more efficient CTL response, presumably through genetic variation. Even with a simulated high-responder, a slowly replicating virus strain elicited only a weak and transient CTL response. This model predicts that the transition from acute to chronic HBV infection could result from a decrease in the replication rate of the virus.

The mathematical model used is reductionist and cannot take into account every aspect of the complex interactions between the virus and the immune system. However, models are useful for predicting and planning experimental work, and this modelling approach could be implemented for other important viruses, such as HIV or cytomegalovirus. This report clearly indicates that the kinetics of virus replication could be important for the outcome of the infection. Slow viruses could sneak past immune surveillance and establish persistence, and therapies that downregulate virus replication could also result in virus persistence and chronic disease.

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References and links

ORIGINAL RESEARCH PAPER Bocharov, G. *et al.* Underwhelming the immune response: effect of slow virus growth on $CD8^+$-T-lymphocyte responses. *J. Virol.* **78**, 2247–2254 (2004)