Early Stochastic Dynamics in Human Cytomegalovirus Infection

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While the dynamics of virus infections have been studied extensively in a variety of settings, the very early dynamics during the establishment phase of an infection remain understudied. A recent paper (1) investigated the early dynamics of cytomegalovirus (CMV) infection in a cohort of highly exposed infants. They found that in a relatively large fraction of newly infected individuals, the infection was transient and self-limiting but that in a few cases, the infection was a fully fledged primary infection. This was explained with stochastic mathematical models of the early infection process. The models could account for the data if the basic reproductive ratio of the virus (R_0) was close to the extinction threshold of 1 and if the infection was initiated from one or a very few infected founder cells. This explanation is based on the stochastic nature of the dynamics at low population levels, where stochastic extinction is a likely event.

The dynamics underlying this observation, however, might be more complex. We recently examined the very early spread of a modified adenovirus in a two-dimensional monolayer of 293 embryonic kidney epithelial cells (2–4), starting from single infected cells. Two distinct patterns of viral spread were observed under identical conditions. About 50% of growth foci in a culture displayed a robust growth pattern, characterized by a plaque-like expansion of the infected cells. The other infection foci resulted in limited growth, characterized by a relatively slow expansion of infected cells, followed by growth cessation. Stochastic fluctuations around small numbers seemed an unlikely explanation for the limited infections, because these were not terminated early at very small population sizes but rather after a period of sustained, albeit slow, growth. Using mathematical models (4), we found that two simultaneously stable outcomes can be observed under the following assumptions: (i) infected cells can establish an interferon (IFN)-induced antiviral state in surrounding uninfected cells, and (ii) this antiviral state can be overcome to a certain extent at higher infection multiplicities, allowing faster infection growth. Under these assumptions, the model predicted an initial race between the spread of the virus and the spread of the antiviral state to uninfected cells. If early stochastic effects push the populations toward the domain of attraction of the robust infection outcome, the virus wins the race, resulting in a fully fledged infection. Otherwise, the race is won by the IFN-induced antiviral state, leading to limited growth. In accordance with predictions, experimental inhibition of IFN responses resulted in a shift of the outcomes from approximately 50% to significantly larger percentages of robust growth (4).

Similar dynamics may provide an alternative explanation for the observations in CMV-infected infants. Type I IFNs reduce CMV replication (5–8), and CMV can overcome this to an extent (9). This mechanism would not require a value of R_0 that is close to the extinction threshold, which might not be evolutionarily robust. Interestingly, an accelerated CMV growth rate was seen at higher virus loads (10), which might be due to increased infection multiplicity, as suggested by our model. Hence, the role of innate immune responses in early CMV dynamics warrants further investigation.

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