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Quantifying the relative contribution of transmission via free virus versus cell-to-cell to the propagation of a hepatitis C virus infection in vitro

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Experiments have shown that hepatitis C virus (HCV) infections in vitro disseminate both distally via the release and diffusion of cell-free virus through the medium, and locally via direct, cell-to-cell transmission. To determine the relative contribution of each mode of infection to HCV dissemination, we developed an agent-based model that explicitly incorporates both distal and local modes of infection. The model tracks the concentration of extracellular infectious virus in the infection medium and the number of intracellular HCV RNA segments within each infected cell over the course of simulated in vitro HCV infections. The model was challenged with data from in vitro HCV infections conducted in the presence and absence of free-virus neutralizing antibodies. We found that direct, cell-to-cell infection accounts for 95% of infection events. In contrast, blocking the 5% of infections occurring via free virus results in a 60% reduction in the number of infection events at 72h post-infection. Taken together, these findings show that while HCV spread via cell-free virus contributes little to the number of infection events, it plays a critical role in speeding up cell-to-cell HCV dissemination in vitro by providing access to distant, uninfected areas, away from the already established large infection foci.

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