GENOME-WIDE RNAi SCREEN IDENTIFIES NOVEL HOST PROTEINS REQUIRED FOR ALPHAVIRUS ENTRY

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The enveloped alphaviruses include important and emerging human pathogens such as Chikungunya virus and Eastern equine encephalitis virus. Alphaviruses enter cells by clathrin-mediated endocytosis, and exit by budding from the plasma membrane. While there has been considerable progress in defining the structure and function of the viral proteins, relatively little is known about the host factors involved in alphavirus infection. We used a genome-wide siRNA screen to identify host factors that promote or inhibit alphavirus infection in human cells. Fuzzy homologue (FUZ), a protein with reported roles in planar cell polarity and cilia biogenesis, was required for the clathrin-dependent internalization of both alphaviruses and the classical endocytic ligand transferrin. The tetraspanin membrane protein TSPAN9 was critical for the efficient fusion of low pH-triggered virus with the endosome membrane. FUZ and TSPAN9 were broadly required for infection by the alphaviruses Sindbis virus, Semliki Forest virus, and Chikungunya virus, but were not required by the structurally-related flavivirus Dengue virus. Our results highlight the unanticipated functions of FUZ and TSPAN9 in distinct steps of alphavirus entry and suggest novel host proteins that may serve as targets for antiviral therapy.