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A Physical Interaction Network of Dengue Virus and Human Proteins*

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Abstract

Dengue virus (DENV), an emerging mosquito-transmitted pathogen capable of causing severe disease in humans, interacts with host cell factors to create a more favorable environment for replication. However, few interactions between DENV and human proteins have been reported to date. To identify DENV-human protein interactions, we used high-throughput yeast two-hybrid assays to screen the 10 DENV proteins against a human liver activation domain library. From 45 DNA-binding domain clones containing either full-length viral genes or partially overlapping gene fragments, we identified 139 interactions between DENV and human proteins, the vast majority of which are novel. These interactions involved 105 human proteins, including six previously implicated in DENV infection and 45 linked to the replication of other viruses. Human proteins with functions related to the complement and coagulation cascade, the centrosome, and the cytoskeleton were enriched among the DENV interaction partners. To determine if the cellular proteins were required for DENV infection, we used small interfering RNAs to inhibit their expression. Six of 12 proteins targeted (CALR, DDX3X, ERC1, GOLGA2, TRIP11, and UBE2I) caused a significant decrease in the replication of a DENV replicon. We further showed that calreticulin colocalized with viral dsRNA and with the viral NS3 and NS5 proteins in DENV-infected cells, consistent with a direct role for calreticulin in DENV replication. Human proteins that interacted with DENV had significantly higher average degree and betweenness than expected by chance, which provides additional support for the hypothesis that viruses preferentially target cellular proteins that occupy central position in the human protein interaction network. This study provides a valuable starting point for additional investigations into the roles of human proteins in DENV infection.

Footnotes

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