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Club de lecture

Genome-wide RNAi screen identifies human host factors crucial for influenza virus replication

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Abstract

Influenza A virus, being responsible for seasonal epidemics and reoccurring pandemics, represents a worldwide threat to public health. High mutation rates facilitate the generation of viral escape mutants, rendering vaccines and drugs directed against virus-encoded targets potentially ineffective. In contrast, targeting host cell determinants temporarily dispensable for the host but crucial for virus replication could prevent viral escape. Here we report the discovery of 287 human host cell genes influencing influenza A virus replication in a genome-wide RNA interference (RNAi) screen. Using an independent assay we confirmed 168 hits (59%) inhibiting either the endemic H1N1 (119 hits) or the current pandemic swine-origin (121 hits) influenza A virus strains, with an overlap of 60%. Notably, a subset of these common hits was also essential for replication of a highly pathogenic avian H5N1 strain. In-depth analyses of several factors provided insights into their infection stage relevance. Notably, SON DNA binding protein (SON) was found to be important for normal trafficking of influenza virions to late endosomes early in infection. We also show that a small molecule inhibitor of CDC-like kinase 1 (CLK1) reduces influenza virus replication by more than two orders of magnitude, an effect connected with impaired splicing of the viral M2 messenger RNA. Furthermore, influenza-virus-infected p27(-/-) (cyclin-dependent kinase inhibitor 1B; Cdkn1b) mice accumulated significantly lower viral titres in the lung, providing in vivo evidence for the importance of this gene. Thus, our results highlight the potency of genome-wide RNAi screening for the dissection of virus-host interactions and the identification of drug targets for a broad range of influenza viruses.

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