How flu succeeds: Investigators identify host factors that help multiple influenza strains thrive

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Investigators at Burnham Institute for Medical Research (Burnham), Mount Sinai School of Medicine (Mount Sinai), the Salk Institute for Biological Studies (Salk) and the Genomics Institute of the Novartis Research Foundation (GNF) have identified 295 human cell factors that influenza A strains must harness to infect a cell, including the currently circulating swine-origin H1N1. The team also identified small molecule compounds that act on several of these factors and inhibit viral replication, pointing to new ways to treat flu. These findings were published online on December 21 in the journal *Nature*.

Influenza A virus contains only enough genetic information (RNA) to produce 11 proteins and must co-opt host cellular machinery to complete its life cycle. Sumit Chanda, Ph.D., of Burnham, Megan Shaw, Ph.D., of Mount Sinai, John Young, Ph.D., of Salk, Yingyao Zhou, Ph.D., of GNF and others used RNAi screening technology to selectively turn off more than 19,000 human genes to determine which human factors facilitate viral entry, uncoating, nuclear import, viral replication and other necessary functions of the virus.

"Because influenza mutates so readily, it has become a moving target for therapeutic intervention, making it difficult to treat circulating strains, including the H1N1 swine flu," said Dr. Chanda. "As a result, there is now widespread resistance to two classes of antiviral drugs. However, by targeting more stable human host factors, we may be able to develop

therapies that prevent or treat a variety of influenza A strains and are more likely to maintain their effectiveness."

"This study has provided us with crucial knowledge of the cellular pathways and factors the influenza virus exploits to replicate" added Dr. Shaw. "Each of these represents an 'Achilles heel' of the virus and vastly increases the number of potential targets for new influenza antiviral drugs."

The team screened human A549 (lung epithelial) cells infected with a modified influenza virus against the genome-wide siRNA library. Conducting two independent screens, they confirmed that selectively impairing each of 295 cellular genes reduced viral infection, effectively illuminating the path followed by influenza viruses during the infection of a cell. Importantly, they found that inhibiting proteins in known drug target classes, such as kinases, vATPases, and tubulin, impairs influenza growth, suggesting that small molecular weight compounds may be developed as host factor-directed antivirals. Protein interactions dataset analysis confirmed 181 host cellular factors that mediate 4,266 interactions between viral or cellular proteins.

Renate Koenig, Ph.D., of Burnham and Peter Palese, Ph.D., Silke Stertz, Ph.D., and Adolfo Garcia-Sastre, Ph.D., of Mount Sinai also collaborated on this research.

"Trying to identify all the host proteins that are required for the replication of influenza viruses is a wonderful challenge and we have come closer to 'knowing' all the genes involved," said Dr. Palese.

Dr. Young added, "These findings, combined with those from other RNAi screens, provide a blueprint of the cellular processes that are exploited more generally by viruses, pointing towards development of future broad-spectrum antiviral approaches."

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