Flu's Evolution Strategy Strikes Perfect Balance

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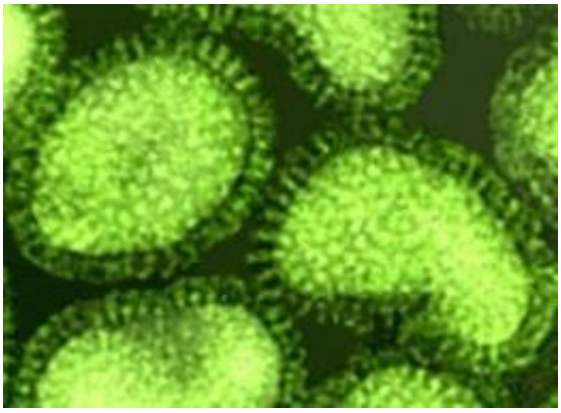

Flu virus

(PhysOrg.com) -- Scientists have uncovered the flu's secret formula for effectively evolving within and between host species: balance. The key lies with the flu's unique replication process, which has evolved to produce enough mutations for the virus to spread and adapt to its host environment, but not so many that unwanted genomic mutations lead to the flu's demise (catastrophic mutagenesis). These findings overturn long-held assumptions about how the virus evolves.

Better understanding how the flu virus replicates and evolves to infect new hosts will help scientists find new ways to fight the flu. One option is the development of therapies that take advantage of the new findings by promoting mutagenesis - treatments designed to generate increased

mutations that will ultimately kill the virus.

"These new findings give us insights into how we may be able to control viral evolution," said Baek Kim, Ph.D., professor in the department of Microbiology and Immunology at the University of Rochester Medical Center and lead study author. "This research presents an attractive strategy for tackling the flu - making the influenza virus kill itself by amplifying the number of mutations made beyond the desired level, which is lethal for the virus."

In the new study, published in the online journal PLoS One, scientists disprove the widely accepted idea that the flu virus evolves so efficiently due to its error-prone replication process. The virus requires a high number of genomic mutations to jump from one species to another, such as from a pig to a human, and up until this point scientists believed the error-prone replication process facilitated the mutations needed for the flu to spread. In reality, its replication process is not prone to errors; rather, the virus goes through multiple rounds of RNA genome replication in each viral infection cycle, allowing it to produce more than enough genomic mutations necessary for viral evolution and host adaptation.

The flu's accurate replication process also keeps the virus in check. Given the flu's multiple rounds of RNA replication per infection, too many mutations would result if the process was highly prone to error, leading to catastrophic mutagenesis.

"The perception has always been that the flu virus mutates a lot, and in order to do that it has to have an enzyme that makes a lot of mistakes, but Kim's work shows that is not the case at all," said David Topham, Ph.D., associate professor of Microbiology and Immunology at Rochester and an expert on how the body fights the flu. "There is a selection pressure, perhaps related to the flu's multiple replication

strategy, which helps certain mutations develop and avoid immunity so that the virus can spread."

Topham, Kim and John Treanor, M.D., chief of the Infectious Diseases Division of the Department of Medicine at Rochester, lead the New York Influenza Center of Excellence (NYICE), which funded the current research. NYICE is one of five centers nationwide designated by the National Institutes of Health to further our understanding of the flu virus through basic research and surveillance studies, and to facilitate the nation's preparations for a potential pandemic.

To pin down the mechanisms behind flu virus evolution, researchers conducted unique biochemical analyses comparing flu virus replication to HIV replication, which has been well characterized in past research. While both viruses require efficient mutation production to adapt and thrive in their host environments, they replicate their genetic information very differently. HIV has evolved so that the virus only has a few chances to replicate its genome per infection and generate sufficient mutations, while the flu virus has ample chances to make and accumulate genomic mutations in each viral infection cycle.

At the center of the new finding are the polymerases, or enzymes, responsible for viral replication. Because the AIDS virus only has a few opportunities to replicate its genome in each infection cycle, its polymerases are highly error prone in order to generate sufficient mutations within its limited replication window. In contrast, the flu virus polymerases are high-fidelity enzymes - they are accurate and not prone to error. Even without copious changes in genetic material, the flu's multiple replication strategy allows the virus to produce genomic mutations sufficient for viral evolution and host adaptation.

"Kim's team has developed some very important new methodology for studying the function of the flu polymerase that could easily result in the

development of new antivirals or other methods to control influenza," said Treanor. "I think this research will stimulate a lot of additional research about the flu polymerase."

Provided by University of Rochester Medical Center