New approaches to understanding influenza may uncover novel therapies

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The influenza virus' ability to mutate quickly has produced new, emerging strains that make drug discovery more critical than ever. For the first time, researchers at Seattle BioMed, along with collaborators at the University of California, San Diego School of Medicine, St. Jude Children's Research Hospital and the University of Washington, have mapped how critical molecules regulate both the induction and resolution of inflammation during flu infection. The results are published this month in the journal *Cell*.

Flu is an elusive foe

The influenza virus mutates extremely quickly, with different strains causing seasonal epidemics each year. Genetic shuffling between different viruses can increase influenza's ability to spread, causing devastating epidemics and pandemics. The 1918 flu pandemic, the first to involve the H1N1 strain, cost the lives of 50 to 100 million people, and even a typical flu season can cost as many as 50,000 lives a year.

Vaccines are a highly effective way to combat the flu, but because manufacturing and distributing vaccines takes such a long time, it is impossible for public health officials to wait until they know for certain which strain of flu will prevail in a given season. "Because of this, drugs are critically important to combat flu infections," says Alan Aderem, Ph.D., principal investigator on the research. "But at the moment, we have very few drugs at our disposal, and resistance is already beginning

to appear against our limited arsenal."

Systems biology yielding new insights

The solution for Aderem and scientist Vincent Tam, Ph.D., was to take a systems approach to better understand the interactions between the flu virus and the human host. They teamed up with Oswald Quehenberger, Ph.D., and Edward Dennis, Ph.D., of the University of California, San Diego School of Medicine to tackle this problem. Systems biology uses computational tools to integrate the study of genes, proteins and lipids. This comprehensive approach unravels the complexities and provides a holistic view of the host-pathogen interaction. This strategy, focusing on lipid components, had never before been applied to the flu infection.

There is a class of lipid mediators that act as signaling molecules to control inflammation, and have long been known to play a role in stimulating an inflammatory response. "But some of these regulatory lipids, including ones derived from the omega-3 fatty acids and known as DHA and EPA, are also involved in resolving inflammation and bringing the body back to homeostasis," observed Quehenberger and Dennis. This dual role makes lipid mediators a critical player in the interaction between the virus and the human immune system.

The research team studied 141 different lipid metabolites and incorporated them into networks comprising lipids, genes and proteins of host responses to two different strains of the flu virus, one mild and one severe. In doing so, they found that infection by the mild H3N2 strain induced a pro-inflammatory response followed by a distinct anti-inflammatory response. This represented a case of a clearly regulated inflammatory response. In contrast, infection by the severe H1N1 strain resulted in overlapping pro- and anti-inflammatory states, indicating that the virus had disturbed the normal methods of controlling inflammation.

Importantly, the study discovered that many of the results found in the mouse model were recapitulated in humans by studying nasal wash samples collected from flu-infected patients. "It is absolutely crucial to confirm the relevance of these molecules in humans if we want to look for effective therapeutics against flu," says Aderem.

Moving to new interventions

"Once an infection starts, it's too late for vaccines," says Dennis, explaining the urgent need for drugs to combat the influenza virus. Emerging strains like H5N1 and H7N9—more commonly known as bird flu—are especially dangerous, killing about 60% of the people they infect, according to data from the Centers for Disease Control and Prevention. Because drugs fight infections that are already underway, they are a critical player in keeping the multitude of flu strains under control.

A more complete understanding of how the flu virus interacts with the human immune system, including the role of lipid mediators, could reveal important new drug targets. "If we can perturb the balance between pro- and anti-inflammatory responses in flu patients, we can help them regulate their immune systems to control their infections," says Tam.

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