Researchers work to determine how H1N1 becomes pandemic

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The last century has seen two major pandemics caused by the H1N1 virus -- the Spanish Flu in 1918 and 2009's Swine Flu scare, which had thousands travelling with surgical masks and clamoring for vaccination. But scientists did not know what distinguished the Swine Flu from ordinary influenza in pigs or seasonal outbreaks in humans, giving it the power to travel extensively and infect large populations.

Until now. Prof. Nir Ben-Tal of Tel Aviv University's Department of Biochemistry and Molecular Biology and his graduate student Daphna Meroz, in collaboration with Dr. Tomer Hertz of Seattle's Fred Hutchinson Cancer Research Center, have developed a unique computational method to address this question. Published in the journal *PNAS*, the research presents a valuable tool for identifying viral mutation strategies, tracking various virus strains and developing vaccinations and anti-virals which can protect the population. It may also lead to more precisely designed vaccines to combat these viral mutations.

Their method reveals that mutations in the virus' amino acids in specific positions, such as antigenic receptor sites, may explain how the new strain successfully spread throughout the population in 2009. These alterations allowed the strain to evade both existing vaccines and the immune system's defenses.

Playing a game of cat and mouse

Viruses and our immune systems are constantly at war. A virus constantly mutates to escape notice, and our immune system strives to play catch-up — to recognize the virus and mobilize the body's defense system.

To determine the spread of the 2009 human pandemic flu, Prof. Ben-Tal and his fellow researchers analyzed the hemagglutinin protein, which controls the virus' ability to fuse to a host cell in the body and transfer the genome which contains the information needed to make more virus. Eventually, he says, our immune system is able to recognize a virus' hemagglutinin, which triggers its reaction to fight against the virus.

Using a statistical learning algorithm, the researchers compared amino acid positions in the 2009 strain of H1N1 against the common flu and the strain of H1N1 found in Swine Flu, and discovered that major sequence changes that had occurred, altering antigenic sites and severely compromising the immune system's ability to recognize and react to the virus.

"Our new computation method showed that the main differences between the pandemic strain and the common seasonal H1N1 strain are in some 10 amino acid positions," Prof. Ben-Tal and Meroz report. "That's all it takes."

Experiments conducted by Sun-Woo Yoon, Dr. Mariette F. Ducatez and, Thomas P. Fabrizio from Prof. Richard J. Webby's lab at St. Jude Children's Research Hospital in Memphis, TN, confirmed some of the theoretical predictions.

Predicting pandemic

Like its 1918 predecessor the Spanish Flu, the 2009 pandemic flu will likely go into "hibernation" — now that this particular strain has been

recognized by the immune system, its power to infect has been compromised. But we were lucky: despite the relatively low death toll of the pandemic in 2009, similar to the number of deaths attributable to common seasonal flu, we might be facing more dangerous future outbreaks of mutated H1N1 varieties.

Because of the enormous mutation rate, says Prof. Ben-Tal, viruses can spread widely and rapidly, and vaccines are fairly inefficient. In the future, a refined version of this computational method may ultimately be used to generically compare various strains of viruses. This in-depth analysis might lead to the ability to predict how a strain will morph and determine if a pandemic could strike.

This is an important step towards revealing the amino acid determinants of the emergence of flu pandemics, but there is more work to be done, the researchers say.

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