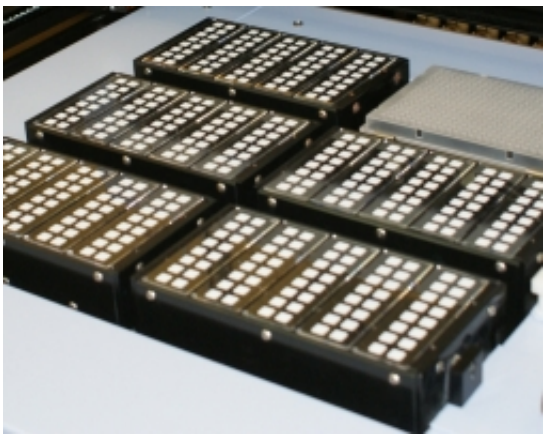
Swine flu variant linked to fatal cases might have disabled the clearing mechanism of lungs

October 22 2010



Glass slides on which carbohydrates resembling cell surface receptors have been arrayed as micro-spots.

(PhysOrg.com) -- A variant of last year's pandemic influenza linked to fatal cases carried a mutation that enabled it to infect a different subset of cells lining the airway, according to new research. The study, due to be published next week in the *Journal of Virology*, suggests that the mutant virus could have impaired the lungs' ability to clear out germs. The researchers behind the study, from Imperial College London, the Medical Research Council National Institute for Medical Research and the University of Marburg said the findings highlight the potential for deadlier strains of flu to emerge and spread.

The 2009 pandemic of H1N1 influenza caused thousands of deaths worldwide, but the majority of cases were relatively mild. A variant of the virus carried a mutation termed D222G in a protein on the surface of the virus, and people infected with this variant were more likely to have severe and fatal illness. According to a World Health Organisation report, the D222G mutation was found in less than two in every hundred cases of 2009 pandemic flu, but was responsible for around seven in every hundred deaths.

iruses infect cells by attaching to receptor molecules on the cell surface. Different receptors are present on different cell types, and a virus can only infect cells that have the right receptors for the protein on its own surface.

The new research shows that flu virus with the D222G mutation can bind to a broader range of receptors in the airway, including receptors that are present on cells called ciliated cells. These cells, found in the lining of the airway, have hair-like projections called cilia. The cilia sway back and forth to move mucus with trapped particles upward toward the mouth, and this is normally swallowed or coughed up. When ciliated cells become infected, the cilia stop moving and this vital clearance function is impaired. Inhaled viruses and bacteria can then reach the lung more easily, where they can potentially cause pneumonia.

The mutant virus has an increased capacity to infect ciliated cells, as shown by the collaborating group at the University of Marburg. Infection of the ciliated cells would sabotage the lungs' clearing mechanism and could be one factor that made the D222G mutation more virulent, the researchers suggest.

"This simple mutation, which swapped one building block of a virus protein for another, apparently resulted in a more virulent version of the H1N1 virus," said Professor Ten Feizi from the Department of Medicine

at Imperial College London, who led the study. "We think this is at least partly due to the virus being able to bind to different receptors, which allowed it to infect ciliated cells and stop them from clearing out germs.

"If the mutant virus were to acquire the ability to spread more widely, the consequences could be very serious. The study goes to show how important it is that the WHO Global Influenza Surveillance Network continues to monitor closely the emergence of new variants of the flu virus. Even though the 2009 pandemic was relatively mild, it's vital that we handle outbreaks cautiously and stay vigilant. The virus is constantly evolving, and it's possible that a new form as dangerous as the 1918 pandemic could emerge."

Professor Feizi and her team study the receptor specificity of different flu viruses by attaching onto a glass surface a range of different carbohydrates, resembling the receptors present on the surface of airway lining cells. The virus is then incubated on top of the glass surface, and using a fluorescent dye, the researchers can see the receptors on the plate to which the virus binds.

The study builds on earlier work by Professor Feizi and her colleagues which showed that compared with seasonal influenza, the 2009 pandemic virus could bind to a broader range of receptor types. The previous study showed that pandemic flu had some affinity for so-called alpha2-3 receptors, as well as the alpha2-6 receptors favoured by seasonal flu. Now they have shown that this affinity for alpha2-3 receptors is substantially enhanced in cases of pandemic flu with the D222G mutation. Whereas alpha2-6 receptors are found in the nose, throat and upper airway, alpha2-3 receptors are prevalent in the lung but also on ciliated cells throughout the respiratory system.

More information: Journal reference: Y. Liu et al. "Altered receptor specificity and cell tropism of D222G haemagglutinin mutants from

fatal cases of pandemic A(H1N1) 2009 influenza." *Journal of Virology*, November 2010, Volume 84, Issue 22.
jvi.asm.org/cgi/content/abstract/JVI.01639-10v1

Provided by Imperial College London