'Immune Camouflage' may explain H7N9 influenza vaccine failure

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The avian influenza A (H7N9) virus has been a major concern since the first outbreak in China in 2013. Due to its high rate of lethality and pandemic potential, H7N9 vaccine development has become a priority for public health officials. However, candidate vaccines have failed to elicit the strong immune responses necessary to protect from infection. A study published in Human Vaccines & Immunotherapeutics has revealed that it may be due to immune camouflage.

One of the ways by which the immune system detects infection is by presenting short peptides derived from the pathogen to T-cells, which distinguish between foreign and self antigens. The study shows that the H7N9 hemagglutinin (HA) surface protein has evolved a set of mutations that make it similar to human proteins, and the presented peptides thus resemble self antigens. The H7N9 influenza strain appears to effectively camouflage itself from the immune system.

The immune-camouflage hypothesis was tested by challenging peripheral blood mononuclear cells from naïve donors with H7N9-derived peptides. Remarkably, the more the peptide resembled a self antigen, the less it was able to elicit a T-cell response. In addition, the predicted human-like antigens expanded and activated regulatory T-cells that are responsible for immune suppression when endogenous peptides are presented, providing further support for the hypothesis.

"It appears that this new mechanism of immune escape may be common to quite a few human pathogens," says Prof. De Groot. "We are working

on validating several other peptides, some from common seasonal strains of influenza and some from pathogens like HIV and M. tuberculosis that do live for a long time inside their hosts."

H7N9 influenza has infected almost 670 people and led to 230 deaths, according to the U.S. Centers for Disease Control and Prevention. These findings could facilitate the development of an effective vaccine and impact vaccine research in general. "It could well explain why some candidate vaccines for pathogens that have co-evolved with human beings – like TB and HIV – do not work so well. It also suggests that 'tweaking' pathogen proteins to remove those camouflaging sequences would result in better, more effective vaccines," concludes Prof. De Groot.

"The original observation of low H7N9 T-cell epitope content was made before any data were available on vaccine efficacy," says senior author Prof. Anne S. De Groot, Director of the Institute for Immunology and Informatics at the University of Rhode Island and CEO at EpiVax, Inc. "It turns out that we were absolutely correct. By comparison with H1N1 and H3N1, H7N9 vaccines are far less immunogenic."

Prof. De Groot's research team has developed a computational tool, JanusMatrix, capable of determining whether a given viral protein is similar to any human protein in residues relevant for antigen presentation.

"JanusMatrix looks at both 'faces' of T-cell epitopes. It starts by looking at the face that binds to HLA or MHC – the downward facing amino acids that bind into the MHC binding pockets. Having determined that a peptide can bind to a specific MHC, the program then looks at the T-cell receptor face (TCR face) and looks in a database of pre-parsed peptides from the human genome that have been identified as binding to the same MHC, for peptides that have the same TCR-facing amino acids."

It turns out that, in addition to having low T-cell epitope content, HA from H7N9, but not from other investigated influenza strains, shows high similarity to several endogenous proteins.

More information: "H7N9 T-cell epitopes that mimic human sequences are less immunogenic and may induce Treg-mediated tolerance." *Hum Vaccin Immunother* 2015; 11(9):2241-52. DOI: 10.1080/21645515.2015.1052197

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