Quick test can predict immune responses to flu shots

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Researchers at the Emory Vaccine Center have developed a method for predicting whether someone will produce high levels of antibodies against a flu shot a few days after vaccination.

After scanning the extent to which carefully selected genes are turned on in white blood cells, the researchers can predict on day three, with up to 90 percent accuracy, who will make high levels of antibodies against a standard flu shot four weeks later.

The results were published online July 10 in the journal *Nature Immunology*.

"It often takes several weeks after vaccination for an individual to develop sufficient levels of protective antibodies against the influenza virus," says senior author Bali Pulendran, PhD, professor of pathology and laboratory medicine at Emory University School of Medicine and Yerkes National Primate Research Center. "The ability to predict who will meet these criteria within a few days after vaccination and identify non-responders would be of great value from a public health perspective."

He adds: "We envision that these predictive signatures could guide the rapid development of vaccines against emerging infections, and aid in the monitoring of suboptimal immune responses in the elderly, infants or people with weakened immune systems."

The first author of the paper is postdoctoral fellow Helder Nakaya. Emory co-authors included Jens Wrammert, PhD, assistant professor of microbiology and immunology and Rafi Ahmed, PhD, director of the Emory Vaccine Center and a Georgia Research Alliance Eminent Scholar. Collaborators included Eva Lee at the Georgia Institute of Technology and investigators at Duke University, Dana Farber Cancer Institute, Institute for Systems Biology and the National Institute of Allergy and Infectious Diseases.

The researchers took a systems biology approach involving immunology, genomics and bioinformatics. Pulendran and his colleagues pioneered this approach studying the yellow fever vaccine, and wanted to extend it to more vaccines, especially those such as flu, against which many people have some preexisting immunity.

Their predictive model is based on a series of clinical studies during the annual flu seasons in 2007, 2008 and 2009. Healthy young adults were vaccinated with a standard flu shot (trivalent inactive vaccine). Others were given live attenuated vaccine nasally.

The researchers comprehensively surveyed the activity levels of all human genes in blood samples from the volunteers. This approach revealed that the activity of many genes involved in innate immunity, interferon and reactive oxygen species signaling were changing after flu vaccination. The team also identified genes in the "unfolded protein response," necessary for cells to adapt to the stress of producing high levels of antibodies.

The gene activity data of subjects from one flu season was then used to "train" a computer model in identifying small groups of genes that can predict high and low responders. Later, the researchers examined whether the model could forecast who would be high or low responders in two other flu seasons.

"The main goal of our study was to demonstrate the feasibility of predicting how strongly a vaccine will stimulate the immune system," Pulendran says. "Along the way, we have developed an assay that focuses on a handful of genes, which could be the basis for a customized vaccine chip to make these predictions cost-effectively."

The researchers want to examine whether the signatures that predict immune responses to flu can predict responses to other vaccines. Encouragingly, a subset of the genes identified in the seasonal flu study were also predictors of the antibody response to vaccination against yellow fever.

The team's comprehensive systems biology approach meant that they were able to discover new functions for genes, even if scientists previously did not suspect their involvement in antibody responses. One example is a gene called CAMK4, well-studied in the brain. Volunteers with stronger antibody responses showed lower CAMK4 gene activity. In collaboration with researchers at Duke University, the Emory team found that mice lacking the CAMK4 gene produced stronger antibody responses to flu vaccines than normal mice. The finding opened up a new avenue of investigation in Pulendran's laboratory, examining how CAMK4 regulates antibody production.

More information: H. Nakaya et al. Systems biology of seasonal influenza vaccination in humans. *Nature Immunol.* (2011).

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