Medical Xpress

Researchers probe why vaccine responses differ from person to person

November 2 2022, by Isabella Backman

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COVID-19 vaccines boast efficacy rates against severe disease and hospitalization as high as 95%. But even among young, healthy adults, this doesn't mean individuals who received the groundbreaking jab acquired equal protection. Why people respond differently to the same immunological exposure is a question that has long evaded scientists.

A team of researchers led by Yale School of Medicine's Steven Kleinstein, Ph.D., Anthony N. Brady Professor of Pathology, is striving to understand why some people's immune systems generate a robust protective response post-vaccination, while others' fail and how this differs across vaccines. Through analysis of systems-level immune profiling data, the team's goal is to create predictive models to better understand why some individuals respond better, and whether the biological mechanisms underlying improved responses are shared between different vaccines. Their work is a part of the Human Immunology Project Consortium (HIPC), a set of national centers studying the range of responses to different infections and vaccinations.

"This is the first time that a number of factors—the diversity of different human vaccine responses, the target pathogen, vaccine type and adjuvant—have been studied as a unit to look for differences and commonalities across such a large number of vaccines," says Kleinstein.

To learn more about an individual's response to a vaccine, researchers can study various signatures—sets of genes, proteins, metabolites, or other biomarkers—associated with antibody response. Previous studies on individual vaccines, such as flu shots, have revealed that specific blood signatures in individuals prior to vaccination are predictive of their antibody responses. However, scientists have not known whether there are any universal signatures shared across vaccines.

Furthermore, researchers can study the immunological changes that happen in individuals in the days following a vaccination. They have been able to predict antibody responses in smaller studies of individual vaccines, but there would be great advantage to knowing if they can tap into a common vaccine mechanism.

Searching for universal signatures

Kleinstein's team wanted to conduct a meta-analysis to see if there are universal gene expression signatures pre- and post-vaccination that were predictive of vaccine responses. But first, they needed to gather a critical mass of data on immune responses across many different vaccines. HIPC members conducted some of those studies, while other data were available in the public domain. The team compiled all the studies and normalized their data so they could be analyzed as a unit. Through partnering with ImmPort, an immune portal funded by the National Institutes of Health (NIH), the NIH's National Institute of Allergy and Infectious Diseases, and its Division of Allergy, Immunology, and Transplantation for making data available to the public, they created a standardized data resource that is accessible to the wider scientific community.

"This is a resource that's available to everyone to enable learning more about vaccines," says Joann Arce, Ph.D., instructor in pediatrics at Harvard Medical School and the lead of data management and analysis core at Precision Vaccines Program at Boston Children's Hospital, and co-first author of an HIPC study published in *Scientific Data*.

"This is a very powerful resource for the community," adds Kleinstein.

After building their data resource, they sought to determine whether there are immunological states prior to vaccination that can predict a stronger response to vaccines. They found that individuals could be classified into three groups that were significantly associated with immune response across 13 vaccines—a high inflammatory group, a low inflammatory group, and a mid-inflammatory group. Counterintuitively, the group that pre-vaccination expressed genes responsible for the highest levels of inflammation had the strongest antibody response.

"We were surprised because inflammation is usually depicted as something that is bad," says Slim Fourati, Ph.D., bioinformatic research

associate at Emory University first author of an HIPC study in *Nature Immunology*. "Usually people undergo therapies to try and reduce their inflammation." This discovery prompted the team to apply single-cell analyses to uncover the two subsets of immune cells—classical monocytes and dendritic cells—that are likely behind this inflammatory signature.

Next, the team looked for signatures that arose post-vaccination that might predict antibody response. They did not find an obvious universal signature. "You can't take any vaccine, look at the same time point after vaccination, take a blood sample, measure something about it, and expect that you're going to be able to predict antibody response across a large number of vaccines," says Kleinstein. "The kinetics [rates of biochemical reaction] of vaccine responses were quite distinct across the 13 vaccines we studied."

Timing adjustment advances the process

However, after adjusting for timing differences among the vaccines, the researchers did identify a common biology that was predictive of antibody responses. "We created what we call a time-adjusted signature," says Kleinstein. "If you look at the biology and vaccine responses, for example the flu vaccine at day seven, but the yellow fever vaccine at day 14 or 21, then you see the same association with antibody responses."

"The difference in kinetics didn't fall neatly along any kind of lines we expected," adds Thomas Hagan, Ph.D., assistant professor in the University of Cincinnati department of pediatrics and first author of a second HIPC study in *Nature Immunology*. "For example, whether the vaccine was against a bacterium or a virus didn't seem to necessarily determine these kinetic differences. It's a much more complicated problem than we thought."

The mechanism of the yellow fever vaccine was especially of interest to the group. It induced an antiviral response significantly later than what was expected based on the other vaccines.

Prior studies have looked at pre- and post-vaccination signatures of individual vaccines in smaller cohorts, and the team wanted to be able to compare the results of this previous work. So finally, the team curated existing publications in the literature and made these signatures available in a machine-readable format. "We essentially created a database of published signatures that allows us to very easily write analysis codes to compare them and see how they behave," says Kleinstein.

"The database will enable researchers to access carefully curated information about a large number of immune signatures, all from one place," says Aris Floratos, Ph.D., assistant professor of systems biology and biomedical informatics at Columbia University Medical Center and co-senior author of another HIPC study. "By aggregating and standardizing immune signatures from a large number of publications, and by providing a user-friendly interface to interrogate this information, we hope to provide the community with a valuable resource to support research in human immune responses."

Improving vaccine science

The team hopes that its work will allow scientists to improve vaccine response across all individuals. Better understanding of how various pre-vaccine immune states impact antibody responses opens the possibility of modulating these states in more vulnerable individuals. For example, scientists may give patients predicted to have a weaker immune response an adjuvant with the vaccine to trigger the inflammatory genes associated with greater protection.

They also believe that their work will help enable improved, more

efficient clinical trials for the development of new vaccines. With improved knowledge of common signatures of antibody responses post-vaccination, clinical trials on upcoming vaccines will be able to work more efficiently and cheaply.

More information: Joann Diray-Arce et al, The Immune Signatures data resource, a compendium of systems vaccinology datasets, *Scientific Data* (2022). DOI: 10.1038/s41597-022-01714-7

Slim Fourati et al, Pan-vaccine analysis reveals innate immune endotypes predictive of antibody responses to vaccination, *Nature Immunology* (2022). DOI: 10.1038/s41590-022-01329-5

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Provided by Yale University