Decoding the human immune system

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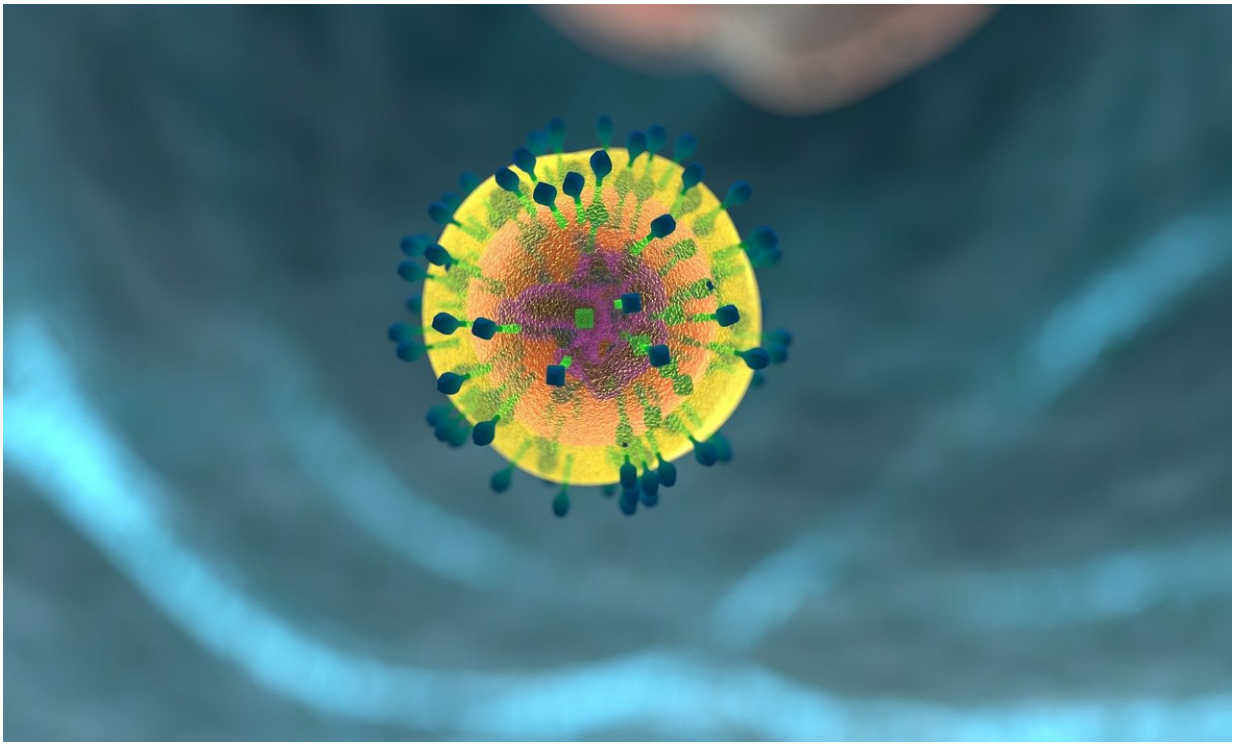

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For the first time ever, researchers are comprehensively sequencing the human immune system, which is billions of times larger than the human genome. In a new study published in *Nature* from the Human Vaccines Project, scientists have sequenced a key part of this vast and mysterious system—the genes encoding the circulating B cell receptor repertoire.

Sequencing these receptors in both adults and infants, the scientists found surprising overlaps that could provide potential new antibody targets for vaccines and therapeutics that work across populations. As part of a large multi-year initiative, this work seeks to define the genetic underpinnings of people's ability to respond and adapt to an immense range of disease.

Led by scientists at Vanderbilt University Medical Center and the San Diego Supercomputer Center, this advancement is possible due to the merging of biological research with high-powered frontier supercomputing. While the Human Genome Project sequenced the human genome and led to the development of novel genomics tools, it did not tackle the size and complexity of the human immune system.

"A continuing challenge in the human immunology and vaccine development fields has been that we do not have comprehensive reference data for what the normal healthy human immune system looks like," says James E. Crowe, Jr., MD, Director of the Vanderbilt Vaccine Center of Vanderbilt University Medical Center, senior author on the new paper, which was published online in *Nature* on Feb. 13. "Prior to the current era, people assumed it would be impossible to do such a project because the immune system is theoretically so large, but this new paper shows it is possible to define a large portion, because the size of each person's B cell receptor repertoire is unexpectedly small."

The new study specifically looks at one part of the adaptive immune system, the circulating B cell receptors that are responsible for the production of antibodies that are considered the main determinant of immunity in people. The receptors randomly select and join gene segments, forming unique sequences of nucleotides known as receptor "clonotypes." In this way, a small number of genes can lead to an incredible diversity of receptors, allowing the immune system to recognize almost any new pathogen.

Conducting leukapheresis on three individual adults, the researchers cloned and sequenced up to 40 billion cells to sequence the combinations of gene segments that comprise the circulating B cell receptors—achieving a depth of sequencing never before done. They also sequenced umbilical cord blood from three infants. The idea was to collect a vast amount of data on a few individuals, rather than the traditional model of collecting only a few points of data on many.

"The overlap in antibody sequences between individuals was unexpectedly high," Crowe explains, "even showing some identical antibody sequences between adults and babies at the time of birth." Understanding this commonality is key to identifying antibodies that can be targets for vaccines and treatments that work more universally across populations.

A central question was whether the shared sequences across individuals were the result of chance, rather than the result of some shared common biological or environmental factor. To address this issue, the researchers developed a synthetic B cell receptor repertoire and found that "the overlap observed experimentally was significantly greater than what would be expected by chance," says Robert Sinkovits, Ph.D., of the San Diego Supercomputer Center at the University of California, San Diego.

As part of a unique consortium created by the Human Vaccines Project, the San Diego Supercomputer Center applied its considerable computing power to working with the multiple terabytes of data. A central tenet of the Project is the merger of biomedicine and advanced computing. "The Human Vaccines Project allows us to study problems at a larger scale than would be normally possible in a single lab and it also brings together groups that might not normally collaborate," Sinkovits says.

Continued collaborative work is now under way to expand this study, including: sequencing other areas of the adaptive immune system, the T

cell repertoire; adding additional demographics such as supercentenarians and international populations; and applying AI-driven algorithms to further mine the datasets for insights. The goal is to continue to interrogate the shared components of the immune system to develop safer and highly targeted vaccines and immunotherapies that work across populations.

"Due to recent technological advances, we now have an unprecedented opportunity to harness the power of the human immune system to fundamentally transform human health," says Wayne Koff, Ph.D., CEO of the Human Vaccines Project. "Decoding the human immune system is central to tackling the global challenges of infectious and non-communicable diseases, from cancer to Alzheimer's to pandemic influenza. This study marks a key step toward understanding how the human immune system works, setting the stage for developing next-generation health products through the convergence of genomics and immune monitoring technologies with machine learning and artificial intelligence."

The new paper, "High frequency of shared clonotypes in human B cell receptor repertoires," was published online in *Nature* on Feb. 13, 2019, and will appear in the Feb. 21, 2019, print issue.

More information: High frequency of shared clonotypes in human B cell receptor repertoires, *Nature* (2019). DOI: 10.1038/s41586-019-0934-8 , www.nature.com/articles/s41586-019-0934-8

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