First detailed map of the body's antibody production could suggest new treatment options for immune disorders

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Stanford researchers led by Professor Stephen Quake have completed the first detailed map of how the human body produces defensive antibodies. Credit: Tricia Seibold

When viruses and bacteria invade the body, the immune system fights back. Defenders called B-cells swarm into affected areas, unleashing antibody molecules that seek to destroy the invaders. This antibody army features a number of specialist classes: Some antibodies envelop invading pathogens or block them from entering healthy cells, while other antibodies create inflammation that can speed the healing process.

Now, for the first time, Stanford researchers have mapped out how the human body creates antibodies of every class, revealing that a diverse set of antibody-producing cells springs from the same kind of ancestor.

"How do we make all the players that protect us?" asked Felix Horns, a biophysics graduate student and first author of a paper published in the journal *eLife*. "What we've done is measure that."

The eight-person research team was led by Horns' adviser, Stanford bioengineering Professor Stephen Quake, who believes that creating a comprehensive overview of the body's natural defense system will enable researchers to develop novel treatments for a variety of immune disorders.

"This map will help us understand what goes awry in immune disease," said Quake, who is also a professor of applied physics and a Howard Hughes Medical Institute investigator. "As a result, we may be able to crack problems like allergies."

Building a family tree of B-cells

To assemble their map, the researchers extracted the B-cells from blood samples from 22 young, healthy adults. Using a high-throughput genetic sequencing machine, which reads out the individual nucleotides that make up a cell's genetic code, they created a large library of antibody-producing genes from all the B-cells in the sample.

They traced the lineage of B-cells by counting the number of acquired mutations in the cells' genes, finding that cells in later generations had more genetic mutations. The researchers also looked for evidence that the B-cells had switched the types of antibody they produced. This switching process allows the immune system to customize its response to incoming threats.

"Each B-cell starts out as a single cell that makes a certain type of antibody," Horns said. "If it protects you, it expands and creates descendants."

Using a variety of analytical techniques, the researchers were able to identify the various classes of antibodies and approximate their prevalence.

About three-quarters of the cells the team analyzed were programmed to create the IgM antibody class. IgM is "the default class in which all antibodies are born," Horns said. "When activated by immune challenge, they undergo class switching."

A large proportion of IgM cells switch to producing the IgG antibody class, the body's most important virus fighters. These cells can give rise to four different IgG sub-classes that have specific anti-viral properties.

A lesser fraction of IgM-producing cells go on to create IgA antibodies, which fend off invading bacteria and also help "good" bacteria in the digestive tract stay in a healthy balance.

The smallest number of IgM cells switch to producing the IgE antibody class, which triggers inflammation in the body and can create an allergic response if it becomes too active.

Switching cells to fight disease

Horns' insights into the class-switching process could lead to a range of new treatment approaches for immune disorders. In rare conditions such as hyper IgM syndrome, patients' cells lack the ability to switch antibody classes, leaving them vulnerable to a wide variety of infections. More common immune conditions may also result from class-switching defects. People with allergies, for instance, produce allergen-specific IgE antibodies, resulting in an overactive immune response.

A few doctors have tried methods like "helminthic therapy," which involves infecting patients with parasitic worms that tweak the body's antibody production. Horns envisions a more precise solution: designing drugs to mimic the signaling molecules that control the antibody class-switching process.

"You can think about the worm as a very blunt instrument," he said, "whereas you can imagine using a designer drug as a scalpel."

As a next step, Horns plans to sequence the genes of people who suffer from immune disorders. Finding out how their antibody production differs from his baseline map would be a key step toward creating drug therapies that would restore an optimal antibody balance.

"Suppose we found someone who cannot make a certain type of antibody or makes it at a low rate," Horns said. "We can convince [their] B-cells to switch to particular classes to fix the deficiency."

More information: "Lineage Tracing of Human B Cells Reveals the In Vivo Landscape of Human Antibody Class Switching." *eLife*, 2016.

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