Flexible targets help immune system make finely-tuned antibodies

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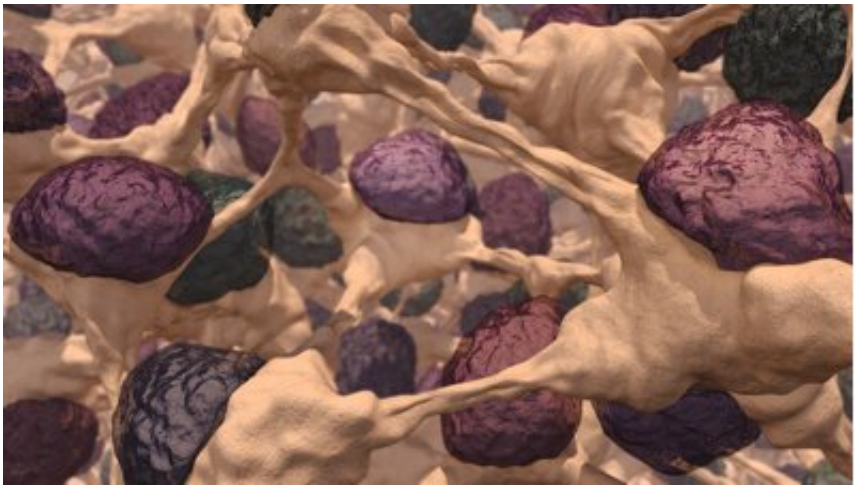

Cellular illustration of the germinal centre (beige), where B cells (purple and blue) multiply and mutate to fine-tune their antibody production. Image credit: Dr Ofir Shein-Lumbroso Credit: Dr Ofir Shein-Lumbroso, Garvan Institute of Medical Research

An in-depth Garvan study of how the immune system generates effective antibodies provides new insights for vaccine design.

Researchers at the Garvan Institute of Medical Research have uncovered a key strategy the immune system uses to generate effective antibodies, which could inform vaccine design for some of the most challenging viruses.

In experimental models, the researchers discovered that the immune system mutated its B cells to generate more finely-tuned antibodies when the targets for those antibodies, referred to as 'antigens', were structurally flexible, rather than rigid. The researchers publish their findings in the journal *PNAS*.

"Our findings address a central issue for developing vaccines—how the immune system generates antibodies that recognize 'foreign' from 'self'," says co-senior author Professor Daniel Christ, Head of Antibody Therapeutics and Director of the Center of Targeted Therapy at Garvan.

"Taking a comprehensive analytical approach, we found that a flexible target allows the immune system to create antibodies more finely-tuned to foreign molecules, which we hope will play a role in informing the design of future vaccines."

Structure matters

Our immune system is constantly challenged by foreign microbes such as viruses. To clear a virus from our body, and to remember and eliminate it more quickly the next time we're exposed, our immune system evolves. This happens in structures called germinal centers within our lymph nodes, where B cells multiply and mutate to produce antibodies more finely-tuned to target the virus.

"Long-lasting immunity is an important challenge for the immune system—antibodies have to bind like glue to foreign threats, such as viruses but avoid any of the body's own molecules as this can lead to autoimmunity," says Dr. Deborah Burnett, co-first author of the paper.

At a sub-microscopic level, some molecules bend and move more than others—some are more rigid, while others are flexible. The same is true for molecules on viruses, for example, the spike protein on the SARS-

CoV-2 virus that causes COVID-19 is highly flexible to adopt multiple different shapes.

"There is a longstanding debate about whether flexible or rigid antigens in vaccines are more likely to elicit a lasting immune response in humans. We wanted to help answer that question," says Dr. Peter Schofield, co-first author of the study.

More paths to reach fine-tuned immunity

"Using an artificial pair of foreign and self-molecules that are very similar, we created different versions of the same antigen, altering one connection that made it either more rigid or more flexible," says Dr. Schofield. The researchers then investigated how the immune system of mice generated antibodies to the different molecules.

The researchers discovered that when the foreign antigen was more flexible, the germinal center could employ a greater number of evolution strategies to make antibodies that bound foreign but not self-molecules.

"Our results showed that the antibodies initially bonded to both the rigid self and flexible foreign antigens in the same way, unable to tell them apart. What surprised us was that, after only a few weeks, when the foreign antigen was flexible, the antibodies were able to specifically mutate to become 67 times more selective for foreign antigens, and 19 times less selective for self," says Dr. Burnett. "The antibodies generated against rigid foreign antigens were more likely to have autoimmune properties."

Informing vaccine design

The ability to produce antibodies that bind foreign but not self-

molecules is a major hurdle for vaccine development, say the researchers.

"It's the major roadblock in the generation of effective HIV vaccines, which have so far been blocked by checkpoints in the body that avoid an autoimmune response," says Professor Chris Goodnow, Garvan's Executive Director and co-senior author of the study. "What we have discovered is fundamental to establishing long-lived immunity, which will inform vaccine design going forward."

"There is circumstantial evidence that antibodies against the spike molecule on the SARS-CoV-2 virus may also recognize 'self'. This may be an explanation for why antibody levels against the novel coronavirus appear to decline in patients quickly after infection," he adds. "Understanding how to increase selection of antibodies that don't bind self may illuminate a pathway to long-lived immunity against COVID-19."

More information: Deborah L. Burnett el al., "Conformational diversity facilitates antibody mutation trajectories and discrimination between foreign and self-antigens," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.2005102117

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