Insights obtained by profiling immune response to repeat viral infections could assist vaccine design efforts

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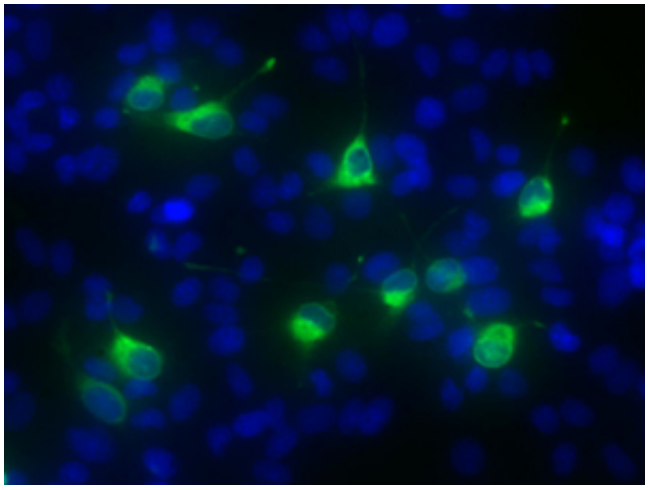

Antibodies (green) isolated from patients with a secondary dengue infection can effectively label cultured infected cells, demonstrating their strong affinity for the viral particle. Credit: 2013 A*STAR Singapore Immunology Network

Patients who successfully beat infection with dengue virus remain vulnerable to reinfection by other dengue variants, and these secondary infections tend to be more severe. The antibodies arising from the immune system's first encounter with the virus can play a complicated role in how these secondary infections unfold.

"Antibodies made during dengue infection can be either protective or disease enhancing," explains Katja Fink of the A*STAR Singapore Immunology Network. Fink and her team wanted to determine whether the antibodies produced very early after infection promote defense or vulnerability. To do this, her team isolated plasmablasts—immature precursors of antibody-secreting plasma cells—from two patients newly diagnosed with secondary infection. After conducting assays to determine the extent to which these cells were targeting the various subtypes of dengue virus, the researchers learned that most patient plasmablasts were specifically generating antiviral antibodies (see image).

The secret of the immune system's success is its diversity, but when the body finds a threat that resembles something it has previously encountered, it specifically stimulates proliferation of cells that secrete antibodies appropriate to that threat. Fink and co-workers characterized the extent to which antibodies produced by individual plasmablasts from such patients neutralized different dengue variants in a mouse model. They found that the antibodies were generally more effective at neutralizing strains from initial infections rather than those involved in secondary infections. This is in keeping with an immunological model called 'antigenic original sin', wherein an initial encounter with a pathogen determines antibody output generated in subsequent encounters.

Importantly, the researchers found that patients with acute secondary infections were also able to successfully mount a new wave of plasmablast-mediated immune defense against the secondary strain, manifested by the generation of a collection of antibodies that effectively recognized and neutralized all four viral subtypes. More than a few very potent antibodies dominate the protective effect, according to Fink. "The immune system responds to dengue with a very diverse repertoire," she notes. Based on the timing with which the antibodies appeared, the researchers were also able to determine that they help rather than hinder the body's antiviral effort.

The cross-protective antibodies generated in this acute plasmablast response preferentially recognized a particular viral coat protein as a target, or 'epitope'. If validated in larger scale

studies, these results could lead to better antiviral protection. "Knowledge about antibody epitopes on the virus that are naturally targeted by the human immune response could be translated into the design of vaccines," says Fink.

More information: Xu, M. et al. Plasmablasts generated during repeated dengue infection are virus glycoprotein–specific and bind to multiple virus serotypes. *The Journal of Immunology* 189, 5877–5885 (2012). www.jimmunol.org/content/early … nol.1201688.abstract

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