Insights into causes of rare genetic immune disorders

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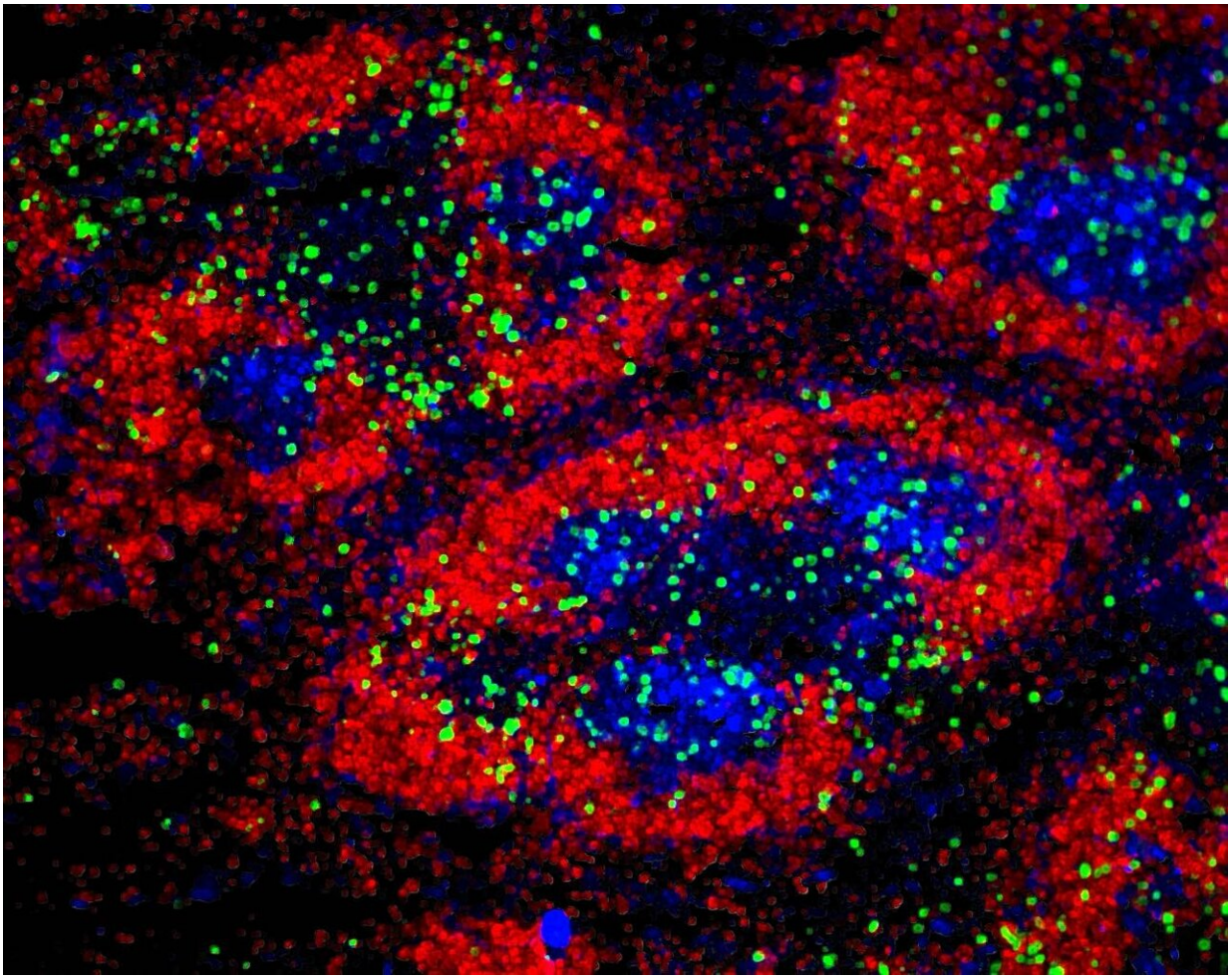


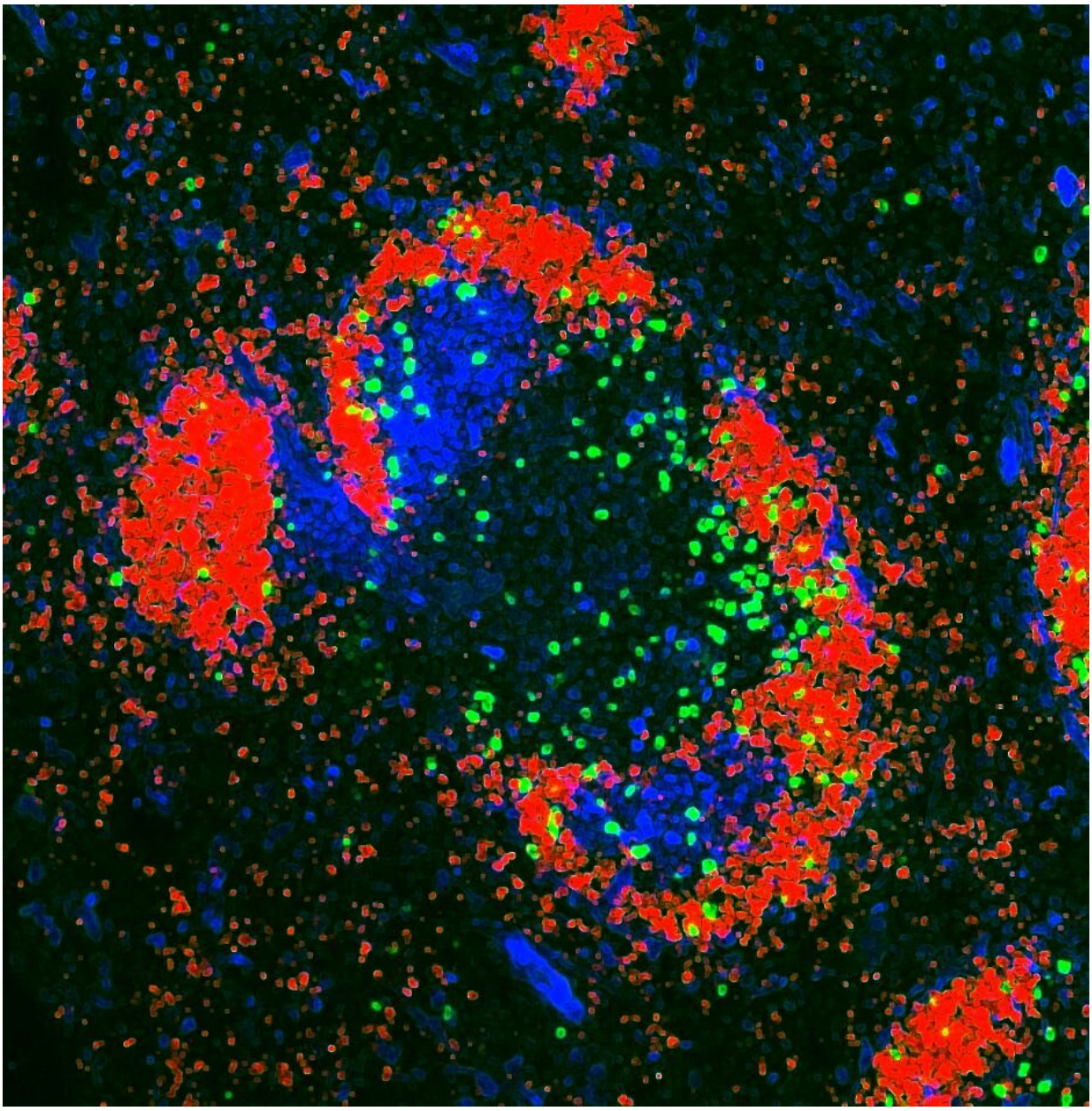
The immune system's T cells (green) helping B cells (in the red zone) to make antibody responses inside the spleen. Credit Garvan. Credit: Garvan

The cellular glitches underlying a rare genetic disorder called activated PI3K Delta syndrome 2 (APDS2) have been identified by researchers at the Garvan Institute of Medical Research. The disorder is caused by genetic variations that disrupt immune cell signaling through a protein called PI3K.

"This study tells us how signaling in the immune system needs to be tightly balanced to make an effective response to infection. Sometimes it's turned down and you have a problem, and sometimes signaling being turned up can interfere with an immune response," says Associate Professor Elissa Deenick, Head of the Lymphocyte Signaling and Activation Lab, co-Lead of the Precision Immunology Program at Garvan and senior author of the paper, published in the *Journal of Experimental Medicine*.

PI3K plays a crucial role in activating immune cells for growth, proliferation, survival, migration and function. The researchers found that the genetic variations in APDS2 and a similar disorder, APDS1, alter PI3K signaling in different ways, leading to distinct effects on the immune system.

The APDS disorders are similar in their impacts but follow different genetic pathways. Variations in the PIK3R1 gene underlie APDS2, while variations in PIK3CD underlie APDS1. Though both result in increased PI3K signaling, their subtle differences—in specific cells, timescales, and mechanisms—yield distinct immune effects. In APDS2, fewer responding B cells are generated in response to vaccination, whereas in APDS1, the number of T cells is reduced. But in both cases, the disorders result in poor antibody responses. In addition, APDS2 variations appear to affect non-immune cells, resulting in growth delays.



The immune system’s T cells (green) helping B cells (in the red zone) to make antibody responses inside the spleen. Credit Garvan. Credit: Garvan

These results also tell us about the signals that are required to achieve good vaccine responses in general. "Even for people who don't have these two rare genetic conditions, other genes can impact these

pathways—which could contribute to why different people have varied responses to vaccinations," says Dr. Tina Nguyen, co-lead author of the study and Research Officer at Garvan.

The findings reveal how finely tuned immune cell signaling must be, and how even minor disruptions can lead to immune deficiency or dysfunction. They are a significant step towards understanding the molecular processes and developing more targeted and effective treatments for the disorders.

"People with mysterious conditions often face challenges in obtaining an accurate diagnosis and understanding the root causes of their health issues. With better access to genomic testing, it's going to become much easier for patients to receive diagnoses for conditions like APDS2. Knowing the genetic basis of a disease can enable targeted, personalized treatment plans that give patients the best chance of effective management or, hopefully over time, a cure," says Professor Stuart Tangye, a senior investigator of the paper and Head of the Immunobiology and Immunodeficiency Lab at Garvan.

The next step is to study how to track individual responses to treatment, developing blood tests to monitor immune health and dysfunction in order to give the right drug, at the right dose, at the right time.

More information: Tina Nguyen et al, Human PIK3R1 mutations disrupt lymphocyte differentiation to cause activated PI3K- delta syndrome 2, *Journal of Experimental Medicine* (2023). DOI: 10.1084/jem.20221020

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