'Rapid response' pathway for immune cell development may improve body's ability to fight recurring infectious threats

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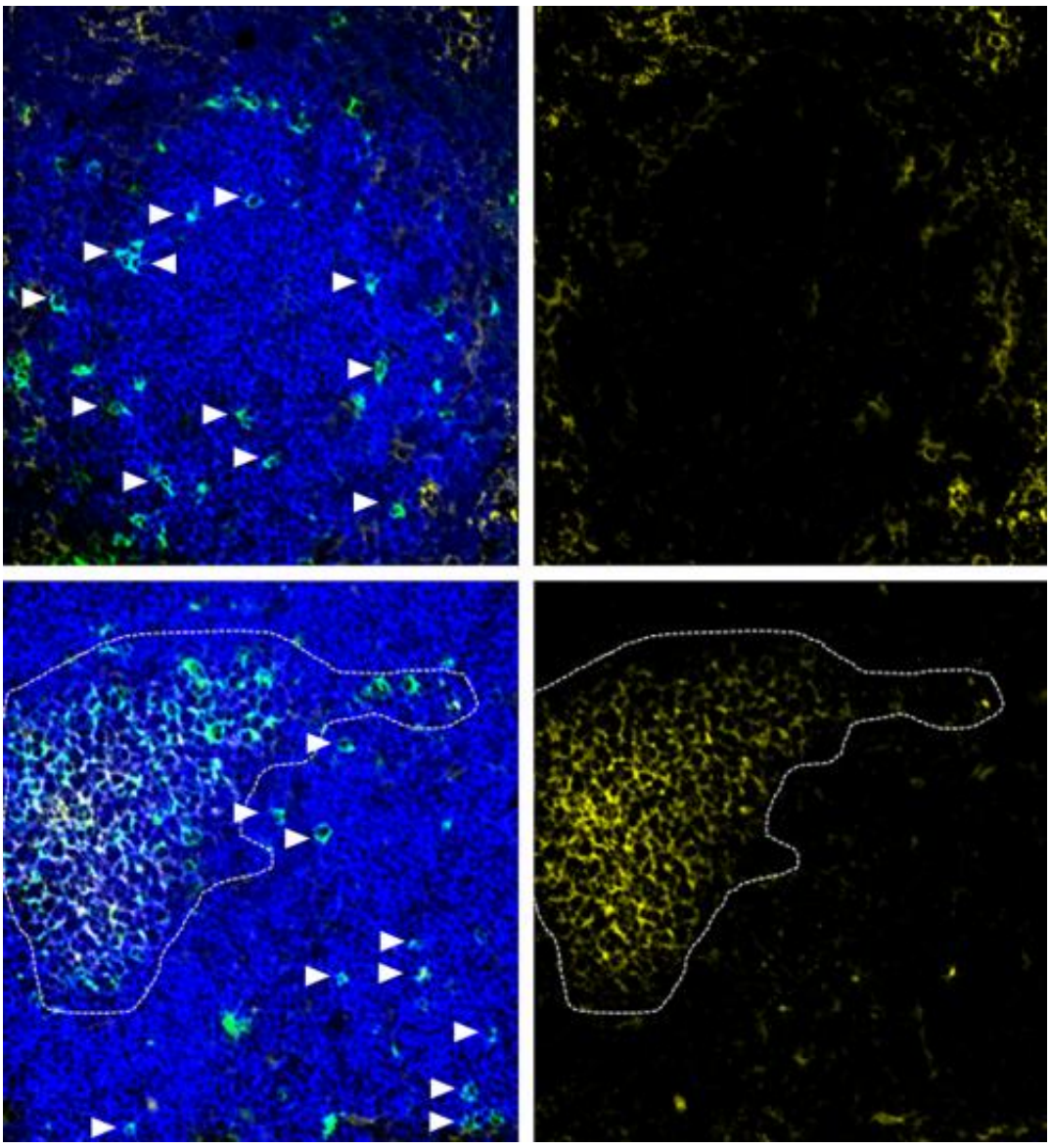

Fluorescent labeling reveals that both conditionally Bcl6-deficient (top) and wild-type (bottom) mice are able to produce functional memory cells (left column, arrowheads). However, these genetically-modified animals lack germinal center (GC) B cells (right column, yellow), revealing a GC-independent pathway for memory cell development. Credit: 2012 Toshitada Takemori, RIKEN Research Center for Allergy and Immunology

Efficient immune protection requires the ability to rapidly recognize intruders that the body has encountered in the past. This is achieved via 'memory' B cells, which develop following immune system activation by a virus, bacterium or other threat.

"Scientists have known about immunological memory for centuries," explains Toshitada Takemori of the RIKEN Research Center for Allergy and Immunology in Yokohama, "but certain critical aspects of this process remain incompletely defined." As a case in point, Takemori's team and Klaus Rajewsky at Germany's Max-Delbrück-Center for Molecular Medicine recently uncovered striking proof of a novel memory B cell production pathway with a potentially distinct role in immune defense.

The initial appearance of an immunity-triggering antigen fuels interaction between B and T cells, which in turn yields activated B cells. These can either differentiate into cells that produce antibodies against the target antigen or migrate to structures called 'germinal centers' (GCs) where their antibody-encoding genes undergo extensive mutation. This somatic hypermutation (SHM) process generates antibodies with optimized target affinity and specificity, and the resulting cells mature into antibody-secreting plasma cells or memory B cells.

However, Takemori has observed evidence that some memory B cells

never undergo SHM, apparently developing via a GC-independent pathway. This has proven difficult to verify experimentally: mice lacking the Bcl6 gene fail to develop GCs but also suffer other defects, making them a poor research model. To overcome this, the researchers engineered rodents where Bcl6 inactivation is limited to a subset of relevant cells.

These animals lacked GCs, but nevertheless generated memory B cells after an immune challenge in numbers roughly equivalent to normal mice. Closer examination confirmed that the memory B cells produced by conditionally Bcl6-deficient animals did not undergo SHM. The researchers also isolated non-mutated memory B cells from wild-type animals, although these were eventually outnumbered by mutated memory B cells, indicating that these non-mutated cells represent a distinct subset of memory B cells that develop in advance of the GC maturation process. "Our analysis indicates that immunological memory is established as soon as possible after the onset of immune response," says Takemori.

As non-GC memory B cells produce relatively low-specificity antibodies, the researchers hypothesize that these cells may complement optimized, post-SHM memory B cells by broadly responding to related but distinct threats: for example, influenza viruses in general rather than one specific strain. "We are now determining whether the GC-independent memory pathway assists the GC-dependent pathway to protect hosts against viral infections," says Takemori.

More information: Kaji, T., et al. Distinct cellular pathways select germline-encoded and somatically mutated antibodies into immunological memory. *Journal of Experimental Medicine* 209, 2079–2097 (2012). jem.rupress.org/content/209/11/2079

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