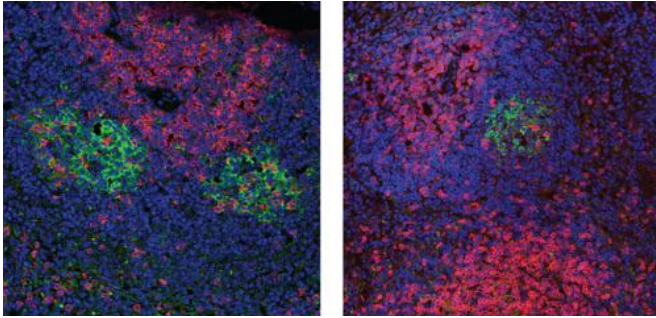


# Recently identified receptor helps trigger first wave of immune response

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In wild-type mice, immune stimuli cause B cells (green) to interact with T cells (red) within structures known as germinal centers (left), giving rise to antibody-secreting plasma cells and memory cells that facilitate long-term immunity. In mice lacking Fc $\gamma$ R, however, these germinal centers are greatly diminished (right). Blue dye indicates cell nuclei. Credit: 2012 Hiroshi Ohno and Ji-Ying Wang, RIKEN Research Center for Allergy and Immunology

B cells can generate different 'classes' of antibodies, each of which carries a specific type of protein chain that triggers a specific downstream cascade of immune responses. Immunoglobulin M (IgM) antibodies, which are the first on the scene, play a particularly important role in fighting off pathogen infection.

It took scientists nearly 40 years to finally isolate Fc $\gamma$ R, a [receptor molecule](#) that enables [immune cells](#) to respond to IgM. Hiroshi Ohno's team at the RIKEN Research Center for Allergy and Immunology (RCAI) in Yokohama was among the first to identify the gene encoding this receptor, and he and his RCAI colleague Ji-Yang Wang recently set out to characterize its function by generating a strain of Fc $\gamma$ R-deficient mice.

Fc $\gamma$ R is predominantly produced by B cells in mice, and Ohno and Wang did not observe any significant differences in overall B cell numbers in

the genetically modified animals. When the researchers triggered an [immune response](#) in B cells from these mice, however, they found that these cells divided more slowly and subsequently began dying off. Fc $\gamma$ R-deficient mice also generated significantly fewer plasma and memory B cells, which are respectively responsible for antibody secretion and coordinating the immune response to recurring infection. Collectively, these results indicate that although this receptor is not required for B cell maturation, it is likely to play a critical role in mounting the initial immune response in the presence of an infectious threat.

As the Fc $\gamma$ R-deficient mice grew older, they produced sharply elevated numbers of antibodies targeting host tissues, similar to those produced in [autoimmune conditions](#) like lupus or [rheumatoid arthritis](#). Such 'auto-antibodies' are of the immunoglobulin G (IgG) subtype, which appears later in the immune response relative to IgM, suggesting that Fc $\gamma$ R is required for [B cells](#) to properly manage the shift from IgM- to IgG-mediated immunity. "Our work defines and closes an auto-regulatory loop that ensures adequate B cell activation during the early phase of an antibody response, yet prevents excess activation at the late phase," explains Wang.

These results do not tell the entire story about IgM signaling, which also employs a parallel network known as the complement pathway, but Wang and Ohno believe their findings could offer clinical opportunities for patients with malfunctions in IgM production as well as other immune disorders. "Fc $\gamma$ R might contribute to human chronic lymphocytic leukemia (CLL) and, if so, inhibition of Fc $\gamma$ R signaling by inhibitors or blocking antibodies could offer therapeutic benefit," says Ohno.

**More information:** Ouchida, R., et al. Critical role of the IgM Fc receptor in IgM homeostasis, B-cell survival, and humoral immune responses. *Proceedings of the National Academy of Sciences*

USA 109, E2699–E2706 (2012).

[www.pnas.org/content/109/40/E2699.abstract](http://www.pnas.org/content/109/40/E2699.abstract)

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