Scientists show how memory B cells stay 'in class' to fight different infections

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Scientists at The Scripps Research Institute have made an important discovery about the internal programming of B cells, the immune cells that make antibodies against infections. The finding opens the way for the development of vaccines that can work more efficiently and hints at therapies for conditions in which B cells cause harm-such as the autoimmune disease lupus erythymatosus, severe allergies, and B-cell lymphomas.

The discovery reveals that B cells produce special proteins to maintain themselves in a particular functional "class," even as they lie dormant in the memory-cell state, awaiting a new infection. The class of a B cell determines how its antibodies marshal other components of immunity, and thus how well they can remove a certain type of threat, say bacteria on the skin versus intestinal parasites.

"This is a real breakthrough, in the sense that we now have a much better understanding of how B cell class is regulated, and how we might target that regulatory process in vaccine and drug design," said Michael McHeyzer-Williams, a Scripps Research professor who was the principal investigator for the study, published in *Nature Immunology*'s advance online edition on May 6, 2012.

Specialized Infection Fighters

Young, "naïve" B cells begin their careers as infection fighters when they are exposed, in the right way, to pieces of an invading microbe that happen to match their main receptor (the B cell receptor, or BCR). Some then become plasma B cells, and slowly ramp up the active production of antibodies. Others instead become memory B cells, which can lie in wait for years, primed to respond very rapidly and nip in the bud any reinfection.

Either way, as B cells move out of the naïve state, helper T cells secrete chemical signals that typically force the B cells into particular classes. IgG-class B cells are the most common in humans, and are broadly effective against viruses and bacteria. IgA-class B cells are predominantly found on mucosal surfaces such as in the throat and intestines. IgE-class cells and their antibodies protect against intestinal worms and other parasites. Some B cells stay in the default IgM class. The class of a B cell is marked by the type of "stem" it has on its Y-shaped antibodies; this stem, or effector, can mobilize other elements of the immune system, such as inflammatory chemicals, when the antibody binds to an invader.

It had been long assumed that the switching of a B cell to a particular class is the result of a one-time signaling event. "The idea was that the signals that produce this switch don't persist in B memory cells, for example," said Nathaniel Wang, a graduate student in the Scripps Research Kellogg School of Science and Technology working in the McHeyzer-Williams laboratory who was first author of the new study.

Testing Assumptions

In the study, Wang, McHeyzer-Williams, and their colleagues tried to determine whether that assumption is true. They knew, for example, that when T cells cause naïve B cells to switch to the IgG2a class, a potent antiviral class, they do so by inducing the production in B cells of a particular protein called T-bet. To clarify T-bet's role, the researchers engineered transgenic mice whose B cells lack the protein.

Without T-bet, they found, the mouse B cells could not be switched to the IgG2a class, even when presented with all the normal stimuli, and even though other IgG classes could be produced normally-or even in higher amounts. Even more surprisingly, in existing IgG2a memory B cells, the abrupt knockdown of T-bet levels caused the cells

to lose their ability to respond to a new infection. In fact, most of the T-bet-deprived memory B cells became undetectable within a few days.

"T-bet turns out to be the central molecule that enforces the IgG2a class in B cells, and if its production stops in IgG2a memory cells, they become dysfunctional and die," Wang said.

The finding that T-bet has this all-important, ongoing function in IgG2a memory cells suggested that other proteins play analogous roles in other classes of memory B cell. Wang therefore turned to memory B cells of the IgA class, and, with a similar set of experiments, showed that these memory B cells depend on the transcription factor ROR?. "It essentially does for IgA memory cells what T-bet does for IgG2a memory cells," said Wang.

Implications for Science and Medicine

Wang and McHeyzer-Williams and their colleagues are now searching for the proteins that keep other memory B cells healthy and in their classes. But already the work has clarified how memory B cells work. "Until now we haven't really had a good conceptual framework for the development and maintenance of these cells," McHeyzer-Williams said.

The findings clearly also have implications for medicine. By supplying a particular class-enforcement protein at the same time that it exposes B cells to microbial proteins, a vaccine could induce a long-term immunity that is heavily weighted towards a desired antibody class. "If you're designing a vaccine for certain types of virus, for example, you would like to have lots of IgG2a and IgA memory cells," said McHeyzer-Williams. "So the goal would be to design a chemical adjuvant for the vaccine that drives B cells into those classes."

Similarly, therapies that knock down class-enforcement signals such as T-bet could usefully reduce or eliminate memory B cells in certain classes. "Some autoimmune, allergic and lymphoma conditions are driven by B cells of a particular class, for example IgE cells in allergies," said McHeyzer-Williams. "Being able to target just that class of B cell would be an obvious advantage over existing therapies, such as steroids, that knock down large parts of the immune system."

More information: "Divergent Transcriptional Programming of Class-Specific B Cell Memory by T-bet and ROR?," *Nature Immunology*.

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