Persistent immunity: Researchers find signals that preserve anti-viral antibodies

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Our immune system is capable of a remarkable feat: the ability to remember infections for years, even decades, after they have first been encountered and defeated. While the antibodies we make last only about a month, we retain the means of making them for a lifetime. Until now, the exact mechanism behind this was poorly understood, but researchers at The Wistar Institute have discovered some of the protein signals responsible for keeping the memory of distant viral infections alive within our bodies.

Their study, presented in the Journal of Clinical Investigation, may aid scientists in creating better, more effective vaccines.

"We are particularly interested in how our bodies generate antibodies against viruses and how we maintain anti-viral antibody secreting cells as a hedge against future infection from the same virus," said Jan Erikson, Ph.D., senior author of the study, professor in Wistar's Immunology Program and a member of The Wistar Institute Vaccine Center. "Our study highlights how protein signals sustain the cells that make antibodies against viruses in perpetuity, which we believe is crucial knowledge for the development of vaccines for lasting protection against the flu, for example."

Despite an annual vaccine against the disease, seasonal influenza remains a potent killer, one associated with nearly half a million deaths each year around the globe. The persistence of antibody memory is why older people, who typically suffer more from influenza, fared much better

than expected during the 2009 avian influenza pandemic. Previous exposure to—or vaccination against—a similar strain provided many older Americans a resistance to the 2009 avian flu. Wistar Vaccine Center researchers are among a number of teams of scientists working toward a universal flu vaccine, one that would forgo the need for an annual flu shot.

The main role of vaccines is to stimulate the production of antibodies that bind to portions of the infectious agent. Once bound, the antibodies provide a target for the immune system, allowing immune cells to attack it or any infected cells in order to clear away disease. Antibodies are highly variable proteins that are produced in huge quantities by a subset of white blood cells, called B cells, that have transformed into antibody factories, termed antibody secreting cells (ASCs). Our immune system produces a broad array of antibodies, but during an infection with a virus, for example, the immune system allows the predominant production of antibodies that are directed against the virus. The cells making these particular antibodies are then selected for preservation.

According to Erikson and her colleagues, this act of preservation requires signals, provided by proteins called BLyS and APRIL. Mice that have been exposed to influenza require these proteins in order to sustain anti-influenza ASCs in their lungs. The researchers found that neutralizing BLyS and APRIL reduced the numbers of anti-viral ASCs found in the lungs and bone marrow, yet interestingly, did not affect the ASCs found in spleen or in lymph nodes nearby the lungs.

BLyS and APRIL bind to another protein called TACI, a receptor found on the surface of ASCs, which the researchers see as an important translator for marking the ASCs that will become long-lived.

"We know from humans that the absence or mutation of the TACI gene leads to common variable immunodeficiency disease (CVID) and these

patients suffer from recurrent respiratory illnesses because of low amounts of certain antibodies in their bronchial secretions," said Amaya I. Wolf, Ph.D., the study's lead author and a postdoctoral fellow in the Erikson laboratory. "Our studies show that mice that lack TACI can mount an initial B cell response to viral infection—and are able to produce antibodies to flu —but these mice fail to maintain anti-viral ASCs over a long period of time. Importantly, we show that this results in lower anti-viral antibody titers, and mice are less protected against a secondary viral attack at a later time."

"After resolution of a viral infection we want to have ASCs in our lungs to guard our mucosal surfaces, the port of microbial entry, in case of a reinfection with the same virus," Wolf said. "The lung microenvironment after a viral infection allows the ASCs to persist as a sort of local base, a place for the local release of protective antibodies."

"To avoid damage of the lung tissue, the immune system wisely evolved means of keeping the secretion of antibodies under tight control," Wolf explained. "The anti-viral ASCs in the lungs are short-lived and require BLyS and APRIL for their more immediate survival, but also the generation of longer-lived ASCs that take up residence in the bone marrow depends on these signals."

According to Wolf, it might be possible to manipulate ASC behavior to prolong or strengthen the effectiveness of vaccines. Drugs that induce targeted production of ASC survival factors, such as BLyS and APRIL or manipulation of their signals through TACI, their receptor, could theoretically help to maintain specific antibodies. While the seasonal flu is constantly mutating—necessitating an annual vaccine —even weakly reactive antibodies could be protective if there are enough of them and if their production is sustained.

One interesting observation from this study, the researchers say, is that

the persistence of ASCs in different tissues appears to be regulated differently. This has spurred plans for the Erikson laboratory to conduct a genome-wide molecular survey in collaboration with Wistar Professor Louise Showe, Ph.D., director of Wistar's genomics facility.

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