Genetic trigger for disease-fighting antibodies discoverd

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A research team led by the La Jolla Institute for Allergy & Immunology has identified the specific gene which triggers the body to produce disease-fighting antibodies -- a seminal finding that clarifies the exact molecular steps taken by the body to mount an antibody defense against viruses and other pathogens. The finding, published online today in the prestigious journal *Science*, has major implications for the development of new and more effective vaccines. The La Jolla Institute's Shane Crotty, Ph.D., was the lead scientist on the team, which also included researchers from Yale University.

"The finding is enormous in terms of its long-term benefit to science and society as a whole because it illuminates a pivotal piece of the vaccine development puzzle -- that is, 'what is the molecular switch that tells the body to create antibodies?' Dr. Crotty has pinpointed the BCL6 gene and, in doing so, has answered a critical question that has long been sought by the scientific community," said Mitchell Kronenberg, Ph.D., president & scientific director of the La Jolla Institute, a nonprofit biomedical research institute. Dr. Kronenberg said this knowledge opens the door to developing ways to boost antibody production, thereby creating stronger and more effective vaccines.

Rafi Ahmed, Ph.D., director of the Emory Vaccine Center, and a professor of microbiology and immunology at the Emory University School of Medicine, called the finding an "important breakthrough."

"Dr. Crotty has defined the gene that regulates the formation of certain

CD4 T cells," said Dr. Ahmed. "Those cells are very critical for antibody production, so describing what regulates the birth of those cells is clearly an important discovery."

Pamela L. Schwartzberg, M.D., Ph.D., a senior investigator in the Cell Signaling Section of the National Human Genome Research Institute, part of the National Institutes of Health, called the discovery a major step forward in the area of vaccine development. "This finding defines the master regulator (gene) that triggers an elaborate cellular interaction necessary to get effective long-term antibody responses, which are required for most successful vaccines," she said. "In making this discovery, Dr. Crotty and his fellow researchers at Yale have made a major contribution that will help provide critical insight into the processes important for successful vaccination and effective immune responses."

The finding is outlined in a paper entitled, "Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper (TFH) cell differentiation." Yale scientist Joseph Craft, M.D., led the Yale research team, which
contributed to the study.

Antibodies, Dr. Kronenberg explained, may be thought of as the body's smart bombs, which seek out infectious agents and tag them for destruction. Twenty-five human vaccines currently exist worldwide, 23 of those work by triggering the production of antibodies. "The scientific community has known for many years that antibodies were key to vaccine development and fighting infections," he continued. "But we didn't know exactly how the process worked at the cellular level and it has long been the subject of speculation, debate and intense interest."

Dr. Crotty said it has been well established that antibody production is a multi-step process that involves interactions between several cellular

players, key among them CD4 "helper" T cells, which are disease-fighting white blood cells that tell other cells to produce antibodies in response to infections. "There were different flavors of these CD4 helper T cells and, for many years, we, in the scientific community, thought that one of the four varieties of CD4 helper type 2 cells (known as TH-2 cells) triggered the antibody process. But about 10 years ago, scientists realized this was incorrect and that there must exist a fifth variety of CD4 helper T cell that initiated antibody production. It was named TFH."

Dr. Crotty's team set out to understand the inner workings of the TFH pathway. "We discovered that the BCL6 gene was like an on and off switch, or master regulator, in this process. In a series of experiments, we showed that if you turn on this gene, you get more CD4 T helper cells (the TFH type) and it's those cells that are telling the B cells to produce antibodies," he said.

Dr. Crotty's group also tested the finding by using a cellular mechanism to turn off the BCL6 gene. Turning off the gene stopped the production of the TFH cells. "Without this genetic trigger, no TFH cells were produced and consequently no antibodies." The researchers also found that the more TFH cells produced, the greater the antibody response.

Yale researchers, who were collaborators on the study, also tested and proved the finding by deleting the BCL6 gene. "Beautifully, they got the same results - antibody production ceased," said Dr. Crotty.

The finding also may have implications for rheumatoid arthritis and some other autoimmune diseases. "Some autoimmune diseases are triggered by antibody-induced inflammation," said Dr. Crotty. "The ability to turn antibody production off may also offer therapeutic opportunities for these people."

Source: La Jolla Institute for Allergy and Immunology