Study Offers Clues to Origins of Autoimmune Disease

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DENVER — Researchers at National Jewish Medical and Research Center have discovered a mechanism in the body that could lead to autoimmune diseases, such as lupus, rheumatoid arthritis, or diabetes. The research team, led by John Cambier, PhD, found that potentially harmful B cells circulating in the body are not permanently silenced as previously thought; they can awaken and regain the ability to launch an attack against the body's own tissue. The findings were published online October 2 by *Nature Immunology*.

"Keeping self-reactive B cells in a quiescent state is crucial for the prevention of autoimmunity," said Dr. Cambier, Professor and Chairman of the Integrated Department of Immunology at National Jewish and the University of Colorado Denver. "Our findings show how these cells can be reactivated and suggest lines of research that may lead to therapies for autoimmune diseases."

B cells are part of the immune system. When properly stimulated, they produce antibodies, which bind to foreign molecules and neutralize them or target the cells they are part of for destruction. The body, in its attempt to protect against any foreign invader, produces a huge variety of B cells, each capable of recognizing a different molecule, also called an antigen.

However, in the course of generating such a variety of B cells, the immune system also produces ones that recognize normal components of the body as antigens. Were those cells to become activated, they would initiate an attack against the body's own tissue. Fortunately, these cells are sent into a sort of suspended animation, known as anergy, when they encounter the antigen but fail to receive additional signals necessary to activate their antibody-producing machinery.

For years, scientists have thought that one encounter with an antigen would send a B cell into permanent anergy. Dr. Cambier and his colleagues showed, however, that self-reactive B cells need constant stimulation by their antigen to remain anergic, and that removing the antigen allows them to regain their normal, ready state.

The researchers suggest that an active infection could draw a self-reactive B cell to a lymphoid organ, such as the tonsils or a lymph node, where there may be no antigen to silence it. There, a robust immune/inflammatory response to the bacterial infection could activate this dangerous B cell and cause it to trigger an autoimmune disease.

"There have been reports linking the onset of autoimmunity with a preceding bacterial infection," said Stephen Gauld, PhD, lead author and post-doctoral fellow in Dr. Cambier's lab. "We are now conducting experiments to determine the role of pro-inflammatory or bacterial products in the loss of B-cell anergy. We are also seeking to better understand the intracellular events that lead to anergy and its loss. Either of these lines of research could uncover potential targets for autoimmune therapy."

National Jewish Health is the leading respiratory hospital in the nation. Founded 120 years ago as a nonprofit hospital, National Jewish Health today is the only facility in the world dedicated exclusively to groundbreaking medical research and treatment of patients with respiratory, cardiac, immune and related disorders. Patients and families come to National Jewish Health from around the world to receive cutting-edge, comprehensive, coordinated care. To learn more, visit the media resources page.

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