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Scientists learn the origin of rogue B cells

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Doctors have long wondered why, in some people, the immune system turns against parts of the body it is designed to protect, leading to autoimmune disease. Now, researchers at the National Institutes of Health's (NIH) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), in collaboration with the Oklahoma Medical Research Foundation, have provided some new clues into one likely factor: the early development of immune system cells called B cells.

B cells are formed in the bone marrow and produce antibodies. Antibodies are generated from the cutting and splicing of immunoglobulin genes early in B-cell development, and have the potential to develop strong and highly specific affinity for different pathogens. When an infectious pathogen (a disease-causing agent) enters the body, B cells are activated and release antibodies into the bloodstream to combat the pathogen. When antibodies encounter the pathogen, they bind to it, rendering it incapable of causing further harm. Antibody molecules also serve as receptors on the surface of B cells.

The problem occurs when the random cutting and splicing of immunoglobulin genes results in an antibody that recognizes a component of one's own body. While the body has a built-in mechanism to correct these errant cells, the NIAMS researchers discovered this doesn't always work the way it was intended. "What happens is that, if the body ever produces a cell with a self-reactive antibody molecule, that cell will get arrested in development at the point where it is actually combining and creating an antibody receptor," says Rafael Casellas, Ph.D., an investigator in NIAMS's Genomic Integrity and Immunity

Group.

Often, rather than killing off the cell, the body edits — or corrects — the receptor, like one might edit a paper, he says. In normal circumstances, this new, good receptor replaces the bad one, but what Casellas and Dr. Patrick C. Wilson of the Oklahoma Medical Research Foundation found was that about 10 percent of the body's B cells retain both receptors: a good, useful one and the faulty self-reactive one that the good receptor was designed to replace. This means that the aberrant B cells have escaped the body's mechanism to correct them. "Our research goes against the theory that B cells should only express a single receptor," says Casellas.

Using a technique in which they inserted a piece of human gene into the cells of laboratory mice, the researchers created a model for visualizing the process in live animals. "Most of what scientists do is to create systems to visualize complex phenomena, then to allow nature to give you the answers to your questions," says Casellas.

Their new findings raise the question of how this knowledge might eventually help people with autoimmune disease. That question, says Casellas, is one that will take time to answer. "This is only one step," he says. "We all carry these cells around, but not all of us develop autoimmunity. Our work provides one explanation for the origin of these self-reactive B cells."

"If you understood the system extremely well and were able to delete the editing cells during development, for instance, then you would only have lymphocytes that don't express self-receptors at all," he says.

For now, the step forward to understand where these self-directed cells are coming from is a big one. "Our objective is to understand the ins and outs of this process," says Casellas.

Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases