BIG IDEA

THE B-CELL OR NOT THE B-CELL

The ravages of chronic fatigue syndrome may be the result of an overlooked but essential part of the body's own immune system.



Chronic fatigue syndrome's debilitating symptoms might be the result of overzealous immune cells.

MYALGIC ENCEPHALOMYELITIS, or chronic fatigue syndrome, is a perplexing disorder that may seem more like a voodoo hex than an illness. Patients might lie bedridden in dark rooms, in chronic pain, often with multiple neurological symptoms like muscle pain, sweating and dizziness. Doctors have targeted various causes, from herpes viruses to retroviruses to depression. But a surprising new explanation suggests that the disorder is an autoimmune disease of the nervous system caused by overactive B-cells, which are normally responsible for churning out pathogen-killing antibodies.

In 2011, two Norwegian oncologists, Oystein Fluge and Olav Mella of Haukeland University Hospital in Bergen, along with colleagues, studied 30 people diagnosed with chronic fatigue immune dysfunction syndrome (CFIDS). Each received either a placebo or a highly specialized chemotherapy drug called rituximab, which rapidly and selectively depletes B-cells. After 12 months, 10 of 15 patients on the drug significantly improved; only two of 15 on the placebo improved.

This study marks just one more step in a growing body of research focusing on the role of B-cells in autoimmune disease. While they're essential for helping the body fend off attacks, if something goes awry, B-cells can generate antibodies that attack healthy tissues.

Until recently, T-cells — cells that activate and regulate the molecules responsible for controlling inflammation and immune response — were considered the great orchestrators of immunity. They were also thought to be the main drivers of autoimmune disorders.

In turn, researchers considered B-cells to be the worker bees taking the T-cells' orders. "T-cells were in fashion for a long time," says retired rheumatologist and researcher Jonathan Edwards. "B-cells were just considered boring." But Edwards was never convinced that T-cells were the alpha and omega of immunity.

B-cell Beginnings

As it turns out, B-cells play a major, and sometimes independent, role in immune function, dancing with T-cells in a fluid and Escher-like loop. For instance, specific anti-T-cell therapies don't work at all for rheumatoid arthritis (RA), and Edwards doesn't think T-cells explained how the disease persisted. He and his colleagues at University College in London worked for a decade piecing together a hypothesis on the role of B-cells in RA, and they then began to test it.

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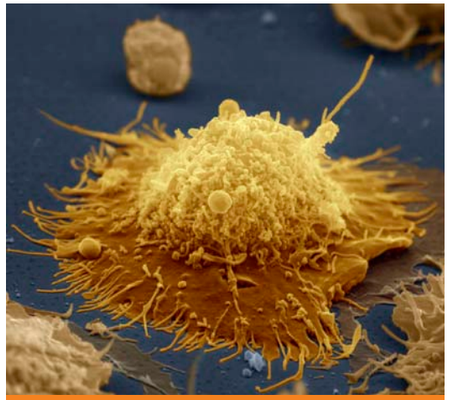

B-cells are more important than previously thought.

In 2004, their landmark study in the *New England Journal of Medicine* changed how researchers approached RA. Their randomized trial followed 161 patients treated either with a conventional immune-suppressing drug called methotrexate, or with methotrexate plus rituximab, the B-cell killer. More than 40 percent of patients given the drug combination experienced major improvement by the end of 24 weeks, and they sustained that improvement for another 24 weeks. Only 13 percent of those receiving methotrexate alone improved.

"T-cells and B-cells cooperate with each other," says Edwards, "and we think the B-cells can sometimes make a mistake, create auto-antibodies and fool the T-cells into giving them permission to continue doing so. We deplete the B-cells, the antibodies gradually disappear, and people improve, but eventually the B-cell population rebounds and people need re-treatment."

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"B-cells are really cool cells," says immunobiologist Mark Shlomchik of Yale University, who studies the interaction between B-cells and two receptors within them, TLR7 and TLR9. These receptors are important for fighting infection. "B-cells actually undergo evolution in real time in your body," says Shlomchik. When B-cells encounter a pathogen, some of them can already bind to it with some accuracy. But then they start dividing and altering their genes, competing with other B-cells to eventually create an antibody that is exquisitely precise. This natural selection process results in a B-cell that binds almost perfectly. At that point, T-cells give it approval to divide rapidly and produce millions of daughter B-cells that can churn out the specific antibody. That process can take days or weeks — which is why you don't recover from the flu in a matter of hours.

"Perhaps the same process is going on with autoimmunity," says Howard Hughes Medical Institute immunologist Philippa Marrack, who also studies B-cells and the TLR7 receptor.

It makes sense, says Edwards. "B-cells are supposed to mutate. That's what they do. Occasionally, they are going to make mistakes that get approved by the T-cells."

Fighting Fatigue

Fluge and Mella, the Norwegian oncologists, credit Edwards with inspiring their work. They also think their results suggest that an unknown antibody — probably an antibody against self, targeting the body's own healthy tissue — is triggering chronic fatigue syndrome. That's because despite rapid B-cell depletion, improvement lagged. Patients who responded to the treatment took two to eight months to show a response.

"We hypothesize that improvement occurred as the B-cell-generated auto-antibodies, which are antibodies to a person's own tissues, were slowly eliminated," says Fluge. "That can take months. This interpretation is supported by the fact that eight of the 10 patients who improved have relapsed. As the B-cell levels recover over time, they begin to churn out antibodies again. These patients have been re-treated."

Fluge and Mella are now working on a multicenter study and monitoring their original patients as they receive booster treatments, to try and determine optimal treatments for CFIDS. So far, their results are in line with their previous hypothesis, though only two-thirds of patients respond to these treatments. That suggests there might be a second mechanism that could independently lead to CFIDS.

For now, drugs such as rituximab that deplete B-cells not only offer potential relief for those with autoimmune illnesses, but a new way of understanding these conditions — as an unintended consequence of the natural selection process B-cells undergo each time they encounter a new pathogen. It's a process that is supremely effective — except when it goes wrong.

JILL NEIMARK

WHAT MAKES B-CELLS TICK?

What determines if an individual B-cell divides, produces an antibody or evolves? Prevailing theories suggest that B-cells react to external cues, such as hormones, but some Australian researchers now believe that the driving forces may be, at least in part, internal.

Immunologist Phil Hodgkin of the Walter and Eliza Hall Institute of Medical Research says the immune system has a sort of default allocation of B-cells corresponding to the various possible outcomes. Each B-cell's basic fate is sealed, in other words, at the outset. Hormones, then, merely stack the deck in favor of specific outcomes.

By devising mathematical models to accurately predict the probability of a B-cell's behavior, the researchers hope to design new vaccines and immune therapies for diseases such as chronic fatigue syndrome. BREANNA DRAXLER