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Cutting the brakes on the immune system

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Your immune system may have more in common with a Corvette than you thought. When a virus or bacteria enters a human body, the immune system revs up to fight and expel the invader. Once the invader is gone, the body puts on the brakes to stop the immune response.

But a new study by Patrick Gaffney, M.D., and Kathy Moser, Ph.D., of the Oklahoma Medical Research Foundation shows that variation of a particular gene—known as TNFAIP3—may cause the immune system to keep going at full speed long after the threat is gone, causing damage to the body.

"TNFAIP3 can be thought of as a critical brake mechanism for the immune system," said Gaffney, the senior author on the study and associate member of OMRF's Arthritis and Immunology Research Program. "When the gene doesn't function properly, the immune system redlines."

The research, done in conjunction with David Altshuler, M.D., Ph.D., a researcher at the Broad Institute of Harvard University and the Massachusetts Institute of Technology, appears in the August edition of the journal *Nature Genetics*.

Lupus is a chronic "autoimmune" disease in which the body's immune system attacks healthy tissues and organs. Symptoms range from skin rashes and joint pain to strokes, seizures and organ failure. The Lupus Foundation of America estimates that as many as 2 million Americans suffer from the disease, which has no known cure and can be fatal.

In healthy individuals, normal versions of the TNFAIP3 gene produce a protein (called A20) that regulates and shuts off the immune response. In lupus patients with the gene variant, the immune system has trouble turning itself off, Gaffney said.

"We suspect that the variant either doesn't make enough of the protein, or it makes a less effective protein," he said. "Our data adds TNFAIP3 to a growing list of lupus-associated genes that may help us diagnose and treat our patients."

Lupus is a multi-genic disease, meaning there's no one gene that causes lupus. But the TNFAIP3 variant may work in concert with other mutant genes to cause lupus in some patients.

"Every single lupus-associated gene we discover is just as important as the others," Moser said. "Each gene can set off new opportunities and new projects for us. You never know which gene is going to give you the best chance to develop new therapeutics or better diagnostics."

Gaffney said they will continue to study the TNFAIP3 variant for links to any other gene variations.

"We also want to know exactly what effect the gene variation has on A20 protein production and function," he said.

Source: Oklahoma Medical Research Foundation