

NIAMS scientists find potential new way to block inflammation in autoimmune disease

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Researchers from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the National Institutes of Health (NIH), have identified a promising new target for autoimmune disease treatment – a cell-surface receptor called DR3. Their research in mice, published on line in the journal *Immunity*, suggests that blocking this receptor could slow or stop the damaging inflammation characteristic of autoimmune diseases, potentially without leaving the body vulnerable to serious infections, as many current therapies do.

DR3 is a protein on the surface of cells. It is a member of the tumor necrosis factor (TNF) family of receptors, which bind to molecules related to TNF, a cell-signaling protein that promotes inflammation. Many of today's most potent treatments for inflammatory diseases, such as rheumatoid arthritis and psoriasis, interfere with the action of TNF, thereby blocking inflammation. Since current anti-TNF therapies don't work in all autoimmune diseases, however, the researchers turned to the study of DR3, which is a close relative of TNFR1, the main receptor for TNF.

Working with mouse models of asthma and multiple sclerosis, both immune system diseases, the researchers found that mice engineered to lack DR3 were resistant to those diseases. "The implication is that blocking DR3 in mice, and possibly in humans, is a potential therapy for these diseases and perhaps others in which the immune system goes awry," said Richard Siegel, M.D., Ph.D., a scientist in the NIAMS' Immunoregulation Group, who led the research effort.

While closely related to TNFR1, DR3 is expressed in T cells, a different kind of immune cell (a white blood cell that identifies and fights infection) than those that express TNFR1, Dr. Siegel said. The NIAMS group collaborated with a laboratory in Cardiff, Wales, which had generated genetically engineered mice deficient in DR3, as well as with a research group at the NIH's National Institute of Allergy and Infectious Diseases (NIAID), which has developed mouse models of disease with strong T cell components, such as asthma and multiple sclerosis. "These findings open up new avenues for therapy of these two diseases as well as to other autoimmune diseases in which T cells play a role in causing or perpetuating the disease," said Siegel.

The researchers hope that DR3-blocking agents will be effective anti-inflammatory treatments someday. Siegel noted that if they were to be used in rheumatic diseases, they would be a complement to strategies that block TNF because they hit a different arm of the immune system. "It could be potentially synergistic or complementary," he said.

Of critical importance, the NIAMS scientists found that removing DR3 did not appear to suppress the immune response or the ability to fight infection within the mice – a problem with many other treatments for autoimmune disease. "We could see the effect of DR3 deficiency in the diseased organ, but when we looked systemically at the immune response at other places in the mouse, it was barely affected," said Dr. Siegel. The group's findings suggest that DR3-blocking agents might be more effective at specifically treating autoimmune disease without breaking down the body's defenses against infections, a long-sought goal of researchers in the field.

Source: NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases

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