

Protein complementarity may offer new insights into autoimmune diseases

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The discovery of "complementary" antibodies against plasminogen in patients with blood vessel inflammation caused by anti-neutrophil cytoplasmic autoantibodies (ANCA) may lead to new approaches to research, testing, and treatment of ANCA vasculitis and other autoimmune diseases, suggests a paper in the December *Journal of the American Society of Nephrology (JASN)*.

"This research is especially important because it opens new avenues for exploration of autoimmune disease that embrace the concepts of protein complementarity," comments Ronald J. Falk, MD, of UNC Kidney Center, University of North Carolina, Chapel Hill, one of the authors of the study. "The power of this approach has gone unappreciated, even though the basic ideas of protein complementarity have been proven in other settings over the years."

The researchers looked for complementary proteins in a group of patients with a rare autoimmune disease called ANCA vasculitis. People with autoimmune diseases have abnormal "autoantibodies" that cause the immune system to attack the body's own cells and tissues. In patients with ANCA vasculitis, the ANCA attack a type of white blood cells called neutrophils, which in turn attack the blood vessel walls. The resulting blood vessel inflammation (vasculitis) can lead to kidney damage (glomerulonephritis) and other complications.

The patients in the study had a particularly aggressive form of vasculitis caused by ANCA against a protein called PR3. They were being treated

with a procedure called plasma exchange therapy (or plasmapheresis), which removes the PR3 ANCA from the blood. "Using an antibody reactive with complementary PR3 protein, produced in the laboratory, we analyzed protein pools removed from the patients' plasma during plasma exchange therapy to identify any existing proteins that were reactive with the anti-complementary PR3 antibody," Dr. Falk explains. Previous studies have suggested that antibodies to complementary proteins may play an important role in the initiation of autoimmune diseases.

The results showed autoantibodies to a complementary protein that, to the researchers' surprise, turned out to be plasminogen—a protein that plays a key role in blood clotting. 22% of the patients with PR3 ANCA vasculitis had anti-plasminogen antibodies, including 56% of those who had serious blood-clotting problems as a complication of their disease. "Identification of potentially pathogenic [disease-causing] anti-plasminogen antibodies provides an explanation of why patients with PR3-ANCA disease have a high incidence of blood clots," says Dr. Falk.

The results may have important implications for the care of patients with ANCA vasculitis—most immediately, in identifying those at high risk of developing blood clots. However, the assay used in the study was inadequate for clinical use. "What is needed is a clinical test that is specific and precise enough to measure anti-plasminogen antibody levels," adds Dr. Falk. Further studies will be needed to establish the clinical value of such a test, including the correlation between complementary antibody levels and the risk of blood clots.

In addition, the study suggests that complementary antibodies may play a more important role in autoimmune diseases than scientists have previously realized. The methods used may lead to the discovery of autoantibodies to complementary proteins in other autoimmune diseases—for example, rheumatoid arthritis or multiple sclerosis.

"Hopefully, our discoveries will entice scientists to consider the potential implications of protein complementarity," says Dr. Falk.

Source: American Society of Nephrology

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