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Team discovers novel anti-NET antibodies in a multinational cohort of antiphospholipid syndrome patients

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Antiphospholipid syndrome is a understudied autoimmune disease that is nevertheless a leading causes of deadly blood clots and late-term

pregnancy loss. An international study led by the University of Michigan researchers Ray Zuo, M.D., and Jason Knight, M.D., Ph.D., has discovered a new class of functional autoantibodies in APS patients that contributes to the disease's development and the systemic inflammation it induces.

Recent studies suggest that APS patients can produce a flurry of overactive immune cells, called neutrophils, that release toxic webs of proteins and DNA called neutrophil extracellular traps, or NETs. These harmful NETs, if not appropriately cleared, can promote inflammation in patients resulting in various clinical complications.

For this study, the team analyzed serum from over 300 APS patients collected by the APS Alliance for Clinical Trials and International Networking international consortium, searching for novel antibodies, called anti-NET antibodies, that might shield the toxic NETs from being destroyed and thereby produce longer lasting noxious effect in the body.

The results reveal elevated levels of the anti-NET in 45% of APS patients worldwide. High anti-NET antibody levels are associated with more circulating toxic NETs in patients' blood and higher levels of inflammation. The team also found that these anti-NET antibodies promote inflammation via a specific pathway called the complement activation pathway.

"While we have suspected the presence of those antibodies based on what we saw in APS patients here at the University of Michigan, this large international study confirmed that these functional anti-NET antibodies are indeed present across a diverse cohort of international patients," said Zuo, lead author and a rheumatologist at Michigan Medicine. "They likely feed into the inflammatory storm responsible for many complications of APS."

Beyond blood clots and adverse pregnancy outcomes, many APS patients suffer from other less-recognized clinical complications, such as low platelet counts, heart valve disease, seizure disorder, kidney damage, and brain lesions. There are few clinically relevant tests that can help physicians predict which APS patients are at risk for these non-clotting complications. The researchers also found that anti-NET antibodies were associated with developing brain "white matter" lesions, which potentially affect the brain's ability to efficiently conduct signals.

"While further studies are needed," said Knight, co-corresponding author of the paper and an associate professor of rheumatology at Michigan Medicine. "Anti-NET antibodies have the potential to help physicians identify patients at risk for certain complications such as the abnormal brain changes that may contribute to difficulties with thinking and memory."

This study stems from APS ACTION, an international research consortium supporting large-scale, multicenter clinical and translational research in APS patients. The consortium has enrolled almost 1,200 antiphospholipid antibody-positive patients as of March 2023, with a collection of detailed demographic and clinical information and blood specimens spanning up to 10 years.

"APS is a relatively rare disease," said Knight. "Without the support of APS ACTION researchers and participants around the world, this study would not have been possible."

"APS ACTION is a unique international research collaborative effort with 43 centers around the globe, including the University of Michigan, open to qualified investigators who are committed to further our understanding of APS and its management," said Doruk Erkan, M.D., M.P.H, founder member and executive committee co-chair of the APS ACTION, Professor of Medicine at Hospital for Special Surgery and

Weill Cornell Medicine, New York, NY. "We will continue to support innovative research and brilliant minds such as Dr. Zuo and Dr. Knight, who are passionate about finding a cure to APS."

NETs themselves are a mixture of DNA, numerous proteins, and other inflammatory molecules, any of which could be targets for "anti-NET antibodies." Utilizing a state-of-the-art high-throughput platform, the team uncovered several specific targets of the identified anti-NET antibodies. Follow-up studies are underway to dive deeper into these particular molecular targets and their associated pathways.

"The better we understand these anti-NET antibodies and their functions, the more equipped we will be to design better therapeutic for APS patients," Zuo said. " As these anti-NET antibodies have been reported in other autoimmune diseases, studying these antibodies will also teach us about the mechanisms of autoimmunity in general."

The study is published in the journal *Arthritis & Rheumatology*.

More information: Yu Zuo et al, Anti-NET antibodies in antiphospholipid antibody-positive patients: Results from the Antiphospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository, *Arthritis & Rheumatology* (2023). DOI: 10.1002/art.42489

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