

Discovery of novel biomarker with remarkable specificity to rheumatoid arthritis

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Rheumatoid arthritis (RA) is an autoimmune disorder that occurs when the immune system mistakenly attacks the body's tissues. Unlike the wear-and-tear damage of osteoarthritis, rheumatoid arthritis affects the lining of the joints, causing painful swelling that can eventually result in bone erosion and joint deformity.

Most RA [patients](#) are positive for anticitrullinated [protein](#) antibodies (ACPA), and these antibodies are highly specific for RA diagnosis. ACPA recognizes various citrullinated proteins, such as fibrinogen, vimentin and glucose- 6-phosphate isomerase. Citrullinated proteins are proteins that have the amino acid arginine converted into the citrulline, which is not one of the 20 standard amino acids encoded by DNA in the genetic code. Autoreactivity to citrullinated protein may increase susceptibility to RA.

While many candidate citrullinated antigens have been identified in RA joints, the involvement of citrullinated proteins in blood serum remains mostly uninvestigated. To that end, a team of University of Tsukuba-centered researchers set out to explore the expression and commonality of citrullinated proteins in peptide glucose-6-phosphate isomerase-induced arthritis (pGIA) and patients with RA, and went one step further to investigate its correlation with RA disease activity. The researchers recently published their findings in *Arthritis Research & Therapy*.

"We examined serum citrullinated proteins from pGIA by western blotting, and the sequence was identified by mass spectrometry. With the same methods, serum citrullinated proteins were analyzed in patients with RA, primary Sjögren's syndrome, [systemic lupus erythematosus](#), and osteoarthritis as well as in healthy subjects," study corresponding author Isao Matsumoto explains. "In patients with RA, the relationship between the expression of the identified protein inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4) and clinical features was also evaluated, and the levels of citrullinated ITIH4 were compared before and after biological treatment."

The researchers found that citrullinated ITIH4 was highly specific to patients with RA, compared with patients with other autoimmune and arthritic diseases or in healthy subjects, indicating a potential role for citrullinated ITIH4 in RA pathogenesis. Notably, its levels were decreased in correlation with the reduction of disease activity score after effective treatment in patients with RA. Moreover, antibody response to citrullinated epitope in ITIH4 was specifically observed in patients with RA.

"Our results suggest that citrullinated ITIH4 might be a novel biomarker to distinguish RA from other rheumatic diseases and for assessing disease activity in patients with RA," Matsumoto says. "To our knowledge, this is the first report of its kind in the literature."

More information: Hoshimi Kawaguchi et al. Identification of novel biomarker as citrullinated inter-alpha-trypsin inhibitor heavy chain 4, specifically increased in sera with experimental and rheumatoid arthritis, *Arthritis Research & Therapy* (2018). [DOI: 10.1186/s13075-018-1562-7](https://doi.org/10.1186/s13075-018-1562-7)

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