Nature Reviews Rheumatology **10**, 3 (2014); published online 19 November 2013; doi:10.1038/nrrheum.2013.182

RHEUMATOID ARTHRITIS

Understanding hypercitrullination in rheumatoid arthritis

The generation of citrullinated antigens in rheumatoid arthritis (RA), as a result of so-called cellular hypercitrullination, is induced by immune-mediated pore-forming pathways, according to new research published in *Science Translational Medicine*. The findings add insights into the role of immune-mediated membranolytic pathways in the development of RA, offering hope for new opportunities for early monitoring and treatment of this disease.

> "Abnormal protein citrullination is suspected of sparking the immune system and driving ... the development of RA"

Existing work has demonstrated that RA joints are enriched in citrullinated proteins. Moreover, autoantibodies against these citrullinated proteins precede the onset of disease and can be used as a biomarker for disease progression. "Abnormal protein citrullination is suspected of sparking the immune system and driving the cause of events leading to the development of RA," explains study author Felipe Andrade.

Andrade and colleagues found a unique pattern of citrullination in cell lysates isolated from synovial fluid from patients with RA. Interestingly, citrullination was observed across a broad range of proteins of different molecular weights, which they termed hypercitrullination.

"Cellular hypercitrullination was not reproduced by cell death and cell-activating pathways previously thought to be responsible for the process," says Andrade. Indeed, the researchers found that hypercitrullination was mediated by perforin and the membrane attack complex (MAC)—both of which are involved in immune-mediated cell membrane lysis and are known to be active in RA joints, although they had been believed to have secondary roles in the development of joint destruction in RA.

Finally, proteomic analysis of neutrophils lysed by either perforin or MAC revealed a similar profile of citrullinated autoantigens as observed in RA synovial fluid cells from patients, including vimentin, histones and collagen. "Pathological citrullination occurring in the rheumatoid joint differs qualitatively and quantitatively from the citrullination occurring under physiological conditions," notes Andrade.

The authors are now working towards determining the mechanisms responsible for abnormal activation of the perforin and MAC pathways in RA joints to hopefully decipher factors that are involved early in the disease process.

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Original article Romero, V. *et al*. Immune-mediated pore-forming pathways induce cellular hypercitrullination and generate citrullinated autoantigens in rheumatoid arthritis. *Sci. Transl. Med.* **5**, 209ra150 (2013)