RHEUMATOID ARTHRITIS

UNRAVELLING THE
ROLES OF NETS IN RA

Neutrophil extracellular traps (NETs) are implicated in several autoimmune diseases, but do they play a part in rheumatoid arthritis (RA)? New research by Mariana Kaplan and colleagues suggests that the production of NETs is indeed increased in patients with RA, resulting in the release of citrullinated autoantigens involved in the disease.

NETs are meshes of chromatin fibres and antimicrobial proteins that are released from neutrophils in a process known as NETosis. They function to trap bacteria, but might also promote autoimmunity. “We became interested in addressing the role of NETosis in RA in part because histone citrullination is required for NET formation,” explains Kaplan. “As responses to citrullinated autoantigens are a characteristic of RA, we hypothesized that externalization of other important RA-related citrullinated autoantigens may occur during NETosis in RA.”

Exploring these ideas, the researchers found that peripheral blood neutrophils from patients with RA had a greater propensity to release NETs than control neutrophils. Moreover, both serum and synovial fluid from patients with RA who had high levels of anti-citrullinated protein antibodies (ACPA) and/or rheumatoid factor could stimulate NET formation in control neutrophils. Similar results were obtained using purified antibody fractions from these patients, whereas control antibodies had less effect. In addition, the proinflammatory cytokines IL-17A and TNF, levels of which are elevated in RA, could together enhance the release of NETs.

Interestingly, NETs produced by neutrophils from patients with RA contained citrullinated vimentin and were recognized by antibodies from such patients, suggesting that they represent a source of RA autoantigens. Furthermore, the researchers uncovered a link between NETosis and joint destruction, by showing that RA NETs can stimulate proinflammatory gene expression in fibroblast-like synoviocytes.

Thus, the authors propose a vicious cycle, whereby RA-associated antibodies and cytokines promote NETosis, which leads to the release of autoantigens that induce further cytokine and ACPA production and joint pathology. “Identifying novel therapeutic targets related to NETs may allow for the development of new drugs in this disease,” concludes Kaplan.

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