RHEUMATOID ARTHRITIS

NETs directly injure cartilage in RA

As one of the most abundant cells in the joints in rheumatoid arthritis (RA), neutrophils have long been associated with the pathogenesis of this disease, but until now, whether they had a direct role in cartilage damage was not known. The results of a new study suggest that neutrophil elastase, an enzyme present in neutrophil extracellular traps (NETs), can both degrade cartilage and stimulate downstream inflammatory processes mediated by fibroblast-like synoviocytes (FLS).

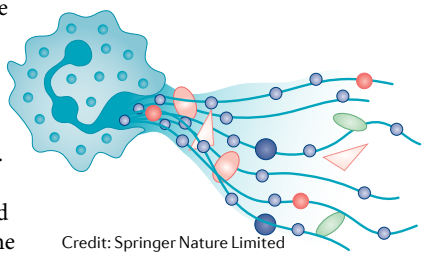
"Our group and others have shown that neutrophils may play an important role in RA initiation and perpetuation," states co-corresponding author Carmelo Carmona-Rivera. "Neutrophils from patients with RA display an enhanced capacity to form NETs, and these lattices externalize citrullinated autoantigens and promote immune dysregulation in the synovium."

"We had previously also found that FLS respond to NETs by exhibiting a pro-inflammatory phenotype, suggesting a connection between neutrophils, FLS and cartilage integrity," adds co-corresponding author Mariana Kaplan.

In their new study, the authors showed that supernatants from NET-treated FLS from patients with RA could degrade aggrecan, one of the main components of cartilage. This degradation was not caused by aggrecanases produced by FLS or present in the NETs, but instead by NET-associated neutrophil elastase. Interestingly, this NET-derived neutrophil elastase also caused the release of peptidylarginine deiminase 2 (PAD2) from FLS.

"The release of PAD2 enhanced citrullination of the formed cartilage fragments that were in turn taken up by FLS and presented to antigen-specific $CD4^+$ T cells, promoting their activation and the production of autoantibodies against citrullinated cartilage fragments," explains Carmona-Rivera. "In turn, these autoantibodies activated macrophages to release pro-inflammatory cytokines that activated synovial neutrophils to release more neutrophil elastase, in a feed-forward loop that exacerbated articular inflammation."

> "neutrophil elastase … can both degrade cartilage and stimulate downstream inflammatory processes"



Credit: Springer Nature Limited

The authors suggest that this new mechanism of cartilage destruction and inflammation could be targeted therapeutically in the future. "Pathways that inhibit NET formation or the effects of molecules present in NETs could be a useful therapeutic approach for RA and its associated organ damage," says Kaplan.

Joanna Clarke

ORIGINAL ARTICLE Carmona-Rivera, C. et al. Neutrophil extracellular traps mediate articular cartilage damage and enhance cartilage component immunogenicity in rheumatoid arthritis. *JCI Insight* https://doi.org/10.1172/jci.insight.139388 (2020)

TARGETED THERAPY

Targeted delivery of immunosuppressant in SLE

Immunosuppressive drugs such as cyclosporine A (CsA) are used for the treatment of various rheumatic diseases, including systemic lupus erythematosus (SLE), but their use is hampered by high non-response rates and adverse effects. Targeted delivery of immunosuppressant drugs could help overcome these issues, as shown in a new study published in *Science Advances*.

"Because CsA strongly inhibits T cell activation and proliferation, and the aetiology of SLE involves abnormal T cell and B cell hyperactivity, there has been a long and ongoing interest in using CsA as a treatment for SLE," explains corresponding author Ravi Kumar. "However, current oral dosage forms of CsA are limited by two major drawbacks: poor bioavailability that necessitates elevated doses and severe nephrotoxicity that arises from the increased dosage."

> "Immunosuppressive drugs … are … hampered by high non-response rates and adverse effects"

To address this issue, his group developed a drug delivery system composed of polyester nanoparticles conjugated to gambogic acid. "We showed that gambogic acid-conjugated nanoparticles are more than six times more likely to bind to T cells than unconjugated nanoparticles," reports Kumar. "As T cells are the primary targets of CsA, having nanoparticles with high affinity for T cells might provide additional drug specificity and disposition to this cell type."

In a mouse model of SLE, Kumar and colleagues tested the effects of nanoparticle-mediated delivery of CsA against treatment with a generic formulation of CsA. "We were entirely surprised to note that almost every inflammatory cytokine marker tested had been normalized by this nanoparticle–CsA formulation, leading to mice that had near wild-type physiological and anatomical characteristics," says Kumar. By contrast, the generic formulation had negligible effects compared with no treatment, in line with current consensus for using CsA as a glucocorticoid-sparing therapy, rather than as a standalone treatment, in SLE.

Credit: Zoonar GmbH/Alamy Stock Photo

Kumar and his group would like to test this delivery system in other animal models, including elucidating the most effective dose and uncovering any associated toxicities, with the long-term aim of translating these findings to human efficacy studies.

Jessica McHugh

ORIGINAL ARTICLE Ganugula, R. et al. A highly potent lymphatic system–targeting nanoparticle cyclosporine prevents glomerulonephritis in mouse model of lupus. *Sci. Adv.* **6**, eabb3900 (2020)