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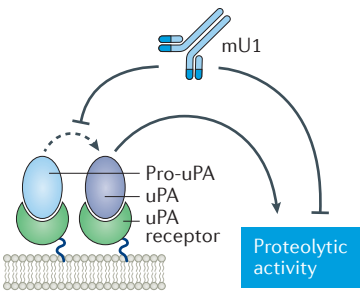
EXPERIMENTAL ARTHRITIS

Targeting proteolysis to halt arthritis

> assessment of affected joints demonstrated a reduction in synovitis and joint destruction

Proteinases are involved in several processes known to contribute to inflammatory arthritis, including coagulation and fibrinolysis. The fibrinolytic proteinase urokinase-type plasminogen activator (uPA) is found in the joints of patients with rheumatoid arthritis (RA), but the exact role of this protein in disease has been unclear. Researchers, working closely with Novo Nordisk, have now demonstrated the effects of blocking the proteolytic action of uPA in experimental arthritis.

"Our aim was to show proof-of-principle for treating inflammatory arthritis in a mouse model using an antibody to uPA," states corresponding author Kasper Almholt. The monoclonal antibody chosen for this study, mU1, had previously been shown to be effective in altering wound healing and fibrinolysis in mice and was known to block the conversion of pro-uPA into uPA, as well as blocking the proteolytic activity of uPA.



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"We chose the widely used collagen-induced arthritis (CIA) mouse as a model of systemic and progressive inflammatory arthritis, and to complement it with a transient arthritis model induced in a single joint, we chose the delayed-type hypersensitivity (DTH)-arthritis model," explains Almholt.

Using these models, the researchers showed that mU1 could reduce established disease compared with a control antibody. Histopathological assessment of affected joints demonstrated a reduction in synovitis and joint destruction in mice with CIA treated with mU1 compared with a control antibody, and reductions in synovitis, bone erosion and cartilage degradation, but not in new bone formation or extra-articular inflammation in mice with DTH-arthritis treated with mU1 compared with a control antibody. In addition, in mice with CIA, mU1 treatment reduced the clinical score over the 2-week observation period to the same level as that seen in mice treated with the anti-TNF treatment etanercept.

Looking towards translating these findings into humans, Almholt and colleagues examined synovial tissue from patients with RA and healthy individuals, discovering that uPA was only present in tissue from patients with RA. Upon further investigation, they found the expression of uPA was restricted to macrophages, neutrophils and some endothelial cells.

"We have now shown that the proteolytic activity of uPA is required for arthritis progression in vivo, and have paved the way for a targeted therapeutic intervention," concludes Almholt.

Joanna Collison

ORIGINAL ARTICLE Almholt, K. et al. Antibody-mediated neutralization of uPA proteolytic function reduces disease progression in mouse arthritis models. *J. Immunol.* **200**, 957–965 (2018)
FURTHER READING Oikonomopoulou, K. et al. Proteinases and their receptors in inflammatory arthritis: an overview. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/nrrheum.2018.17 (2018)