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CONNECTIVE TISSUE DISEASES

Initiating fibrotic manifestations of SSc

Tackling the fibrotic complications of systemic sclerosis (SSc) by blocking the extrinsic coagulation system might be a new avenue for therapy in the disease, according to new data from Konstantinos Ritis and colleagues, published in *Arthritis & Rheumatism*. The researchers describe a signaling amplification loop that links thrombin, tissue factor, connective tissue growth factor (CTGF, also known as CCN2) and endothelin-1 in SSc fibrosis.

CTGF—expression of which can be induced by thrombin—promotes the activation of fibroblasts, leading to fibrosis (deposition of collagen), and has been implicated in the pathological fibrosis of SSc. Another feature of SSc pathology, vasculopathy, involves endothelin-1. The researchers investigated the role of crosstalk between the thrombin and endothelin-1 signaling axes in SSc fibrosis, using colonic myofibroblasts (HCMFs) isolated from patients with SSc. Compared with control HCMFs, they found that these cells had enhanced expression of CTGF, which was abrogated by inhibition of either thrombin or its receptor, proteinase-activated receptor 1. Similarly, SSc HCMFs expressed higher levels of tissue factor than their control counterparts, and expressed more of the endothelin-1 receptor ETA (and less of ETB) than the controls. Culturing the control HCMFs with low doses of thrombin induced *ETA* expression, and a combination of thrombin pretreatment and addition of endothelin-1 caused increased expression of tissue factor in the control HCMFs. As tissue factor in turn induces thrombin, the findings point to a vicious circle that causes aberrant activation of fibroblasts in SSc.

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Original article Chrysanthopoulou, A. *et al.* Tissue factor–thrombin signaling enhances the fibrotic activity of myofibroblasts in systemic sclerosis through endothelin-1 receptor A up-regulation. *Arthritis Rheum.* doi:10.1002/art.30586