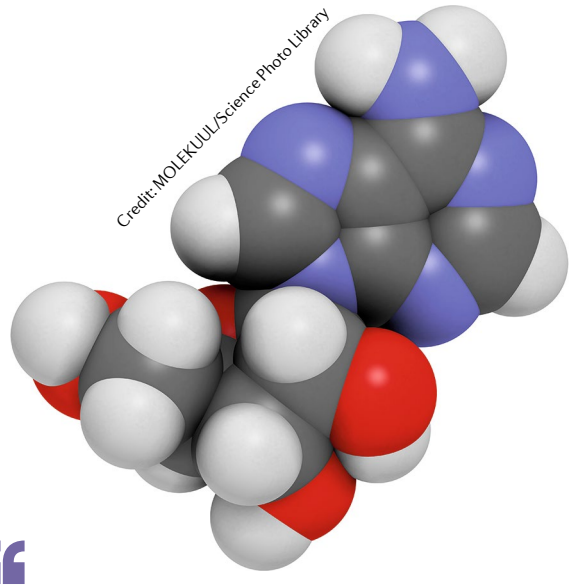
SYSTEMIC SCLEROSIS

Targeting adenosine in SSc


Credit: MOLEKUUL/Science Photo Library

Aberrant activation of adenosine-dependent signalling has been implicated in a number of fibrotic diseases, including systemic sclerosis (SSc). The results of a new study indicate that adenosine depletion with recombinant pegylated adenosine deaminase (PEG-ADA) improves the three cardinal features of SSc, namely fibrosis, inflammation and vasculopathy, in preclinical models of the disease.

PEG-ADA is currently used as enzyme replacement therapy for patients with adenosine deaminase severe combined immunodeficiency (ADA-SCID). "As PEG-ADA is already used for the treatment of ADA-SCID and is well tolerated even with long-term application, our findings could have clinical implications and stimulate clinical trials with PEG-ADA in SSc," notes Yun Zhang, first author of the study.

Targeting adenosine signalling in SSc has been attempted before, primarily by inactivation of CD73 (an ectonucleotidase important in adenosine production) or by targeting individual adenosine receptors. However, neither approach has yielded an effective treatment for SSc.

In the present study, Zhang and colleagues investigated the effects of PEG-ADA in two mouse models of SSc: *Fra2*-transgenic mice and the sclerodermatous chronic graft-versus-host disease (Scl-GVHD) mouse model. In both models, treatment with PEG-ADA inhibited myofibroblast differentiation and ameliorated fibrosis in the skin, lungs and intestines, organ systems commonly affected in SSc. "The antifibrotic effects in the mouse models were also translated to the human context using a full-thickness skin model," notes Zhang.

> "treatment with PEG-ADA inhibited myofibroblast differentiation and ameliorated fibrosis in the skin, lungs and intestines"

Treatment with PEG-ADA also prevented vascular manifestations in *Fra2*-transgenic mice and dampened the inflammatory response in both the Scl-GVHD and *Fra2*-transgenic mouse models. RNA-Seq analysis demonstrated that PEG-ADA treatment normalized the expression of several genes related to fibrosis, vasculopathy and inflammation in *Fra2*-transgenic mice.

Sarah Onuora

ORIGINAL ARTICLE Zhang, Y. et al. Recombinant adenosine deaminase ameliorates inflammation, vascular disease and fibrosis in preclinical models of systemic sclerosis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41259 (2020)

OSTEOARTHRITIS

PDGF-BB is the key to unlocking pathological angiogenesis in OA

Subchondral bone angiogenesis and neovascularization of the articular cartilage are features known to develop at an early stage during osteoarthritis (OA), but the exact mechanisms behind these processes have been unclear. A new study has uncovered a role for platelet-derived growth factor (PDGF)-BB in subchondral bone angiogenesis and in the development of OA in mice.


Credit: Tetra Images/Getty

"Our study provides the first evidence that PDGF-BB derived from preosteoclasts is a key promoter of pathological subchondral bone angiogenesis during OA development," states corresponding author Mei Wan.

To assess the role of PDGF-BB in disease, Wan and colleagues used the destabilization of the medial meniscus (DMM) model of OA. "In mice after joint destabilization, mononuclear preosteoclasts in the subchondral bone secreted excessive amounts of PDGF-BB, which activated PDGF receptor-β signalling in pericytes for neovessel formation," explains Wan.

The researchers used conditional PDGF-BB-knockout and transgenic mice that either lacked or overexpressed *Pdgfb* in osteoclast lineage cells. In this way, they could specifically assess the role of PDGF-BB production by preosteoclasts. "By using conditional PDGF-BB-knockout mice and conditional PDGF-BB transgenic mice, we found that PDGF-BB derived from preosteoclasts is both sufficient and necessary for the development of subchondral bone angiogenesis and subsequent joint degeneration," says Wan.

> "conditional PDGF-BB transgenic mice spontaneously developed OA-like disease"

Conditional PDGF-BB-knockout mice had reduced subchondral bone angiogenesis compared with wild-type mice following DMM and developed less severe disease than sham-operated mice. Interestingly, the conditional PDGF-BB transgenic mice spontaneously developed OA-like disease. "Our transgenic mice can serve as an ideal spontaneous OA model that should help investigators study the pathogenesis of joint degeneration and OA pain, develop early interventions and test the efficacy of new treatments for human OA," suggests Wan.

Joanna Clarke

ORIGINAL ARTICLE Su, W. et al. Angiogenesis stimulated by elevated PDGF-BB in subchondral bone contributes to osteoarthritis development. *JCI Insight* https://doi.org/10.1172/jci.insight.135446 (2020)