Clinical Connections

Inhibition of the Progression of Skin Inflammation, Fibrosis, and Vascular Injury by Blockade of the CX3CL1/CX3CR1 Pathway in Experimental Mouse Models of Systemic Sclerosis

Luong et al, Arthritis Rheumatol 2019;71:1923–1934

CORRESPONDENCE
Minoru Hasegawa, MD, PhD: minoruha@u-fukui.ac.jp

KEY POINTS
- Anti-CX3CL1 (anti-fractalkine) mAb inhibits skin fibrosis in mouse models induced by subcutaneous bleomycin or growth factor administration.
- Anti-CX3CL1 mAb therapy attenuates inflammation and vascular injury in bleomycin-damaged skin.
- Anti-CX3CL1 mAb suppresses extracellular matrix production by normal skin fibroblasts via inhibition of TGFβ1/Smad signaling.

SUMMARY
Interaction between the chemokine CX3CL1 (fractalkine) and its receptor CX3CR1 induces cell adhesion and chemotaxis. In systemic sclerosis (SSc), cytokines produced by inflammatory cells are believed to contribute to the development of tissue fibrosis and vascular injury. Luong et al used the bleomycin-induced and growth factor–induced mouse models of SSc to demonstrate that anti-CX3CL1 monoclonal antibody (mAb) therapy suppressed the progression of inflammation, fibrosis, and vascular injury in skin. Interestingly, anti-CX3CL1 mAb reduced the extracellular matrix expression by normal fibroblasts via inhibition of transforming growth factor β1 (TGFβ1)/Smad signal transduction. Thus, anti-CX3CL1 mAb treatment may be effective for skin fibrosis by reducing leukocyte infiltration and extracellular matrix synthesis from fibroblasts in SSc. These conclusions suggest that anti-CX3CL1 mAb may be a promising candidate for clinical trials of inflammation-driven skin fibrosis such as SSc.
Clinical Connections

Osteoclast-Derived Autotaxin, a Distinguishing Factor for Inflammatory Bone Loss


**CORRESPONDENCE**

Irma Machuca-Gayet, PhD: irma.machuca-gayet@inserm.fr
Fabienne Coury, MD, PhD: fabienne.coury-lucas@chu-lyon.fr

**SUMMARY**

Osteoclasts are responsible for focal bone erosions and systemic bone loss in rheumatoid arthritis (RA). Autotaxin (ATX), encoded by the *ENPP2* gene, is a lysophospholipase D that converts lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA). Prior studies have shown that LPA controls both osteoclastogenesis and osteoclast bone resorption through its receptor LPA_1 and that ATX is up-regulated in the synovial fluid of RA patients and contributes to synovial inflammation. Flammier et al demonstrated that ATX is expressed in osteoclasts present at inflammatory sites and is up-regulated by tumor necrosis factor (TNF). Pharmacologic inhibition of ATX significantly mitigated focal and systemic bone loss without affecting synovial inflammation in a human TNF–transgenic (*hTNF*+/−) mouse model. Conditional deletion of ATX in osteoclasts was found to be protective against systemic bone loss and bone erosion in a mouse model of RA. In the circumstance of noninflammatory bone loss observed in mice after ovariectomy, ATX inactivation in osteoclasts did not prevent bone loss. The authors concluded that ATX is a new factor that controls inflammation-induced bone loss without interfering in osteoclast function in noninflammatory conditions and may be a promising therapeutic target for the prevention of bone erosion in RA.

**KEY POINTS**

- ATX is highly up-regulated in osteoclasts by TNF.
- ATX is a key autocrine factor in osteoclast-mediated bone resorption in inflammatory settings.
- Selective inhibition of osteoclast-derived autotaxin prevents bone destruction in inflammatory models of RA.
- ATX abrogation does not affect physiologic osteoclast-mediated resorption, suggesting a possible therapeutic approach for preventing bone erosion in RA.