

# **THROMBIN-INDUCED CCN2 EXPRESSION AS A TARGET FOR ANTI-FIBROTIC THERAPY IN SCLERODERMA**

Andrew Leask

CIHR Group in Skeletal Development and Remodeling, Division of Oral Biology,  
Department of Dentistry, Schulich School of Medicine and Dentistry, Dental Sciences  
Building, University of Western Ontario, London ON, Canada, N6A 5C1

Andrew.leask@schulich.uwo.ca

## **ABSTRACT**

**Scleroderma (systemic sclerosis, SSc) is a fibrotic disease for which there is no therapy. CCN2 (connective tissue growth factor, CTGF) is a marker and mediator of fibrosis. Previously, it has been shown that thrombin induces CCN2 expression in fibroblasts. In a recent fascinating report, Bogatkevich and colleagues (Arthritis Rheum. 60:3455-3464, 2009) show that dabigatran, an inhibitor of thrombin action, blocks the overexpression of CCN2 by scleroderma fibroblasts and reverses the contractile phenotype of these cells. These results strongly suggest that dabigatran may be a potential antifibrotic drug for the treatment of fibrosing diseases such as scleroderma.**

SSc is a prototypical multisystem disease with a significant fibrotic component; patients often die due to lung fibrosis (Varga and Abraham, 2007). There is no therapy for SSc; however, recent studies have shown that, as for other fibroproliferative diseases, a particular type of differentiated fibroblast, termed the myofibroblast, contributes to scar formation in this disease (Chen et al., 2005). Myofibroblasts are characterized by an

increased proliferative and contractile capacity and abundant expression of  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), collagens, and other ECM proteins ([Hinz et al., 2007]. Overexpression of CCN2 is also considered to be a key marker of fibrotic fibroblasts; the levels of CCN2 expression correlate well with the severity of fibrosis in SSc (Leask, 2004; Dzadzio et al., 2005; Leask et al., 2009). Thus, targeting the action of the myofibroblast is essential for developing rational therapies for SSc. Of note, it is essential to remember that, in spite of the fact that in vitro the potent pro-fibrotic cytokine transforming growth factor  $\beta$  (TGF $\beta$ ) induces  $\alpha$ -SMA expression and myofibroblast differentiation, blocking canonical TGF $\beta$  signaling does not affect the  $\alpha$ -SMA or CCN2 expression in scleroderma fibroblasts (Leask, 2006; Chen et al., 2006).

When applied to lung fibroblasts, thrombin, a multifunctional serine protease and a key enzyme of blood coagulation that catalyzes the conversion of fibrinogen to fibrin (Green, 2006), induces myofibroblast formation and CCN2 expression (Chambers et al., 2000; Bogatkevich et al., 2001). Dabigatran is a selective direct thrombin inhibitor that reversibly binds to thrombin and prevents the cleavage of fibrinogen to fibrin (Sorbrera et al., 2005). In a recent study by Bogatkevich and colleagues, dabigatran blocked thrombin-induced myofibroblast differentiation, and suppressed CCN2,  $\alpha$ -SMA, and collagen overexpression by scleroderma fibroblasts.

Previously, it was shown that inhibition of endothelin-1, but not canonical TGF $\beta$  signaling, reverses the  $\alpha$ -SMA and CCN2 overexpression by SSc fibroblasts (Shi-wen et al., 2004, 2007; Chen et al., 2006). Thrombin itself has been demonstrated to induce

endothelin-1 (Lepailleur-Enouf et al., 2000). These data suggest that thrombin activity may be responsible for the overexpression of endothelin-1,  $\alpha$ -SMA and CCN2 in SSc fibroblasts and thus for the fibrosis observed in this disease.

This study suggests that dabigatran might prove to be a promising drug for the treatment of fibrotic conditions where there is thrombin overexpression. However, studies using additional in vivo preclinical models are required first, prior to conducting extensive clinical trials.

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