

**CCN2: DECORIN INTERACTIONS**  
**A NOVEL APPROACH TO COMBATING FIBROSIS?**

Andrew Leask  
Department of Dentistry  
University of Western Ontario  
London ON Canada N6A 5C1  
[Andrew.leask@schulich.uwo.ca](mailto:Andrew.leask@schulich.uwo.ca)

**ABSTRACT**

**CCN2 (connective tissue growth factor, CTGF), a member of the CCN family is overexpressed in fibrotic disease and is essential for the development of experimental fibrosis. Drugs targeting CCN2 action may therefore prove to be useful anti-fibrotic approaches. CCN2 acts via integrins and heparan sulfate-containing proteoglycans (HSPGs). In a recent study, Vial and colleagues (2011) show that decorin can bind CCN2. A peptide corresponding to the leucine rich repeats peptide 12 region of decorin can neutralize CCN2-mediated activity on C2C12 cells in vitro. Thus it is conceivable that this peptide could be used in the future as a novel antifibrotic approach.**

Fibrotic disorders represent one of the largest groups of diseases for which there is no therapy. It has long been known that the matricellular protein CCN2 (connective tissue growth factor, CTGF) is (a) rapidly induced by fibrogenic cytokines such as TGF $\beta$  and (b) highly expressed in a wide range of fibrotic conditions (Igarishi et al., 1993; Blom et al., 2002). Based on these observations, and that fibrogenic activities can be attributable to CCN2, the notion emerged that CCN2 could represent a novel target for anti-fibrotic

drug intervention (Goldschmeding et al., 2000; Moussad and Brigstock, 2000; Leask et al., 2002). As discussed in an earlier Bits and Bytes, precise evidence using has finally emerged that clearly indicates that CCN2 is indeed required for experimental fibrosis (Leask, 2011).

Several different strategies that target the profibrotic action of CCN2 have emerged; for example, using siRNA, a hammerhead ribozyme, antisense RNA or specific antibodies (Sisco et al., 2008; Gao and Brigstock, 2009; Brigstock, 2009; Ponticos et al., 2009; Wang et al., 2011). These strategies are aimed at generally blocking CCN2 expression or action. However, CCN2 has functions other than promoting fibrosis (Leask and Abraham, 2006); thus a better approach may be to uncover methods of directly targeting CCN2's pro-fibrotic actions.

To develop such a selective anti-fibrotic approach, it might be wise to block specific interactions between CCN2 and its receptors/ligands. The mechanism of action for CCN2 is complex, owing to the fact that CCN2, as an adhesive protein, can bind many different ligands including integrins and components of the extracellular matrix (Leask and Abraham, 2006; Chen and Lau, 2009; Perbal, 2004). For example, CCN2 possesses a heparin-binding domain; indeed, CCN2 can interact with a variety of heparan sulfate-containing proteoglycans (HSPGs) (Leask and Abraham, 2006; Chen and Lau, 2010; Gao and Brigstock, 2005). These latter proteins, although found on the cell surface, can also be soluble; thus it is possible that individual HSPGs could represent novel, anti-fibrotic therapeutic approaches through their ability to block CCN2 action.

In a recent report, Vial and colleagues (2011) test this latter hypothesis by exploring whether the HSPG decorin, which has previously been shown to suppress TGF $\beta$  activity (Kolb et al., 2001), regulates CCN2 action on cells. To begin to investigate this issue, the authors used a C2C12 myoblast cell line deficient in decorin to show, that in the absence of decorin, CCN2 potently induces expression of fibronectin. Moreover, they showed that recombinant decorin blocked the ability of CCN2 to induce fibronectin expression in C2C12 cells. Decorin and CCN2 bound each other directly; the authors delineated the

precise region of decorin (in leucine rich repeats peptide 12) that was responsible for this interaction. CCN2 was also able to induce decorin expression, providing a method of controlling the action of endogenous CCN2 protein.

These exciting data not only provide evidence of yet another HSPG that can interact with CCN2, but also provide a biologically-based method of selectively interfering with the pro-fibrotic action of CCN2 using a relatively small peptide. It would be interesting to ascertain whether the leucine rich repeats peptide 12 region of decorin could reverse experimental fibrosis *in vivo*.

## **REFERENCES**

Blom IE, Goldschmeding R, Leask A. (2002) Gene regulation of connective tissue growth factor: new targets for antifibrotic therapy? *Matrix Biol.* 21:473-82

Brigstock DR. (2009) Strategies for blocking the fibrogenic actions of connective tissue growth factor (CCN2): From pharmacological inhibition *in vitro* to targeted siRNA therapy *in vivo*. *J Cell Commun Signal.* 3:5-18.

Chen CC, Lau LF. (2009) Functions and mechanisms of action of CCN matricellular proteins. *Int J Biochem Cell Biol.* 41:771-83.

Chen CC, Lau LF. (2010) Deadly liaisons: fatal attraction between CCN matricellular proteins and the tumor necrosis factor family of cytokines. *J Cell Commun Signal.* 4:63-9

Gao R, Brigstock DR. (2005) Connective tissue growth factor (CCN2) in rat pancreatic stellate cell function: integrin  $\alpha 5 \beta 1$  as a novel CCN2 receptor. *Gastroenterology.* 129:1019-30.

Gao RP, Brigstock DR. (2009) Connective tissue growth factor hammerhead ribozyme attenuates human hepatic stellate cell function. *World J. Gastroenterol.* 15:3807-13.

Goldschmeding R, Aten J, Ito Y, Blom I, Rabelink T, Weening JJ. (2000) Connective tissue growth factor: just another factor in renal fibrosis? *Nephrol Dial Transplant.* 15:296-9.

Igarashi A, Okochi H, Bradham DM, Grotendorst GR. (1993) Regulation of connective tissue growth factor gene expression in human skin fibroblasts and during wound repair. *Mol Biol Cell.* 4:637-45.

Kolb M, Margetts PJ, Sime PJ, Gauldie J. (2001) Proteoglycans decorin and biglycan differentially modulate TGF-beta-mediated fibrotic responses in the lung. *Am J Physiol Lung Cell Mol Physiol.* 280:L1327-34.

Leask A 2011 CCN2: a bona fide target for antifibrotic drug intervention, *J. Cell Commun Signal*, epub

Leask A, Abraham DJ. (2006) All in the CCN family: essential extracellular signaling modulators emerge from the bunker. *J Cell Sci.* 119:4803-10.

Leask A, Holmes A, Abraham DJ. (2002) Connective tissue growth factor: a new and important player in the pathogenesis of fibrosis. *Curr Rheumatol Rep.* 4:136-42.

Moussad EE, Brigstock DR. (2000) Connective tissue growth factor: what's in a name? *Mol Genet Metab.* 71:276-92

Perbal B. (2004) CCN proteins: multifunctional signalling regulators. *Lancet.* 363:62-4

Ponticos M, Holmes AM, Shi-wen X, Leoni P, Khan K, Rajkumar VS, Hoyles RK, Bou-Gharios G, Black CM, Denton CP, Abraham DJ, Leask A, Lindahl GE. (2009) Pivotal role of connective tissue growth factor in lung fibrosis: MAPK-dependent transcriptional activation of type I collagen. *Arthritis Rheum.* 60:2142-55.

Sisco M, Kryger ZB, O'Shaughnessy KD, Kim PS, Schultz GS, Ding XZ, Roy NK, Dean NM, Mustoe TA. (2008) Antisense inhibition of connective tissue growth factor (CTGF/CCN2) mRNA limits hypertrophic scarring without affecting wound healing in vivo. *Wound Repair Regen.* 16:661-73.

Vial C, Gutierrez J, Santander C, Cabrera D, Brandan E. Decorin interacts with CTGF/CCN2 through LRR12 inhibiting its biological activity. *J Biol Chem.* 2011 Mar 23. [Epub ahead of print]

Wang Q, Usinger W, Nichols B, Gray J, Xu L, Seeley TW, Brenner M, Guo G, Zhang W, Oliver N, Lin A, Yeowell D. (2011) Cooperative interaction of CTGF and TGF- $\beta$  in animal models of fibrotic disease. *Fibrogenesis Tissue Repair.* 4:4.