Yin and Yang revisited: CCN3 as an anti-fibrotic therapeutic?

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Abstract Fibrotic diseases are a significant cause of mortality. It is being increasingly appreciated that the cellular microenvironment plays a key role in promoting pathological fibrosis. A previous Bits and Bytes described an elegant series of experiments published by Bruce Riser and colleagues (Am J Pathol. 2009; 174:1725–34) that showed that CCN3 (nov) antagonizes the fibrogenic effects of CCN2 and hence could represent a novel anti-fibrotic therapy. They have continued their excellent work and have recently used the ob/ob mouse as a model of obesity and diabetic nephropathy to show that CCN3 could block the induction of profibrotic gene expression, fibrosis and loss of kidney function (Am J Pathol. 2014; 184:2908–21). Also, reversal of fibrosis was observed. Thus this paper provides strong evidence that CCN3 may be used as a novel therapy to treat diabetes caused by obesity.

Keywords CTGF · CCN2 · CCN3 · Nov · Fibrosis

There are no Food and Drug Administration–approved drugs that specifically target fibrotic disease. Diabetic nephropathy (DN) associated with fibrosis is a significant complication of diabetes and may contribute to renal failure. In many patients, angiotensin II inhibitors

can slow the progression of renal failure (Melchior et al. 1993). However, novel methods that block or reverse renal fibrosis are needed.

The CCN family of matricellular proteins (Brigstock et al. 2003) are known to be dysregulated and participate in organ fibrosis; e.g., CCN2 is both a marker and mediator of fibrosis (Blom et al. 2002; Trojanowska 2009) and anti-CCN2 strategies (antibodies and antisense strategies) are currently in clinical trials for pulmonary fibrosis. Indeed, CCN2 is a well-established downstream mediator of fibrosis (Abdel Wahab and Mason 2004; Phanish et al. 2010; Fragiadaki et al. 2012; Liu et al. 2013). However, issues of possible functional redundancy among CCN family members exist; for example, both CCN4 and CCN6 have been proposed to be potent fibrogenic mediators (Königshoff et al. 2009; Jian et al. 2014; Batmunkh et al. 2011). Moreover, owing to potential issues relating to achieving proper tissue penetration with an antibody and knockdown efficiency with antisense, additional methods of targeting CCN2 are might be warranted.

A possibility has been raised that CCN3, also known as nov, may be an endogenous inhibitor of CCN2 and hence could be used as an antifibrotic agent. The expression of CCN3 is reciprocally regulated to CCN2; for example, in a prior report referred to in a previous Bits and Bytes, Riser and colleagues found that CCN3 was constitutively expressed by mesangial cells in culture (Riser et al. 2009; Leask 2009). In this report, the authors exposed mesangial cells to TGF- β and found that, although CCN2 and type I collagen expression were elevated, CCN3 expression was reduced. Moreover, they found that CCN3 could directly suppress CCN2 and type I collagen expression.

In a subsequent paper published in JCCS, Riser and colleagues showed that, in an animal model of obesity (ob/ob), the level of renal cortex CCN2 mRNA shows markedly elevated expression early, but falls gradually to baseline; conversely, CCN3 levels show essentially the opposite pattern

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(Riser et al. 2010). The same authors have now gone on to show that rCCN3 can prevent the development of diabetes-induced fibrosis (Riser et al. 2014). rCCN3 was injected into db/db mice at a time when the onset of albuminuria occurred. rCCN3 was delivered by i.p. injection three times per week, and treatment was stopped after 8 weeks (i.e., at 17 weeks of age) CCN3 blocked the progression of fibrosis in this model, as visualized by several criteria. For example, CCN3 blocked the induction of CCN2, type I collagen mRNA and TGF β 1 mRNA expression. Moreover, CCN3-treated db/db mice showed reduced mesangial cell expansion and levels of plasma creatine and albuminuria. CCN3 also blocked of renal cortical CCN2 protein expression, glomerular laminin deposition, and podocyte loss, all characteristics of human DN.

Thus CCN3 or peptides derived from CCN3 may represent a viable anti-fibrotic treatment in DN.

References

- Abdel Wahab N, Mason RM (2004) Connective tissue growth factor and renal diseases: some answers, more questions. *Curr Opin Nephrol Hypertens* 13:53–58
- Batmunkh R, Nishioka Y, Aono Y, Azuma M, Kinoshita K, Kishi J, Makino H, Kishi M, Takezaki A, Sone S (2011) CCN6 as a profibrotic mediator that stimulates the proliferation of lung fibroblasts via the integrin β 1/focal adhesion kinase pathway. *J Med Invest* 58:188–196
- Blom IE, Goldschmeding R, Leask A (2002) Gene regulation of CTGF: new targets for antifibrotic therapy? *Matrix Biol* 21:473–482
- Brigstock DR, Goldschmeding R, Katsube KI, Lam SC, Lau LF, Lyons K, Naus C, Perbal B, Riser B, Takigawa M, Yeger H (2003) Proposal for a unified CCN nomenclature. *Mol Pathol* 56(2):127–128
- Fragiadaki M, Hill N, Hewitt R, Bou-Gharios G, Cook T, Tam FW, Domin J, Mason RM (2012) Hyperglycemia causes renal cell damage via CCN2-induced activation of the TrkA receptor: implications for diabetic nephropathy. *Diabetes* 61:2280–2288
- Jian YC, Wang JJ, Dong S, Hu JW, Hu LJ, Yang GM, Zheng YX, Xiong WJ (2014) Wnt-induced secreted protein 1/CCN4 in liver fibrosis both in vitro and in vivo. *Clin Lab* 60:29–35
- Königshoff M, Kramer M, Balsara N, Wilhelm J, Amarie OV, Jahn A, Rose F, Fink L, Seeger W, Schaefer L, Günther A, Eickelberg O (2009) WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. *J Clin Invest* 119:772–787
- Leask A (2009) Yin and Yang: CCN3 inhibits the pro-fibrotic effects of CCN2. *J Cell Commun Signal* 3:161–162
- Liu S, Parapuram SK, Leask A (2013) Fibrosis caused by loss of PTEN expression in mouse fibroblasts is crucially dependent on CCN2. *Arthritis Rheum* 65:2940–2944
- Melchior WR, Bindlish V, Jaber LA (1993) Angiotensin-converting enzyme inhibitors in diabetic nephropathy. *Ann Pharmacother* 27:344–350
- Phanish MK, Winn SK, Dockrell ME (2010) Connective tissue growth factor-(CTGF, CCN2)—a marker, mediator and therapeutic target for renal fibrosis. *Nephron Exp Nephrol* 114:e83–e92
- Riser BL, Najmabadi F, Perbal B, Peterson DR, Rambow JA, Riser ML, Sukowski E, Yeger H, Riser SC (2009) CCN3 (NOV) is a negative regulator of CCN2 (CTGF) and a novel endogenous inhibitor of the fibrotic pathway in an in vitro model of renal disease. *Am J Pathol* 174:1725–1734
- Riser BL, Najmabadi F, Perbal B, Rambow JA, Riser ML, Sukowski E, Yeger H, Riser SC, Peterson DR (2010) CCN3/CCN2 regulation and the fibrosis of diabetic renal disease. *J Cell Commun Signal* 4:39–50
- Riser BL, Najmabadi F, Garchow K, Barnes JL, Peterson DR, Sukowski EJ (2014) Treatment with the matricellular protein CCN3 blocks and/or reverses fibrosis development in obesity with diabetic nephropathy. *Am J Pathol* 184:2908–2921
- Trojanowska M (2009) Noncanonical transforming growth factor beta signaling in scleroderma fibrosis. *Curr Opin Rheumatol* 21(6):623–629