CCN3: a novel anti-fibrotic treatment in end-stage renal disease?

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Abstract Fibrosis is a major cause of end-stage renal disease (ESRD), a progressive loss in renal function that occurs over a period of months or years, is characterized by a decreased capability of the kidneys to excrete waste products. There is no specific treatment unequivocally shown to slow the worsening of chronic kidney disease. Plasma levels of CCN2, a fibrogenic agent, is a predictor of ESRD and mortality in patients with type 1 diabetic nephropathy. CCN3 has been hypothesized to have antagonistic effects to CCN2 both in vitro and in vivo, including in cultured mesangial cells. In a recent study, van Roeyen and colleagues (Am J Pathol in press, 2012) showed that in vivo overexpression of CCN3 in a model of anti-Thy1.1-induced experimental glomerulonephritis resulted in decreased albuminuria, glomerulosclerosis and reduced cortical collagen type I accumulation. CCN3 enhanced angiogenesis yes suppressed mesangial cell proliferation. Thus CCN3 protein may represent a novel therapeutic approach to help repair glomerular endothelial damage and mesangioproliferative changes and hence prevent renal failure, glomerulosclerosis and tubulointerstitial fibrosis.

Keywords CCN2 · CCN3 · Diabetes · Fibrosis · PDGF · Fibrosis · Connective tissue growth factor · Nov

Diabetic nephropathy and glomerulonephritides, which are characterized by glomerular mesangial cell proliferation and/or matrix accumulation, account for more than 50 % of end-stage renal disease cases in most Western countries (Klahr et al.

1988). Major contributing factors to diabetic nephropathy include transforming growth factor- β 1 (TGF- β 1) and platelet-derived growth factor (PDGF)-BB (Nakamura et al. 1993; Lassila et al. 2005; Ziyadeh et al. 2000; Floege et al. 2008; van Roeyen et al. 2011). During early stages, PDGF-BB potentially increases proliferation and matrix synthesis of mesangial cells and induces the expression of TGF- β 1 (Lassila et al. 2005; Di Paolo et al. 1996). PDGF receptor antagonists attenuate diabetic nephropathy (Lassila et al. 2005). Activation of the TGF- β 1 loop leads to cell cycle arrest, induction of cyclin-dependent kinase inhibitors, and further ECM synthesis (Wolf 2002). Of the members of the CCN family of matricellular proteins, CCN2 is upregulated in models of diabetes and appears to contribute to the fibrosis observed in this disease; an anti-CCN2 antibody has been used in a phase 1 clinical trial and was shown to be safe and to be associated with a decrease in albuminuria (Mason 2009; Twigg 2010; Adler et al. 2010).

However, little is known about endogenous proteins that might counteract and terminate the progression of diabetes. The CCN family member CCN3 has been shown to have activities opposing CCN2, at least in vitro (Riser et al. 2009; Leask 2009; Riser et al. 2010; Kawaki et al. 2011). CCN3 is downregulated in PDGF-B- or -D-stimulated mesangial cells (van Roeyen et al. 2008). To assess whether overexpression of CCN3 could rescue anti-Thy1.1 nephritis, van Roeyen and colleagues (2012) overexpressed CCN3 in skeletal muscle by electroporation and studied the effects of elevated systemic CCN3 production. CCN3 overexpression led to a downregulation of PDGFR- β mRNA expression at day 5 after disease induction. CCN3 overexpression resulted in increased capillary repair. In progressive glomerulonephritis, CCN3 reduced glomerulosclerosis and cortical accumulation of collagen type I. CCN3 overexpressing rats displayed reduced albuminuria compared to controls. CCN3 overexpression downregulates CCN2 expression in healthy

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but not nephritic rats. Thus CCN3 had pro-angiogenic and anti-mesangioproliferative effects in experimental glomerulonephritis, both of which helped to preserve and reconstitute normal glomerular architecture.

CCN3 therefore represents a potentially novel therapeutic tool to help repair glomerular endothelial damage and mesangioproliferative changes. Further efforts need to be expended in evaluating whether CCN3 could be used as a biological agent to prevent or revert diabetes, for example, in humans.

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