Yin and Yang Part Deux: CCN5 inhibits the pro-fibrotic effects of CCN2

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Abstract There is no treatment for fibrotic disease is a significant cause of mortality. CCN2 Members of the CCN family of matricellular proteins have a characteristic four domain structure. CCN2 (connective tissue growth factor) is believed to play an essential role in fibrogenesis. In a recent paper, data are provided that CCN5 (wisp2), which lacks the carboxy-terminal heparin-binding domain shared by the other CCN proteins, may act as a dominant-negative protein to suppress CCN2-mediated fibrogenesis. These data are consistent with the notion that different CCN proteins may enhance or suppress each other's action and also suggest that CCN5, may be used as a novel anti-fibrotic therapy.

Keywords CTGF · CCN2 · wisp2 · Fibrosis

The CCN family of matricellular proteins consists of six members (CCN1-6) which are secreted, cell- and matrix-associated proteins with diverse roles in cell function, including wound repair, vascular disease, fibrosis, angiogenesis, tumorigenesis, cell differentiation and survival (Perbal 2004; Leask and Abraham 2006).

Fibrosis, a group of chronic disorders characterized by excessive scarring resulting in organ failure and death, is a significant contributor to the overall health care costs in the

world. Previous studies have indicated that CCN2, also known as CTGF (Connective Tissue Growth Factor), is both a marker and mediator of fibrosis and hence may represent a novel target for anti-fibrotic intervention (Leask and Abraham, 2004; Leask 2004; Leask et al. 2009). For example, CCN2 can promote TGF β signaling and fibroblast activation (Grotendorst 1997; Shi-wen et al. 2006; Kennedy et al. 2007), and its amino-terminal half is considered an excellent surrogate marker for the severity of fibrosis (Dziedzic et al. 2005). Moreover, strategies targeting CCN2 are effective at suppressing animal models of fibrosis in vivo (Gao and Brigstock 2009; Ponticos et al. 2009).

CCN2, a cysteine-rich secreted protein of 36 to 38 kDa (Chen et al. 2001), has four distinct modules which are shared the members of the CCN family of matricellular proteins; however CCN5 (wisp2) lacks the carboxy-terminal heparin-binding domain (Leask and Abraham 2006). How these proteins act remains incompletely understood but is likely related their modular nature and the ability of these modules to support interactions with a wide range of regulatory proteins and ligands (including transforming growth factor β , heparan sulfate-containing proteoglycans (HSPGs), integrins and fibronectin), which identity differs depending on which CCN protein is considered (Perbal 2001; Holbourn et al. 2008). Inherent in this model is the intriguing possibility that different CCN proteins can either enhance or suppress the activity of other CCN proteins. Indeed, recent evidence suggests that CCN3 can block the fibrogenic action of CCN2 (Kawaki et al. 2008; Leask 2009; Riser et al. 2009).

The carboxy-terminal domain (domain IV) of CCN2 appears to be essential for its function as this module alone can recapitulate many of the effects of CCN2 including its ability to promote cell adhesion and bind integrins and

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HSPGs (Gao and Brigstock 2004). Based on this fact, Yoon et al. (2010) conducted an elegant series of experiments in which they showed that whereas CCN2 induced hypertrophic growth of cardiomyocytes CCN5, which lacks domain IV, suppressed this action of CCN2. Removal of domain IV from CCN2 resulted in a molecule that also acted as a dominant negative of full length CCN2. Crucially, a hybrid CCN5 protein which contained domain IV of CCN2 behaved like CCN2 and promoted hypertrophic growth. In vivo, CCN2 transgenic mice showed enhanced TGF β signaling, whereas CCN5 transgenic mice showed impaired TGF β . Moreover pressure overload-induced cardiac fibrosis was increased in CCN2 overexpressing mice but suppressed in CCN5 overexpressing mice.

Although direct evidence was not provided in this paper, these data are consistent with the notion that the carboxy-terminal domain of CCN proteins is essential for their ability to bind cell surface receptors and signal. Moreover, these data suggest that CCN5 may be a novel, biological anti-fibrotic therapy.

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