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BITS AND BYTES

It's a knockout: CCN3 suppresses neointimal thickening

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Abstract The role of CCN proteins in vivo is only just becoming understood. A prototypical member of the CCN family, CCN3 suppresses proliferation. In a study in press, Shimoyama and colleagues show that mice lacking CCN3 have a hyperproliferative response to vascular injury. These data, along with other recent observations, suggest that CCN3 may represent a novel therapy for hyperproliferative diseases.

Keywords CCN3 · Nov · Hyperplasia · Vasculature · Injury

Proteins which are members of the CCN family of multicellular signaling regulators consist of four common domains, and regulate the activities of a variety of signaling molecules including TGFβ, BMPs and integrins (Leask and Abraham 2006). While CCN1 (cyr61) and CCN2 (CTGF) promote cell proliferation, CCN3 (NOV) has a potent antiproliferative effect in vitro (Perbal 2008). Although the developmental roles of CCN1 and CCN2 have been investigated using knockout models (Mo et al. 2002; Ivkovic et al. 2003), the in vivo function of CCN3 is unclear.

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In spite of several attempts, the isolation of ccn3 null mice has remained elusive until recently. A recent manuscript by Heath et al. (2008) reported the generation of Novdel3-/- mice which produce no full length NOV protein and express at a barely detectable level a mutant NOV protein lacking exon 3 of CCN3. By replacing exon 3 of Nov with a TK-neomycin cassette, they generated mutant mice which possessed abnormal skeletal and cardiac development, cardiomyopathy, muscle atrophy and cataracts. However, as discussed in previous Bits and Bytes, these are not true null CCN3 mice (Leask 2007; Perbal 2007), and thus the developmental functions for which CCN3 is required remain unclear.

A study in press (Shimoyama et al. 2010) reports that true CCN3 null mice have finally been generated. This study confirmed the expression of CCN3 in the medial layer of aortas. CCN3 suppressed vascular smooth muscle cell proliferation and migration in vitro. When subjected to vascular injury, CCN3 null mice possessed a 6-fold enhancement of neointimal thickening compared with the wild-type, coinciding with an enhanced cell proliferation.

Collectively, these results are consistent with the notion that CCN3 suppresses angiogenesis and fibrosis, and that this member of the CCN family has opposing effects to CCN1 and CCN2 (Bleau et al. 2005; Kawaki et al. 2008; Riser et al. 2009) which are considered to promote angiogenesis and fibrosis (Leask 2009). These data raise the exciting possibility that CCN3 is a critical negative growth regulator could be used as a novel therapy to combat a variety of pathologies in which CCN1 and CCN2 are overexpressed, namely cancer, fibrosis and cardiac disease.

References

Bleau AM, Planque N, Perbal B (2005) CCN proteins and cancer: two to tango. Front Biosci 10:998–1009

Heath E, Tahri D, Andermarcher E, Schofield P, Fleming S, Boulter CA (2008) Abnormal skeletal and cardiac development, cardiomyopathy, muscle atrophy and cataracts in mice with a targeted disruption of the Nov (Ccn3) gene. BMC Dev Biol 8:18

Ivkovic S, Yoon BS, Popoff SN, Safadi FF, Libuda DE, Stephenson RC, Daluiski A, Lyons KM (2003) Connective tissue growth factor coordinates chondrogenesis and angiogenesis during skeletal development. Development 130:2779–2791

Kawaki H, Kubota S, Suzuki A, Lazar N, Yamada T, Matsumura T, Ohgawara T, Maeda T, Perbal B, Lyons KM, Takigawa M (2008) Cooperative regulation of chondrocyte differentiation by CCN2 and CCN3 shown by a comprehensive analysis of the CCN family proteins in cartilage. J Bone Miner Res 23:1751–1764

Leask A (2007) CCN3: a novel function in vivo. J Cell Commun Signal 1:227–228

Leask A (2009) Yin and Yang: CCN3 inhibits the pro-fibrotic effects of CCN2. J Cell Commun Signal 3:161–162

Leask A, Abraham DJ (2006) All in the CCN family. J Cell Science 119:4803–4810

Mo FE, Muntean AG, Chen CC, Stolz DB, Watkins SC, Lau LF (2002) CYR61 (CCN1) is essential for placental development and vascular integrity. Mol Cell Biol 22:8709–8720

Perbal B (2007) CCN3-mutant mice are distinct from CCN3-null mice. J Cell Commun Signal 1:229–230

Perbal B (2008) CCN3: doctor Jekyll and mister Hyde. J Cell Commun Signal 2:3–7

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

Shimoyama S, Hiraoka S, Takemoto M, Koshizaka M, Tokuyama H, Tokuyama T, Watanabe A, Fujimoto M, Kawamura H, Sato S, Tsurutani Y, Saito Y, Perbal B, Koseki H, Yokote K (2010) CCN3 inhibits neointimal hyperplasia through modulation of smooth muscle cell growth and migration, in press