

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.

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 TGFbeta, 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.

In spite of several attempts, the isolation of *ccn3* null mice has remained elusive until recently. A recent manuscript by Heath and colleagues (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 Nov exon 3 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.* 130:2779-91.

Kawaki H, Kubota S, Suzuki A, Lazar N, Yamada T, Matsumura T, Ohgawara T, Maeda T, Perbal B, Lyons KM, Takigawa M.(2003) 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(11):1751-64.

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.* 119:4803-10.

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.* 22:8709-20.

Perbal B. (2007) CCN3-mutant mice are distinct from CCN3-null mice. *J Cell Commun Signal.*1:229-30.

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(5):1725-34. Epub 2009 Apr 9.

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. CCN3 inhibits neointimal hyperplasia through modulation of smooth muscle cell growth and migration