J. Cell Commun. Signal. (2007) 1:229–230
DOI 10.1007/s12079-008-0020-8

COMMENTARY

CCN3-mutant mice are distinct from CCN3-null mice

B. Perbal

Received: 14 April 2008 / Accepted: 14 April 2008 / Published online: 4 June 2008

Abstract A recent manuscript reported phenotypic alterations associated to the expression of a CCN3 protein deleted for the Von Willebrand type C repeat that is common to the various members of the CCN family of proteins. In this comment, the biological significance of these alterations is briefly discussed.

Soon after the isolation of ccn3 in chicken (Joliot et al. 1992), collaborative projects were initiated to identify the functions of CCN3 in vivo. Along this line, cloning of the mouse ccn3 gene by us and our collaborators (Perbal 2006) permitted to undertake the construction of CCN3 null mice. In the original project in which my laboratory was a co-applicant for funding in the early 90's, P. Schofield, C. Boulter and myself agreed upon a strategy aimed at knocking out the whole ccn3 gene. Unfortunately, this approach did not permit the isolation of null mice. The possible reasons for this failure were discussed at the first international workshop on the CCN (Cyr61, cystein-rich 61; Ctgf, connective tissue growth factor; Nov, nephroblastoma overexpressed) family of genes and in subsequent meetings. The antiproliferative activity of CCN3 that was established by my laboratory was proposed to be one among the possible causes explaining the difficulties to obtain null mice, and the construction of conditional mutants was envisioned to overcome these problems. In spite of several other attempts from various groups, the isolation of ccn3 null mice remained elusive until recently. The manuscript by Heath et al. (2008) reports abnormal skeletal and cardiac development, cardiomyopathy, muscle atrophy and cataracts as a result of ccn3 disruption in mice.

Their strategy is now based on the disruption of ccn3 exon 3 which encodes the CCN3 module 2 that contains a Von Willebrand type C repeat (VWC).

Based on reports indicating that the VWC of CCN proteins is involved in physical interactions with transforming growth factor beta and bone morphogenetic protein (Leask and Abraham 2006), the production of a mutated CCN3 protein lacking this module is expected to have profound biological consequences and be responsible, at least in part, for the abnormal phenotype of the mice engineered by the authors.

Although the authors themselves quote that variant proteins lacking the VWC domain may be functionally distinct from full length proteins, they do not address the possibility that the phenotype of the mutant mice results from the production of the CCN3del3 variant protein. Furthermore, although many of the functional effects of CCN proteins result from modules acting in concert it is generally accepted that some functions of the CCN proteins are directly related to each individual module. Along this line, the production of small amounts of a rearranged protein containing only three modules may be quite sufficient to permit essential biological functions that are played by the same modules in the full length protein.

Several independent reports have established that CCN proteins lacking the VWC module show oncogenic properties and are expressed in a variety of human tumors (Tanaka et al. 2001; Yanagita et al. 2007). We have recently

This commentary also appears on line under Newsletter section of the ICCNS Website at http://ccnsociety.com

B. Perbal (✉)
Department of Dermatology,
University of Michigan Medical School,
Medical Science I, 1150 W. Medical Center Dr.,
Ann Arbor, MI 48109-0609, USA
e-mail: perbalbernard@yahoo.com

observed that CCN3 lacking the VWC module is expressed in Ewing's tumor samples (Perbal et al. unpublished). The authors also quote unpublished observations in support of transcripts lacking the VWC domain in several tissues in the wild type mouse embryo at E16.5. Since the potential effects and specific activities of variant CCN3 proteins lacking the VWC module are presently unknown, one cannot exclude that the low amounts of mutated CCN3 protein expressed in the animal model developed by Heath et al. play a critical role and interfere with differentiation processes leading to abnormalities described by the authors. Although the manuscript by Heath et al. brings interesting preliminary observations that confirm potential developmental functions of variant CCN3 protein lacking the VWC module, it seems premature to conclude that the phenotype of mutant mice expressing such a variant results from the disruption of ccn3.

The isolation of true CCN3-null mice will certainly permit the clarification of these exciting problems.

References

Heath E, Tahri D, Andermarcher E, Schofield P, Fleming S, Boulter A (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

Joliot V, Martinerie C, Dambrine G, Plassiart G, Brisac M, Crochet J, Perbal B (1992) Proviral rearrangements and overexpression of a new cellular gene (nov) in myeloblastosis-associated virus type 1-induced nephroblastomas. Mol Cell Biol 12:10–12.

Leask A, Abraham DJ (2006) All in the CCN family: essential matricellular signaling modulators emerge from the bunker. J Cell Sci 119:4803–4810

Perbal B (2006) NOV story: the way to CCN3. Cell Commun Signal 4:3 Feb 20

Tanaka S, Sugimachi K, Saeki H, Kinoshita J, Ohga T, Shimada M, Maehara Y (2001) A novel variant of WISP1 lacking a Von Willebrand type C module overexpressed in scirrhous gastric carcinoma. Oncogene 20:5525–5532

Yanagita T, Kubota S, Kawaki H, Kawata K, Kondo S, Takano-Yamamoto T, Tanaka S, Takigawa M (2007) Expression and physiological role of CCN4/Wnt-induced secreted protein 1 mRNA splicing variants in chondrocytes. FEBS J 274:1655–1665