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BITS AND BYTES

Et tu, CCN1….

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Abstract
The CCN family of matricellular proteins are recognized bona fide targets for therapeutically targeting so-called chronic inflammatory diseases, including fibrosis and cancers. The majority of the work supporting this contention has been derived from examining CCN2, formerly, and unhelpfully, termed "connective tissue growth factor." Both CCN2, and its related protein, CCN1, formerly termed "cysteine-rich protein 61", are positively regulated by not only TGFbeta, but also by the hippo/YAP/TAZ mechanotransduction pathway that appears to drive these pathologies. Indeed, increasing evidence indicates that CCN1 also contributes to these fibrosis and cancers and, consequently, targeting both CCN2 and CCN1 simultaneously could be of therapeutic value. This commentary focuses on a recent, exciting paper (Ju et al., 2020, *Scientific Reports*, *10*, 3201) suggesting that CCN1 is a target for non-alcoholic steatohepatitis (NASH).

Keywords CCN1 · Cyr61 · CCN family · NASH · Non-alcoholic steatohepatitis · Fibrosis · Steatosis · Matricellular proteins

Non-alcoholic fatty liver disease (NAFLD), a liver disease affecting people who drink little to no alcohol, is characterized by the excessive storage of fat in liver cells. NAFLD is the most common liver disease in Canada affecting about 20% of Canadians. The most common cause of NAFLD is obesity. Certain conditions that often accompany and may contribute to fatty liver disease include: diabetes mellitus, hyperlipidemia, insulin resistance and high blood pressure.

Non-alcoholic steatohepatitis (NASH), a serious form of NAFLD, is characterized by liver fibrosis and cirrhosis. In most cases, NASH seems to be a slowly progressive disease. However, NASH patients can have liver cancer or liver failure and an increased risk of cardiovascular disease and diabetes. Inflammation in the liver plays a critical role in the development of NASH, and NASH-associated liver fibrosis. However, the underlying mechanisms have not been completely elucidated.

The CCN family, including CCN1 [cysteine-rich protein 61 (Cyr61)], CCN2 (connective tissue growth factor), and CCN3 (nephroblastoma overexpressed), are matricellular proteins that play critical roles in development, differentiation, angiogenesis, and extracellular matrix regulation (Perbal 2018). CCN1, like CCN2, has been associated with cancers, fibrotic and inflammatory disease (Leask 2020a, 2020b). Although deregulated expression of these proteins has been suggested to be specifically associated with chronic connective tissue disease, it is perhaps more accurate, as they are stereotypical YAP/TAZ targets (Leask et al. 2003; Peidl et al. 2019; Moon et al. 2020), to consider them as markers of mechanically loaded states such as those caused by a stiff, fibrotic extracellular matrix (Chaqour 2020) and are likely to act within these states to promote pathological responses. That is, like CCN2, CCN1 is an emerging target for therapeutic intervention; for example, in both lung and skin fibrosis (Quesnel et al. 2019; Kulkarni et al. 2020)

A recent report (Ju et al. 2020) adds to this thesis. In summary, the authors found that, inNASH models, CCN1 caused increased macrophage infiltration and hepatic inflammation. In NASH patients, CCN1 was overexpressed, and correlated with steatosis. They concluded that increased CCN1 may act as an initiation factor in steatosis in NASH.

Specifically, the authors found that, in patients with NASH, the levels of hepatic CCN1 mRNA and protein were significantly increased compared to those seen in healthy individuals. Also, in mice fed a methionine choline deficient or a high-fat (HF) diet, CCN1 expression was significantly increased in serum and liver, compared with mice fed control chow diets. In these models and in patients, CCN1

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expression in livers was positively associated with steatosis. Mice overexpressing CCN1 developed more steatosis when fed a HF diet for 11 weeks, and had higher expression of fatty acid metabolism-associated genes. Conversely, mice in which CCN1 was targeted using an adenoviral-delivered shRNA showed reduced steatosis.

Of extreme importance, when localization of F4/80, a well-established histological marker of murine macrophages, was examined, the number of F4/80-positive cells was increased in the livers with increased CCN1 expression and was decreased upon CCN1 knockdown, compared with control mice subjected to the NASH model. That is, CCN1 promoted inflammation in NASH.

In conclusion, in NASH, CCN1 acts in response to inflammation to promote the formation of fatty liver. Therefore, CCN1 is likely to be a therapeutic target in NASH. These exciting data are of importance as they support the contention that targeting CCN1 along with CCN2, for example by adding CCN3 or CCN3-derived peptides, may be of critical importance (Riser et al. 2009).

References

Chaqour B (2020) Caught between a "rho" and a hard place: are CCN1/CYR61 and CCN2/CTGF the arbiters of microvascular stiffness? J Cell Commun Signal 14(1):21–29

Ju L, Sun Y, Xue H, Chen L, Gu C, Shao J, Lu R, Luo X, Wei J, Ma X, Bian Z (2020) CCN1 promotes hepatic steatosis and inflammation in non-alcoholic steatohepatitis. Sci Rep 10(1):3201

Kulkarni T, Kurundkar AR, Kim YI, de Andrade J, Luckhardt T, Thannickal VJ (2020) The senescence-associated matricellular protein CCN1 in plasma of human subjects with idiopathic pulmonary fibrosis. Respir Med 161:105821

Leask A (2020a) Conjunction junction, what's the function? CCN proteins as targets in fibrosis and cancers. Am J Physiol Cell Physiol 318(6):C1046–C1054

Leask A (2020b) A centralized communication network: recent insights into the role of the cancer associated fibroblast in the development of drug resistance in tumors. Semin Cell Dev Biol 101:111–114

Leask A, Holmes A, Black CM, Abraham DJ (2003) Connective tissue growth factor gene regulation. Requirements for its induction by transforming growth factor-beta 2 in fibroblasts. J Biol Chem 278(15):13008–13015

Moon S, Lee S, Caesar JA, Pruchenko S, Leask A, Knowles JA, Sinon J, Chaqour B (2020) A CTGF-YAP regulatory pathway is essential for angiogenesis and Barriergenesis in the retina. *iScience 23*(6):101184

Peidl A, Perbal B, Leask A (2019) Yin/Yang expression of CCN family members: transforming growth factor beta 1, via ALK5/FAK/MEK, induces CCN1 and CCN2, yet suppresses CCN3, expression in human dermal fibroblasts. PLoS One 14(6):e0218178

Perbal B (2018) The concept of the CCN protein family revisited: a centralized coordination network. J Cell Commun Signal 12(1):3–12

Quesnel K, Shi-wen X, Hutchenreuther J, Xiao Y, Liu S, Peidl A, Naskar D, Siqueira WL, O'Gorman DB, Hinz B, Stratton RJ, Leask A, (2019) CCN1 expression by fibroblasts is required for bleomycin-induced skin fibrosis, Matrix Biol Plus 3, 2019,

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):1725–1734