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BITS AND BYTES

# Sonic advance: CCN1 regulates sonic hedgehog in pancreatic cancer

**Andrew Leask**

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**Abstract** Pancreatic ductal adenocarcinoma (PDAC) is the fifth leading cause of cancer internationally. As the precise molecular pathways that regulate pancreatic cancer are incompletely understood, appropriate targets for drug intervention remain elusive. It is being increasingly appreciated that the cellular microenvironment plays an important role in driving tumor growth and metastasis. CCN1, a member of the CCN family of secreted matricellular proteins, is overexpressed in pancreatic cancer, and may represent a novel target for therapy. Sonic hedgehog (SHh) is responsible for PDAC cell proliferation, epithelial-mesenchymal transition (EMT), maintenance of cancer stemness, migration, invasion, and metastatic growth; in a recent report, it was shown that CCN1 is a potent regulator of SHh expression via Notch-1. CCN1 activity was mediated, at least in part, through altering proteosome activity. These results suggest that CCN1 may be an ideal target for treating PDAC.

**Keywords** CCN1 · Pancreatic cancer · Sonic hedgehog · Notch · Microenvironment

Pancreatic ductal adenocarcinoma (PDAC), an aggressive malignant disease of the exocrine pancreas with a 5-year survival rate of less than 5 %, it represents the fourth-leading cause of cancer-related deaths in the United States with an estimated 37,390 deaths in 2012 (Feig et al. 2012) PDAC is resistant to systemic therapies, possibly to the extensive, fibrous (desmoplastic) stroma that surrounds the tumor cells. Bidirectional signaling between tumors and cells within the tumor stroma is believed to play a major role in the initiation and promotion of pancreatic cancer; indeed, the role of the tumor microenvironment in mediating the growth and metastasis of cancers is being increasingly appreciated (Jewer et al. 2012).

Matricellular proteins, such as the CCN family of proteins, provide signals that support tumorigenic activities such as epithelial-to-mesenchymal (EMT) transition, angiogenesis, tumor cell motility, proliferation and invasion (Chong et al. 2012). CCN1, formerly referred to as cyr61, is dysregulated in a variety of cancers including pancreatic cancer. As discussed in a recent Bits and Bytes (Leask 2011a), Haque and colleagues (2011) showed that CCN1 mRNA and protein expression was elevated in ~85 % of pancreatic cancer specimens and, in pancreatic cell lines, silencing CCN1 blocked cell migration, EMT and tumor in the backs of nude mice.

Owing to wide range of potential signalling pathways modified by the CCN proteins, the precise mechanisms underlying the action of the CCNs are, in general, poorly understood. The authors of the prior report relating to the potential role of CCN1 in pancreatic ductal adenocarcinoma (PDAC) have now gone on to show that CCN1 impacts both the sonic hedgehog (SHh) and the notch pathways (Haque et al. 2012). SHh influences tumor growth by contributing to the formation of desmoplasia (i.e., the growth of fibrotic tissue that promotes tumor invasion) in pancreatic cancer (Bailey et al. 2011). Solid tumors are characterized by an intrinsic tumor-promoting inflammatory response; crosstalk between Tnf-α/Ikk2 and Notch sustains the intrinsic inflammatory profile of transformed cells suppressing PPARγ expression (Maniati et al. 2008), a protein which also potently suppresses fibroproliferative responses (Wei et al. 2012). Moreover, Notch suppresses phosphatase and tensin homolog (PTEN) phosphorylation and hence enhances Akt

A. Leask (✉)
Department of Dentistry, Schulich School of Medicine and Dentistry, Dental Sciences Building, University of Western Ontario, London, ON, Canada N6A 5C1
e-mail: Andrew.Leask@schulich.uwo.ca

A. Leask
Department of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, Dental Sciences Building, University of Western Ontario, London, ON, Canada N6A 5C1

phosphorylation (Vo et al. 2011); reduced PTEN expression and/or activity plays a key role both in cancers and in fibrotic disease (Song et al. 2012; Parapuram et al. 2011; Lai et al. 2011).

In their current report, Haque and colleagues (2012) investigate the mechanism underlying CCN1 action in PDAC. In pancreatic cancer cells, expression of CCN1 correlates with that of SHh, and is highest in the most aggressive cell lines. In Panc-1 cells, silencing of CCN1 using shRNA reduced SHh, cyclin D1 and Bcl-2 expression and also resulted in a near complete loss of active *Notch-1* protein expression. Significantly, in the absence of CCN1, the proteasome activity was significantly increased. As might be expected, addition of recombinant CCN1 protein to Panc-1 cells in which CCN1 was silenced (Panc-$1^{CCN1KO}$) restored the elevated proteasome activity to essentially normal; moreover, treatment of Panc-$1^{CCN1KO}$ with the proteosome inhibitor lactacystin restored *Notch-1* expression. Thus CCN1 acts, at least in part, by altering proteosome activity. Neutralizing anti-integrin αv or anti- integrin β3 antibodies markedly blocked CCN1-induced activation of *Notch-1* and SHh expression in Panc-$1^{CCN1KO}$ cells, emphasizing the importance of these integrins in CCN1-mediated activity.

Collectively, these data are consistent with the emerging concept that the CCN family of matricellullar proteins represent viable therapeutic targets for drug intervention in a wide variety of disorders including cancers, concepts that were presented recently both in a review (Jun and Lau 2011) and at the 2011 International CCN Society-sponsored meeting in Vancouver (Leask 2011b). Moreover, the results suggest a novel mechanism of CCN1 action, namely by modulating the activity of the proteosome.

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