

CCN1: a novel target for pancreatic cancer

Andrew Leask

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Abstract Members of CCN family of matricellular proteins are being increasingly recognized by the translational research community as representing excellent targets for drug intervention. Although much effort has been expended in outlining the mechanisms involved in pancreatic carcinogenesis, the precise molecular pathways involved remain incompletely understood, and appropriate targets for drug intervention remain elusive. A recent exciting report by Haque and colleagues (*Mol Cancer*. 2011 Jan 13;10:8) provides strong evidence that CCN1 (*cyr61*) is a potential therapeutic target in pancreatic cancer.

Keywords CCN1 · Pancreatic cancer · miRNA · *cyr61*

Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth leading cause of cancer deaths in North America, with a median survival rate of 6.4 months (Aikawa et al. 2006; Li et al. 2004). Owing to the difficulty in treatment of PDAC due to the late presentation and the lack of an effective treatment strategy, understand of the mechanism(s) underlying PDAC is absolutely essential.

Expression of the CCN family of matricellular proteins, including CCN1, is dysregulated in a variety of cancers (Tsai et al. 2002; Xie et al. 2004). CCN1 promotes

migration, adhesion, angiogenesis and tumor growth through an integrin-dependent mechanism (Babic et al. 1998; Chen et al. 2004). In the case of prostate carcinoma cells, CCN1 has been shown to be essential for proliferation (Franzen et al. 2009).

There has been relatively little information supplied on the potential role of CCN1 in pancreatic cancer; however, a few years ago it was shown that, in a model of pancreatic adenocarcinoma, CCN1 expression was increased (Holloway et al. 2005). In a report recently published (Haque et al. 2011), CCN1 was shown to have elevated mRNA and protein expression in ~85% of pancreatic cancer specimens compared to adjacent normal samples where expression was essentially absent. In cell lines, the highest expression of RNA and protein was detected in Panc-1 cells followed by AsPC-1, Capan-1 and BxPC-3. It is interesting to note that CCN2 (CTGF) is also found in Panc-1 cells (Pickles and Leask 2007).

Epithelial-mesenchymal transition (EMT) marks the formation of motile cells from non-motile, parent epithelial cells and hence is essential for cancer progression/metastasis. Silencing CCN1 with either siRNA or neutralizing antibody blocked the migration of pancreatic cancer cell lines; moreover, expression of epithelial markers (E-cadherin, β -catenin) increased, whereas expression of mesenchymal/stem cell markers (Vimentin, Notch-1, Oct-4, ABCG2 and CD44) decreased (Haque et al. 2011). Recombinant CCN1 induced markers of EMT in CCN-1 negative BxPC3 cells. Cells in which expression of CCN1 had been silenced with siRNA were unable to form tumors in the back of nude mice. CCN1 knockout Panc-1 cells possessed increased expression of the miR-200 family (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) which is known to regulate EMT and tumor aggressiveness (Gregory et al. 2008). Thus CCN1-induced EMT, stemness

A. Leask (✉)

CIHR Group in Skeletal Development and Remodeling, Division of Oral Biology and Department of Physiology and Pharmacology, 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

and migration activity may be driven, at least in part, through the regulation of miRNAs.

It is interesting to note that CCN2 has also been postulated to represent a therapeutic target for pancreatic cancer therapy, in particular in relation to hypoxia (Aikawa et al. 2006; Bennewith et al. 2009; Leask 2009). It remains unclear whether CCN1 and CCN2 perform identical or complementary functions in pancreatic cancer, and therefore whether therapies targeting CCN1 or CCN2 individually or CCN1 and CCN2 together should be considered. Moreover, it has been suggested that CCN6 itself may represent a novel anti-cancer therapy (Huang et al. 2010; Leask 2010). That said, it is becoming increasingly apparent that the CCN family of matricellular proteins may represent good targets for drug intervention in cancers.

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