CCN6: a novel method of aTAKing cancer

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Abstract It is well-established that the expression of CCN family of matricellular proteins is altered in essentially all cancers and, hence, targeting these proteins may be a novel therapeutic approach to treating these diseases. For example, CCN6 (WISP3) is downregulated in aggressive breast cancers, and this phenomenon appears to result in the tumor survival by promoting Akt phosphorylation. In a recent report by Pal et al. (Cancer Res 72(18):4818–4828, 2012), CCN6 knockdown was shown to promote BMP4-mediated activation of the Smad-independent TAK1 and p38 kinases. CCN6 expression was inversely associated with BMP4 and phospho-p38 levels in 69 % of invasive breast carcinomas. TAK1 inhibition has been previously shown to decrease tumor progression in preclinical models of TAK1-dependent cancers. These data are consistent with the idea that CCN6 may represent a novel therapeutic approach, as compared to attacking TAK1 directly, to selectively target breast cancers.

Keywords CCN6 · TAK1 · Breast cancer · Metastasis · CCN family · Microenvironment

The CCN family of matricellular signalling modifiers consists of 6 members, namely CCN1–6 (Perbal 2001; Leask and Abraham 2006; Holbourn et al. 2008). Members of the CCN family of matricellular proteins contribute to inflammation, wound healing and injury repair in adulthood. Dysregulation of CCN protein expression or activity exists in various chronic diseases, including fibrosis, atherosclerosis, arthritis and cancer. As such, their potential as therapeutic targets is being increasingly recognized (Jun and Lau 2011).

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CCN6 (formerly known as WISP3) is downregulated in aggressive cancers, including that of the breast; whereas normal epithelium expresses CCN6, CCN6 is reduced or lost in the majority of invasive carcinomas (Huang et al. 2008). Huang et al. (2010) used shRNA-mediated knockdown of CCN6 to show that reduction of CCN6 expression in caused growth factor-independent survival, anchorage-independent growth and protection from both apoptosis and anoikis (detachment-induced apoptosis, which is a protective mechanism resulting in death of cells resulting from diminished contract with the extracellular matrix).

In a recent report (Pal et al. 2012), the same laboratory continued their prior studies (Huang et al. 2008, 2010) to show that knockdown of CCN6 in human mammary epithelial (CCN6 KD HME) cells resulted in highly invasive cells, compared to control cells, in 3D cell culture concomitant with reduced E-cadherin expression at cell-cell borders. The invasiveness of CCN6 KD HME cells was completely reversed by recombinant human CCN6 protein. In CCN6 KD HME cells, mRNA levels of TGF- β 1, TGF- β 2, BMP1, 2, 3, 5, and 6 were unaffected, but mRNA levels of BMP4 were induced a 21-fold. The TGF β /BMP pathway consists of canonical Smad-dependent and non-canonical Smad-independent components; CCN6 KD cells showed elevated TAK1 phosphorylation as well p38 phosphorylation which occurs downstream of TAK1. Specific inhibition of BMP4, TAK1, or p38 reduced invasion and restored acinar-like organization of CCN6 KD HME cells. Conversely, CCN6 overexpression decreased invasion in MDA-MB-231 cells and this effect was rescued by rhBMP4. rhCCN6 protein bound rhBMP4. Finally, overexpression of CCN6 in tumor cells resulted in elevated metastasis free survival in vivo. Finally, in tumor samples CCN6 expression correlated inversely with BMP4/p-p38.

Consistent with prior observations, these data show that CCN6 protein acts to suppress metastasis via the BMP4/TAK1/p38 axis. TAK1 has been proposed to represent a

novel therapeutic target for cancers, yet, in addition to its role in mediating TGF β /BMP signaling, also is a key mediator of innate immunity (Sakurai 2012). It is possible, then, that CCN6 may be a more selective, rational therapeutic target for development of treatments to halt breast cancer metastasis and improve clinical outcome.

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