CCN6 (WISP3): a new anti-cancer therapy?

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Abstract The CCN family of matricellular proteins are dysregulated in cancers, and may strategies targeting them may represent novel approaches to treating these diseases. A recent study from Huang and colleagues (Cancer Res. 70: 3340–50, 2010) suggests that CCN6 (WISP3) is down-regulated in aggressive breast cancers, and this phenomenon may result in the promotion of tumor survival. CCN6 may represent a novel therapeutic approach to breast cancer.

Keywords Cancer · CCN proteins · WISP3 · CCN6

The CCN family of matricellular signalling modifiers consists of 6 members (Brigstock 2003; Leask and Abraham 2006; Holbourn et al. 2008; Chen and Lau 2009). CCN proteins are generally secreted, and are proposed to promote the interaction among signaling pathways between epithelium and stroma (Holbourn et al. 2008; Chen and Lau 2009; Chu et al. 2008).

Of the CCN family, probably CCN6 (WISP3) is the least-studied. In contrast to several of the other family members notably CCN2 (connective tissue growth factor) (Leask 2009b), CCN6 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). The high frequency of reduction or loss of CCN6 in breast cancer suggests a potential role in initiation and/or progression of human breast cancer.

A recent study attempts to shed light on the mechanistic role of CCN6 in epithelial biology (Huang et al. 2010). Using MCF10A and HME cell lines, the authors found that shRNA-mediated knockdown of CCN6 caused growth factor-independent survival and proliferation. Mammary epithelial cells with reduced CCN6 expression failed to arrest in G₁/S under serum deprivation. Reduced CCN6 expression also resulted in trigger anchorage-independent growth. Moreover, loss of CCN6 expression protected cells from apoptosis and anoikis (detachment-induced apoptosis, which is a protective mechanism resulting in death of cells resulting from diminished contract with the extracellular matrix). The phenotype resulting from reduced CCN6 expression was caused by the activation of the pro-survival PI3K/Akt pathway.

It is now increasingly apparent that the relative abundance of individual CCN family members, which often have opposing activities (Perbal 2001), can have a profound effect on pathological conditions (Leask 2009a, 2010). For example, CCN1 appears to promote angiogenesis and breast cancer invasion (O’Kelly et al., 2008; Leu et al. 2002). Furthermore, CCN2 appears to play a similar role at least for osteolytic metastasis (Leu et al. 2002; Shimo et al., 2006). These data suggest that the relative abundance of CCN6 (compared to CCN1 and CCN2) may be important for cancer survival; CCN6 may be a novel therapeutic approach to highly invasive cancers.

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