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BITS AND BYTES

CCN6: a modulator of breast cancer progression

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Abstract The expression of the CCN family of matricellular proteins is highly dysregulated in connective tissue pathologies such as fibrosis and highly metastatic cancers. Strategies targeting members of this family, especially CCN2, are under development as novel therapeutic approaches to highly metastatic cancers such as pancreatic cancer. In prior reports, the Kleer laboratory and colleagues have linked reduced expression of CCN6 (WISP3) with aggressive breast cancers. Loss of CCN6 was associated with elevated Akt phosphorylation and TAK1 activation. In a recent report, the same group reports that, by modulating Notch signaling, CCN6 can promote the maintenance of an epithelial phenotype and also reduce cancer cell migration and invasion, tumor initiation, and metastasis (Oncotarget in press DOI:10.18632/oncotarget.7734). These results are consistent with the hypothesis that addition of CCN6 peptides may represent a novel, viable therapeutic approach to blocking aggressive breast cancers.

Keywords CCN6 · WISP3 · CTGF · CCN family · CCN2 · Breast cancer · Metastasis

As initially defined by Paul Bornstein, matricellular proteins are a subset of dynamically expressed secreted proteins that are found in the extracellular matrix; they exert regulatory rather than structural roles in and are highly dysregulated in cancers (Bornstein and Sage 2002). The CCN of matricellular proteins (named after Cyr61, CTGF, and NOV) have roles in development and fibrogenesis, and are increasingly appreciated as having functions and roles in tumorigenesis, particularly in cancers that are highly metastatic and have extensive tumor stroma (Holbourn et al. 2008). As such, their role as therapeutic targets in cancers (notably those of the pancreas) is being increasingly appreciated (Jun and Lau 2011; Ohgawara et al. 2011, Zarogoulidis et al. 2015; Hutchenreuther et al. 2015).

Prior publications from the Kleer laboratory and colleagues have shownt that CCN6 (formerly known as WISP3) is downregulated in aggressive breast cancers; reduction of CCN6 expression promotes growth factor–independent survival, anchorage-independent growth and protects from apoptosis and anoikis (Huang et al. 2008, 2010). Knockdown of CCN6 in human mammary epithelial cells caused cells to be highly invasive; this phenotype was reversed by recombinant CCN6 (Pal et al. 2012). CCN6 knockdown cells showed elevated phosphorylation of TAK1 and p38, which was required for the phenotype of these cells. Thus the authors hypothesized that CCN6 suppresses metastasis by blocking the activation of TAK1/p38 (Pal et al. 2012).

In a study recently published, the same laboratory elucidated another mechanism whereby CCN6 may elicit anti-oncogenic effects (Huang et al. 2016). CCN6 overexpression in aggressive breast cancer cells induced mesenchymal-to-epithelial transition (MET) and cancer cell migration and invasion, as well as metastasis,. CCN6 overexpression or treatment with recombinant CCN6 downregulated Slug and was sufficient to reduce Notch1 signaling and transcriptional activity and hence to reverse EMT. Slug levels had been previously shown to correlate with increased metastatic potential and tumor grade (Liu et al. 2013). Thus CCN6 is a novel regulator of Slug in breast cancer progression further supporting the notion that modulation of CCN6 levels and

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activity may be a potential strategy to prevent or halt breast cancer development.

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