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BITS AND BYTES

Death of a tumor: targeting CCN in pancreatic cancer

Andrew Leask

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Abstract The matricellular protein CCN2 (connective tissue growth factor, CTGF) has been previously implicated in tumorigenesis. In pancreatic cancer cells, CCN2 expression occurs downstream of ras/MEK/ERK. Direct evidence that CCN2 mediates tumor progression in pancreatic cancer has been lacking. An exciting recent report by Bennewith et al. (Cancer Res 69:775–784, 2009) has used shRNA knockdown of CCN2 to illustrate that CCN2 contributes to growth of pancreatic tumor cells, both in vitro and in vivo. This report briefly summarizes these findings.

Keywords CTGF · CCN2 · PANC-1 · Pancreatic cancer

The 5-year survival rate for pancreatic cancer is ~5% (Jemal et al. 2008). Members of the CCN family, including CCN2, are dysregulated in cancers and promote angiogenesis and metastasis through an integrin-mediated pathway (Babic et al. 1998; Rachfal et al. 2004; Jiang et al. 2004; Xie et al., 2004; Shimo et al. 2006; Pickles and Leask 2007). In the case of pancreatic cancer cells, CCN2 was expressed downstream of ras/ MEK/ERK (Pickles and Leask 2007). Immunologic inhibition of CCN2 inhibits the growth and metastasis of xenografted human pancreatic tumors in mice (Aikawa et al. 2006; Dornhöfer et al. 2006). However, from these latter studies it was unclear precisely whether the antibody targeted CCN2 expressed by the tumor cells, derived from the human, or stromal cells, derived from the mouse. That is, these studies did not explore the basis of why the anti-CCN2 antibody was impeding tumor formation and expansion.

Bennewith and colleagues (2009) generated PANC-1 tumor cell lines stably transfected with different shRNA sequences recognizing CCN2. These tumor lines displayed impaired growth in soft agar, as well as delayed tumor growth when pools of shRNA-possessing cells injected subcutaneously into mice. Intriguingly, the growth kinetics was delayed owing to clonal selection of tumor cells displaying high CCN2 expression, indicating that the stromal microenvironment favored the outgrowth of cells expressing high CCN2 levels. When clonal populations of cells were injected into mice, those cells displaying more efficient knockdown of CCN2 resulted in proportionately decreased tumor growth and elevated survival. CCN2 is upregulated in response to hypoxia (Higgins et al. 2004; Hong et al. 2006), and PANC-1 cells in which CCN2 expression was reduced showed increased susceptibility to hypoxia-induced apoptosis. The authors reported that CCN2, significantly, did not affect the growth of PANC-1 cells cultured in normoxia. Finally, CCN2 expression was found in areas of hypoxia and tumor growth in clinical pancreatic adenocarcinoma samples.

It was somewhat disappointing that the authors did not assess, for example, if knockdown of CCN2 affected cell migration or proliferation, features that CCN2 is known to promote in other cell types (Blom et al. 2001; Kennedy et al. 2007; Gao et al. 2004). Moreover, signaling pathways mediating CCN2 action were not explored. For example, it may be that while CCN2 expression is downstream of ras/MEK/ERK (Pickles and Leask 2007) CCN2 may also promote tumorigenic activities by stimulating this pathway as well. Indeed, the involvement in CCN2 in acting through ERK is well-established (Gao et al. 2004; Chen et al. 2004;

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

Kennedy et al. 2007). Thus it remains possible that CCN2 may be involved in promoting a loop of constitutive ERK activation resulting in tumorigenesis.

Nonetheless, the results from Bennewith and colleagues (2009) strongly support the notion that CCN2 plays a key role in oncogenesis and that blocking the action of CCN2 may be suitable for precisely targeted drug therapy in cancer.

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