

CCN2 YAPs at cancer

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ABSTRACT

The YAP transcription coactivator has been implicated as an oncogene and is amplified in human cancers. Previously, it has been shown that CCN2 (connective tissue growth factor, CTGF) is a target of the tumor promoting YAP and its transcription factor target TEAD. A recent report in *Genes and Development* by Zhao and colleagues (2008) has extended these initial observations to show that CCN2 plays an important role in the growth-promoting function of YAP. These data confirm the role of CCN2 as a key oncogenic mediator. This report briefly summarizes these findings.

A large body of evidence has indicated that the expression of the CCN family of proteins is dysregulated in cancers and promotes angiogenesis and metastasis by 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). CCN2 expression appears to correlate with high tumor grade and metastasis (Deng et al., 2007). Collectively, these results suggest that CCN2 expression may be both a marker and mediator of metastasis and that studying the basis of why CCN2 is overexpressed in cancers may enhance our understanding of the molecular basis of cancers as well as the role that CCN2 may play in these pathologies (Blom et al., 2002). Indeed, it was recently shown that CCN2 was expressed downstream of ras in pancreatic cancer cells (Pickles and Leask, 2007).

In NIH 3T3 fibroblasts, The CCN2 promoter is activated by the oncogenic transcriptional coactivator YAP and regulated by the YAP target TEAD (Leask et al., 2003). In an intriguing recent report, Zhao and colleagues (2008) extend this observation by first confirming that YAP and members of the TEAD family interact (Vassilev et al., 2001). Among the confirmed YAP-inducible genes in NIH 3T3 fibroblasts and MCF10A breast cancer cells was CCN2, and this response depended on TEAD transcription factors (Zhao et al., 2008). Chromatin immunoprecipitation experiments verified that TEAD and YAP bound the endogenous CCN2 promoter. Zhao and colleagues (2008) YAP activated the CCN2 promoter via previously identified TEAD/YAP response elements (Leask et al., 2003). Zhao and colleagues (2008) used siRNA to knockdown CCN2 expression in the YAP-overexpressing MCF10A cells, and showed that reduction in CCN2 expression decreased the acini growth and reversed the rough surface morphology in 3D culture. However, CCN2 knockdown did not affect the apparent epithelial-mesenchymal transition (EMT) in monolayer culture. These results indicate that in CCN2 may play an important role in the growth-promoting function but may not be required for the EMT-inducing activity of YAP.

It is interesting to note that the TEAD/YAP response elements of the CCN2 promoter are also functional binding elements for the Ets family (ETS) of transcription factors (van Beek et al., 2006) which also are implicated in the pathology of cancer (Libermann et al., 2006). ETS transcription factors are characterized by an evolutionally conserved Ets domain and play important roles in cell development, cell differentiation, cell proliferation, apoptosis and tissue remodeling. Most of them are downstream nuclear targets of Ras-MAP kinase signaling, and the deregulation of ETS genes results in the malignant transformation of cells (Oikawa, 2004). Possible functional interactions between the TEAD/YAP and ETS transcription factors have not been speculated on before. However, it is interesting to note that Ets1 is required, but TEAD1 blocks, the TGF β -induction of CCN2 in fibroblasts (Leask et al., 2003; van Beek et al., 2006).

Collectively the above results suggest that although the TEAD/YAP and ETS factors may have similar activities in some contexts, alteration in TEAD/YAP:ETS ratios may have

profound effects on other areas, such as the resistance of cancer cells to TGF β . But, perhaps more important from the context of the CCN family, the results from Zhao and colleagues (2008) strongly support the notion that CCN2 plays a key role in oncogenesis and that blocking the action of CCN2, or other members of the CCN family, may be suitable for precisely targeted drug therapy.

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