Editorial

Editorial on "Transcription factor SPZ1 promotes TWIST-mediated epithelial—mesenchymal transition and oncogenesis in human liver cancer"

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Twist1, a basic helix-loop-helix (bHLH) transcription factor, has been implicated in epithelial mesenchymal transitions (EMTs) in a variety of cancers including lung cancer (1-3). As a result, Twist1 is thought to play an important role in metastasis through a variety of described mechanisms (4-9). In addition, overexpression of Twist1 is associated with chemotherapy resistance and is associated with poor prognosis (3,10-12). Twist1 overexpression is also associated with cancer stemness, a phenotype thought to be responsible for cancer initiation, metastasis, and therapy resistance (2). Twist1 is an attractive target in cancer because it is overexpressed in cancer while minimally expressed in normal tissues. Although small inhibitory RNA suppression of Twist1 has been effective in reducing cancer growth *in vitro*, therapies targeting Twist1 that can be used *in vivo* have not yet been reported. As a result, understanding the regulation of Twist1 may reveal new ways of blocking Twist1 expression that may lead to new effective cancer therapies.

In this manuscript, Wang and colleagues report spermatogenic bHLH transcription factor Zip 1 (SPZ1) binds to the promoter region of Twist1 and activates Twist1 expression in hepatocellular carcinoma (HCC) cell lines (13). They support this conclusion through experiments showing binding of SPZ1 to a short portion of the TWIST promoter and a series of knockout and overexpression studies of SPZ1 that show increases in TWIST expression. In addition, the association of TWIST1 and SPZ1 expression in human samples supports their data. They also show that SPZ1 expression is associated with more aggressive tumor phenotype (larger tumor size, increased number of tumors, higher stage, and lymphovascular invasion) in human HCC cancer specimens, and that SPZ1 is associated with expression of Twist1 in human HCC tumor samples. Because of the important role of Twist1 in EMT and cancer stemness, the authors conclude that SPZ1 may be a master regulator of EMT in HCC leading to transcription of key EMT genes and pathways including Snail1 and Slug as well as other markers of cancer stemness.

The study is methodologically sound and has a number of strengths, in particular the correlation of SPZ1 and Twist1 expression with clinical outcomes in a large number of human samples. Other strengths of the study are the use of a transgenic mouse model and correlation with downstream signaling pathways of EMT and cell migration, which make inferences on the possible effects of SPZ1 expression on development of metastasis.

There are important limitations to this study though. First, although Twist1 is reported to be high in most tumors and low in normal tissues, SPZ1 expression is low in the majority of liver cancers that are reported in this study. In fact, only about 29% of tumors studied had high SPZ1. If SPZ1 in fact is the major regulator of Twist1, one would assume that levels of SPZ1 and Twist1 would be

more concordant. While the authors do show a statistical correlation between SPZ1 and Twist1 levels, it is clear that the regulation of Twist1 is not just under the control of SPZ1, and that SPZ1 is involved in transcription of other cancer related genes, as others have shown. There are a number of interrelated pathways involving regulation of EMT and the relative importance of SPZ1 is not clear (1). Moreover, although mRNA expression levels of SPZ1 were associated with poor prognosis, it is unclear how the cut point of high and low expression levels were selected and whether the selection of this cut-point was validated by any means. The lack of use of a validation method for the cutpoints limits may lead to falsely identifying an effect.

In addition, there are many unanswered questions about the role of SPZ1 in TWIST expression and in the malignant phenotype that ought to be answered before focusing on targeting SPZ1 for cancer therapy. First, does forced expression of SPZ1 in benign immortalized cells lead to malignant transformation? If not, what other oncogenic pathways are required? Since TWIST1 is thought to be a gene involved early in carcinogenesis, is SPZ1 expression or TWIST1 expression sufficient for malignant transformation or are other oncogenic drivers required? Next, what other genes are regulated by SPZ1? Although a handful of epithelial to mesenchymal transformation genes were evaluated in this paper, evaluation across the genome in cancer cells may detect other important cancer related genes that are under the control of SPZ1. In addition, rescue experiments whereby TWIST1 is knocked down after overexpression of SPZ1 may help elucidate the effect of SPZ1 on TWIST1 relative to other oncogenes. Along the same lines, it is unclear what other transcription factors regulate TWIST expression. Even though TWIST1 expression is lower with SPZ1 knockdown, additional transcription factors may still play an important role in the regulation of TWIST1 in human cancers. Finally, although this manuscript focuses on HCC, is SPZ1 equally important for TWIST1 expression in other cancers?

Although the authors demonstrate that SPZ1 is a potential target for cancer therapy, targeting bHLH transcription factors with peptides is challenging (14). In addition, off target effects on the many other critical bHLH transcription factors are likely.

In summary, Wang and colleagues provide important information on the regulation of TWIST1 via SPZ1 in HCC, a finding which is likely to be relevant to other malignancies. Both Twist1 and SPZ1 are appealing targets for therapy. Additional investigation on the other roles of SPZ1 in cancer is important, and it may shed light on possible TWIST targeting therapies.

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Footnote

Conflicts of Interest: DJ Raz is a consultant for Cireca.

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