Editorial

Transcription factor SPZ1 may promote TWIST-mediated epithelial-mesenchymal transition in thoracic malignancies

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Epithelial-mesenchymal transition (EMT) is characterized by decreased epithelial properties and increased mesenchymal attributes, and is believed to play an important role in cancer metastasis (1). EMT contributes to the circulating tumor cell load in epithelial cancers because it increases tumor cell invasiveness, promotes tumor cell intravasation and promotes tumor cell survival in the peripheral system. EMT not only enhances cancer motility and dissemination through the disruption of intercellular junctions, but it also allows cells to acquire stem-like properties (2). Recently, EMT has been reported to influence the tumor microenvironment and possibly contribute to tumor immune escape (3). Tripathi *et al.* reported that EMT was associated with significantly reduced expression of immunoproteasome components and their regulators in non-small cell lung cancer (NSCLC) cell lines (4). In addition, they demonstrated that low expression of immunoproteasome subunits in early stage NSCLC patients was associated with recurrence and metastasis. Therefore, EMT is a candidate predictive marker to be explored for immunotherapy outcome and targeting EMT may offer important perspectives for current immunotherapy approaches (3).

In cancers, EMT is triggered by diverse signaling pathways through the regulation of EMT transcription factors (TFs) and/or microRNAs (2). Overexpression of TFs, such as TWIST, SNAIL, ZEB, and FOXC families, is known to induce EMT in a variety of cancers (5,6). Among these TFs, TWIST1, a basic helix-loop-helix transcription factor (bHLH), is a master regulator of gastrulation and mesoderm specification (7,8) and has recently been demonstrated to be essential in mediating cancer metastasis (9). Ectopic expression of TWIST1 upregulates mesenchymal cell markers and a loss of epithelial markers, and induces EMT (10). Under hypoxic condition, a principal feature of malignancies, HIF-1 alpha promotes EMT through the induction of TWIST1 (11).

Although TWIST1 is silent in most healthy adult tissues, it was found to be overexpressed in many types of cancers, including lung and esophageal carcinomas (12,13). Pallier *et al.* investigated the implication of TWIST1 reactivation on the acquisition of a mesenchymal phenotype in *EGFR* mutated lung cancer and showed that TWIST1 expression was linked to *EGFR* mutation, to low CDH1 expression and to low disease-free survival (12). Yuen *et al.* reported that TWIST was upregulated in esophageal squamous cell carcinoma and a high level of TWIST expression was significantly associated with a greater risk of developing distant metastasis within one year of esophagectomy (13). Wushou *et al.* conducted a systematic review and meta-analysis to determine the association of TWIST1 expression with the prognosis of carcinoma patients (14). The analysis included 17 studies, four of which evaluated lung cancer and two evaluated esophageal cancer, and revealed that expression of TWIST1 was associated with worse survival in carcinoma. These findings suggest that TWIST1-mediated EMT plays an important role in the progression of thoracic malignancies.

Spermatogenic bHLH transcription factor Zip 1 (SPZ1) is a TF expressed primarily during the embryonic development stage, and shows a testis-specific expression in germline and somatic cells in the adult stage (15,16). Hsu *et al.* reported that SPZ1 directly binds to phosphorylated ERK1/2 and is activated by phosphorylation (17). The activated SPZ1 translocates into the nucleus and activates downstream genes. Ectopic expression of SPZ1 promotes cell cycle progression and proliferation, and leads to tumor formation. However, the function of SPZ1 is not fully understood and little is known about the implication of SPZ1 reactivation in human cancer.

In a recent article in *Oncogene*, Wang *et al.* investigated the expression of SPZ1 and TWIST1 in hepatocellular carcinoma (HCC) and noncancerous liver tissue, and found that increased expression of *SPZ1* mRNA and nuclear localization of SPZ1 protein was observed in HCCs (18). HCC patients with high *SPZ1* expression had significantly worse survival than those with low *SPZ1*. The forced expression of *SPZ1* in the HCC cell lines significantly increased the expression of several genes related to cell proliferation, while the knockdown of *SPZ1* in the cell lines with higher endogenous expression significantly repressed expression. The forced expression of *SPZ1-GFP* enhanced the expression of EMT markers, including TWIST1, Snail1, Slug, Wnt5a, HIF-1, CD133, CD44, ZEB1, and BMI1. The knockdown of *SPZ1* repressed cell proliferation both *in vitro* and *in vivo*. In addition, they demonstrated that SPZ1 transcriptionally activates *TWIST* gene expression. Based on these findings, the authors concluded that SPZ1 was able to regulate cellular proliferation, invasion, and tumorigenic activity in a TWIST1-dependent manner. They also suggested that the cascade of SPZ1 on TWIST1 activation was a prerequisite for EMT activation to initiate oncogenesis, and was therefore a possible therapeutic target in HCC.

Hsu *et al.* previously established a *SPZ1* transgenic mouse (16), and found that ectopic *SPZ1* expression led to tumor progression (17). Wang *et al.* demonstrated the detailed information about SPZ1-induced tumors in the transgenic mice in this article (18). Eighteen of sixty *SPZ1* transgenic mice developed tumors in the lung, liver, kidney, small intestine, and uterine tissues at six to eight months of age. Hepatoma, which was their focus, was observed in 13 out of 60 transgenic mice. Interestingly, the most frequently observed tumor in the transgenic mice was lung cancer with 18 of 60 mice having lung tumors. This result indicates that expression of SPZ1 may play an important role in lung carcinogenesis.

TWIST1, one of TFs that mediate EMT, is known to be often reactivated in lung and esophageal cancers. SPZ1, a newly described molecule, may promote TWIST1-mediated EMT in thoracic malignancies. Further analysis of the expression status of SPZ1 as well as the biologic implication of its expression in lung and esophageal cancer is needed.

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Footnote

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