LETTER TO THE EDITOR

Epithelial–Mesenchymal Transition and LOXL2: Consideration Continues

TO THE EDITORS:

We appreciate the interest in our recent publication in the *Annals of Surgical Oncology*.¹ We thank Clara Balsano and colleagues for their comments.

As a new promoter of EMT, LOXL2 is found in several epithelial cancer cell lines. We found that LOXL2 was highly expressed in cholangiocarcinoma (CC) tissues and was associated with CC invasion and metastasis through EMT. Accordingly, we provided evidence for the hypothesis that HCVc can promote EMT in CC cell through LOXL2. We estimate that the mechanism may have two aspects: on the one hand, HCVc may interact with LOXL2, making its expression atopic and increasing its activity; on the other hand, HCVc may promote LOXL2 transcription.

Many results support LOXL2 as a new poor prognosis marker or novel therapeutic target in squamous cell carcinomas and gastric cancer.^{2,3} LOXL2 promotes migration in noninvasive breast cancer cells but not in normal breast epithelial cells.⁴

Furthermore, LOXL2 activity might be a crucial modulator of Snail, providing an additional control mechanism of EMT and tumor progression. To better understand the participation of Snail and LOXL2 molecules, Peinado et al. have performed in-depth in vitro and in vivo studies of HaCa4 cells with silenced expression of Snail or LOXL2. These results suggest that LOXL2 influences the Snail-dependent invasion properties and, perhaps, the Snail-prosurvival action, but, in addition, LOXL2 has

specific functions in the negative control of the epidermal differentiation program, apparently through the direct or indirect regulation of Snail-independent target genes.

Subsequent mechanistic studies showed that LOXL2 could activate both the Snail/E-cadherin and Src kinase/focal adhesion kinase (Src/FAK) pathways. However, secreted LOXL2 induced gastric tumor cell invasion and metastasis exclusively via the Src/FAK pathway but not the Snail/E-cadherin pathway.²

**Dajiang Li, PhD, Tianyu Li, PhD,
and Shuguang Wang, PhD**

Institute of Hepatobiliary Surgery of PLA, Southwest Hospital, Third Military Medical University, Chongqing, People's Republic of China
e-mail: sgwang90@yahoo.com

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