LETTER TO THE EDITOR

Regarding: Epithelial-Mesenchymal Transition Induced by Hepatitis C Virus Core Protein in Cholangiocarcinoma

TO THE EDITORS:

We appreciate the article by Li et al. in a recent issue of the *Annals of Surgical Oncology*.¹ In this study, the authors demonstrated that HCV, in particular HCV core protein (HCVc), was associated with epithelial and mesenchymal transition (EMT) in cholangiocarcinoma (CC). They demonstrated that HCVc may participate in CC invasion and metastasis with the downregulation of epithelial markers, as E-cadherin (E-cad), and the upregulation of mesenchymal markers, as vimentin and fibronectin. In addition, they investigated the role of lysyl oxidase such as protein 2 (LOXL2), a new promoter of EMT and an important factor for HCV infection. They demonstrated that LOXL2 was highly expressed in CC tissues and was associated with invasion and metastasis through EMT. Thus, they hypothesized that HCVc can promote EMT in CC through LOXL2 activity. To test this hypothesis, LOXL2 expression was measured after HCVc gene transfection. They observed that LOXL2 level was increased in CC/HCVc, and after the inhibition of LOXL2 expression they observed a downregulation of LOXL2 and of mesenchymal markers and a simultaneous upregulation of epithelial markers. These results support the relationship between HCVc, LOXL2, and EMT.

All these findings are very intriguing but they could be more interesting with the comprehension of the role of Snail, the EMT master gene.² The transcription factor Snail controls epithelial-mesenchymal transitions (EMT) by repressing E-cad expression and other epithelial genes. Peinado et al. show that LOXL2 interacts and cooperates with Snail to downregulate E-cadherin expression.³

The functional collaboration of these two proteins to repress E-cadherin expression is strictly dependent on the presence in Snail protein of two specific lysine residues: K98 and K137. Snail's lysine residues 98 and 137 are essential for Snail stability, functional cooperation with LOXL2, and induction of EMT.⁴

All these observations highlight that LOXL2 might be a key molecule during progression of tumors related or not to HCV infection. Furthermore, LOXL2 activity might be a crucial modulator of Snail, providing an additional control mechanism of EMT and tumor progression. It would be interesting to analyze the role of LOXL2 and Snail in hepatocarcinoma induced by HCV. In particular, it could examine how HCVc is really involved in the induction of LOXL2/Snail-mediated EMT. This evidence also raises the possibility of using LOXL2 expression as an additional predictive/prognostic marker for carcinoma progression.

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