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2018-04-25


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Pranoti Mandrekar
University of Massachusetts Medical School

Et al.

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Repository Citation

Mandrekar P, Cardinale V. (2018). Periostin and mesothelin: Potential predictors of malignant progression in intrahepatic cholangiocarcinoma. Open Access Articles. <https://doi.org/10.1002/hep4.1189>. Retrieved from <https://escholarship.umassmed.edu/oapubs/3437>

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Periostin and Mesothelin: Potential Predictors of Malignant Progression in Intrahepatic Cholangiocarcinoma

SEE ARTICLE ON PAGE 155

Cholangiocarcinoma (CCA), a heterogeneous group of malignancy arising at any level of the biliary tree based on their anatomical location, is classified into intrahepatic (iCCA), perihilar, and distal subtypes. iCCA, which arises distally to the second-order bile ducts, is a highly heterogeneous and

aggressive malignancy with overall poor prognosis. The rate of iCCA is increasing rapidly, particularly in Western countries; however, its precise etiology and pathogenesis remain elusive.⁽¹⁾ While surgical resection is the first line of treatment, liver transplantation is the potential curative treatment for unresectable tumors in patients with iCCA, and posttransplantation 5-year survival rates are 51% in these patients. Currently, there are no curative medical therapies or targeted molecular therapies approved for use in iCCA. The complex plethora of cell types, extracellular matrix, and soluble factors that influence tumor progression should be considered to understand its pathogenesis and to devise effective strategies for its clinical management.⁽¹⁾ Furthermore, identification of biomarker signatures relevant to disease progression and aggressiveness may not only aid in diagnosis but also have prognostic value that will help build a precision approach for the treatment of iCCA.

Recent studies exploring mechanisms related to iCCA progression have focused on the role of cancer stem cells, mesenchymal stem cells, and microRNAs in driving iCCA progression.⁽²⁾ Additional mechanisms related to iCCA development have investigated genetic alterations as well as molecular aberrations that include the significance of fibroblast growth factor signaling, hepatocyte growth factor–mesenchymal epithelial transition signaling, myeloid leukemia cell differentiation protein-1 (Mcl-1), Kirsten sarcoma virus oncogene (KRAS), and the phosphoinositide-3-kinase–protein kinase B–mammalian target of rapamycin complex pathway as well as mesothelin expression.⁽³⁾ Immune checkpoint proteins programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), which have also been explored in surgically resected iCCA specimens, showed high expression, suggesting a potential for exploiting these pathways/inhibitors for therapeutic regimens.

The stroma of iCCA undergoes profound changes in its composition during cholangiocarcinogenesis and modulates the biology of epithelial tumor cells.⁽³⁾ Cells endowed in CCA stroma, comprising mainly cancer-associated fibroblasts, tumor associated macrophages, and vasculature cells, contribute to tumor mass

Abbreviations: 3D, three-dimensional; CCA, cholangiocarcinoma; EMT, epithelial–mesenchymal transition; iCCA, intrahepatic cholangiocarcinoma.

Received February 22, 2018; accepted March 31, 2018.

Supported by the National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Public Health Service grants 2R01AA017986 (to P.M.) and 5R01AA025289-02 (to P.M.) and Department of Defense grant W81XWH-13-1-0498 (to P.M.).

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DOI 10.1002/hep4.1189

Potential conflict of interest: Nothing to report.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Pranoti Mandrekar, Ph.D.
Gastrointestinal Division, Department of Medicine
LRB Rm #221
University of Massachusetts Medical Center
364 Plantation Street
Worcester, MA 01605
E-mail: Pranoti.Mandrekar@umassmed.edu
Tel: +1-508-856-5391

Or

Vincenzo Cardinale, M.D.
Department of Medico-Surgical Sciences and Biotechnologies
Sapienza University of Rome
Rome, Italy
E-mail: vincenzo.cardinale@itroma.it
Tel: +39-349-560-1492

formation and significantly affect iCCA biology.⁽¹⁾ Considering the desmoplastic nature of iCCA and its origin in chronic inflammatory conditions, the role of extracellular matrix proteins in driving pathogenesis cannot be undermined. Matricellular glycoproteins, such as periostin and mesothelin, have been under investigation for their contribution to the progression of iCCA, and hence their prognostic value as biomarkers to determine aggressiveness and invasiveness is emerging.^(4,5)

In *Hepatology Communications*, Manzanares et al.⁽⁶⁾ investigated the modulation of periostin and mesothelin, predictors of poor survival for patients with iCCA, in tumor progression in an orthotopic tumor model in rat and in a three-dimensional (3D) culture model. The authors found a strong positive correlation between tumor and serum periostin and mesothelin and increasing liver tumor mass and associated peritoneal metastases but also provided data *in vitro* showing these markers reflected differences in CCA cell aggressiveness and malignant grade. Expression levels of periostin and its pattern were most prominent in the desmoplastic stroma of larger sized more aggressive liver tumors and peritoneal metastases. In comparison, mesothelin was more highly expressed in CCA cells. The results of *in situ* expression reflected that serum levels of both biomarkers positively and linearly correlated with signs of aggressiveness.

Periostin is a crucial extracellular remodeling factor and in cancer cells binds to integrins leading to activation of phosphoinositide-3-kinase-protein kinase B-mediated and focal adhesion kinase-mediated signaling, resulting in invasion, metastasis, cell survival, and epithelial-mesenchymal transition (EMT).⁽⁴⁾ Previous observations reported increased periostin staining in human surgically resected iCCA, and this was associated with poor prognosis, which has been noted in other cancers, including pancreatic and breast tumors. Further studies evaluating the molecular mechanisms of periostin related to cancer progression and invasion could provide promise to develop this glycoprotein as a biomarker and/or therapeutic target.

Mesothelin, another glycoprotein important in extracellular matrix modeling has also been suggested for its potential as a prognostic marker in human iCCA.⁽⁵⁾ Increased mesothelin expression has been associated with shorter postoperative survival outcomes in iCCA.⁽⁵⁾ Because all previous studies relied on immunostaining to score expression in human tumors, Manzanares et al.⁽⁶⁾ designed a systematic investigation of mesothelin, using an orthotopic tumor model of

iCCA and 3D cultures of CCAs. Interestingly, increased serum mesothelin correlated with size of the orthotopic iCCA tumor. Remarkably, Manzanares et al. identified two molecular weight forms of mesothelin in iCCA tumors. The 50-kDa mesothelin, expressed predominantly at the apical luminal surface, is predictive of a more differentiated less aggressive iCCA phenotype. On the other hand, the 40-kDa cytoplasmic mesothelin is associated with increased malignant progression. Complementary to these *in vivo* studies, *in vitro* 3D cultures showed that coculturing of α -smooth muscle actin-positive cancer-associated fibroblasts contributed to an increase in the 40-kDa mesothelin form and correlated with an increase in iCCA anaplasia and ductal-like cell polarity. The precise mechanisms that influence expression of the 40-kDa cytoplasmic mesothelin associated with malignancy remains to be determined. Future extensive characterization is justified to determine the relevance of the two molecular weight forms in human iCCA.

Given the complexity in diagnosis of iCCA and lack of therapeutics, identifying molecular markers that not only contribute to pathogenesis but also serve as potential biomarkers or therapeutic targets is an attractive premise. The *in vivo* and *in vitro* results described by Manzanares et al.⁽⁶⁾ guarantee additional work using clinical samples of iCCA but also perihilar and distal CCA to provide a scientific and clinical basis for future development of periostin and/or mesothelin as diagnostic and prognostic markers. More importantly, understanding the role of periostin and mesothelin in EMT and cancer progression could not only uncover their function but also provide support for a future basis of targeting EMT for cancer treatment.

EMT is an important event that occurs during metastasis and is essential in the migration and invasion of cancer cells from the primary site. This transition of tumor epithelial cells is accompanied by genetic reprogramming, guided by the main EMT-inducing transcription factors SNAIL, TWIST, and ZEB, with repression of genes of the epithelial phenotype and acquisition of mesenchymal markers, such as α -smooth muscle actin, vimentin, and fibronectin. The prognostic value of different EMT markers has been analyzed in CCA.⁽⁸⁾ For example, nuclear expression of the S100A4 mesenchymal marker by neoplastic ducts was a strong predictor of metastasis and reduced survival in patients with CCA undergoing surgical resection. The modulation of EMT is a candidate strategy to counteract cancer local invasiveness and metastases, although to develop an effective anti-EMT treatment,

redundancies and bypasses among the pathways regulating EMT should be addressed.⁽⁷⁾

Whether periostin regulates the induction of EMT and hence malignant progression as well as metastasis is unknown. Interestingly, Mino et al.⁽⁸⁾ investigated the role of periostin in regulating EMT in iCCA. These studies provide a functional basis for periostin in iCCA and unravel its crucial role in pathogenesis. Mino et al. showed that periostin is highly expressed in surgically resected human iCCA tumors compared to adjacent nontumor tissue. Importantly, increased periostin expression in undifferentiated iCCA cell lines compared to moderately differentiated iCCA cell lines suggests that periostin expression correlates to the malignant potential of iCCA. Further, pronounced release of periostin from undifferentiated iCCA cells compared to moderately differentiated iCCA cells supports its role in malignancy. In fact, knockdown of periostin in undifferentiated iCCA cells exhibits decreased EMT markers and up-regulation of epithelial markers, suggesting reversal of EMT and reduction of the malignant potential, including diminished invasion and migration. These studies unravel a role for periostin in EMT and the malignant potential of iCCA, reinforcing its potential as a biomarker of tumor progression and poor prognosis.

Pranoti Mandrekar, Ph.D.¹

Vincenzo Cardinale, M.D.²

¹Department of Medicine
University of Massachusetts Medical School
Worcester, MA

²Department of Medico-Surgical Sciences and
Biotechnologies
Sapienza University of Rome, Rome, Italy

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