

Friend or foe: role of E-cadherin in prostate cancer metastasis

Ching-Yu Lin¹, Chih-Pin Chuu^{1,2,3}

¹Institute of Cellular and System Medicine, National Health Research Institutes, Miaoli, Taiwan; ²Graduate Institute of Basic Medical Science,

³Graduate Program for Aging, China Medical University, Taichung City 40402, Taiwan

Correspondence to: Dr. Chih-Pin Chuu, Institute of Cellular and System Medicine, National Health Research Institutes, 35, Keyan Road, Zhunan Town, Miaoli County 35053, Taiwan. Email: cpchuu@nhri.org.tw.

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Alteration of E-cadherin protein level during epithelial-mesenchymal transition (EMT) or mesenchymal-epithelial transition (MET) plays important role in cancer metastasis (1). In a recent paper “Liver Protects Metastatic Prostate Cancer From Induced Death by Activating E-cadherin Signaling” by Ma *et al.* (2) reported that the interaction between liver cells and metastatic prostate cancer (PCa) cells provokes re-expression of E-cadherin in PCa cells, which protects PCa cells from cell death induced by chemotherapeutic drugs. E-cadherin fabricates this protection via activation of canonical survival signaling pathways, including the extracellular signal-regulated kinases (ERK), protein kinase B (AKT), and the Janus kinase (JAK) signaling. Ma *et al.* used DU-145, an androgen-receptor (AR)-negative androgen-independent PCa cell line which expresses very low level of E-cadherin on the cell membrane to determine the role of E-cadherin in PCa chemotherapy resistance. The researchers found that either co-culture with primary hepatocytes to mimic liver cell microenvironment or addition of PD153035 (inhibitor suppressing the kinase activity of epidermal growth factor receptor, EGFR) induced the re-expression of E-cadherin in DU-145. These E-cadherin-high DU-145 cells were much more resistant to chemotherapeutic drugs treatment and TNF-related apoptosis-inducing ligand (TRAIL) both *in vitro* and *in vivo*.

The finding that elevation of E-cadherin in metastasized DU-145 PCa cells protects PCa cells from chemotherapy is very interesting and may stimulate novel therapies for advanced PCa targeting E-cadherin. However, the

difference in AR expression level and phosphatase and tensin homolog (PTEN) status may complicate the effect of E-cadherin on PCa metastasis. In PCa cells, AR modulates the expression of proteins regulating cell cycle, survival and growth. Increase in AR mRNA and protein is observed in castration-resistant prostate cancer (CRPC) as compared to the primary prostate tumors (3). Ligand-activated AR has been reported to bind E-cadherin promoter, to downregulate E-cadherin expression, to activate Snail, to induce EMT, and thus promotes cancer metastasis (4,5). Re-expression of AR in PC-3 cells, another AR-negative PCa cells, increases E-cadherin but represses EMT, migration, and invasion of PC-3 cells in the absence of androgen (6). PTEN is a negative regulator for phosphoinositide 3-kinase (PI3K)-Akt signaling pathway. Deletion of PTEN was observed in 40–70% of PCa patients, resulting in upregulation of PI3K-Akt signaling. Deletion or mutation of PTEN is associated with poor prognosis, cancer metastasis, and progression towards castration-resistant status or PCa (7,8). DU-145 is an AR-negative PCa cell line expressing wild type PTEN. Whether the phenomenon observed in DU-145 is the general case for all PCa cells requires further investigation. It is a good idea to use both LNCaP (AR-positive, mutant PTEN) and PC-3 (AR-negative, PTEN null) for validation. Ma *et al.* pointed out that E-cadherin promotes protection against chemotherapy drugs partially via activation of Akt1 and Akt2. As Akt3 has been reported to play important role in PCa (9), it will be worthy to examine if Akt3 is involved in

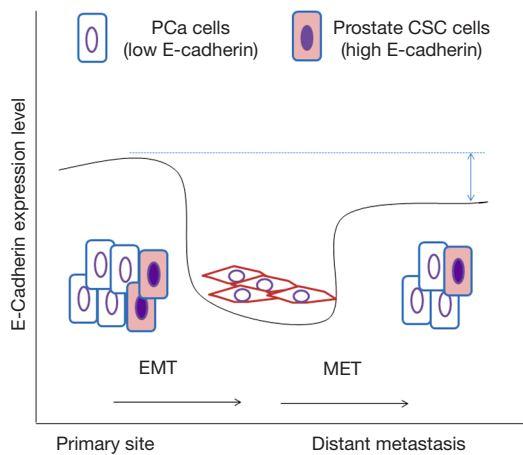


Figure 1 Alteration of E-cadherin level during PCa metastasis. During the EMT and cancer metastasis, the E-cadherin decrease in prostate CSCs cells to proceed migration and invasion. At the metastatic site, the CSCs cells regain E-cadherin expression and generate low E-cadherin PCa cells. The average level of E-cadherin of the metastatic prostate tumors may be lower than the primary tumors to accommodate the tough micro-environment at the metastatic lesion. PCa, prostate cancer; EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition; CSC, cancer stem cell.

the chemotherapeutic protection of E-cadherin.

During the EMT, level of E-cadherin decreases to assist the metastasis of cancer cells. Ma *et al.* suggested that after PCa cells launch at liver tissue to form metastatic colony, the interaction between PCa cells and hepatocyte cells stimulates the expression of E-cadherin. The elevation of E-cadherin will then protect PCa cells from chemotherapy but also hinder the proliferation of PCa cells. As liver metastasis only counts for 25% of all PCa metastasis, less than the PCa metastasis incidence in lymph node, bone, and lung, it is critical to determine if cells in lymph node, bone, and lung or immune cells may interact with PCa cells to stimulate the expression of E-cadherin.

E-cadherin positive prostate cancer stem cells (CSCs) subpopulation has been reported to express the reprogramming factors SOX2 and OCT3/4 (10). This subpopulation of prostate CSCs is highly invasive and is capable of altering its E-cadherin expression during the process of invasion (10). As CSCs population is well known for being chemotherapy-resistant, we believe that this prostate CSCs population account for most, if not all, of the chemotherapy protective effects being observed by Ma *et al.* The CSCs population will first decline the expression

of E-cadherin to promote cancer metastasis, possibly via epigenetic modification of methylation of the CDH1 promoter (11) and uncoupling of ZEB1 and E-cadherin expression in metastatic PCa (12). At the metastatic lesion, the CSCs population will elevate the expression of E-cadherin. Putzke *et al.* analyzed 185 PCa metastases and discovered significantly higher E-cadherin expression in bone than in lymph node and soft tissue metastases (12). Using DU-145 sublines with different E-cadherin expression level, Putzke *et al.* found that DU-145 xenografts positive for E-cadherin exhibit higher aggressiveness and the metastases frequency, suggesting that high E-cadherin expression in metastatic PCa is associated with aggressive tumor growth. This E-cadherin-positive DU-145 cells also demonstrate the highest expression of genes associated with stem cells (12), supporting our hypothesis that CSCs play essential role in E-cadherin-induced chemotherapy resistance.

Ma *et al.* mentioned in the papers that according to the analysis of TCGA, lower E-cadherin level was found in patients with distant metastasis. Our analysis using Oncomine database also indicates that expression of E-cadherin is lower in metastatic prostate tumors as compared to primary tumors (*Figure S1*). This obviously seems to be contradictory to the chemotherapy-protective role of E-cadherin as suggested by Ma's paper. We believe that this can be explained by the fact that high E-cadherin expression hampers proliferation of PCa cells at metastatic lesion. Therefore, a mixture of larger population of PCa cells with low E-cadherin expression and a small population of prostate CSCs with high E-cadherin expression forms the primary prostate tumors. During the EMT and cancer metastasis, the E-cadherin decrease in prostate CSCs cells to proceed migration and invasion. At the metastatic site, the CSCs cells regain E-cadherin expression and generate low E-cadherin PCa cells. The average level of E-cadherin of the metastatic prostate tumors may be lower than the primary tumors to accommodate the tough micro-environment at the metastatic lesion (*Figure 1*).

In summary, Ma *et al.* provided evidence to demonstrate that E-cadherin is not only a tumor suppressor protein, but can also diminish the effects of chemotherapy via activation of ERK, Akt, and JAK signaling pathway. Development of novel therapy for advanced PCa should take E-cadherin and these signaling pathways into consideration.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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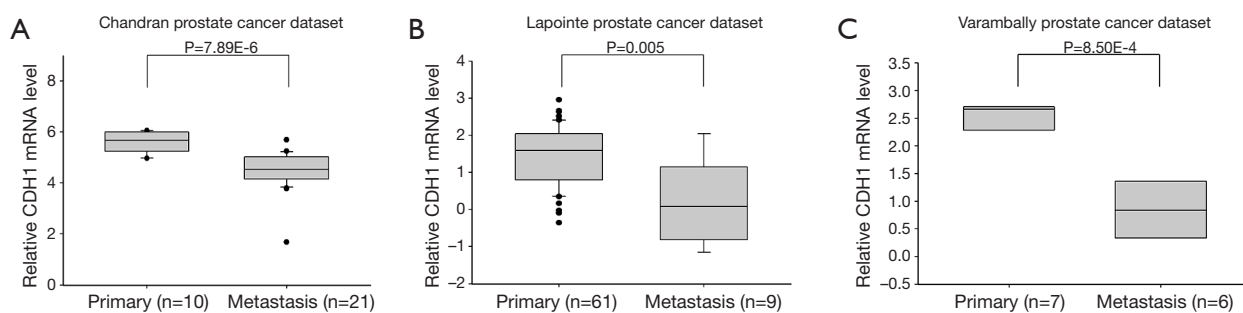


Figure S1 Oncomine database for CDH1 expression of human prostate cancers. The mRNA level of (A) Chandran; (B) Lapointe; (C) varambally in primary *vs.* metastatic prostate tumors was analyzed from online gene array data extracted from Oncomine.