Letter to the Editor

Friend turned foe: E-cadherin perversely protects micrometastases

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We thank Drs. Lin and Chuu for their recent insightful Commentary in *TAU*, on our paper in Hepatology concerning the role of E-cadherin in the survival and chemoresistance of prostate cancer metastases (1). We would like to take this opportunity to amplify or explain some of the findings as they discussed.

First, the transient expression of E-cadherin at the earliest stages of metastatic seeding appears to be widespread if not universal for carcinomas. That small metastatic nodules express E-cadherin at levels higher than the primaries has been noted by many pathologists, and documented by ourselves for cancers originating in the prostate, breast, and colon and metastasizing to the liver, lung, brain or even bone (1,2). This stage of epithelial reversion of carcinoma cell phenotypes is often not fully appreciated due to its transient nature in the epithelial-mesenchymal plasticity (EMPathy) continuum.

A plethora of studies points out the essential role of epithelial-mesenchymal cell plasticity in tumors metastasis. An initial epithelial to mesenchymal transition (EMT) helps tumor cells separate and escape from the primary site. We have shown that this converts back to an epithelial phenotype (MErT) to enhance survival in an inhospitable metastatic microenvironment. MErT confers tumor cells survival advantage including resistance to death cytokines released in a non-specific foreign body response, a property which also renders them generally chemoresistant (3). The ectopic organs induce the tumor cells to re-express E-cadherin; epithelial tissues like liver and lung allow for cell heterotypic and homotypic E-cadherin binding while mesenchymal tissues like bone and brain show tumor cell homotypic E-cadherin binding. As noted, this is a phenotypic switch, not only involving E-cadherin but also gap junctions (e.g., connexin 43, 26 and 32), and cytokeratins, with reciprocal downregulation of mesenchymal markers (2). However, it must be noted that this EMPathy is not complete or exact with tumor cells often expressing both mesenchymal and epithelial markers simultaneously. This epithelial phenotype is meta-stable as large metastatic nodules appear to undergo a second EMT, so that by the time these metastases are clinically detectable, they appear as mesenchymal (2). This second EMT is selected as the epithelial phenotype retards or even stops proliferation.

Liver metastases are very common in prostate cancer (4), contrary to general impressions. As the liver metastases are usually clinically silent until late in progression, their presence is underappreciated. However, autopsy series have shown that these are as common as bone marrow metastases. As noted above, small bone metastases have been reported to express E-cadherin. Lymph node tumor growths do present an exception, as they tend to be phenotypically similar to the primary lesion, usually mesenchymal.

As Lin and Chuu note, we examined advanced Castrate Resistant Prostate Cancer as these reflect the tumor types that pose clinical conundrums. We have not queried androgen responsive tumors such as LNCaP as they are not spontaneously metastatic in model systems. Still, the points made concerning AR are relevant. AR expression is maintained throughout prostate cancer progression, and the majority of androgen-independent or hormone refractory

prostate cancers express AR (5). Over 80% of patients show a positive response to androgen ablation. However, patients with metastatic prostate cancer eventually experience disease progression in a median of 12 to 18 months after androgen deprivation therapy and are failed with secondary hormone therapy. It is indicated prostate cancer cells in these patients developing additional survival pathways, such as PTEN mutations, or hormone-autonomous AR signaling. Still, the microenvironment overrides this signaling. According to our data, both AR negative classic prostate cancer cell lines, DU145 ($PTEN^{WT}$) and PC3 ($PTEN^{null}$), have shown conversion and chemoresistance in liver microenvironments *in vivo* and *in vitro* (1). Thus, while AR and PTEN mutations may contribute, there appears to be an E-cadherin-dependent survival.

The E-cadherin-linked chemoresistance is due to mobilization of the canonical survival pathways, including those through ERK and AKT. Interestingly, these kinases appeared relatively quiet at baseline, with chemotherapeutic drug challenge activating them (1). We found the subtherapeutic doses of kinase inhibitors sensitized the cells to killing by death cytokines and chemotherapy, so that the cells acted similar to their mesenchymal E-cadherin-negative cognates. We focused on AKT1 and AKT2 as these were increased in E-cadherin high tumors, but AKT3 had comparable expression levels in both E-cadherin high/low tumors. Still these studies examined protein levels but did not finely discern activation, thus not excluding AKT3 involvement. In the ongoing studies, we are discerning the varied roles of AKT isoforms in both the cadherin switch and chemoresistance, which appear to be non-overlapping roles.

Lin and Chuu raise the issue of whether these resistant cells represent prostate cancer stem cells. This is complex in that it appears that for carcinomas (as opposed to lymphomas/leukemias) the cancer stem cell population is not a fixed, asymmetrically dividing population but a plastic phenotype. Furthermore, at least *in vitro* and in small metastatic nodules *in vivo*, the phenotype appears to encompass the vast majority of the tumor cells, and not a small fraction usually thought of when discussing stem cells. Moreover, a recent study unlinked epithelial-mesenchymal plasticity from metastasis-enhancing stem cell capacity. In this study, epithelial and mesenchymal circulating CSCs had the similar metastatic potential and upon arrival to the secondary sites, mesenchymal cells converted to epithelial state to have the comparable proliferative capacity with their epithelial counterparts (6). Given this, the E-cadherin low tumor nodules in the liver could be transiently E-cadherin high, which was not noted before reversion to a mesenchymal outgrowth. This is further verified by the fact that preventing E-cadherin re-expression with shrank hampers liver metastases (1). The study mentioned in Commentary by Uptake *et al.*, exploring the more aggressive tumor growth of DU145 with high E-cadherin in tibia engraft mouse model, support our findings again that E-cadherin confers tumor cells survival advantage in the ectopic sites (7). Lastly, we did not see cancer stem cell markers tracking with E-cadherin expression in our study (data not shown), but only the E-cadherin high tumors were resist to induced cell death.

Lin and Chuu come to an important and potentially impactful conclusion that new approaches are needed for the androgen-independent metastatic tumors, and before late stage disease ensues. They propose that understanding these survival pathways may lead to new ways to render occult metastases sensitive to the drugs we have, and that even newer agents still must overcome the survival advantage conferred by E-cadherin re-expression. With this, we fully concur.

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Footnote

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

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