Asian Journal of Andrology (2011) 13, 179–180
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RESEARCH HIGHLIGHT

Epithelial–mesenchymal transition in prostate cancer: providing new targets for therapy

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Asian Journal of Andrology (2011) **13,** 179–180; doi:10.1038/aja.2010.169; published online 3 January 2011

The ability of epithelial cells to undergo phenotypic transitions during embryogenesis, wound healing and malignant progression is now widely accepted as a core biological process termed epithelial–mesenchymal transition (EMT).[1] During cancer progression, the process of EMT has been associated with the acquisition of stemness properties, treatment resistance and metastatic progression, hallmarks of malignancy.[2,3] Indeed, induction of EMT in breast cancer model systems generates properties of self-renewal, metastasis and chemotherapy resistance, demonstrating causality.[2,3] The hijacking of this core biological process during malignant progression is likely related to key initiating events, including genetic mutations and activation of oncogenic pathways that in turn regulate cell proliferation, migration, epithelial–mesenchymal signaling and cross-talk, and angiogenesis.[4] In prostate cancer, this link between EMT and progression has been circumstantial, but definitive evidence is emerging.[5,6] For instance, new data indicate that expression of the fusion protein TMPRSS2-ERG, which is created through interstitial deletion of chromosome 22 in over half of all prostate cancers,[7] can lead to activation of the beta-catenin pathway and EMT.[8] Additionally, overexpression of the polycomb-repressive complex protein EZH2 has been linked to EMT, metastasis and castration resistance.[9] In prostate cancer model systems, activated stromal signaling from the tumor microenvironment may induce EMT and stemness properties in prostate cancer, contributing to castration resistance and metastatic progression through this molecular cross-talk, often mediated by cytokines and other paracrine factors.[10] We have recently shown that several EMT factors, such as vimentin and N-cadherin, are commonly expressed in circulating tumor cells from men with castration-resistant metastatic prostate cancer.[11] This E-cadherin to N-cadherin switch has been associated with EMT in many tumor types, and in prostate cancer has previously been associated with relapse after surgery and development of metastatic disease.[5]

In a very exciting manuscript in 7 November 2010 advance online publication of *Nature Medicine*, Tanaka *et al.* found that N-cadherin may be more than just a marker of EMT; it may be a useful therapeutic target.[12] In a series of elegant preclinical and clinical correlative studies, they found that N-cadherin was upregulated in castration-resistant prostate cancer cell lines, and increased in expression during serial passage of prostate cancer cell lines in the setting of castration. They next found that N-cadherin expression was increased in clinical metastases from men with castration-resistant disease compared with benign prostate conditions or localized or hormone-sensitive disease, although nearly one-third of men with hormone-naive disease expressed N-cadherin, implying likely some degree of pre-existing expression in tumors rather than complete induction during castration-resistant progression. More importantly, in a series of experiments in which N-cadherin was ectopically expressed and in which N-cadherin was silenced, Tanaka *et al.* demonstrated that N-cadherin induced prostate cancer cells toward castration-resistant growth, promoted muscle invasion, and led to loss of E-cadherin, increased expression of vimentin, and a more mesenchymal phenotype. RNAi-mediated knockdown of N-cadherin reduced invasion and castration-resistant tumor growth, implying that N-cadherin is both necessary and sufficient for malignant growth in these model systems. All of these features point toward a central role of N-cadherin in metastatic spread. Interestingly, N-cadherin expression led to loss of androgen receptor expression, suggesting an inverse relationship between EMT and androgenic signaling in prostate cancer. Finally, Tanaka *et al.* demonstrated the possibility of targeting N-cadherin through the generation of two monoclonal antibodies against extracellular N-cadherin domains. Anti-N-cadherin antibody administration reduced expression of other EMT markers, tumor growth and invasion, and delayed castration resistance, lymph node metastases and angiogenesis. These changes were accompanied by increased E-cadherin expression. Forced N-cadherin over expression was associated with BCL-2 overexpression, transforming growth factor-beta signaling, and IL-8 and IL-6 expression, all factors implicated in castration-resistant prostate cancer and tumor metastasis.[10] Moreover, targeting antibodies against N-cadherin reduced Akt activation and IL-8 and IL-6 expression during tumor regression, suggesting at least one oncogenic mechanism behind the downstream effects of N-cadherin expression and the mediation of treatment resistance.

Collectively, this work suggests that N-cadherin, an EMT factor, is important in castration-resistant progression in prostate cancer, as well as in contributing to metastasis and the lethal phenotype. It is interesting to speculate that the switch to N-cadherin expression in prostate cancer may induce homotypic adhesion to neural structures, which are known to express N-cadherin, as

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well as to activated prostate stroma, which may also undergo N-cadherin induction.[13,14] This cross-talk and change in adhesion preference may lead to perineural invasion, nodal and disseminated hematogenous metastases. Combined with the existing data linking EMT to stemness, chemoresistance and metastasis in multiple epithelial tumors, the new data by Tanaka *et al.* suggest a new approach targeting EMT directly using N-cadherin monoclonal antibodies or potentially small molecule inhibitors of EMT drivers as a novel approach to prostate cancer therapy and for other solid tumors. Further proof of this will require testing of N-cadherin antibodies in additional preclinical models of prostate cancer that more closely resemble human disease as well as in orthotopic or transgenic models of prostate cancer that undergo hematogenous rather than lymph node spread. It would be of great interest if N-cadherin antibodies were able to reduce the circulating tumor cell count and development of new metastatic foci in these settings, given the detection of this antigen on circulating tumor cells.[11] Finally, further testing of the safety of N-cadherin targeting will be needed, given its normal role in development, adhesion and mesenchymal cell function.

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