Cancer cells adapt by hijacking embryonic developmental processes. One such phenomenon, referred to as the epithelial–mesenchymal transition (EMT), is considered a hallmark of cancer and plays a dominant role in facilitating cancer cell invasion and metastasis (1). Both early precursor lesions and neoplastic cells can derive a selective advantage by modulating their microenvironment. The selection process can take advantage of not one but many routes to co-opt existing normal cellular processes. Examples include the expression of neovasculature to provide growth advantage, the production of chemokines to recruit enabling cells (e.g., lymphocytes and macrophages), or the suppression of the local immune response to avoid T-cell surveillance. Each of these processes represents major avenues of research and the focus of drug target development to limit the spread and progression of cancer cells.

Is this selection process largely random or are there local organ-specific habitat traits that favor specific mechanisms of adaptation? Emerging observations provide clinically relevant clues to how adaptations may be niche specific. One recent example comes from the burgeoning field of immune-oncology. In a series of clinical trials targeting lymphocytes and macrophages, or the suppression of the local immune response to avoid T-cell surveillance. Each of these processes represents major avenues of research and the focus of drug target development to limit the spread and progression of cancer cells.

In this issue of Cancer Discovery, Lucas and colleagues (7) describe a nearly prostate cancer–specific serine protease that enhances EMT signaling through c-MET activation. In 1999, Lin and colleagues (8) first described the transmembrane serine protease 2 (TMPRSS2) as highly expressed in normal prostate tissue when compared with a spectrum of other human tissues. Low levels of transcription were seen in colon and lung tissues as well. Abundant TMPRSS2 expression in cells of prostate origin, including cancer cells, was explained through the presence of androgen responsive elements in the 5′ promoter. In short, this serine protease achieves organ specificity through the androgen receptor, similar to another well-known prostate-specific serine protease, prostate-specific antigen (PSA) or human kallikrein 3 (hK3).

The serine protease role of PSA is believed to enable anticoagulation of the seminal fluid, representing an important evolutionarily conserved function to preserve fertility. In the current study, Lucas and colleagues provide novel insights into a potential signal transduction role of TMPRSS2 in the setting of prostate cancer disease progression.
organ specificity plays a pivotal role in the TMPRSS2 story. This is the ideal setting for cancer cells to hijack this process for selective activation of EMT signaling, facilitating the metastatic process. A number of studies over the past several years have demonstrated that AR signaling is activated throughout the course of prostate cancer progression, even in the face of potent antiandrogen therapy. TMPRSS2 is clearly one of the downstream proteins regulated by AR that provides tumor cells with a selective advantage. It is noteworthy to add that around 40% to 50% of prostate cancers harbor a common recurrent gene fusion involving the TMPRSS2 5′ promoter and ERG (11, 12). Lucas and colleagues demonstrate that despite inactivation of one copy of TMPRSS2 through rearrangement, the other copy maintains a similar level of gene expression. It is also worth noting that with the exception of the neuroendocrine prostate cancer cell line NCI-H660 there are few cases of biallelic loss of TMPRSS2 in cancer cells. Thus, as noted in early work by Lucas and colleagues, TMPRSS2 expression is maintained in aggressive and metastatic cancer in the cytoplasm (10), and expression is completely lost in AR-negative prostate cancer, such as neuroendocrine prostate cancer. Therefore, targeting TMPRSS2 is an appealing concept to reduce metastatic burden. The nomination of BHH as a putative inhibitor of TMPRSS2 is intriguing as it is already FDA approved for other indications.

In summary, this study provides important insight into the dual roles of a highly prostate-specific serine protease in health and cancer cells. The work also highlights our need to consider organ-specific gene expression as a route for cancer cells to gain selective opportunities for growth, invasion, evasion of the immune system, and metastasis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Grant Support
M.A. Rubin is supported by the Prostate Cancer Foundation, the NCI (R01 CA116337), and the NCI Early Detection Research Network (U01 CA11275).

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Insights into the Mechanism of Organ-Specific Cancer Metastasis

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Cancer Discovery 2014;4:1262-1264.

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