Cancer cells adapt by hijacking embryonic development 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 the programmed death 1 (PD-1) receptor or its ligand immune-oncology (2), results have been excellent to insignificant, based on either the programmed death 1 (PD-1) receptor or its ligand PD-L1 antibodies. The rationale for targeting these checkpoints with anticytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), anti–PD-1, or anti–PD-L1 antibodies has shown impressive results in the treatment of a subset of patients with metastatic melanoma (3–5). Activity has also been observed in a small percentage of patients with renal cell cancer and non–small cell cancer (4). Yet, no activity was observed in pancreatic or colon cancer. Work continues to understand not only how to improve the effectiveness of these approaches but also the failures. One important observation is that tissue-specific factors may contribute significantly to immune surveillance, as was recently demonstrated in pancreatic cancer, suggesting that cells in the microenvironment maintain immunosuppression in addition to the cancer cells (6). Therefore, mechanisms exploited by cancer cells and by the microenvironment may be more predictable, and thus exploitable, than expected once we begin to elucidate the organ-specific rules of play.

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 type II (TMPRSS2) as highly expressed in prostate cancer, achieving 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.
TMPRSS2 belongs to the type II class of serine transmembrane proteases. This class also includes hepsin (TMPRSS1), known also to be overexpressed in prostate cancer (9). After determining the high expression of TMPRSS2 in prostate tissue, Lucas and colleagues (10) established that high expression of TMPRSS2 was also associated with mislocalization from the apical surface into the cytoplasm in high-grade and metastatic prostate cancer, potentially suggesting an alternate role in disease progression. To begin to understand a potential mechanistic role of TMPRSS2 in prostate cancer disease progression, they turned to a Tmprss2-/- mouse that they had previously described. The mouse has no recognizable phenotype save for the lack of TMPRSS2 expression. Crossing an established prostate cancer mouse model with the Tmprss2-/- mice, they observed decreased metastases in mice lacking TMPRSS2 expression. TMPRSS2 expression increased the likelihood of distant metastases to liver and lung. In vitro experiments demonstrated that TMPRSS2-expressing tumor cells have increased capabilities of proliferation and invasion as compared with Tmprss2-/- cells.

Is TMPRSS2’s role in disease progression solely related to canonical protease activity? An intriguing experiment from their study would suggest otherwise. Lucas and colleagues injected tumor cells into the tail veins of recipient mice. The Tmprss2-/- and Tmprss2+/- tumor cells could both be detected in circulation early on. However, by 24 hours, the Tmprss2-/- cells were no longer detectable, in contrast with the Tmprss2+/- cells, which persisted and established distant metastases. Taken together, these observations suggested that potential substrates could also be modulated to help reverse the metastatic role of TMPRSS2. To this end, they performed positional scanning of synthetic combinatorial peptide libraries (PS-SCL). This nominated motifs for possible activation sequences in zymogen precursors of PLAT and hK2. hK2 is expressed in the normal prostate epithelial cells, and when secreted into the glands, it activates PSA, thus nominating a novel upstream role of TMPRSS2 in initiating and maintaining the prevention of the coagulation of seminal fluid proteins in the normal state. Another motif nominated by the screen corresponded to a precursor form of the hepatocyte growth factor (HGF), suggesting a role for TMPRSS2 in HGF/c-MET signaling. Indeed, they demonstrated that intact TMPRSS2 could activate MET and that this could be reversed with a c-MET inhibitor. Consistent with these findings, a transcriptomic signature of TMPRSS2 as compared with Tmprss2 null cells demonstrated an EMT signature with high expression of CXCL12/CXCR4, consistent with prior HGF signatures, and the elevation of the EMT marker N-cadherin. Finally, a compound library screen identified bromhexine hydrochloride (BHH) as a putative inhibitor of TMPRSS2. Treatment of Tmprss2+/- cells compared with Tmprss2-/- cells significantly decreased the number of distant metastases.

Lucas and colleagues have begun to elucidate the role of TMPRSS2 in normal prostate physiology and its role in cancer. Similar to the example of immune regulation therapy, organ specificity plays a pivotal role in the TMPRSS2 story. TMPRSS2 is potentially crucial to reproductive homeostasis and highly prostate specific due to androgen receptor (AR) regulation. 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 CA111275).

Published online November 3, 2014.

REFERENCES


Insights into the Mechanism of Organ-Specific Cancer Metastasis

Mark A. Rubin

Cancer Discovery 2014;4:1262-1264.

Updated version
Access the most recent version of this article at:
http://cancerdiscovery.aacrjournals.org/content/4/11/1262

Cited articles
This article cites 12 articles, 5 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/4/11/1262.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://cancerdiscovery.aacrjournals.org/content/4/11/1262.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.