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Insights into the mechanism of organ specific cancer metastasis

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Summary

Nelson and colleagues nominate the Transmembrane Serine Protease Type II (TMPRSS2) as an important player in the initiation of epithelial-mesenchymal transition (EMT) in prostate cancer. Cancer cells maintain AR-regulated cytoplasmic TMPRSS2 expression, which facilitates EMT invasion and metastasis in model systems through hepatocyte growth factor and c-MET signaling. In addition to providing data rationale for potentially targeting this organ-specific enabler of metastatic disease progression, this study also highlights the importance of understanding how organ/tissue specific-genes are co-opted in the context of cancer.

Cancer cells adapt by hijacking embryonic developmental processes. This phenomenon referred to as 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 coopt existing normal cellular processes. Examples include the expression of neo-vasculature to provide growth advantage, the production of chemokines to recruit enabling cells (e.g., lymphocytes, 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 either the Programmed Death 1 (PD-1) receptor or its ligand PD-L1, results have been excellent to insignificant based on the organ site and genetic background. The rationale for these trials is

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that cancer cells can effectively hide from the immune system by using immune-cell-intrinsic checkpoints that are activated by T-cells(2). A blockade of these checkpoints with anti-cytotoxic 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 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*, Nelson and colleagues describe a nearly prostate cancer-specific serine protease that enhances EMT signaling through c-MET activation(7). In 1999, Nelson et al. first described the transmembrane serine protease 2 (TMPRSS2) as highly expressed in normal prostate tissue when compared to a spectrum of other human tissues(8). 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, Nelson and colleagues provide novel insights into a potential signal transduction role of TMPRSS2 in the setting of prostate cancer disease progression. TMPRSS2 belongs to the type II class of serine transmembrane proteases. This class also includes hepsin (TMPRSS1) known also to be over-expressed in prostate cancer(9). After determining the high expression of TMPRSS2 in prostate tissue, the Nelson group 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(10). 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. TMPRRS2 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 to tmprss2$^{-/-}$ cells.

Is TMPRSS2's role in disease progression solely related to canonical protease activity? An intriguing experiment from their study would suggest otherwise. Nelson and colleagues

injected tumor cells into the tail vein of recipient mice. The tmprrs2$^{-/-}$ and tmprss2^{wt} tumor cells could both be detected in circulation early on. However, by 24 hours, the tmprrs2$^{-/-}$ cells were no longer detectable in contrast to the tmprss2^{wt} 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 secreted into the glands, it activates PSA, thus nominating a novel role of TMPRSS2 in initiating and maintaining the upstream role of preventing the coagulation of seminal fluid proteins in the normal state. Another motif nominated by the screen corresponded to a precursor form of hepatocyte growth factor (HGF), suggesting a role for TMPRSS2 in HGF/c-MET signaling. To address this, they demonstrated that intact TMRPSS2 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 to TMPRSS2 null 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 library screen identified bromhexine hydrochloride (BHH) as a putative inhibitor of TMPRSS2. Treatment of TMPRSS2^{wt} compared to TMPRSS2$^{-/-}$ significantly decreased the number of distant metastases.

Nelson 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 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 anti-androgen therapy. TMPRSS2 is clearly one of the downstream proteins regulated by AR that provides tumors cells with a selective advantage. It is noteworthy to add that around 40–50% of prostate cancers harbor a common recurrent gene fusion involving the TMPRSS2 5′ promoter and ERG(11, 12). Nelson and colleagues demonstrate that despite inactivation of one copy of TMRPSS2 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, NCIH660, there are few cases of bi-allelic loss of TMRPSS2 in cancer cells. Thus, as noted in early work by the Nelson group, 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 TMRPSS2 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.

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