

# The TMPRSS2 Protease Promotes Prostate Cancer Metastasis

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The vast majority of prostate cancer deaths are caused by metastasis, yet the mechanisms that allow primary tumor cells to become invasive are largely unknown. A new study led by Dr. Jared Lucas and Cynthia Heinlein in the laboratory of Dr. Pete Nelson (Human Biology and Clinical Research Divisions), along with their collaborators, tackled this question by modeling in mice the role of a protease (TMPRSS2) in prostate cancer metastasis. TMPRSS2 is a Type II transmembrane serine protease (TTSP) that was previously known to be expressed in normal prostate epithelium and to be upregulated in aggressive prostate cancers (Lucas et al., 2008), but its role in normal and neoplastic prostate development had not previously been determined. "A critical aspect of this study involved the multi-disciplinary collaboration with Fred Hutch and UW faculty that brought in expertise ranging from pathology to high-throughput small molecule screens", explained Dr. Nelson.

The authors first directly compared the transcript levels of TMPRSS2, relative to two other TTSPs, hepsin and matriptase, both of which had been implicated in prostate cancer, in microdissected epithelium from localized or metastatic prostate cancers. Notably, they found that TMPRSS2 was the most highly expressed protease. To confirm that TMPRSS2 was elevated in metastatic tissue samples, the authors examined metastatic cancer foci from 44 men, and discovered that the majority of foci (132 of 166) exhibited high levels of TMPRSS2. Next, the researchers employed pharmacological inhibition of androgen signaling in men with localized prostate cancer, as well as a castration-resistant mouse xenograft model, to show that TMPRSS2 expression was regulated by androgen ligands. Importantly, deletion of TMPRSS2 in a mouse model of prostate cancer (TRAMP model) attenuated metastasis to distant solid organs. Further, TMPRSS2-positive, but not TMPRSS2-depleted, primary tumor cells injected into mouse tibias promoted tumor growth and bone destruction. Together, these results showed that TMPRSS2 indeed promotes prostate cancer metastasis and permits survival and growth of prostate cancer cells at distant sites.

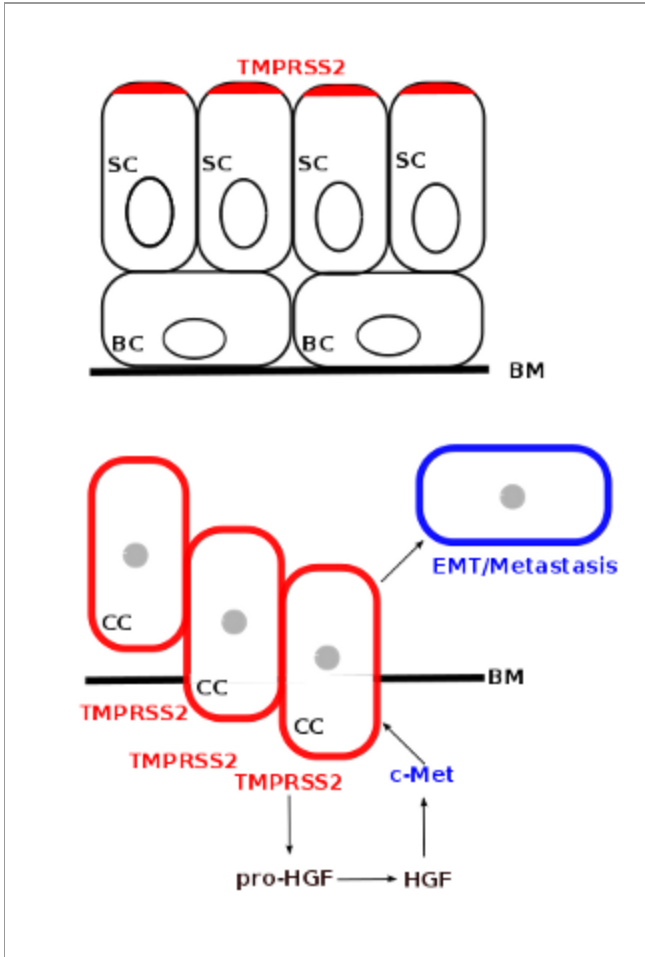
To uncover potential substrates of TMPRSS2 that could account for its metastatic activity, the authors screened a large library of synthetic peptides and found a sequence identical to the activation sequence of the precursor form of hepatocyte growth factor (pro-HGF). HGF is a ligand for

c-Met, an oncogenic receptor tyrosine kinase known to be relevant to prostate cancer invasion. Consistent with pro-HGF being a TMPRSS2 substrate, active, but not protease-inactive form of TMPRSS2, was able to cleave pro-HGF in vitro, which resulted in c-Met activation. Since HGF- c-Met signaling has been linked to epithelial to mesenchymal transition (EMT), the authors wondered whether such link could be extended to TMPRSS2. Indeed, transcriptional profiling of TRAMP tumor cells with or without TMPRSS2 revealed that EMT-associated genes were downregulated in the absence of TMPRSS2. Finally, to assess if TMPRSS2 would constitute a therapeutic target, the researchers screened several different chemical libraries for TMPRSS2 inhibitors and identified a bioavailable, FDA-approved compound called bromhexine. *In vivo* studies showed that intraperitoneal injection of bromhexine in TRAMP mice reduced the frequency of metastasis. Overall, these studies show that androgen-induced expression of TMPRSS2 potently activates HGF- c-Met signaling, which endows prostate tumor cells with invasive and mesenchymal properties. According to Dr. Nelson, "The identification of a bioavailable inhibitor of TMPRSS2 provides an opportunity to determine if suppressing TMPRSS2 activity can reduce the spread of prostate cancer and consequently impair metastatic growth".

[Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, Morrissey C, Corey E, Montgomery B, Mostaghel E, Clegg N, Coleman I, Brown CM, Schneider EL, Craik C, Simon J, Bedalov T, Nelson PS](#). 2014. The Androgen-Regulated Protease TMPRSS2 Activates a Proteolytic Cascade Involving Components of the Tumor Microenvironment and Promotes Prostate Cancer Metastasis. *Cancer Discov* pii: CD-13-1010. Epub ahead of print

See also:

[Lucas JM, True L, Hawley S, Matsumura M, Morrissey C, Vessella R, Nelson PS](#). 2008. The androgen-regulated type II serine protease TMPRSS2 is differentially expressed and mislocalized in prostate adenocarcinoma. *J Pathol* 215(2): p. 118-25.



*Image by Alexandre Neves*

In normal prostate epithelium, TMPRSS2 cannot access stromal pro-hepatocyte growth factor (pro-HGF). In neoplasia however, high levels of TMPRSS2 cleaves pro-HGF, which in turn activates c-Met in cancer cells (CC) to promote metastasis and epithelial to mesenchymal transition (EMT). SC: secretory epithelial cell; BC: basal epithelial cell; BM: basement membrane.