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PROSTATE CANCER

TMPRSS2 promotes metastasis through proteolysis

Transmembrane protease serine 2 (TMPRSS2) has been shown to be expressed in high levels in metastatic prostate cancer, and is regulated by androgen receptor signalling. Furthermore, TMPRSS2 promotes metastasis by proteolytic activation of hepatocyte growth factor (HGF), and chemical inhibition of TMPRSS2 suppresses metastasis.

Metastatic disease is the major cause of death from prostate cancer, but the biochemical mechanisms underlying progression from localized disease are poorly understood. TMPRSS2—and related proteases hepsin and matriptase—have previously been shown to have elevated expression in localized prostate cancers compared with benign tissues, and are thought to influence cancer invasiveness. Comparison of these proteins in neoplastic epithelium from 14 localized and 40 metastatic prostate cancers has now shown that TMPRSS2 is the most highly expressed protease. TMPRSS2 expression was also high in 132 of 166 tissue samples from metastatic cancer foci, suggesting a functional role in tumour cell dissemination and survival in foreign sites.

> “...chemical inhibition of TMPRSS2 suppresses metastasis”

Involvement of the androgen receptor in regulation of TMPRSS2 expression was shown by positive correlation of expression in microdissected primary and metastatic tumour epithelia. Chemical castration in men with localized prostate cancer reduced *TMPRSS2* expression. Furthermore, in a xenograft model, development of a castration-resistant phenotype, accompanied by reactivation of androgen receptor signalling, was related to an increase in *TMPRSS2* expression.

In mouse models of prostate cancer, the presence of functional Tmprss2 was significantly associated with metastasis to solid organs, and with the viability and metastatic potential of tumour cells injected into wild-type mice. Similarly, targeted reduction of *TMPRSS2* expression in LNCaP cells significantly reduced cell proliferation and invasion.

A TMPRSS2 proteolytic cleavage sequence present in HGF was identified by screening pools of synthetic peptides. HGF cleaved by TMPRSS2 activated c-Met and promoted invasiveness of DU145 prostate cancer cells. TMPRSS2 activity induced an epithelial–mesenchymal transition phenotype in a mouse model. Screening of nearly 70,000 chemical compounds identified five inhibitors of TMPRSS2 protease activity. The FDA-approved bromhexine inhibited metastasis in a mouse model, suggesting that targeting TMPRSS2 might be clinically viable.

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Original article Lucas, J. M. *et al.* The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. *Cancer Discov.* doi:10.1158/2159-8290.CD-13-1010