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RESEARCH HIGHLIGHT

PRSS3/mesotrypsin in prostate cancer progression: implications for translational medicine

Evette S Radisky

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Prostate cancer morbidity and mortality are caused by metastasis to other vital organs and tissues. Metastatic prostate cancer is a terminal disease in need of improved therapies. Hockla *et al.* have identified prostate cancer cell upregulation of the digestive protease PRSS3/mesotrypsin in association with metastasis and recurrence. Gene silencing of *PRSS3* led to pronounced reductions in invasion and metastasis in cell culture and in an orthotopic mouse model of prostate cancer. Importantly, a recently developed inhibitor of mesotrypsin was equally effective in suppressing invasion. These results identify mesotrypsin as a potential therapeutic target in metastatic prostate cancer.

Prostate cancer is a disease that can lie latent for decades or can progress rapidly to systemic metastasis and death—and the molecular pathways that distinguish between indolent and aggressive cancers are not well defined. Assessment of patient prognosis is therefore a critical challenge—who is likely to benefit from further interventions, and who should be spared further treatment? Prostate-specific antigen assays provide a valuable surveillance tool, but prostate-specific antigen is not a specific marker for aggressive prostate cancers, and only a fraction of the many men who experience prostate-specific antigen relapse after initial treatment will ever develop overt metastasis.[1,2] Thus, there is an unmet clinical need for additional and more specific biomarkers that define subsets of patients at greatest risk of metastatic progression. An additional unmet need is encountered by patients with advanced disease—current therapies are inadequate, since metastatic prostate cancer inevitably develops resistance to androgen deprivation therapy, at which time subsequent treatment of castration-resistant prostate cancer with standard chemotherapy agent docetaxel, and even with newer regimens incorporating agents that block androgen signaling via alternative mechanisms, can provide only modest survival benefits.[3] Thus, the search for biomarkers prognostic of future metastasis goes hand-in-hand with pursuit of new strategies for therapeutic intervention in metastatic prostate cancer, and these two efforts converge upon an underlying need to unravel the biology of metastasis. By understanding the molecular mechanisms that drive metastasis, the hope is that basic scientists will both identify rational molecular targets for therapy and, in parallel, develop functionally linked biomarkers that can accurately identify the patients who will benefit.[4,5] In the recent report of Hockla *et al.*,[6] our research team has identified the protease PRSS3/mesotrypsin as such a candidate therapeutic target for metastatic prostate cancer.

Among the many characteristics of cancer, it is the ability to invade tissues and create distant metastases that most clearly distinguishes a deadly cancer from a less threatening tumor.[7] Proteases that are aberrantly expressed in the tumor microenvironment, either by tumor cells themselves or by tumor-associated stromal cells, represent key contributors to metastatic progression. Proteolytic enzymes can shed cell adhesion molecules and stimulate epithelial–mesenchymal transition to enhance cell motility, they can degrade basement membranes and remodel extracellular matrix to stimulate invasion, they can aid entry and exit from the vascular system, and they can also be required for effective colonization of metastatic sites.[8,9] Identifying proteases that drive tumor progression and metastasis, and defining their specific mechanisms of action, can potentially reveal novel druggable targets and underexplored avenues for slowing or halting the spread of metastatic disease.[10] Moreover, as extracellular molecules with binding sites for highly specific substrate ligands, secreted proteases are more amenable to pharmacological inhibition that are many oncogenic signaling pathways within the cell.

The serine protease mesotrypsin, encoded by the *PRSS3* gene, is normally expressed by the pancreas and secreted into the digestive tract as a digestive enzyme. A high level of mesotrypsin expression has recently been implicated as an important mediator of progression and metastasis in pancreatic cancer, a malignancy characterized by rapid and aggressive dissemination.[11] In examining open source data from microarray studies of prostate cancer, we made the observation that the *PRSS3* gene was ectopically expressed in many prostate cancers, especially in metastatic tissues, and that its expression in primary tumors was significantly associated with cancer recurrence after tumor resection.[6] In subsequent investigations of the potential role of mesotrypsin in functionally driving metastasis, we found that gene silencing of *PRSS3* led to a pronounced reduction in metastasis in an orthotopic mouse model of human prostate cancer. In cultured cells, *PRSS3* silencing suppressed anchorage-independent growth, migration, invasion and invasive 3D growth morphology, while treatment with active recombinant mesotrypsin had an opposite effect, suggesting that mesotrypsin functions at multiple levels to facilitate prostate cancer cell spread throughout the body and colonization of distant organs. Significantly, a recently developed polypeptide inhibitor of mesotrypsin[12] was equally effective in suppressing the invasion of cultured prostate cancer cells. Our results

Department of Cancer Biology, Mayo Clinic Comprehensive Cancer Center, Jacksonville, FL 32224, USA
Correspondence: Dr ES Radisky (radisky.evette@mayo.edu)

identify mesotrypsin as a potential therapeutic target in metastatic prostate cancer.[6]

At present, mesotrypsin is at the beginning of the translational journey to usefulness in the clinic. Most pressing from the clinical point of view is the necessity for validation of PRSS3/mesotrypsin expression as a marker of aggressive disease in larger clinical cohorts. It may then become possible to use measurement of mesotrypsin expression as a stratification tool to identify a molecular subtype of aggressive prostate cancer likely to respond to a specialized treatment approach. A further developed example of this translational scenario is found in the definition of SPINK1 as a functional marker of a rare but unusually aggressive subtype of prostate cancer.[13] Recent investigations of the molecular mechanisms of SPINK1 signaling in prostate cancer have led to the discovery of a SPINK1–EGFR signaling axis, creating the possibility for use of SPINK1 as a biomarker to identify poor prognosis patients potentially responsive to EGFR-targeted therapies.[14] For mesotrypsin, additional questions remain with regard to the basic mechanisms by which the protease drives prostate cancer metastasis. Most importantly, what is the specific, functionally relevant protein substrate of mesotrypsin, cleavage of which stimulates invasive behavior? Once this target and its cleavage site(s) or products are identified, perhaps they can be detected in clinical samples, and ultimately used as biomarkers of response to therapy. Finally, the development of mesotrypsin inhibitors with therapeutic potential is a remaining challenge. While we have demonstrated that mesotrypsin activity can be targeted for inhibition with resulting suppression of tumor cell malignancy and invasion,[6,12] mesotrypsin is but one of a large family of related proteases, and it will be difficult but likely necessary to develop inhibitors with greatly improved selectivity for success in the clinic. The payoff for these efforts may be a new, and potentially more effective, molecularly targeted therapy for controlling the spread of metastatic prostate cancer.

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