

Novel insights of how prostate cancer causes secondary tumors

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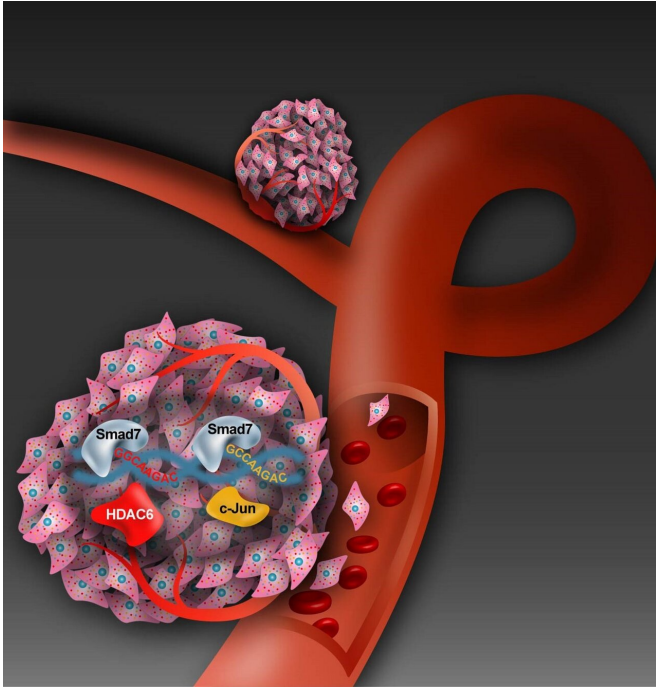


Illustration of how the protein Smad7 enhances the development of tumors by regulating the gene expression of HDAC6 and c-Jun. Credit: Kemal Avican

An increased awareness of what molecular-level mechanisms prostate cancer cells use to become mobile and spread may provide new opportunities for the treatment of aggressive prostate cancer. This according to a new study by researchers at Umeå University, Sweden, in collaboration with researchers in Uppsala and Tokyo.

"We can show that one specific amino acid in a signaling molecule plays an important role in mobilizing the [cancer cells](#) and in that way increase the risk of metastases," says Professor Maréne Landström, Umeå University.

This researchers studied the growth factor TGF- β (Transforming Growth Factor Beta), which

regulates how cells grow and specialize. Previous studies have shown an overproduction of TGF- β in many [cancer](#) forms, one being [prostate](#) cancer. High levels of TGF- β have proven to be strongly linked with poor prognosis and low survival rates as a consequence of the growth factor stimulating cancer cells to spread in the human body and cause life-threatening secondary tumors—so-called metastases.

TGF- β regulates the expression of the protein Smad7—an active component in the TGF- β signaling chain. In healthy cells, Smad7 can prevent continued TGF- β signaling via negative feedback. However, Maréne Landström and her research group and colleagues can now show, contrary to previous belief, that, in cancer cells, Smad7 can reinforce the development of tumors by regulating the gene expression of HDAC6 and c-Jun.

The specific amino acid that has caught the researchers' attention is called Lys102 and is found in Smad7. This amino acid binds to particular gene-regulating functions in DNA to increase production of the gene expression HDAC6 and c-Jun. This has the effect that cancer cells become more mobile and more prone to form metastases. Researchers have been able to see a clear connection between all these variables and a negative prognosis for prostate cancer.

"The good news is that by using treatment with an HDAC6 inhibitor, we can make prostate cancer [cells](#) lose their mobility. In that way, novel opportunities can open up for treatments that reduce the risk of metastases," says Maréne Landström.

Clinical trials are now taking place in the UK to find specific HDAC6 inhibitors in patients with solid tumors, which means that treatments using HDAC6 inhibitors can become a complement in the cancer treatment of patients with hard-to-treat forms of

disease. Future studies can explore the benefit of indicating expressions of Smad7, HDAC6 and c-Jun to enable new and more specific treatments for men with aggressive prostate cancer.

The study also shows an entirely new function of Smad7 in the way that it can recruit Smad2 and Smad3 to the place of transcription for these genes. Previously, it has been thought that Smad7 held the role of inhibitor for TGF beta-Smad2/3 transcriptional activity.

The study is published in *iScience*.

More information: Smad7 enhances TGFbeta-induced transcription of c-Jun and HDAC6 promoting invasion of prostate cancer cells, *iScience*, DOI: [10.1016/j.isci.2020.101470](https://doi.org/10.1016/j.isci.2020.101470)

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