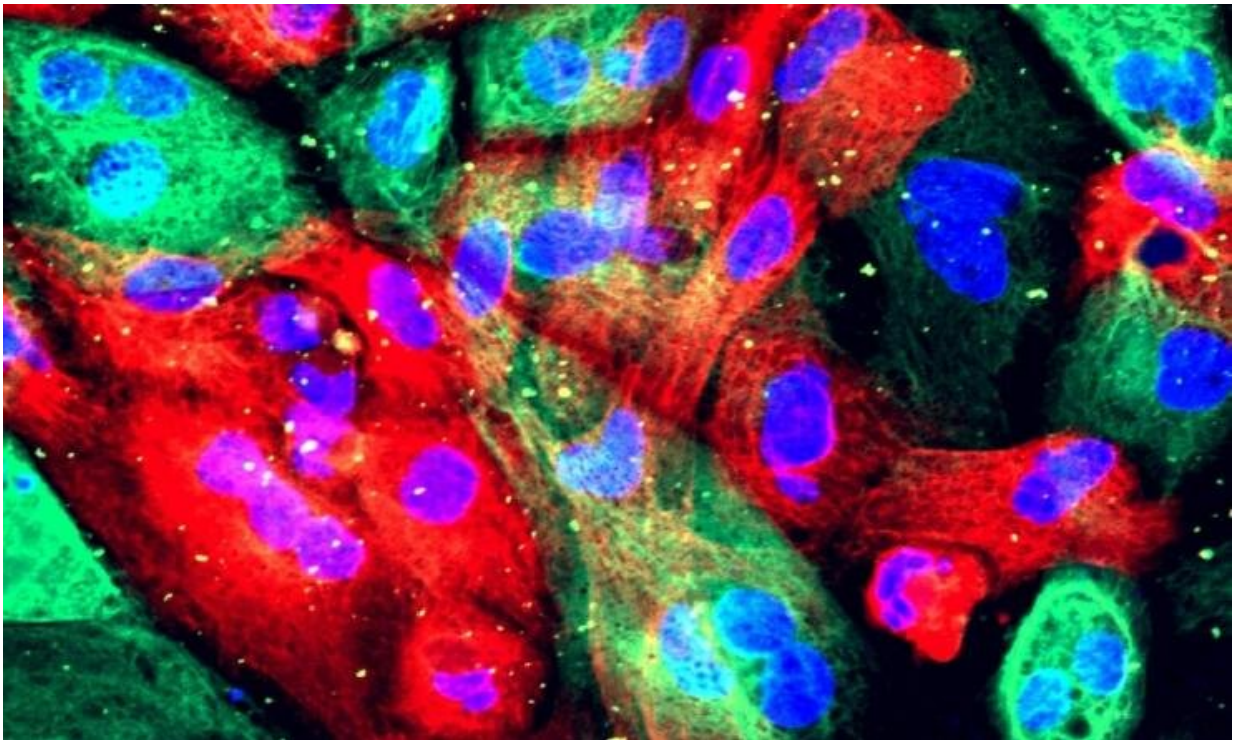


Protein NSD2 found to drive early prostate cancer development

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Prostate cancer cells. Credit: NIH Image Gallery

Researchers at the University of Michigan Health Rogel Cancer Center have uncovered a key reason that a typically normal protein goes awry and fuels cancer.

They found that the protein NSD2 alters the function of the [androgen](#)

receptor, an important regulator of normal prostate development. When an androgen receptor binds with NSD2, it causes rapid cell division and growth, leading to [prostate cancer](#). The study, [published](#) in *Nature Genetics*, may suggest a new way to therapeutically target prostate cancer.

The findings illuminate a phenomenon not previously understood. The androgen receptor's normal function is to define the development of the prostate. It tells the [cells](#) to stop growing and maintain a normal prostate. But in cancer, the androgen receptor does the opposite: It tells the cells to continue growing and drive cancer development.

"Our study is one of the first molecular explanations for this functional duality of the androgen receptor," said study first author Abhijit Parolia, Ph.D., Rogel fellow and assistant professor of pathology at Michigan Medicine. "NSD2 is a cancer specific collaborator of the androgen receptor that essentially rewires its activity to support prostate cancer development."

Researchers started with a CRISPR screening to look for co-factors involved in the androgen receptor and prostate cancer. They scoured the enhanceosome, a complex of multiple proteins, including transcription factors and other [epigenetic factors](#), that assemble on the DNA at specific sites to drive the expression of genes. They contrasted this with what's called the neo-enhanceosome. It's an analogous machinery, but cancer-causing [transcription factors](#) find their way in, reorganize the careful assembly and drive expression of cancer-causing programs.

The androgen receptor typically sits along a specific line of sites within DNA. When NSD2 is present, it rearranges where the androgen receptor "enhanceosome" sits on the DNA, setting it next to sites occupied by known cancer-causing genes and drivers.

"This is the machinery around the genes we know are involved in prostate cancer development, including androgen receptors, ERG and FOXA1. They all use this machinery to regulate oncogenic expression. We're now working to indirectly target the genes of interest by affecting these epigenetic components like NSD2," said study co-senior author Arul M. Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and S.P. Hicks Professor of Pathology at Michigan Medicine.

Researchers found that NSD2 is expressed in prostate cancer cells, but not in normal prostate cells. NSD2 was previously known to be involved in metastatic prostate cancer. This is the first study to show that it is fundamental to the earliest stage of prostate cancer development.

The team used multiple methods to knock down or halt NSD2 expression in prostate cancer cells, and found that doing so returns the cells to a more normal state, slowing the growth and spread of the cancerous cells but not eliminating the cancer. A related protein called NSD1 works along with NSD2, they found.

A compound that degrades both NSD1 and NSD2 successfully destroyed prostate cancer cell lines. The degrader targeted the cancer cells specifically without affecting normal cells. More work is needed to refine the degrader, as the initial version could not be translated to a mouse model.

"By degrading NSD1 and NSD2, we can more directly target cancer and avoid the normal tissue," Chinnaiyan said. "Our study suggests if we're able to develop NSD1/2-targeting agents, they could potentially be combined with FDA-approved [androgen receptor](#) antagonists and have a synergist effect in terms of treatment."

More information: NSD2 is a requisite subunit of the AR/FOXA1

neo-enhanceosome in promoting prostate tumorigenesis, *Nature Genetics* (2024). DOI: [10.1038/s41588-024-01893-6](https://doi.org/10.1038/s41588-024-01893-6) ,
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