

Scientists show how frequently mutated prostate cancer gene suppresses tumors

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Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

The gene SPOP is mutated in up to 15 percent of all cases of prostate cancer, making it one of the most mutated genes in the disease. However, when the gene is functioning properly, it acts as a tumor suppressor. Despite what's known about SPOP, scientists have not been able to determine exactly how the gene is able to halt the progression of disease.

Now, new research from The Wistar Institute has found how SPOP is able to halt tumors by inducing senescence, a state of stable cell cycle arrest, which means that the cells have stopped dividing and growing. With this new information, scientists may be able to design therapeutic strategies that can halt cancers caused by these mutated genes that are able to bypass senescence.

The findings were published online by the journal *Cell Reports*.

In a paper published in 2012, a large study analyzed mutations in [prostate cancer](#) tumors and found that the SPOP gene was the most frequently mutated among genes identified in this cohort, suggesting that tumors exhibiting a mutation of SPOP could be characterized as a specific subtype of the disease. Further studies found several proteins that interact with SPOP, but this information still failed to explain exactly how SPOP is able to suppress tumors.

"Since this mutation appears so frequently in prostate cancer, understanding how it functions as a [tumor suppressor](#) when it operates normally helps us determine why the mutated version causes cancer," said Hengrui Zhu, Ph.D., first author of the study and a postdoctoral fellow in the laboratory of Rugang Zhang, Ph.D., associate professor in Wistar's Gene Expression and Regulation program. "Our study shows how SPOP is not only able to induce senescence but how mutated SPOP is able to bypass senescence."

The Zhang laboratory began to unravel this mystery by determining if there was a connection between SPOP and senescence. Indeed, they were able to show that SPOP was found in higher concentrations in [senescent cells](#). Next, they compared samples of wild-type (not mutated) SPOP with their mutated counterparts, which were associated with cancer. Wild-type SPOP samples showed senescent behavior, whereas their cancer-associated mutants were impaired in their ability to induce

senescence.

In this study, the research team directly linked this behavior of SPOP to an enzyme called SENP7. The function of SENP7 is not entirely clear, but this study showed just how important it is with regard to SPOP. When SPOP is not mutated, SENP7 remains in check and senescent cells are able to keep cancer activity at bay. To test what happens when SPOP is not functioning properly, the researchers inactivated the gene and observed the effect this had on SENP7. They found that the levels of SENP7 increase enough that cells are able to overcome senescence and become cancerous. Notably, when SENP7 activity was inhibited, [prostate cancer cells](#) showed senescent behavior and stopped growing, suggesting that SENP7 might be an important therapeutic target.

"These findings give us reason to believe that we may be able to develop better treatment strategies for SPOP-mutated prostate cancer," said Zhang, the lead author of the study. "Patients with mutated SPOP may be less sensitive to treatments that induce senescence, so that could help them avoid unnecessary treatment and allow physicians to pursue alternate treatment strategies. Likewise, inhibiting SENP7 directly in combination with other targeted therapies for prostate cancer may provide a synergistic effect."

Provided by The Wistar Institute

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