Loss of tumor suppressor SPOP releases cancer potential of SRC-3

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Mutations in a protein called SPOP (speckle-type POZ protein) disarm it, allowing another protein called steroid receptor coactivator-3 (SRC-3) to encourage the proliferation and spread of prostate cancer cells, said researchers led by those at Baylor College of Medicine in a report that appears online in *Proceedings of the National Academy of Sciences*.

Normally SPOP acts as a tumor suppressor gene by marking SRC-3 for destruction, said Dr. Nicholas Mitsiades, assistant professor of medicine – hematology/oncology and molecular and cellular biology, and corresponding author of the report. SRC-3 is an oncogene or cancer-promoting gene that fosters the growth of cancer cells and their spread or metastasis.

"The protein SPOP is normally there to decrease the levels of SRC-3," said Mitsiades, who is also a member of the Dan L. Duncan Cancer Center at BCM. About a year ago, several groups reported that mutations in SPOP were the most common single point mutation or change in a single nucleotide or base pair (A,T,C,G) that is part of the "alphabet" of DNA or the genetic material of prostate cancer tumors.

What Mitsiades and his group found was that mutated SPOP is no longer an effective suppressor of the cancerous effects of SRC-3. He and his colleagues found the mutation in both the primary or original prostate cancer and in the metastatic tumors that it spawned.

In laboratory studies they showed that when cells produce high levels of normal SPOP, SRC-3 is potently degraded and no longer available to encourage prostate cancer growth.

Mitsiades said that it remains to be examined whether the SPOP mutations affect the prognosis for patients with prostate cancer and their response to treatment.

"To make things more difficult, there is not just one SPOP mutation," he said. "There are many different mutations. Our study and some other data as yet unpublished shows that while all mutations act similarly as far as the mechanism of action, all are not equally potent in their effect. That means additional research needs to be done to examine whether different mutations carry a different prognoses," he said.

"An important question for us is how can you treat prostate cancer with an SPOP mutation," he said.

The mutation results in a loss of function because the mutated gene cannot carry out its task of reducing SRC-3 levels.

"Right now we are not good at replacing something with drugs," he said. "We are much better at inhibiting functions. If we could inhibit SRC-3, then we might overcome the cancer-promoting effects of the mutations in SPOP."

Dr. Bert O'Malley, chair of molecular and cellular biology at BCM and a co-author of the report, is working on inhibitors of SRC-3.

Those inhibitors are important because SRC-3 plays a role in many cancers, including breast cancers, said Mitsiades. It could prove an important target for treatment of many cancers – along with breast and prostate tumors.

"Its regulation is quite complex," he said. "It can be degraded and SPOP is only one mechanism by which that occurs."

Provided by Baylor College of Medicine