Researchers clarify role of SMYD3 enzyme in prostate cancer progression

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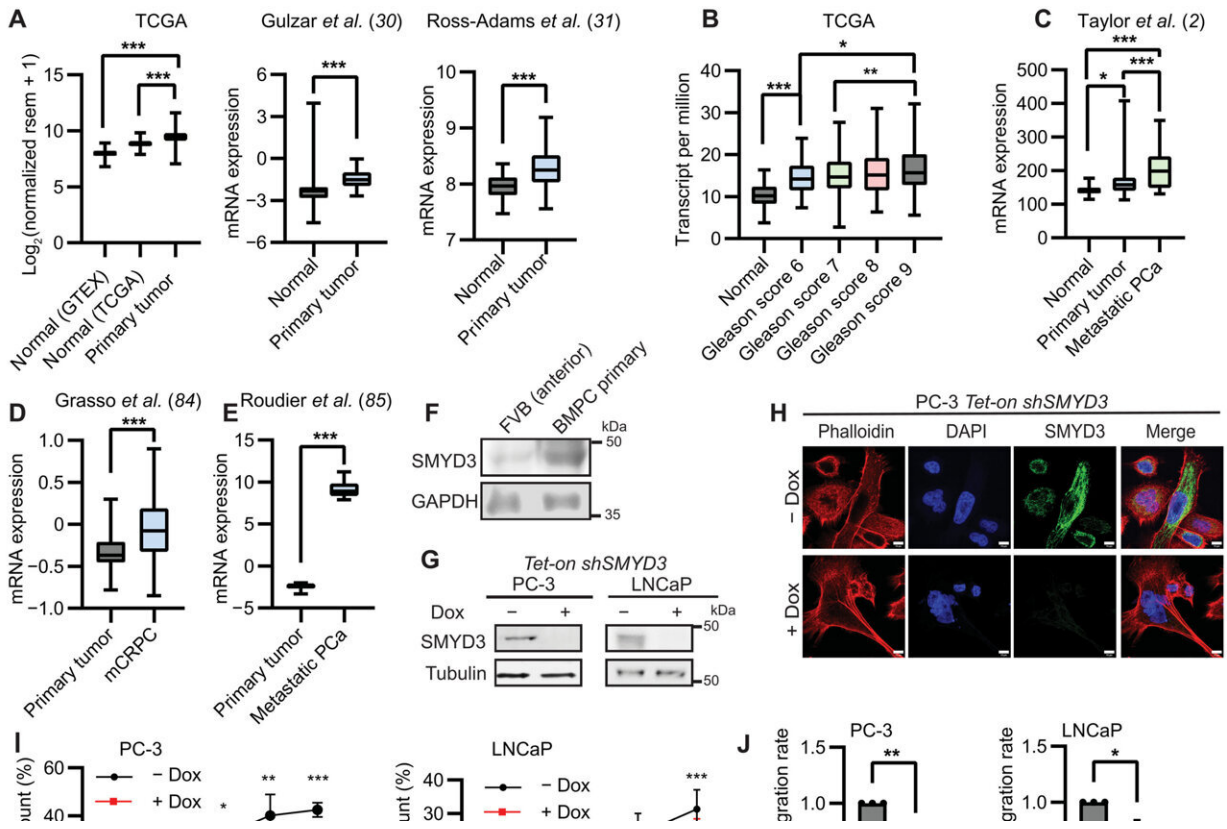

SMYD3 loss impedes PCa progression.(**A**) Expression of *SMYD3* mRNA from TCGA [GTEX normal (*n* = 105), TCGA tumor adjacent normal (*n* = 49), primary tumors (*n* = 495)], Gulzar *et al.* [normal (*n* = 35), primary tumor (*n* = 43)] (*30*), and Ross-Adams *et al.* [normal (*n* = 73), primary tumor (*n* = 126)] (*31*). Significance determined using one-way analysis of variance (ANOVA) and Tukey's multiple comparisons test for TCGA dataset. (**B**) Expression of *SMYD3* mRNA from TCGA–Prostate Adenocarcinoma in tumor-adjacent normal prostate tissues (*n* = 52), Gleason score 6 (*n* = 45), Gleason score 7 (*n* = 247),

Gleason score 8 (n = 64), and Gleason score 9 (n = 136) prostate tumors. (**C** to **E**) Expression of SMYD3 mRNA from PCa datasets. (C) Taylor *et al.* [normal (n = 29), primary tumor (n = 131), metastases (n = 19)] (*2*). (D) Grasso *et al.* [primary tumor (n = 59), metastases (n = 32)] (*84*). (E) Roudier *et al.* [primary tumor (n = 11), and metastases (n = 48)] (*85*). (**F**) SMYD3 immunoblot in primary tumor from BMPC mice (*Hoxb13-MYC*$^{+/-}$ *Hoxb13-Cre*$^{+/-}$ *Pten*$^{Fl/Fl}$) (*32*) compared to normal, anterior prostate lobe of FVB mice. (**G**) Immunoblot of PC-3 and LNCaP *Tet-on shSMYD3* cells with and without doxycycline (0.2 μg/ml; −/+ dox) using anti-SMYD3. (**H**) Immunofluorescence of PC-3 *Tet-on shSMYD3* −/+ dox using anti-SMYD3. Scale bars, 10 μm. (**I**) Cell viability time course of PC-3 and LNCaP *Tet-on shSMYD3* cells −/+ dox (n = 6). Significance evaluated using two-way ANOVA and Sidak's multiple comparisons test. (**J**) Normalized migration rate of PC-3 and LNCaP *Tet-on shSMYD3* cells −/+ dox (n = 3). (**K**) Soft agar assay of PC-3 (n = 42) and LNCaP (n = 8) *Tet-on shSMYD3* cells −/+ dox. (**L**) Adhesion of PC-3 *Tet-on shSMYD3* cells −/+ dox to human fibronectin (HFN; n = 5) (left), to wild-type PC-3 cells (n = 6) (middle), and to NIH3T3 fibroblasts (n = 5) (right). (**M**) Invasion capacity of PC-3 and LNCaP *Tet-on shSMYD3* cells (n = 3). Significance evaluated using two-tailed unpaired Student's t test. Error bars represent SD, and P values are indicated as follows: *P P P Science Advances (2023). DOI: 10.1126/sciadv.adi5921

Prostate cancer is the most common cancer in men other than skin cancer, and more than 288,000 new cases are diagnosed every year, according to the American Cancer Society. The disease's fatality rate has decreased by more than half since the 1990s, but there is still room for progress—especially in treating or preventing advanced, metastatic disease, which is much more likely to be fatal.

A new paper published in *Science Advances* clarifies how an enzyme called SMYD3 may be involved in prostate cancer's progression to a more dangerous and aggressive stage. The enzyme's newly confirmed role makes it a prime potential drug target for preventing metastatic disease.

Redefining an enzyme's role

Researchers have been attempting to explain SMYD3's role in cancer since observing that it is unusually abundant in cancerous tumors compared to healthy tissue, explains Erin Green, associate professor of biological sciences at the University of Maryland, Baltimore County (UMBC) and senior author on the paper.

"There is a lot of interest in this protein," Green says. "However," she adds, "the literature has been muddled."

Several previous studies suggested that SMYD3 acted inside a cell's nucleus and regulated which genes the cell expressed by directly modifying DNA. But research led by Nicolas Reynoird, a scientist at the Institute for Advanced Biosciences in Grenoble, France and a co-author on the new study, suggested a different mechanism.

In a key 2014 paper published while Reynoird was a postdoctoral fellow at Stanford, he and collaborators found that SMYD3 was working outside the nucleus and activating a type of protein called MAP kinase. MAP kinases are overactive in cancer cells and can promote tumor growth.

The new *Science Advances* paper, led by Sabeen Ikram, a postdoctoral fellow at Stanford University, built on Reynoird's previous work. Ikram's experiments showed conclusively and in detail how SMYD3 may be triggering metastatic prostate cancer via the MAP kinase signaling pathway. The new paper ties together the overabundance of SMYD3 and excessive activation of MAP kinase signaling for the first time in prostate cancer, renewing interest in SMYD3 as a therapeutic target.

Exciting findings from every angle

The research team showed in cells in a petri dish and in mice that adding methyl groups (a carbon atom bound to three hydrogen atoms) to the MAP kinase is probably SMYD3's role in driving metastasis. Experiments with inactivated SMYD3 were much less likely to lead to metastasis.

Compounds that can inactivate SMYD3, called inhibitors, are already available, Green says. Ikram ran experiments with one of these and found that it effectively killed cancer cells in a petri dish. The team would like to run the same experiments in mice to further confirm the compound's effect. They'd also like to explore whether targeting SMYD3 could help tackle cancers that develop resistance to other treatments.

Ikram's experiments also found that SMYD3 led to increased activity of a protein called vimentin, which is well-studied as a marker of cancer progression. Interestingly, SMYD3's effect was specific to vimentin, even though it is a member of a large group of similar proteins.

Finally, the new study found for the first time that SMYD3 creates a positive feedback loop in the cell, where high levels of SMYD3 contribute to maintaining its overabundance.

A new direction and new hope for patients

Green sees many avenues for future work.

"We've only checked this mechanism in prostate cancer so far, but I think it's likely happening in other cancer cell types," Green says. "That's another thing that we want to keep investigating: How common is this?"

Green is also excited for SMYD3's potential use as a therapeutic target for prostate or other cancers. SMYD3 inhibitors already exist, so the

new findings may encourage companies to invest in discovering new uses for them.

"There's drugs out there that haven't been fully explored because people decided there was not a good target," Green says. "So there's a lot more that could be done there."

More information: Sabeen Ikram et al, The SMYD3-MAP3K2 signaling axis promotes tumor aggressiveness and metastasis in prostate cancer, *Science Advances* (2023). DOI: 10.1126/sciadv.adi5921

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