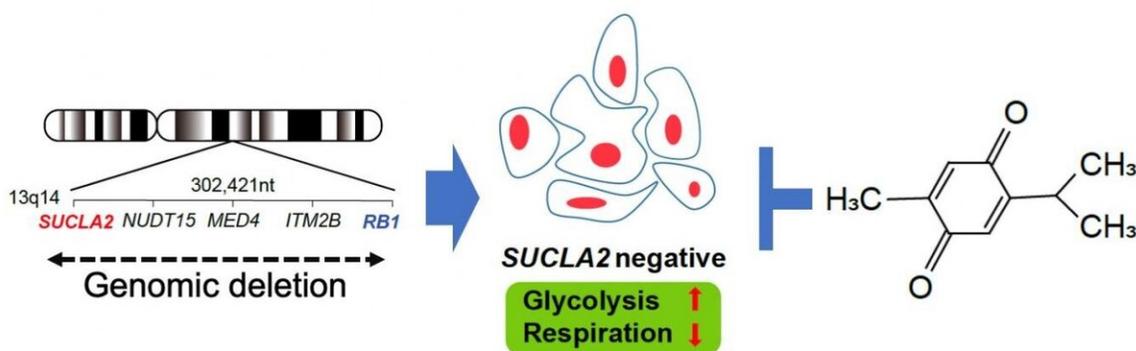


# Advanced prostate cancer has an unexpected weakness that can be targeted by drugs

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SUCLA2 gene is frequently involved in the deletion of RB1 gene region, which occurs in 10 - 30 % of advanced prostate cancers. SUCLA2 deletion gives rise to a metabolic vulnerability. By screening chemical compounds, thymoquinone appeared to selectively kill SUCLA2-deficient prostate cancer cells. Credit: Kanazawa University

The compound thymoquinone (TQ) selectively kills prostate cancer cells at advanced stages, according to a new study published in *Oncogene*. Led by researchers at Kanazawa University, the study reports that prostate cancer cells with a deletion of the *SUCLA2* gene can be therapeutically targeted. *SUCLA2*-deficient prostate cancers represent a significant fraction of those resistant to hormone therapy or metastatic, and a new therapeutic option for this disease would have immense benefits for patients.

Hormone therapy is often chosen for the treatment of metastatic prostate cancer but nearly half of patients develop resistance to the treatment in as little as 2 years. A mutation in *RB1*, a tumor suppressor gene that keeps [cell growth](#) under control, has been pegged as a particularly strong driver of treatment resistance and predicts poor outcome in patients.

"Mutations in [tumor suppressor genes](#) are enough to induce initiation and malignant progression of prostate cancer, but so far we haven't been able to directly target these mutations with drugs to treat prostate cancer," says the lead author Susumu Kohno. "We wanted to find a genetic aberration associated with that of a tumor suppressor gene which we could target therapeutically."

In the genome, *SUCLA2* neighbors *RB1*. An analysis of [prostate cancer cells](#) showed that cells with a *RB1* deletion were also missing *SUCLA2*, pairing up the *SUCLA2* deletion with the *RB1* deletion present in advanced stage prostate cancer. Kohno and colleagues analyzed prostate cancer tissue and found that 11% of cases were missing both *SUCLA2* and *RB1*.

The researchers screened compounds to identify drugs that would selectively kill cells with a *SUCLA2* deletion. Out of around 2,000 compounds, TQ emerged as a hit compound. TQ already has known anti-cancer effects and was shown to be safe in a phase I clinical trial. Kohno

and colleagues applied the TQ treatment to a mouse model of SUCLA2-deficient prostate cancer and TQ selectively suppressed tumor growth.

"These findings show that TQ treatment could be an effective therapy for treating prostate cancer cells that harbor SUCLA2 deficiency," says the senior author Chiaki Takahashi.

In a search of genetic databases from patients with prostate cancer, the researchers found that the frequency of SUCLA2 loss was almost perfectly aligned with RB1 loss at every disease stage—meaning the SUCLA2 deletion could identify people with prostate cancer needing advanced therapy.

Finding this drug-targetable vulnerability opens a crack in the barrier of treatment resistance for [prostate](#) cancer. More work needs to be done to improve efficacy of TQ and identify patients that would benefit from this type of treatment, but the compound provides a promising route for new treatment options for advanced [prostate cancer](#).

**More information:** Susumu Kohno et al, Pharmacologically targetable vulnerability in prostate cancer carrying RB1-SUCLA2 deletion, *Oncogene* (2020). [DOI: 10.1038/s41388-020-1381-6](https://doi.org/10.1038/s41388-020-1381-6)

Provided by Kanazawa University

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