Prostate cancer study reveals molecular switch linked to lineage plasticity, therapy resistance

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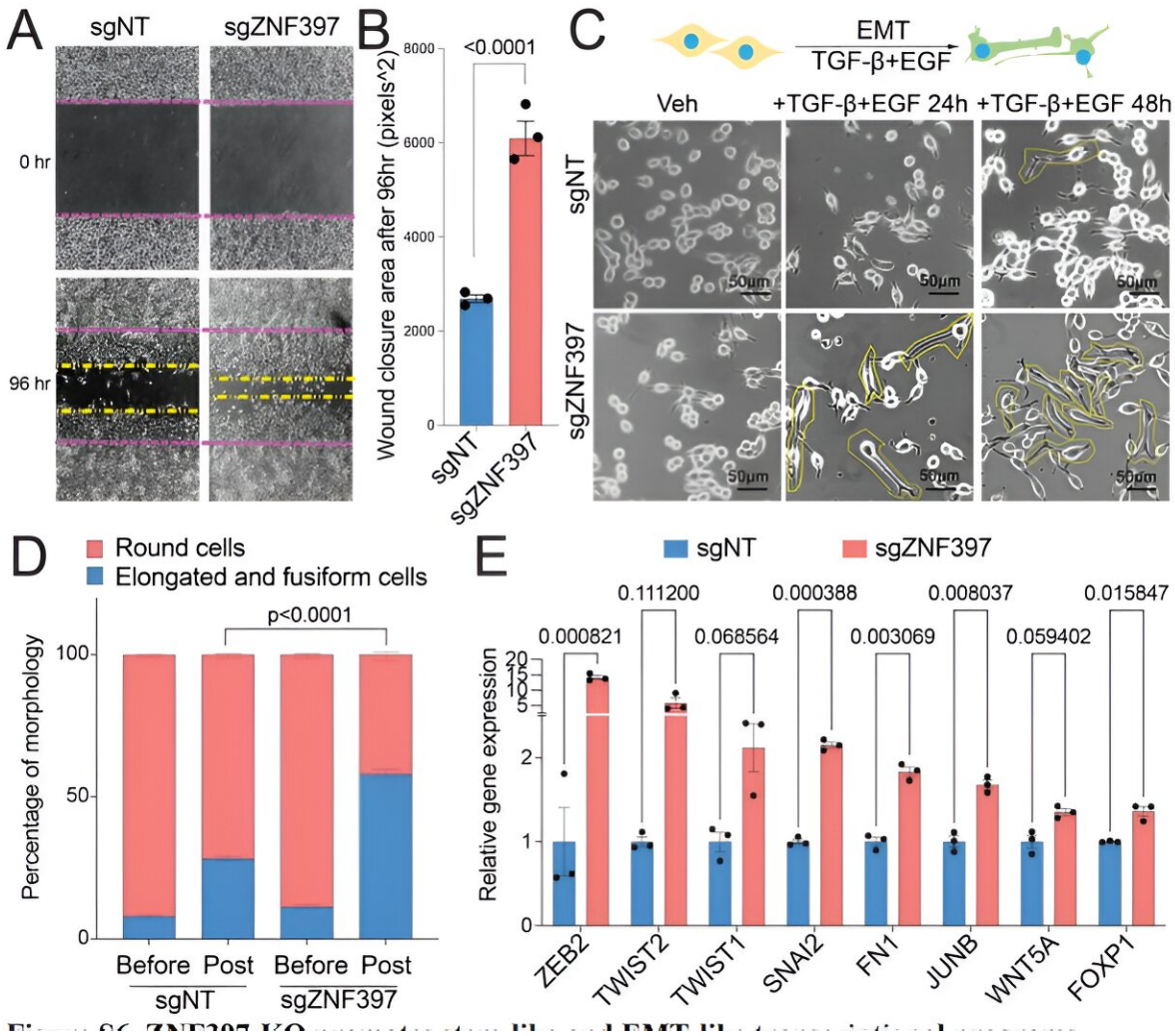

ZNF397-KO promotes stem-like and EMT-like transcriptional programs. Credit: *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-23-0539

Two genes working in tandem play a critical role in shaping the identity and behavior of prostate cancer cells and their response to treatment, UT Southwestern Medical Center researchers report.

The findings, published in *Cancer Discovery*, offer crucial insights into how cancer cells evade the current standard-of-care treatments and provide a potential target for the development of novel prostate cancer therapies.

"Our study reveals a new genetic and molecular process that controls how tumor cells change their type and respond to treatment," said study leader Ping Mu, Ph.D., Assistant Professor of Molecular Biology and a member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern.

"These important discoveries enhance our understanding of what drives drug resistance and introduce a new approach for treating prostate cancer."

Nearly one out of every eight men will get prostate cancer during their lifetime, making it the most common cancer among men, according to the American Cancer Society.

Prostate cancer's ability to adapt has proved a formidable challenge, with therapy resistance emerging as a significant obstacle. Advanced prostate cancer, including metastatic castration-resistant prostate cancer (mCRPC), is particularly difficult due to its capacity to develop resistance to conventional therapies, such as androgen receptor (AR) inhibitors.

This resistance can arise due to lineage plasticity, where cancer cells

undergo "identity switches," enabling them to evade targeted treatments. Lineage plasticity allows cancer cells to switch from their original luminal lineage, driven by androgen receptor (AR) signaling, to alternative lineages, such as neuroendocrine or stem-like phenotypes, which are resistant to AR-targeted therapies originally designed to target their previous identities.

In this study, researchers identified a deficiency of Zinc Finger Protein 397 (ZNF397) as a critical trigger for this transformation in prostate cancer cells. This deficiency prompts a shift from a reliance on AR signaling for cell growth (the luminal lineage) to increased dependence on activity involving the gene Ten Eleven Translocation 2 (TET2), which encodes an enzyme that regulates DNA methylation, a critical epigenetic mechanism.

The transition consequently renders cancer cells more flexible and adaptable, ultimately leaving them resistant to therapies targeting AR signaling.

The research also revealed the pivotal role of TET2 in driving epigenetic rewiring, which contributes to lineage plasticity and therapy resistance in prostate cancer, shedding light on how prostate cancer cells can adapt through epigenetic reprogramming.

In addition, the study demonstrates that inhibiting TET2 can reverse resistance to AR-targeted therapies in ZNF397-deficient tumors. By genetically and pharmacologically inactivating TET2, the researchers effectively reversed resistance to AR-targeted therapies in ZNF397-deficient tumors.

The study builds upon previous research from the Mu Lab, furthering the understanding of lineage plasticity and drug resistance mechanisms and paving the way for personalized treatment strategies tailored to

combat lineage plasticity-driven therapy resistance in prostate cancer.

"The possibility of reversing this type of resistance by targeting TET2 with drugs offers new paths for developing treatments for patients with advanced prostate cancer," Dr. Mu said.

"These insights could lead to clinical trials testing TET2 inhibitors in treating metastatic castration-resistant prostate cancer patients, potentially improving treatment results and increasing survival rates."

More information: Yaru Xu et al, ZNF397 Deficiency Triggers TET2-driven Lineage Plasticity and AR-Targeted Therapy Resistance in Prostate Cancer, *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-23-0539

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