Absence of tumor-suppressing gene derails DNA replication, leaving cells vulnerable to cancer

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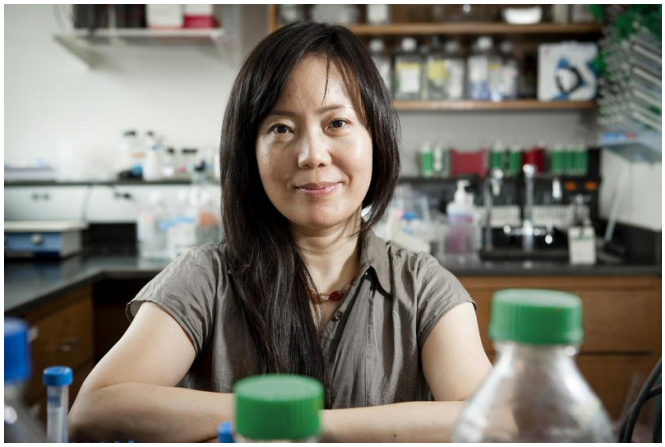

Dr. Wen Shen. Credit: Carlos Rene Perez

Cell duplication and growth is essential to sustaining life, and in order for this critical function to take place, cells must unwind the tight ball of DNA in their nucleus and then duplicate their genomic information. This is a delicate maneuver, ripe for errors or omissions, and if PTEN, a known tumor-suppressor gene, has mutated or is absent, the replication process derails and can lead to cancer development, Weill Cornell Medical College researchers found in a new study.

Because of the new insights it reveals, this research, published July 9 in *Nature Communications*, might influence how future cancer patients are treated based on their genetic make-up.

"Tumors without PTEN are more sensitive to chemotherapies that work by targeting DNA replication, while normal cells or cancers with active PTEN resist these treatments," said Dr. Wen H. Shen, the study's lead investigator and an assistant professor of cell biology in radiation oncology at Weill Cornell. "Based on our research, knowing PTEN status is critical for guiding treatment choices."

In the late-1990s, scientists discovered the PTEN gene and growing evidence has shown that PTEN is a powerful tumor suppressor. Less clear, however, was whether and how PTEN works when it comes to DNA replication—and if loss of PTEN could impact this central process of genome transmission to allow development and progression of cancer. The Weill Cornell research team found that when the PTEN gene is missing or mutated, DNA is left unprotected in the duplication process and can become damaged or corrupted.

"DNA replication is an error-prone process," said Dr. Shen, who is also a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell. "As the DNA double helix unwinds and separates, forming a Y-shaped open structure, it is vulnerable to stress signals and damages.

"Our study shows that PTEN acts as a guardian of this process by sitting right on the replication fork to recruit other essential protective partners," she continued. "Without PTEN, this protection machinery falls apart. DNA is then unprotected, which leads to fork stalling and failure to restart."

Without PTEN or the protective proteins that PTEN recruits, Dr. Shen said, the DNA may become fragile and corrupted, leading the cell to produce stress signals. Cancer can result when the stress signals accumulate or when cells with un-replicated DNA rush into cell division prematurely to produce an abnormal number of chromosomes in a cell, a condition called aneuploidy.

PTEN function is absent in a wide variety of

cancers—for example, 70 percent of prostate cancers have PTEN mutation or deletion. Because of this, researchers are currently testing PTEN to see if it's a marker of aggressive cancer and for personalized cancer treatment.

"Patients whose cancers have lost PTEN or harbor mutations in the gene are known to have poorer outcomes than patients with active PTEN," Dr. Shen said. "Our expectation is that a PTEN blood test in the near future will help clinicians decide on the right therapies for each cancer patient, and in particular, to benefit this subgroup of cancer patients carrying PTEN mutations."

More information: "PTEN regulates DNA replication progression and stalled fork recovery." *Nature Communications* 6, Article number: 7620
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