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Discovery opens door to new treatments for prostate, brain and skin cancers

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Researchers at the Lady Davis Institute for Medical Research of the Jewish General Hospital and McGill University in Montreal have discovered a previously unsuspected link between two different genetic pathways which suppress the growth of cancer tumours. This breakthrough, they say, could lead to new treatments for some of the deadliest and most intractable forms of cancer; including prostate cancer, brain cancer and melanoma.

The scientists discovered a novel link between a tumour-suppressing gene known as the phosphatase and tensin homolog (PTEN) and a protein called PKR, which is known to inhibit protein synthesis. The researchers discovered that when PTEN is mutated or absent, PKR loses its inhibitory ability, and protein synthesis within the affected cells runs wild.

"This leads to high proliferation of cells with a survival advantage over normal cells," explains Dr. Antonis E. Koromilas of the JGH Lady Davis Institute for Medical Research and McGill's Department of Oncology. "That is a condition that facilitates tumour development."

PTEN plays a vital role in the suppression of humans cancers by inhibiting a genetic pathway called phosphoinositide-3 kinase (PI3K). Clinicians often target PI3K with drugs when treating cancer patients, but this does not work in all cases, because not all mutant forms of PTEN interact with PI3K. In 1992, in a study published in the journal Science, Dr. Koromilas and Dr. Nahum Sonenberg of McGill University

identified PKR as a potential tumour suppressor, but its association with PTEN was unsuspected at the time.

The new discovery was made by Koromilas's graduate researcher Zineb Mounir, the study's first author, along with colleagues in the United States. Their findings were published December 22 in the journal *Science Signalling*.

"Because they are not mediated by the known PI3K pathway, existing cancer treatments don't always work on tumours with PTEN mutations," explains Mounir.

"That's why this discovery has such tremendous implications," continues Koromilas."If we start to understand how these mutants of PTEN function, we should be able to design drugs that can activate PKR, essentially switch on its protein synthesis inhibitory function."

These treatments, Koromilas adds, don't necessarily have to be tailored from scratch to pinpoint PKR.

"We also have learned from our work that DNA damage can actually activate the PKR pathway, and some chemotherapy treatments are known to damage DNA. So you have the option to design drugs that are specific to PKR, or you can use drugs that have a more general effect and activate this pathway almost as a side-effect."

Provided by Jewish General Hospital