Common genetic defect in prostate cancer inspires path to new anti-cancer drugs

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Like security screening to make sure nothing harmful makes its way into a crowded area, cells in the human body use checkpoints to control their growth and prevent harmful mutations from making their way into new

cell populations and causing trouble. Every cell that divides and replicates its DNA must clear at least three checkpoints—all of which call on specialized genes known as tumor suppressors.

Tumor suppressor genes encode proteins that work with other molecules in cells to put the brakes on cell division when DNA damage or other defects are detected. This process prevents mutations that harm cells or that lead to uncontrolled cell growth and cancer from being passed along to new cells. Fortunately, tumor suppressors are fairly robust. Under normal circumstances, they stop working only when mutations affect both of the tumor suppressor gene's alleles, which are the different forms of a gene inherited from each parent.

But in the case of prostate cancer, researchers at the Lewis Katz School of Medicine at Temple University (LKSOM) and Fox Chase Cancer Center recently discovered an important exception to this two mutation rule. Working in human cells and animal models, they found that a mutation leading to the loss of just one allele of a tumor suppressor gene known as PPP2R2A is enough to make a tumor caused by other mutations worse.

In a study published in the journal *Oncogenesis*, the team, led by Xavier Graña, Ph.D., Professor of Medical Genetics and Molecular Biochemistry, and in the Fels Institute for Cancer Research and Molecular Biology at LKSOM, found that patients whose prostate tumors carry only one copy of PPP2R2A do not survive as long as those whose tumors have two copies of the gene. They also showed that in cells deficient in PPP2R2A, reconstitution of the PP2A protein encoded by the gene ultimately kills prostate cancer cells.

The study is the first to show that reactivating PP2A in affected cells can slow or stop the advance of prostate cancer in an animal model.

"The majority of prostate tumors have only one functional copy of the PPP2R2A gene," Dr. Graña explained. "Because this alteration occurs so frequently, many patients could benefit from treatments that restore the gene's activity."

Dr. Graña's team mapped out specifically what happens when cells lose a copy of PPP2R2A, and what happens when PP2A is reconstituted. When lost, they found that cells were more likely to divide and replicate, thereby generating more cells—a process that fuels cancer progression. This occurred because cells just breezed through the so-called mitotic checkpoint, which normally ensures that a cell's chromosomes are organized properly for cell division. PP2A reactivation, on the other hand, resulted in sustained activation of the mitotic checkpoint—to the point that the cellular machinery responsible for separating replicated chromosomes for division collapsed, killing the cells.

"Restoring PP2A to normal levels in these cancer cells caused a weakening of their centrosome, which is the organizer of the cell machinery in charge of faithfully separating chromosomes," Dr. Graña explained. "The combination of a sustained checkpoint and a weakened centrosome results in collapse of the mitotic apparatus, with chromosomes not knowing where they have to go."

"Our findings indicate that prostate tumors often kick off a copy of the PPP2R2A gene to facilitate their growth and that bringing PP2A levels back to normal results in abnormal chromosome sorting and cell death."

Small molecules that activate PP2A and that have the potential to be developed into drugs have already been identified. Whether they specifically activate PP2A in prostate cancer remains unclear, however.

"More work is needed to find a specific drug for this complex, but we have a promising start," Dr. Graña added.

More information: Ziran Zhao et al, PPP2R2A prostate cancer haploinsufficiency is associated with worse prognosis and a high vulnerability to B55α/PP2A reconstitution that triggers centrosome destabilization, *Oncogenesis* (2019). DOI: 10.1038/s41389-019-0180-9

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