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Scientists discover new subtype of prostate cancer

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Researchers led by the University of Michigan Rogel Cancer Center have identified a new subtype of prostate cancer that occurs in about 7 percent of patients with advanced disease



The subtype is characterized by loss of the gene CDK12. It was found to be more common in metastatic prostate cancer compared to early stage tumors that had not spread.

Tumors in which CDK12 was inactivated were responsive to immune checkpoint inhibitors, a type of immunotherapy treatment that has overall had limited success in prostate cancer.

Researchers at the Rogel Cancer Center will lead a multisite clinical trial to assess checkpoint inhibitors as a treatment for metastatic prostate cancer with CDK12 loss.

In this study, published in Cell, researchers looked at DNA and RNA sequencing data from 360 tumor samples from patients with metastatic castration-resistant prostate cancer.

This is an aggressive, advanced form of the disease in which the cancer has spread throughout the body and no longer responds to traditional hormone-based treatments.

Tumor samples were from U-M's Mi-ONCOSEQ program and from samples collected through the Stand Up to Cancer-Prostate Cancer Foundation Dream Team.

Researchers found the loss of CDK12 in only about 1 percent of early prostate cancer samples. That jumped to 7 percent for metastatic cancer, which indicates a more-aggressive form of the disease.

"It suggests that those early stage patients who have CDK12 loss are the ones who will develop metastatic disease. This could be a harbinger in early cancer," Chinnaiyan says.

By following the mechanism of how CDK12 loss impacts the cell, researchers found a process in which cells create neoantigens that are foreign to the immune system. This boosts immune-fighting T-cells, which may explain why these patients benefit from immune checkpoint blockade.

This suggests that a precision medicine approach to prostate cancer could help better direct immunotherapy treatment. It could also explain why some prostate cancer patients have had exceptional responses to immunotherapy while the treatment has had lackluster results overall in prostate cancer.

The team had first recognized a possible role for CDK12 in a 2015 paper that evaluated the genomic landscape of advanced prostate cancers. CDK12 has also been linked to ovarian cancer.

Little is known about CDK12 on a molecular basis but scientists do know that CDK12 regulates several critical cellular processes and is essential for development. Eliminating it is likely lethal to most cell types.

So why can tumors lose CDK12 and survive? Researchers suspect cancer must inherit something that allows it to grow in the face of CDK12 loss. More study is needed to understand this.

"This very promising study suggests that CDK12 loss may be a biomarker for identifying prostate cancer patients who may respond to checkpoint immunotherapy," says Howard Soule, Ph.D., executive vice president and chief science officer of the Prostate Cancer Foundation.