New clues to common and elusive KRAS cancer gene

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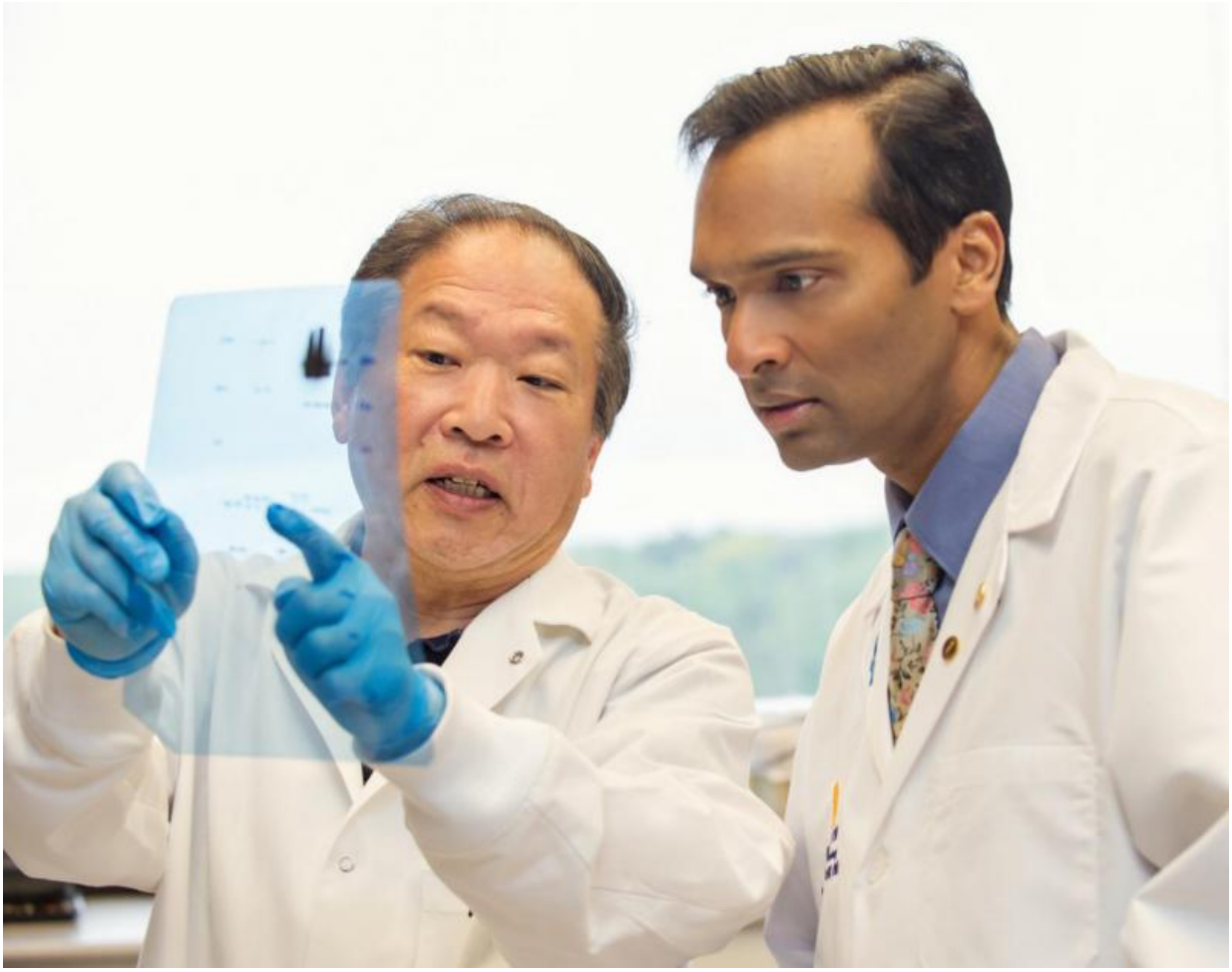

Arul Chinnaiyan, right, consults with one of his lab associates. Credit: University of Michigan Comprehensive Cancer Center

One of the most common cancer-causing genes has continuously stymied researchers' efforts to develop treatments against it.

Now, researchers at the University of Michigan Comprehensive Cancer Center have dug deeper and exposed a key interaction that may contribute to why mutations in KRAS lead to cancer.

Nearly a third of all cancers have mutations in the RAS family of genes, including KRAS. In pancreatic cancer, a particularly aggressive and difficult-to-treat disease, almost every tumor is driven by KRAS mutations. But KRAS has been thought to be "undruggable" - researchers cannot identify an effective therapy against it.

"We came at this from a different angle," says study author Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology. "Knowing how critical KRAS is in cancer development, we looked for important protein interactions that we might try to disrupt. We picked up on an interactor called AGO2. It was a very robust interaction,"

AGO2 plays a role in silencing genes and processing microRNA - so it impacts many genes. The researchers found AGO2 interacted with both mutated and normal KRAS. The link appeared in all 12 of the cell lines tested.

The study appears in *Cell Reports*.

Studies in cell lines and mouse models showed that AGO2 enhanced the cancer-causing ability of KRAS. The higher the level of AGO2, the more cancerous activity, the researchers found. At the same time, KRAS inhibits AGO2's ability to process microRNA. This impacts the downstream oncogenes and tumor suppressor genes controlled by microRNA.

The finding suggests potential to explore interrupting the KRAS-AGO2 interaction as a possible therapy. Additional research is needed. The study authors plan next to try to replicate their cell findings in a mouse model to confirm the interaction. They will also begin to map it in 3D to begin to identify opportunities for potential therapies.

"This is not a near-term solution. It is a basic science discovery that has potential to be translated. It's exciting to consider that KRAS may not be the undruggable target we thought it is," Chinnaiyan says.

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