

'Achilles heel' of pancreatic cancer identified

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A research team at Georgetown Lombardi Comprehensive Cancer Center reports that inhibiting a single protein completely shuts down growth of pancreatic cancer, a highly lethal disease with no effective therapy.

Their study, published online today in *Science Signaling*, demonstrates in animal models and in human cancer cells that while suppressing Yes-associated protein (Yap) did not prevent pancreatic cancer from first developing, it stopped any further growth.

"We believe this is the true Achilles heel of pancreatic cancer, because knocking out Yap crushes this really aggressive cancer. This appears to be the critical switch that promotes cancer growth and progression," says the study's senior investigator, Chunling Yi, PhD, an assistant professor of oncology at Georgetown Lombardi.

Yi added that because Yap is over-expressed in other cancers, such as lung, liver and stomach tumors, researchers are already working on small molecule drugs that will inhibit activity of the protein and its partnering molecules.

The study was conducted in mouse models of [pancreatic ductal adenocarcinoma](#) (PDAC), which accounts for all but five percent of human pancreatic cancers. These mice have a mutation in the KRAS gene, as well as a mutation in their p53 gene. "More than 95 percent of pancreatic cancer patients have a KRAS mutation and about 75 percent have a mutation in p53, so these mice provide a natural model of the

human disease," she says.

Because it has been very difficult to devise drugs that target either KRAS or p53, in this study the researchers looked for other potential druggable targets involved in uncontrolled growth of pancreatic cancer.

They found that Yap was over-expressed in both mouse models and human samples of PDAC, and they discovered that the KRAS mutation found in most pancreatic cancer activates Yap. "The KRAS mutation uses Yap to make [cancer cells](#) grow, so shutting down Yap defuses the mutated gene's activity," Yi says.

Yap also shuts down activity of the p53 oncogene, though the link between p53 and Yap is not yet known.

"KRAS and [p53](#) are two of the most mutated genes in human cancers, so our hope is that a drug that inhibits Yap will work in [pancreatic cancer](#) patients—who have both [mutations](#)—and in other cancers with one or both mutations," Yi says.

Provided by Georgetown University Medical Center

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