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Scientists identify possible KRAS downstream target for pancreatic cancer therapy

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While the mutated KRAS oncogene is associated with many cancers, it has not yet been successfully targeted by a therapeutic agent. Scientists are trying to find another way to target the gene by blocking signals from another protein downstream.

A University of North Carolina School of Medicine team offers first evidence of the role of a protein called GSK-3 alpha in promoting oncogenic KRAS function. When the scientists inhibited GSK-3 in a model of pancreatic tumors, the team got a strong anti-tumor response, thus offering a potential therapeutic option. Their findings are published in the June issue of the journal *Cancer Discovery*.

Albert Baldwin, William Rand Kenan Professor of Biology, study senior author, and associate director of UNC Lineberger Comprehensive Cancer Center, says, "GSK-3 promotes activity of a protein called NF-kappa B. Our lab has been studying NF-kappa B for a number of years and has published that this protein is important in KRAS signaling. But how KRAS activates NF-kappa B has not been well understood. We have found a link."

GKS-3 has alpha and beta forms. The beta form has been studied and is considered to be a tumor suppressor. GSK-3 alpha was considered to be redundant to GSK-3 beta. The research team studied GSK-3 alpha in mice with human pancreatic tumors and found through their experiments

that its function is different from GSK-3 beta.

"Our data suggest that GSK-alpha is really an onco-protein and that KRAS utilizes GSK-alpha to activate both NF-kappa B pathways, called canonical and noncanonical. This finding is important because GSK-3 alpha sits on top of the two pathways and inhibits them both, thus making it a viable therapeutic target. We are conducting further pharmacologic studies," said Baldwin.

Provided by University of North Carolina Health Care