

Targeting FGFR2 May Prevent or Delay Some KRAS-Mutated Pancreatic Cancers

Preclinical study suggests inactivating KRAS with targeted therapies might slow progression of precancerous pancreatic lesions to cancer.

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Precancerous pancreatic lesions and some pancreatic ductal adenocarcinoma (PDAC) tumors harboring KRAS mutations had higher-than-normal expression of the FGFR2 protein, and FGFR2 inactivation delayed KRAS-mutated PDAC development in mice, according to results of a study published in [Cancer Research](#), a journal of the [American Association for Cancer Research](#).

PDAC is the most common type of [pancreatic cancer](#), a highly lethal malignancy that is often preceded by precancerous lesions. These lesions are [relatively common](#), but only a small portion will progress to PDAC, explained first author [Claudia Tonelli, PhD](#), a research investigator in the laboratory of [AACR Past President David A. Tuveson, MD, PhD, FAACR](#), at Cold Spring Harbor Laboratory.

While mutations in the KRAS protein are known to drive pancreatic cancer, these do not appear to be sufficient to promote the transition from precancerous lesions to cancer, Tonelli noted. “Understanding the additional pathways that promote progression from a precancerous pancreatic lesion to a malignant tumor could help identify more viable treatment strategies as well as cancer interception approaches to stop PDAC from developing in the first place,” she added.

By analyzing murine and human pancreatic tissue specimens, Tonelli and colleagues found that, compared with normal tissue, FGFR2 expression was higher in KRAS-mutated precancerous lesions and some KRAS-mutated PDAC. Notably, FGFR2 expression in murine precancerous lesions correlated with an increase in mutant KRAS signaling.

“We know that precancerous pancreatic lesions often carry KRAS mutations,” said Tonelli. “Our observation that FGFR2 expression was associated with increased KRAS signaling suggests that FGFR2 may play a key role in driving the progression of KRAS-mutated precancerous lesions to malignancy.”

Consistent with this hypothesis, the researchers found significantly fewer precancerous lesions

and delayed PDAC tumors formation in KRAS-mutated mice in which the FGFR2 gene had been deleted compared with those with an intact FGFR2 gene. In addition, the combined inhibition of FGFR2 and another signaling protein, EGFR, significantly reduced the formation of precancerous lesions in mice carrying mutated KRAS.

According to Tonelli, the findings suggest that targeting FGFR2 could potentially benefit patients at high risk of their precancerous lesions progressing to PDAC. While FGFR inhibitors are clinically available, Tonelli cautioned that their effectiveness in intercepting PDAC would first need to be tested in clinical trials before they could be used for this purpose.

“Our study provides critical insights into pancreatic cancer development and could guide the development of strategies for the interception and prevention of pancreatic malignancies,” she summarized.

A limitation of the study is that it did not directly examine whether FGFR2 inactivation in precancerous lesions would also block or delay subsequent PDAC. This could be addressed in future studies by performing long-term FGFR2 inhibition, or alternatively by genetic experiments, Tonelli noted.

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