

Study confirms protein as potential cause of most common type of pancreatic cancer

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Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Researchers at The University of Texas MD Anderson Cancer Center have confirmed a protein as an oncogene responsible for the most common and lethal form of pancreatic cancer known as pancreatic ductal adenocarcinoma (PDAC). The team's findings, which validated ubiquitin specific protease 21 (USP21) as a frequently amplified gene and a potential druggable target, appear in the Sept. 5 online issue of *Genes & Development*.

"The USP family is the largest group of enzymes known as cysteine proteases, which play an important role in [tumor development](#) and cancer stem cell biology," said Ronald DePinho, M.D., professor of Cancer Biology. "Genomic analysis identified frequent amplification of USP21 in PDAC. This overexpression correlated with cancer progression in PDAC patient samples, drove malignant transformation of human pancreas cells, and promoted mouse tumor growth."

The researchers also found that depletion of USP21 impairs pancreatic tumor growth, achieved through USP21's ability to deubiquitinate and stabilize TCF7, a transcription factor that promotes cancer cell stemness. Protein ubiquitination is one of the most common post-translational modifications and can affect [protein function](#) in several ways, including [protein](#) stability regulation.

The findings are important, given that current therapeutic options are ineffective in PDAC. Previous genomic profiling of PDAC has provided a comprehensive atlas of recurrent genetic aberrations that promote PDAC tumorigenesis, said DePinho.

"These genetic events include known oncogenes and [tumor suppressor genes](#), as well as numerous novel genetic aberrations," he said. "Moreover, classification of PDAC based on molecular signatures suggests the existence of distinct potential oncogenic drivers for different PDAC subtypes."

These observations prompted the team to explore newly characterized genetic alterations in PDAC with the goal of identifying and understanding new oncogenes that may expand therapeutic strategies for PDAC.

"Moreover, USP21 knockout mice are normal, suggesting that targeting USP21 may represent a cancer-specific vulnerability," said DePinho.

More information: *Genes & Development* (2019). DOI: [10.1101/gad.326314.119](https://doi.org/10.1101/gad.326314.119)

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