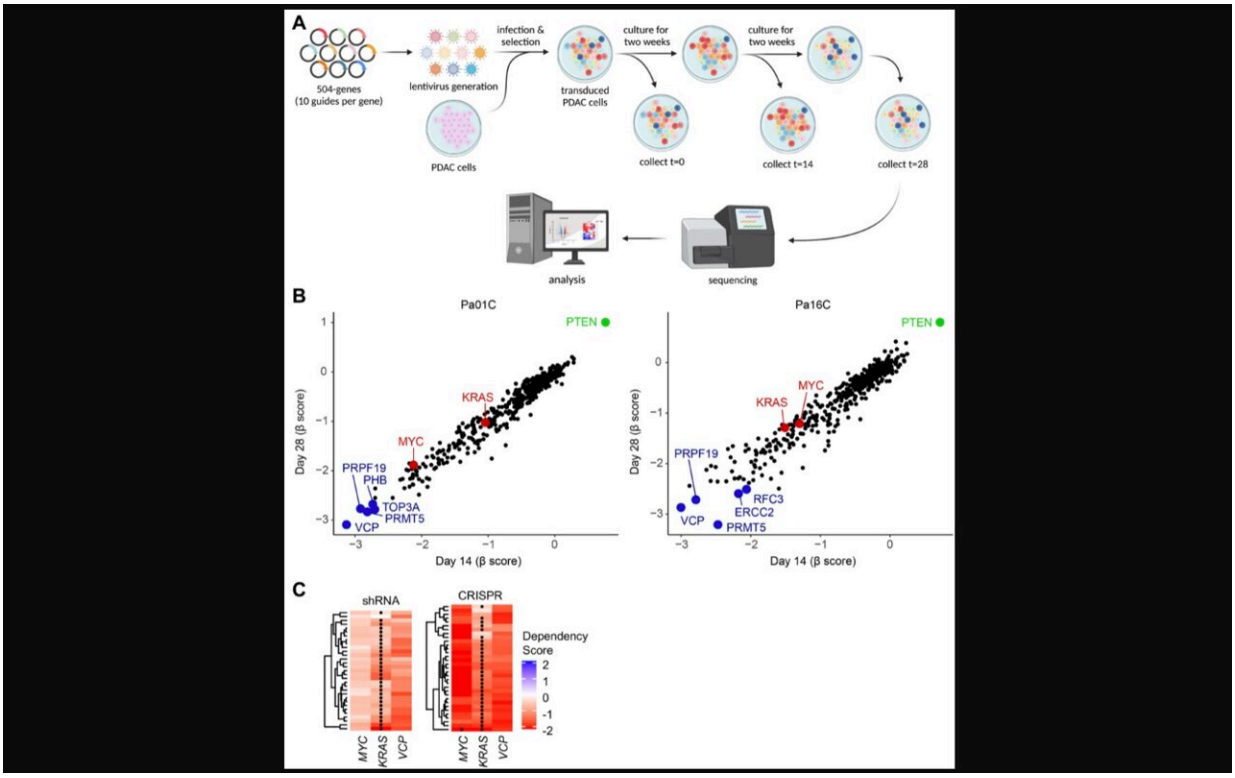
VCP/p97 as a therapeutic target in KRAS-mutant pancreatic cancer

March 24 2023



VCP is an essential gene for KRAS-mutant PDAC. Credit: 2023 Lee et al.

A new research paper, titled "VCP/p97, a pleiotropic protein regulator of the DNA damage response and proteostasis, is a potential therapeutic target in KRAS-mutant pancreatic cancer," was published in *Genes & Cancer* on March 10, 2023.

Researchers have recently shown that proteins involved in the DNA damage response (DDR) are critical for KRAS-mutant pancreatic ductal adenocarcinoma (PDAC) cell growth in vitro. However, the CRISPR-Cas9 library that enabled the identification of these key proteins contained limited representation of DDR-related genes. In their recent study, researchers from the University of North Carolina at Chapel Hill performed a comprehensive, DDR-focused CRISPR-Cas9 loss-of-function screen to further investigate the DDR in this context.

"Our search was directed toward DDR proteins, stemming from our previous identification of this pathway as an important mechanism for PDAC survival," write the researchers.

This screen identified valosin-containing protein (VCP) as an essential gene in KRAS-mutant PDAC cell lines. The team observed that genetic and pharmacologic inhibition of VCP limited cell growth and induced apoptotic death. To address the basis for VCP-dependent growth, they first evaluated the contribution of VCP to the DDR and found that loss of VCP resulted in accumulation of DNA double-strand breaks.

Next, they addressed its role in proteostasis and found that loss of VCP caused accumulation of polyubiquitinated proteins. The researchers also found that loss of VCP increased autophagy. Therefore, the team reasoned that inhibiting both VCP and autophagy could be an effective combination. Accordingly, they found that VCP inhibition synergized with the autophagy inhibitor chloroquine. Their conclusion was that concurrent targeting of autophagy can enhance the efficacy of VCP inhibitors in KRAS-mutant PDAC.

"We identified VCP as an important protein for PDAC growth and proteostasis via its regulation of protein degradation. VCP has therapeutic potential; however, explorations of this potential in preclinical studies were limited to the use of VCPi CB-5083," conclude

the researchers.

More information: Ye S. Lee et al, VCP/p97, a pleiotropic protein regulator of the DNA damage response and proteostasis, is a potential therapeutic target in KRAS-mutant pancreatic cancer, *Genes & Cancer* (2023). DOI: 10.18632/genesandcancer.231

Provided by Impact Journals LLC

Citation: VCP/p97 as a therapeutic target in KRAS-mutant pancreatic cancer (2023, March 24) retrieved 25 April 2024 from https://medicalxpress.com/news/2023-03-vcpp97-therapeutic-kras-mutant-pancreatic-cancer.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.