Study points to new combination strategy for pancreatic cancer

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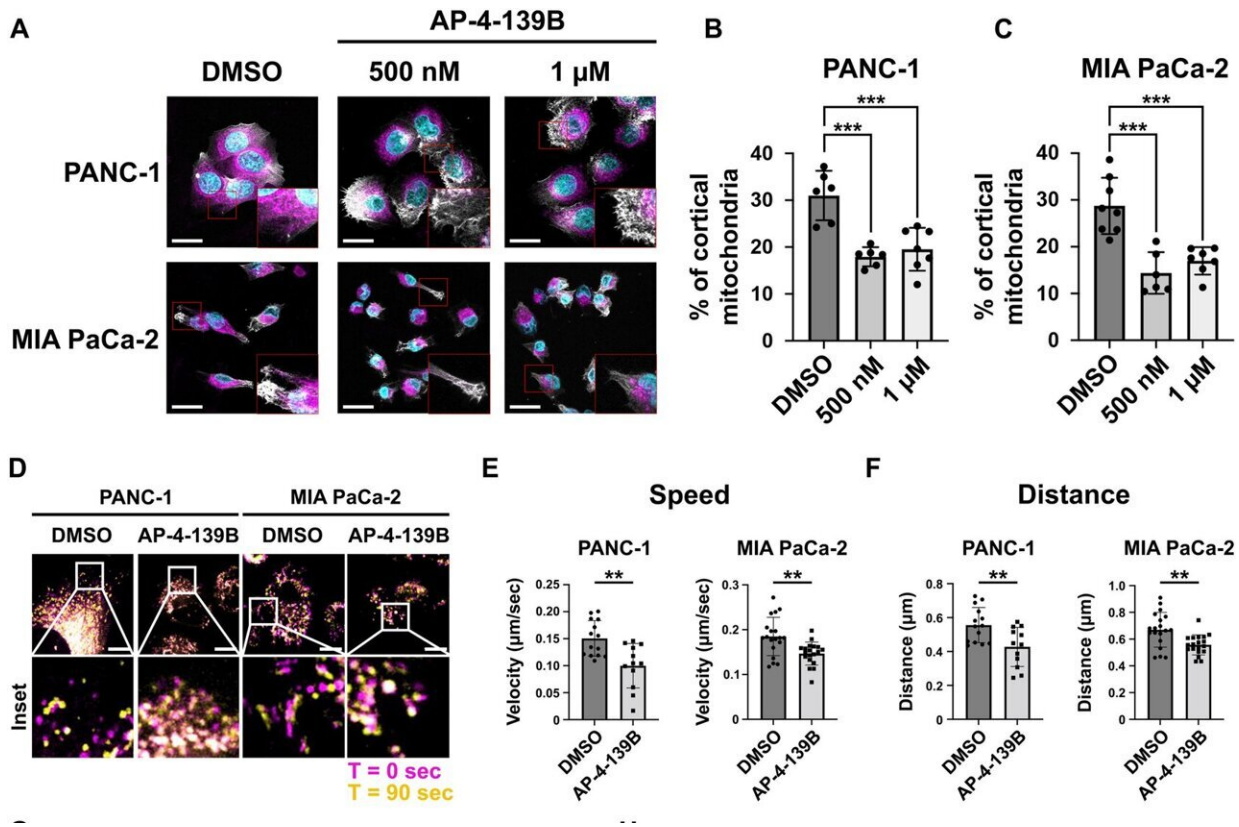

HSP70 inhibition affects mitochondrial subcellular localization and dynamics. Credit: *Cell Death & Differentiation* (2024). DOI: 10.1038/s41418-024-01310-9

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and is projected to become the second-leading cause

of cancer-related death by 2030. Although progress has been made in improving outcomes, the five-year survival rate remains stubbornly low at just 13%.

Now, researchers at MUSC Hollings Cancer Center have identified a promising therapeutic strategy. Published in *Cell Death and Differentiation*, the study describes a new role of HSP70, or heat shock protein 70, and suggests that simultaneously blocking HSP70 and a survival mechanism called autophagy may reduce the growth of pancreatic cancer.

This is the inaugural publication for the Barnoud Lab, headed by Tim Barnoud, Ph.D., who joined Hollings in late 2021. Co-first authors on the paper are Colleen Quaas, Ph.D., and Giulia Ferretti, Ph.D., who have both been awarded fellowships by Hollings. Ferretti is a current HCC Abney Fellow while Quaas has completed her T32 ITOS fellowship and is headed a few blocks north to a faculty position at The Citadel.

Quaas pointed out that this investigation required a significant amount of research effort and collaboration from everyone in the lab as well as other labs at the Hollings Cancer Center.

"A lot of techniques were involved, and one of the benefits of the fellowship is that we were able to have the funds to use a lot of really cutting-edge techniques—such as live cell video-microscopy to study mitochondrial dynamics in real-time—and to perform all of the preclinical efficacy studies of our inhibitors in mouse models.

"And we're fortunate that we have an environment at Hollings where we are all collaborative and work really well together," she said.

Why is HSP70 important in cancer?

Cells utilize heat shock proteins (HSPs) especially when they are under stress. These HSPs act as "chaperones," ensuring that other proteins are folded correctly in order to do their jobs when facing a stressful environment.

Barnoud explained that cancer cells, because they grow and divide at abnormally fast rates, are in a constant state of stress, which includes instances where they have limited oxygen and nutrients necessary to grow.

Because of this, they produce significantly more HSP70 than normal cells. Researchers' attention was drawn to HSP70 as a therapeutic target, although there were still unknowns about everything it was doing in cancer cells.

During his postdoctoral fellowship at The Wistar Institute in Philadelphia, Barnoud found that there was an especially large amount of HSP70 in the mitochondria of tumor cells, including pancreatic cancer cells. Mitochondria, the "powerhouse" of the cell, supplies the energy that cells need to live. However, HSP70 wasn't showing up in the mitochondria of normal cells.

"This was quite surprising. But these findings led us to ask a simple question: What is HSP70 doing in the mitochondria of cancer cells?" Barnoud said.

At his lab at Hollings, Barnoud set out to find out.

Mitochondrial dynamics, a process that regulates the size, shape and position of mitochondria within cells, has been implicated in pancreatic cancer progression and metastasis. The mechanisms that regulate mitochondrial dynamics still aren't fully understood, however.

Barnoud's lab showed that inhibiting HSP70 with a small-molecule inhibitor impaired the function of a protein called DRP1, which is critical for mitochondrial health and integrity. The buildup of compromised mitochondria in turn can lead to the death of cancer cells.

However, another consequence of HSP70 inhibition is the buildup of reactive oxygen species and oxidative stress in the mitochondria, which can activate a critical metabolic sensor in cells known as AMPK. In turn, AMPK activation triggers a survival mechanism known as autophagy, which cancer cells often use to combat a variety of stresses, including chemotherapy.

"Autophagy is an interesting way for pancreatic cancer cells to survive, in that cells essentially undergo 'self-eating' to obtain critical nutrients needed for important biological processes," Barnoud said.

"What was fascinating is that blocking HSP70 made this self-eating process go into over-drive in order for the pancreatic cancer cells to survive the stress we were throwing at it," Ferretti said.

The team showed that blocking autophagy improved the efficacy of HSP70 inhibition and slowed the growth of pancreatic tumors in mice. As with other cancers, research is showing that a multi-faceted intervention is more effective.

"The exciting part of our story is that there is an FDA-approved drug that can block autophagy. Now, more potent autophagy-specific inhibitors are currently in clinical trials for pancreatic cancer," Barnoud said.

"The long-term goal of the lab is to advance the first small molecule HSP70 inhibitor to the clinic, which we hope will be beneficial in the fight against pancreatic cancer but perhaps also for other cancers that are

'addicted' to HSP70."

More information: Giulia D. S. Ferretti et al, HSP70-mediated mitochondrial dynamics and autophagy represent a novel vulnerability in pancreatic cancer, *Cell Death & Differentiation* (2024). DOI: 10.1038/s41418-024-01310-9

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