Study finds cancer cells use a new fuel in absence of sugar

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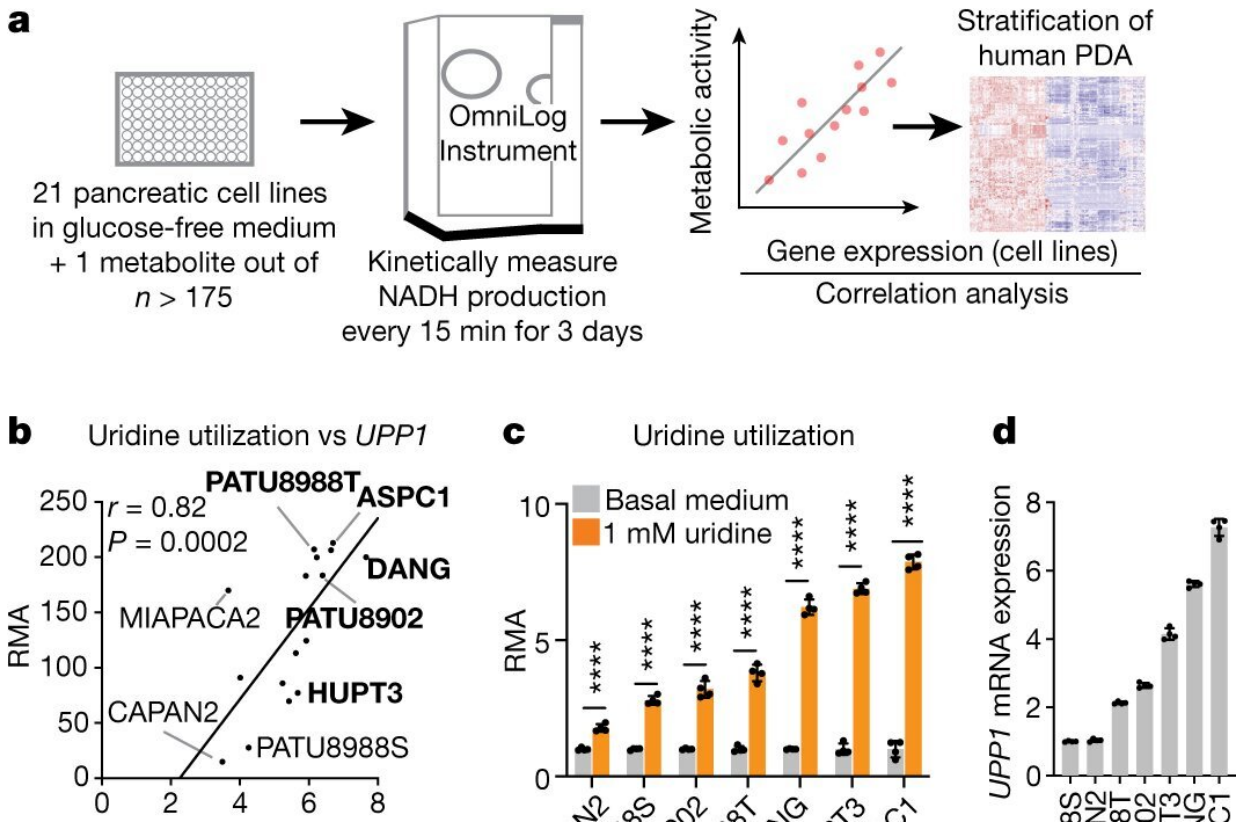

Profiling of metabolite utilization in PDA cells identifies uridine. Credit: *Nature* (2023). DOI: 10.1038/s41586-023-06073-w

Researchers at the University of Michigan Rogel Cancer Center have discovered a new nutrient source that pancreatic cancer cells use to grow. The molecule, uridine, offers insight into both biochemical

processes and possible therapeutic pathways.

The findings, published in *Nature*, show that cancer cells can adapt when they don't have access to glucose. Researchers have previously identified other nutrients that serve as fuel sources for pancreatic cancer; this study adds uridine to the catalog.

Pancreatic tumors have few functioning blood vessels and can't easily access nutrients that come from the bloodstream, like glucose. Costas Lyssiotis, Ph.D., Maisel Research Professor of Oncology and lead investigator of the study, explained that without the right nutrients, the cancer cells get hungry. "We know they still grow, obviously, but what are they using to grow?" he said. "These findings show that, under certain circumstances, uridine is one of those fuels."

Asked about the impact, Zeribe Nwosu, Ph.D., one of the co-first authors in the study, says "the ability of cancer to switch to alternative nutrients has fascinated me for a long time. Blocking such compensatory switches could lead us to new treatments and that's the door we hope this study will open."

Uridine is present in the tumor microenvironment, but its exact source, and how cancer cells access it, remains a mystery. "Part of the picture is it's in the bloodstream, but we don't know where it's coming from specifically," said Lyssiotis. "Likely, it's coming from multiple places, and so far we haven't been able to pin it to a single source."

Events that Lyssiotis refers to as "times of crisis"—when cells don't have enough nutrients, because of limited blood access and/or intense competition between cells—could be a clue as to why, and where, cells turn to uridine. "The cancer cells seem to be sensing the concentrations of glucose and uridine in the local environment to inform their adaptation," says Matt Ward, another co-first author. Lyssiotis' team

recognize this unknown regulatory process, as well as a cancer-promoting mutation in the KRAS gene, which is common in pancreatic cancer, as two ways that cancer cells control their usage of uridine.

Lyssiotis and his team have been working on this research for nearly a decade alongside their collaborators in the Sadanandam lab at the Institute for Cancer Research in London. They used a technology that screens hundreds of different nutrients to see which ones support pancreatic cancer growth. Typically, researchers look at standard nutrients like sugar, protein and fat, but Lyssiotis's team took an unbiased approach.

"We used a large panel with over 20 pancreatic cell lines and around 200 different nutrients to assess different ways pancreatic cancer cells grow," he explained. "What do they actually metabolize? This method led us to discover uridine."

This method offers therapeutic insight, too. The findings showed that uridine is metabolized by the enzyme uridine phoshorylase-1, or UPP1. Blocking UPP1 had a major impact on the growth of pancreatic tumors in mice, findings that suggest the importance of testing drugs that block uridine as possible new treatment options.

"There's potential to better understand and treat pancreatic cancer with new drug targets and new therapeutic approaches," said Sadanandam, co-author on the study.

More research is needed to determine the best way to move this discovery to the clinic.

More information: Zeribe C. Nwosu et al, Uridine-derived ribose fuels glucose-restricted pancreatic cancer, *Nature* (2023). DOI: 10.1038/s41586-023-06073-w

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