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Scientists use organoid model to identify potential new pancreatic cancer treatment

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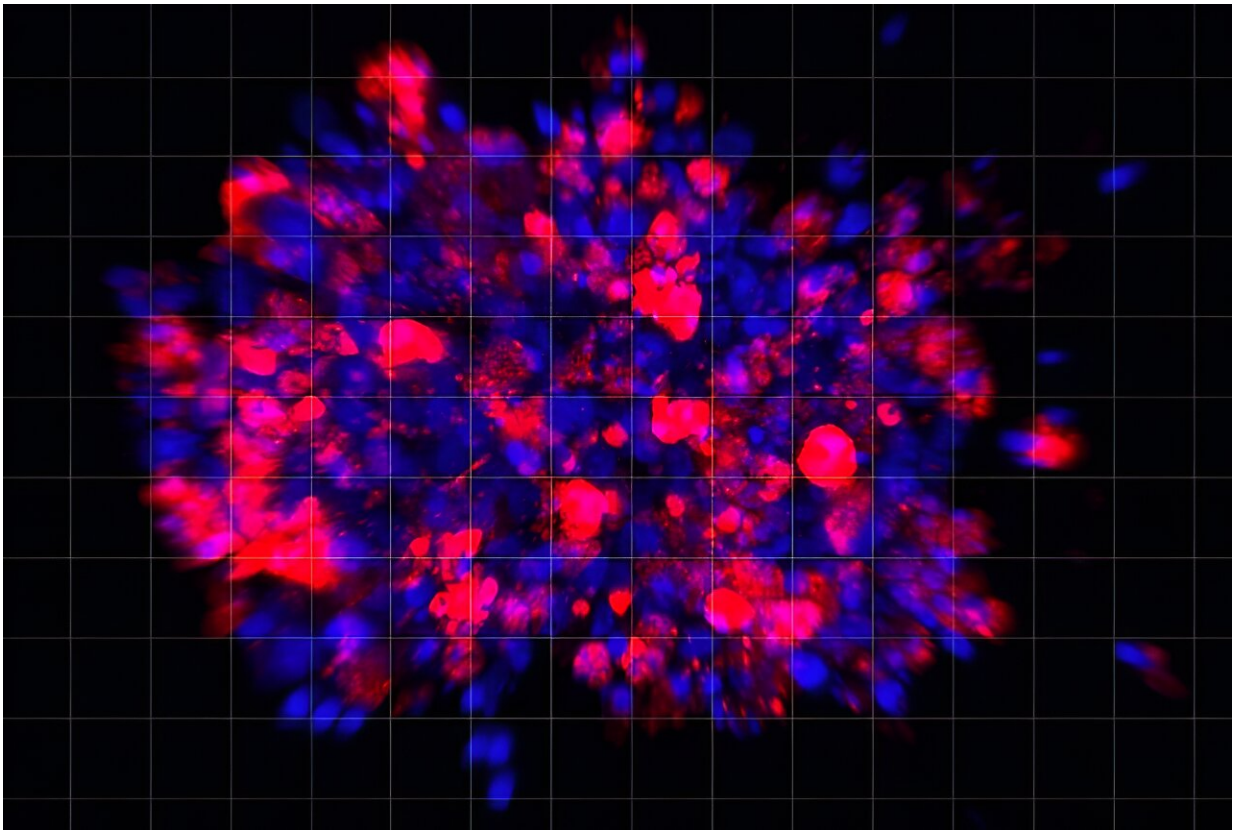

Perhexiline maleate induces cell death of human pancreatic cancer organoids. (Red: Cell death marker; Blue: DAPI). Credit: Xiaohua Duan

A drug screening system that models cancers using lab-grown tissues called organoids has helped uncover a promising target for future

pancreatic cancer treatments, according to a new study from researchers at Weill Cornell Medicine.

In the study, published Dec. 26 in *Cell Stem Cell*, the scientists tested more than 6,000 compounds on their pancreatic tumor organoids, which contain a common pancreatic cancer-driving mutation. They identified one compound—an existing heart drug called perhexiline maleate—that powerfully suppresses the organoids' growth.

The researchers discovered that the cancer-driving mutation in the organoids forces the abnormally high production of cholesterol, which the drug largely reverses.

"Our findings identify hyperactive cholesterol synthesis as a vulnerability that may be targetable in most pancreatic cancers," said study co-senior author Dr. Todd Evans, vice chair for research in surgery, the Peter I. Pressman MD Professor in Surgery, and a member of the Hartman Institute for Therapeutic Organ Regeneration at Weill Cornell Medicine.

"This study also highlights the value of using genetically well-defined organoids to model cancer and discover new treatment strategies," said co-senior author Dr. Shuibing Chen, director of the Center for Genomic Health, the Kilts Family Professor Surgery and a member of the Hartman Institute for Therapeutic Organ Regeneration at Weill Cornell Medicine.

A tumor organoid-based screening system

Organoids have become popular tools for studying tissues in health and disease. They can be made from human or animal tissue, they can recreate much of an organ's complex architecture, and they can be genetically engineered for precision modeling. Organoids can also model

specific tumor types with their cancer-driving gene mutations. Indeed, when these tumor organoids are derived from human tissue, they have the potential to model human cancers better than any animal model.

In the study, the researchers set up an organoid-based automated drug-screening system for the most common form of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC)—one of the most untreatable and lethal of cancers. The organoids, made from normal mouse pancreatic tissue, were engineered to contain various sets of mutations known to drive human pancreatic tumors. All the organoids contained KrasG12D, the mouse version of a cancer-driving mutant gene found in most cases of PDAC.

The researchers tested a library of more than 6,000 compounds, including FDA-approved drugs, on the organoids, identifying several that could substantially disrupt their growth. The best of these was perhexiline maleate, an older drug used to treat the heart condition called angina. A modest dose of the drug blocked growth in all the KrasG12D-containing organoids, destroying some of them outright within days, while having no adverse impact on healthy organoids lacking the mutation. The drug had similar effects against mouse and human PDAC-derived tumor organoids transplanted into mice, and in human tumor organoids carrying other types of Kras mutation.

By comparing gene activity patterns in treated and untreated organoids, the researchers found that cancer-associated mutant Kras greatly boosts the production of cholesterol in organoid cells, and that perhexiline maleate opposes this effect by inhibiting a key cholesterol metabolic pathway regulatory factor called SREBP2.

Cholesterol as an emerging cancer target

The discovery of cholesterol's role was not entirely surprising, since

cholesterol is an essential building-block used in making new cells, and a promoter of cell survival; it is already known to be an important sustainer of malignant growth for some other tumors, including lung tumors. Now, the results suggest that targeting it may be an effective new treatment strategy against PDAC.

Perhexiline maleate's effectiveness in human organoids harboring several different Kras mutations also suggests that turbo-charged cholesterol synthesis can be a general treatment target in KRAS-mutant cancers.

"We hope that our cholesterol-targeting strategy will be independent of particular KRAS mutations and will make it hard for treated tumors to evolve resistance," said Dr. Evans, who is also a member of the Sandra and Edward Meyer Cancer Center.

Perhexiline maleate is unlikely to be used as-is for treating PDAC. Although it is still prescribed as an angina drug in Australia and some other countries, it can have serious side effects, including liver damage and peripheral nerve damage—which is why it was withdrawn from several European markets in the 1980s, and was never approved in the United States.

"We want a better compound for cancer treatment," said Dr. Chen. The simplicity of the drug's chemical structure suggests that it probably can be modified to improve its potency, safety, bloodstream half-life and other properties, she said.

The team now plans to use perhexiline maleate as a starting point for the development of a more refined candidate PDAC drug, and as a laboratory tool for studying cholesterol synthesis in PDAC and other cancers.

More information: Xiaohua Duan et al, A pancreatic cancer organoid platform identifies an inhibitor specific to mutant KRAS, *Cell Stem Cell* (2023). DOI: 10.1016/j.stem.2023.11.011