

Discovery of a molecular switch in pancreatic cancer cells that triggers metastatic disease

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

More than 62,000 people in the United States will be diagnosed with pancreatic cancer by the end of this year, with the vast majority having a deadly and aggressive subtype known as pancreatic ductal

adenocarcinoma (PDA). PDA affects more than 90% of patients with pancreatic cancer and has an average 5-year survival rate of less than 10%.

Now, researchers at the Herbert Irving Comprehensive Cancer Center (HICCC) at New York-Presbyterian/Columbia University Irving Medical Center have discovered a protein whose level of expression functions as a molecular switch between primary [cancer](#) growth and metastatic dissemination in PDA cells. The study, published online June 24 in *Molecular Cell*, provides key insights towards a possible treatment that can toggle this molecular switch to block the spread of the disease to other organs.

"Metastasis underlies the lethality of many cancer types, and this is particularly prominent in [pancreatic cancer](#)," says Iok In Christine Chio, Ph.D., assistant professor of genetics and development in the Institute for Cancer Genetics (ICG) at Columbia University Vagelos College of Physicians and Surgeons (VP&S), member of the HICCC's Tumor Biology and Microenvironment program, and the study's principal investigator. "Understanding metastasis and developing therapies that target and prevent metastatic dissemination is essential to change the landscape for pancreatic cancer patients."

The protein, named methionine sulfoxide reductase A (MSRA), caught the attention of Dr. Chio and her colleagues due to its unusually low levels of expression in metastatic pancreatic cancer cells. To figure out its purpose, they used the genome editing technique CRISPR-Cas9 to delete the code for MSRA from PDA cells, which substantially increased their likelihood of metastasis.

Eventually, they realized that a high level of MSRA expression kept the growing cells as part of the primary tumor, whereas a low level of MSRA expression seemed to push the cells to metastasize. In other

words, MSRA expression level appeared to operate like a [molecular switch](#).

Next, the researchers studied pancreatic organoids, which are 3D representations of a tumor that can mimic its biological activity *in vitro*, to analyze how the switching is achieved. Dr. Chio had previously developed the organoid model system for pancreatic cancer as a postdoctoral researcher at Cold Spring Harbor Laboratory. Applying chemoproteomics—a technique that uses chemical probes to identify protein oxidative changes—revealed that MSRA controls the oxidation of certain target proteins involved in glucose metabolism, a process required for the proliferation and migration of cancer cells.

"Specifically, we found that pyruvate kinase M2 (PKM2), a key enzyme in the glucose [metabolic pathway](#), exhibits an oxidation mark in metastatic cancer cells but not primary tumor cells," she says. "To put it simply, think about PKM2 as a traffic light at an intersection. This oxidation mark on PKM2 acts as the green light that permits cancer cells to spread and metastasize, a lethal outcome for pancreatic cancer patients."

Once it has the oxidation mark, the PKM2 enzyme becomes activated, altering [glucose metabolism](#) in a manner that enables tumor cells to move to distant organ sites.

As a next step, Dr. Chio and her colleagues are testing whether the restoration of MSRA expression will inhibit the spread of pancreatic cancer [cells](#) to other parts of the body. Their [genetic experiments](#) show that this approach is feasible and are now exploring the use of a "molecular glue" system that can restore MSRA expression in their organoid and mouse models.

"Patients who are diagnosed with pancreatic cancer generally undergo

neoadjuvant treatment, then surgical resection, followed by adjuvant treatment," Dr. Chio says. "In principle, restoring MSRA expression at the time patients undergo [surgical resection](#) should impede tumor dissemination and recurrence."

More information: Dan He et al, Methionine oxidation activates pyruvate kinase M2 to promote pancreatic cancer metastasis, *Molecular Cell* (2022). [DOI: 10.1016/j.molcel.2022.06.005](https://doi.org/10.1016/j.molcel.2022.06.005)

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