Turning a pancreatic cancer cell's addiction into a death sentence

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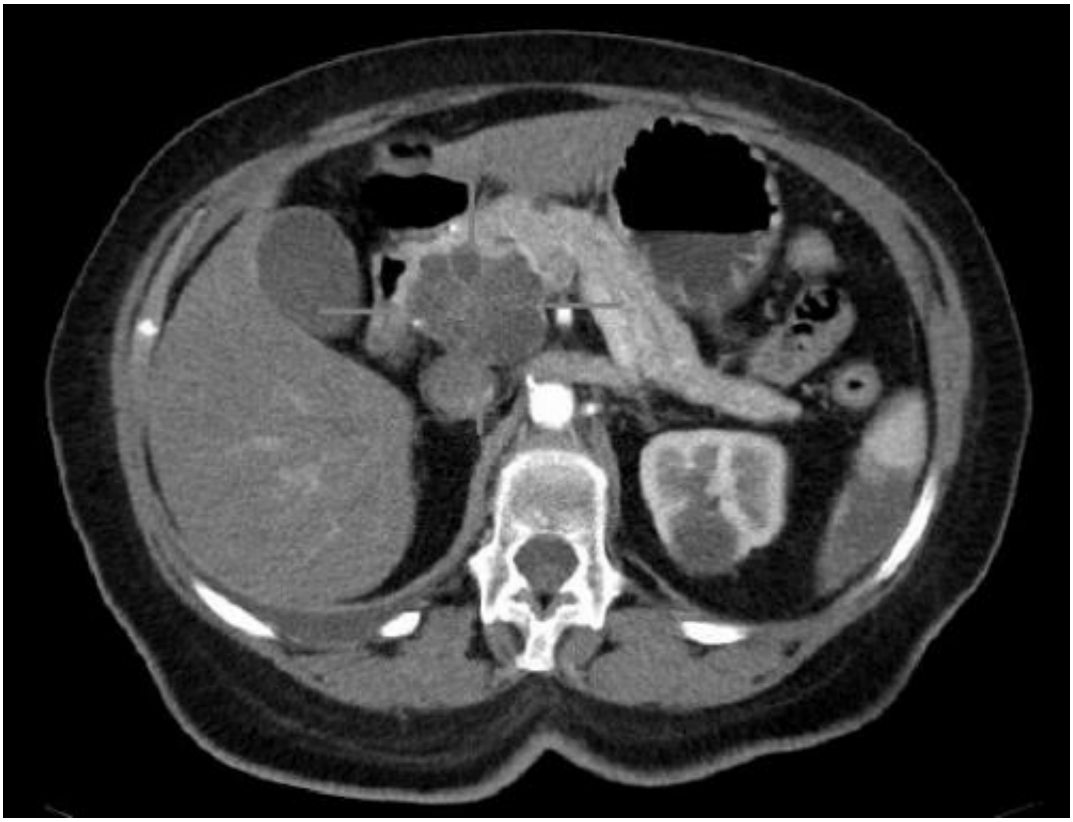

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Probing the unique biology of human pancreatic cancer cells in a laboratory has yielded unexpected insights of a weakness that can be used against the cells to kill them.

Led by Princess Margaret Cancer Centre (PM) Scientist Dr. Marianne Koritzinsky, researchers showed that about half of patient-derived pancreatic cancer cell lines are highly dependent or "addicted" to the protein peroxiredoxin 4 (PRDX4), as a result of the altered metabolic state of the cancer cell.

This addiction is vital for the cancer cell's survival, thereby also making it a precise, potential target against the cancer.

Pancreatic cancer is a deadly disease with an overall five-year survival of only eight percent. Moreover, 36% to 46% of patients who undergo surgery with curative intent develop a recurrence of pancreatic cancer, despite adjuvant chemotherapy.

Research results are published on May 7, 2021 in *Science Advances*.

It's been known for decades that cancer cells acquire key changes in their metabolism to support their continuous need for building blocks from nutrients to divide and grow faster, explains Dr. Koritzinsky, who is the senior author of the study, and an Associate Professor in the Departments of Radiation Oncology, Medical Biophysics and the Institute of Medical Science at the University of Toronto.

This latest research reveals that the same metabolic deregulation that fuels cell growth, can create novel vulnerabilities in cancer.

It was previously known that pancreatic cancer cells increased levels of a key metabolite known as NADPH which acts to fuel uncontrolled levels of cell growth. Dr. Koritzinsky discovered that high levels of NADPH in the pancreatic cancer cells created a novel form of oxidative stress and a corresponding requirement for PRDX4 to survive.

Essentially, cancer cells need PRDX4, an antioxidant protein, to destroy

the toxic byproducts resulting from the uncontrolled metabolism.

Dr. Koritzinsky showed that targeting PRDX4 in patient-derived cancer cells lines led to toxic accumulation of oxidative stress, resulting in DNA damage, and cell death, and impaired tumour growth in preclinical models. Equally important, loss of PRDX4 had no measurable effect on normal cells.

Taken together, this body of work reveals the potential of targeted therapies to exploit unique metabolic features of cancer cells that are far more specific than, for example, chemotherapy which affects both cancer and normal cells.

"It's not hard to kill cancer cells," says Dr. Koritzinsky, "It's hard to kill cancer cells without harming the cancer patient."

She goes on to explain that targeting a specific protein that is needed by a cancer cell, but not a normal one, opens up a wider therapeutic window, with potentially less toxicity to normal tissue.

For this research, Dr. Koritzinsky teamed up with Dr. Jason Moffat, Professor, Donnelly Centre for Cellular and Biomolecular Research, University of Toronto and PM Senior Scientist/Staff Physician Dr. David Hedley to mine large functional genomics data sets and validate findings in patient-derived tumour cells, including recent samples from Princess Margaret patients.

Through this data set mining, they were able to assess about 20,000 different proteins for a comprehensive picture of which ones are important in helping cancer cells survive. PRDX4 turned out to be key.

Based on these discoveries, Dr. Koritzinsky would like to develop new drugs against PRDX4 that could be tested in preclinical models, and

eventually translated to the clinic.

She adds that there may be other ways to take advantage of these new biological insights, including combining this targeted approach with other DNA damaging treatments such as radiotherapy, and establishing biomarkers that can identify the patients who will benefit from PRDX4 targeting.

More information: "NOX4 links metabolic regulation in pancreatic cancer to endoplasmic reticulum redox vulnerability and dependence on PRDX4" *Science Advances* (2021). advances.sciencemag.org/lookup … .1126/sciadv.abf7114

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