Disrupting cells' 'powerhouses' can lead to tumor growth, study finds

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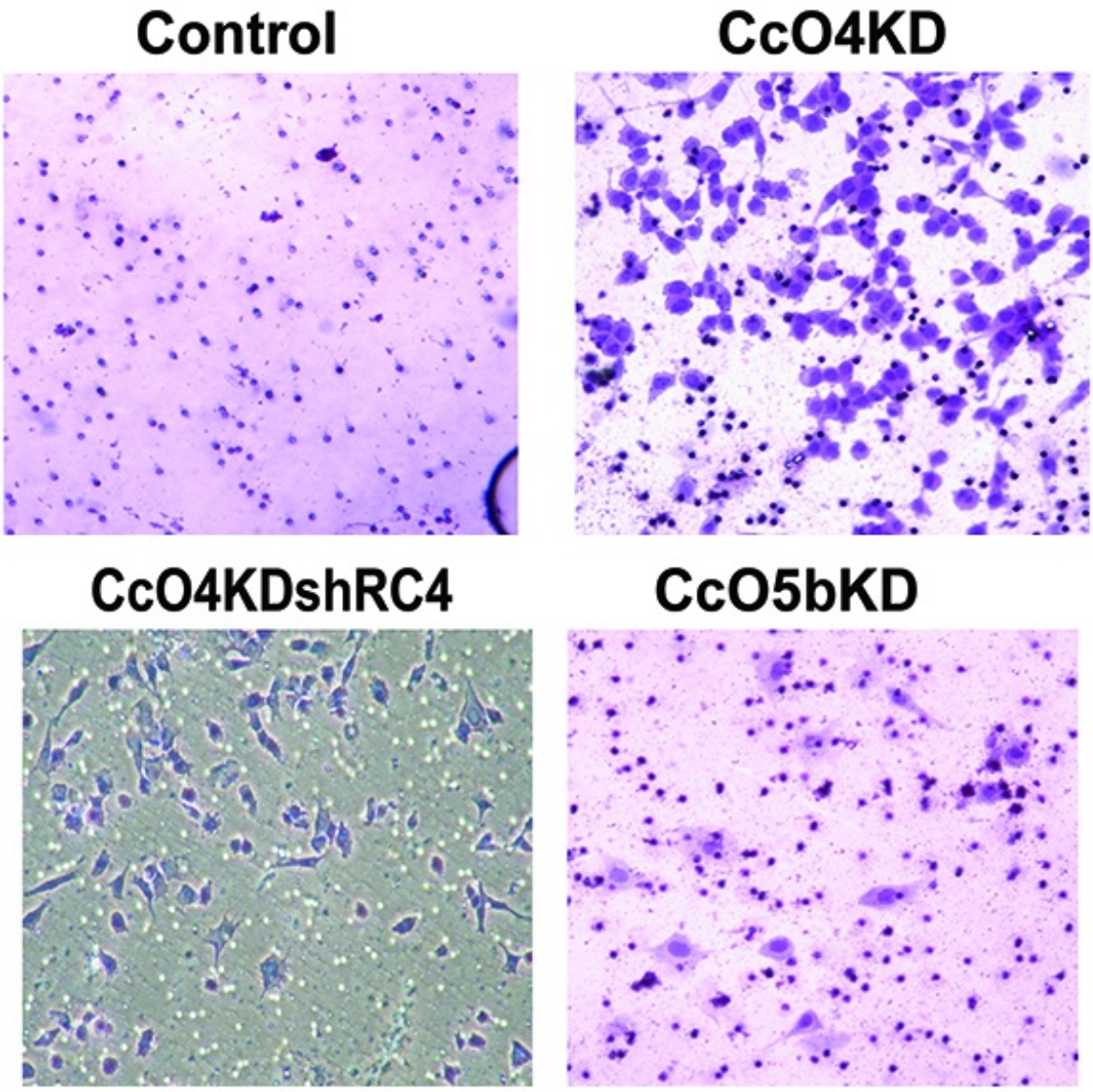

Disrupting the function of the mitochondria (panels on right) made cells highly invasive compared to control cells.

Cancer cells defy the rules by which normal cells abide. They can divide without cease, invade distant tissues and consume glucose at abnormal rates.

Now a study by University of Pennsylvania researchers implicates defects in mitochondria, the energy-production centers of cells, as playing a key role in the transition from normal to cancerous. When the Penn scientists disrupted a key component of mitochondria, otherwise normal cells took on characteristics of cancerous tumor cells.

The research is published in the journal *Oncogene* and was led by members of the lab of Narayan G. Avadhani, the Harriet Ellison Woodward Professor of Biochemistry in Penn's School of Veterinary Medicine's Department of Biomedical Sciences, in collaboration with the lab of Hiroshi Nakagawa from the Gastroenterology Division in Penn's Perelman School of Medicine. Satish Srinivasan, a research investigator in Avadhani's lab, was the lead author. Manti Guha, Dawei Dong and Gordon Ruthel of Penn Vet and Kelly A. Whelan of Penn Medicine also contributed, along with Yasuto Uchikado and Shoji Natsugoe of Japan's Kagoshima University.

In 1924, German biologist Otto Heinrich Warburg observed that cancerous cells consumed glucose at a higher rate than normal cells and had defects in their "grana," the organelles that are now known as mitochondria. He postulated that the mitochondrial defects led to problems in the process by which the cell produces energy, called oxidative phosphorylation, and that these defects contributed to the cells becoming cancerous.

"The first part of the Warburg hypothesis has held up solidly in that most proliferating tumors show high dependence on glucose as an energy source and they release large amounts of lactic acid," Avadhani said. "But the second part, about the defective mitochondrial function causing cells to be tumorigenic, has been highly contentious."

To see whether the second part of Warburg's postulation was correct, the Penn-led research team took cell lines from the skeleton, kidney, breast and esophagus and used RNA molecules to silence the expression of select components of the mitochondrias' cytochrome oxidase C, or CcO, a critical enzyme involved in oxidative phosphorylation. CcO uses oxygen to make water and set up a transmembrane potential that is used to synthesize ATP, the molecule used for energy by the body's cells.

The biologists observed that disrupting only a single protein subunit of cytochrome oxidase C led to major changes in the mitochondria and in the cells themselves.

"These cells showed all the characteristics of cancer cells," Avadhani said.

They displayed changes in their metabolism, becoming more reliant on glucose and reducing their synthesis of ATP. Instead of conducting oxidative phosphorylation, they largely switched over to conducting glycolysis, a less efficient means of making ATP that is common in cancer cells.

The cells lost contact inhibition and gained an increased ability to invade distant tissues, both "hallmarks of cancer cells," Avadhani noted. When they were grown in a 3D medium, which closely mimics the natural environment in which tumors grow in the body, the cells with disrupted mitochondria formed large, long-lived colonies, akin to tumors.

The researchers also silenced cytochrome oxidase C subunits in an already-tumorigenic breast and esophageal cancer cell lines.

"We found that the cells became even more invasive, heightening their malignant potency," Srinivasan said.

Finally the Penn team looked at actual tumors from human patients and found that the most oxygen-starved regions, which are common in tumors, contained defective versions of cytochrome oxidase.

"That result alone couldn't tell us whether that was the cause or effect of tumors, but our cell system clearly says that mitochondrial dysfunction is a driving force in tumorigenesis," Avadhani said.

The researchers observed that disrupting CcO triggered the mitochondria to activate a stress signal to the nucleus, akin to an "SOS" alerting the cell that something is amiss. Avadhani and his colleagues had previously seen a similar pathway activated in cells with depleted mitochondrial DNA, which is also linked to cancer.

Building on these findings, Avadhani and members of his lab will examine whether inhibiting components of this mitochondrial stress signaling pathway might be a strategy for preventing cancer progression.

"We are targeting the signaling pathway, developing a lot of small molecules and antibodies," Avadhani said. "Hopefully if you block the signaling the cells will not go into the so called oncogenic mode and instead would simply die."

In addition, they noted that looking for defects in cytochrome oxidase C could be a biomarker for cancer screening.

More information: *Oncogene* , dx.doi.org/10.1038/onc.2015.227

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