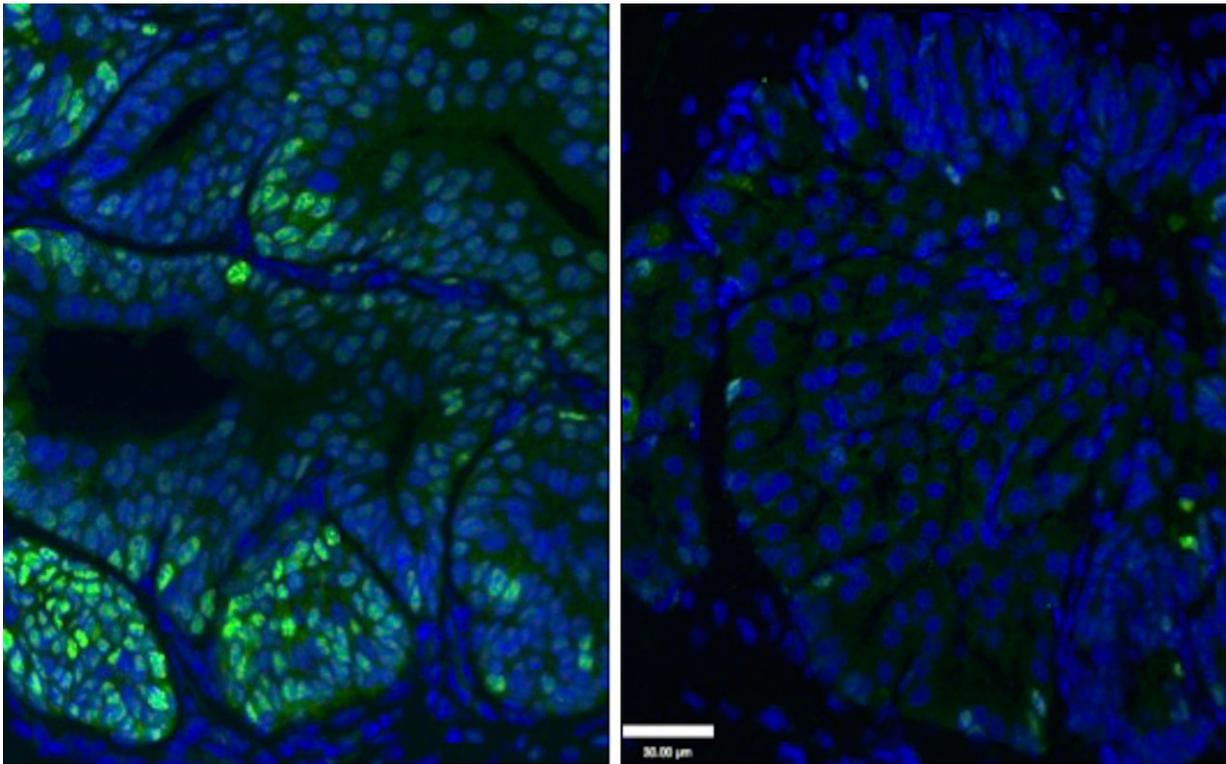


Study reveals a way to make prostate cancer cells run out of energy and die

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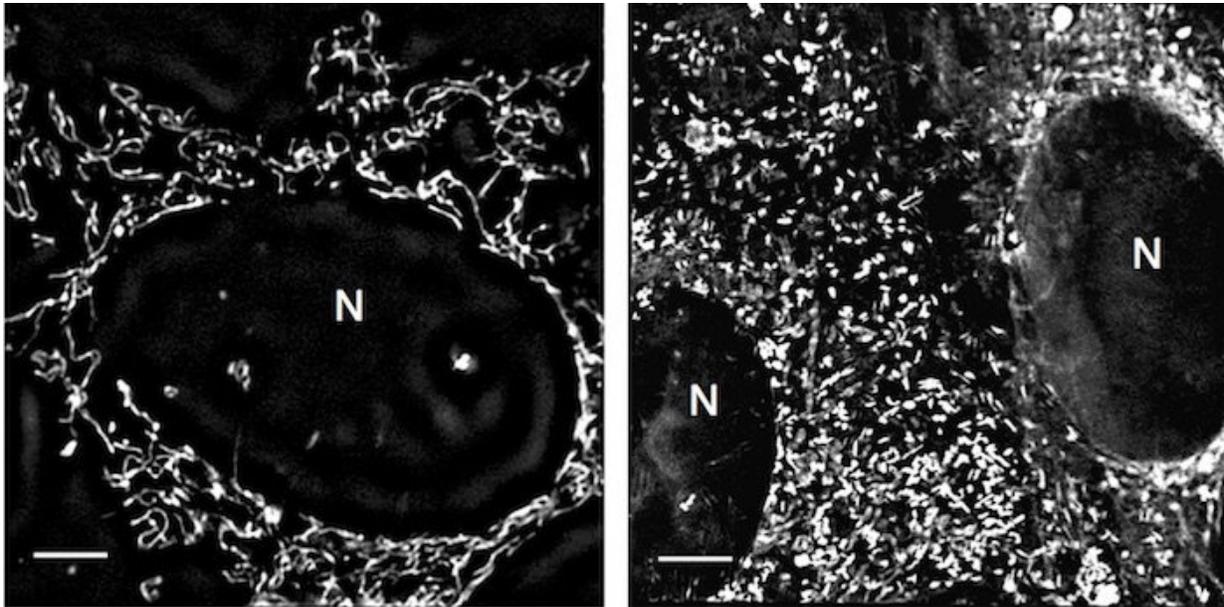
Deguelin, an inhibitor of mitochondria in cells, can be used to target lethal prostate cancers lacking the gene PTEN. Left: cancerous mouse prostate cells glow green. Right: After 10 weeks of treatment with deguelin, only a few cancer cells remain. This compound and another called rotenone, kill cells missing PTEN but don't harm normal cells by exploiting cancer cells' dependency on glucose. Credit: Trotman Lab, CSHL

Scientists at Cold Spring Harbor Laboratory (CSHL) have discovered that cells lacking the tumor-suppressor protein PTEN—a feature of many cancers—are particularly vulnerable to drugs that impair their energy-producing mitochondria. Such drugs induce them to literally eat themselves to death, the research shows.

Unlike normal [cells](#), cells without PTEN seem driven to preserve their mitochondria at all costs, says the team leader, CSHL Professor Lloyd Trotman. He and colleagues have found that when such cells are treated with certain mitochondrial inhibitors, they consume vast quantities of glucose to fuel these efforts. As a result, they quickly run out of energy and die.

Some mitochondrial inhibitors, including the widely prescribed diabetes medication metformin—one of the most widely taken drugs in the world—are already being evaluated in clinical trials for their ability to prevent or treat many types of cancer.

The new findings, reported today in *Cell Reports*, suggest that such drugs have the potential to eliminate [cancer cells](#) at doses that leave [healthy cells](#) intact. The timing is critical, however. When glucose levels are high, this window of opportunity is completely lost. "The hope is that carefully timed administration of these drugs can generate a much better window of selective killing," Trotman says.



Left: nucleus (N) of a healthy cell, surrounded by networks of mitochondria, whose networks form spaghetti-like strands just outside the nucleus. Right: After treatment with mitochondrial inhibitor deguelin, mitochondria have fragmented and are now separated in the space between two cellular nuclei. Administered when glucose is low, such inhibitors effectively induce cancer cells to eat themselves to death. Normal cells survive. Credit: Trotman Lab, CSHL

Two related compounds, both derived from the root of the same plant, emerged from a screen performed by the team. Both killed cells missing PTEN and another tumor suppressor, p53. Loss of these together is common among men with advanced prostate cancer and is associated with highly metastatic disease.

The two drugs had little effect on nearly identical cells with functional PTEN. One, rotenone, is a known mitochondrial inhibitor. In collaboration with Navdeep Chandel at Northwestern University, Trotman's lab established that the second compound, deguelin, works in much the same way.

Oddly, further experiments with deguelin revealed that it shuts down mitochondrial function just as well in cells with PTEN as it does in cells that lack it. So why did cells with PTEN tolerate the toxic compound so much better?

The answer has to do with how cells use glucose, say co-first authors of the paper, postdoctoral researchers Adam Naguib and Grinu Mathew. They found that cells without PTEN use glucose from their environment to generate the energy-rich molecule ATP, which they import into mitochondria to keep them intact. "That's the exact opposite of what mitochondria are supposed to be doing," Trotman points out. "Mitochondria are supposed to generate ATP for the rest of the cell." For these cells lacking PTEN, unless there is an endless supply of glucose, they quickly use up the sugar and die.

Eventually, any cell subjected to mitochondrial inhibitors will run out of energy and die. Cells without PTEN just get there much faster, Trotman says. That means it could be critical to administer mitochondrial inhibitors to cancer patients when their blood sugar is low, he says. That's counter to how metformin and related medications are currently tested in [cancer](#), because the protocol used to manage diabetes calls for the drugs to be taken immediately after meals.

More information: Naguib A. et al, "Mitochondrial complex I inhibitors expose a vulnerability for selective killing of Pten-null cells" *Cell Reports*, April 3, 2018.

Provided by Cold Spring Harbor Laboratory

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