Researchers describe how acidity makes oxygen-starved cancer cells dormant and drug resistant

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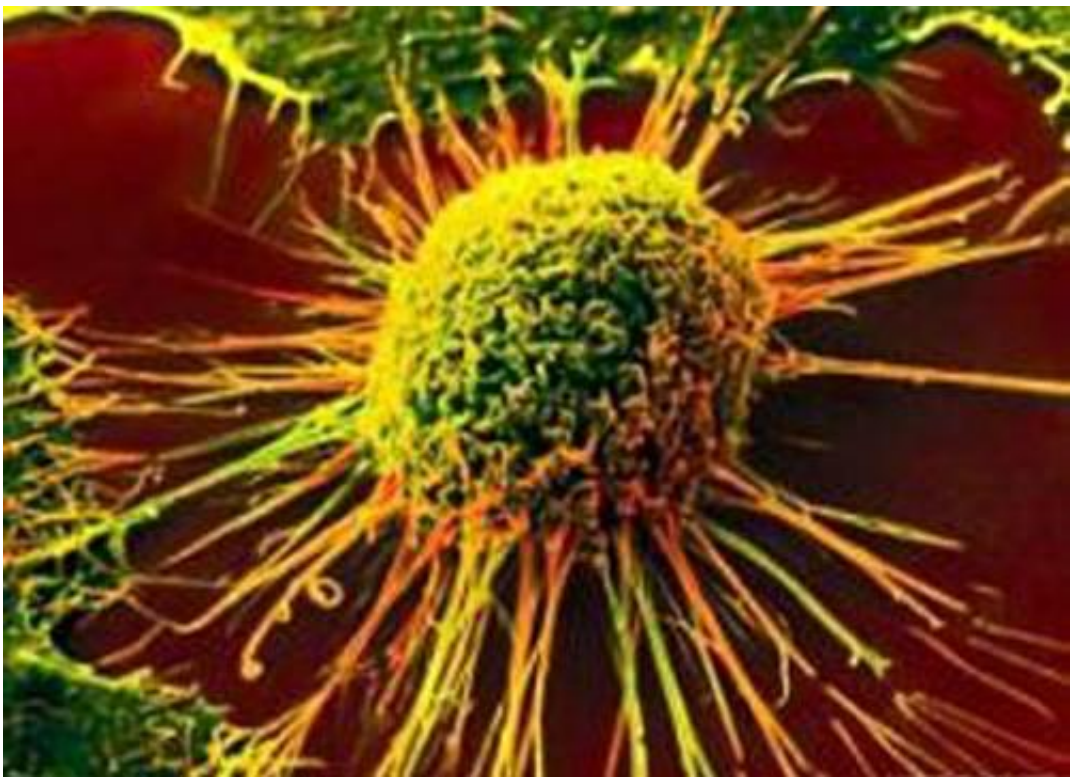

Cells enter a state of dormancy as tissues starved of oxygen become increasingly acidic, according to new research led by investigators from the Perelman School of Medicine at the University of Pennsylvania, the Ludwig Institute for Cancer Research, and The Wistar Institute. The *Cell*

study found that this dormancy, thought to be a major cause of drug resistance and disease relapses in cancer, might be relatively easy to reverse when it is induced by acidity. If confirmed, the finding could help improve a variety of cancer therapies.

Penn MD-Ph.D. student Zandra Walton discovered that acidic conditions halt protein synthesis in cells. Walton studies cancer biology in the lab of former Abramson Cancer Director Chi Van Dang, MD, Ph.D., Ludwig Institute scientific director and a professor in the Molecular & Cellular Oncogenesis Program at Wistar.

Dang, Walton, and their colleagues connected the pause in protein synthesis to another long known (and long neglected) phenomenon: When a cell becomes acidic, lysosomes—sac-like organelles that break down proteins and recycle their amino acids—rapidly disperse from their location near the nucleus to the periphery.

The study detailed how, in response to acidity, cells turn off a critical molecular switch called mTORC. In ordinary conditions mTORC gauges the availability of nutrients before giving cells the green light to grow and divide. The silencing of mTOR shuts down production of proteins, disrupting the cells' metabolic activity and circadian clocks, pushing them into quiescence. The researchers also demonstrate that this acid-mediated effect could be turned off—a finding that could help improve a variety of cancer therapies.

Looking at tumors that had been grafted into mice, the researchers observed a lack of mTOR activity in places in which no oxygen was present. But tumors taken from mice that had been given baking soda in their drinking water light up with mTOR activity. It is possible that if baking soda can be used to reawaken such dormant cells, tumors might become far more sensitive to therapy.

Baking soda has been reported in the past to enhance cancer immunotherapy but the mechanism underlying that effect was unclear.

In acidic conditions, lysosomes rapidly disperse carrying mTOR away to the cell's periphery and separating it from a protein called RHEB found near the nucleus and required for mTOR activation. Lacking one of its key activation signals, mTOR remains dormant, suspending the synthesis of proteins. The team observed that baking soda can reverse this effect, sending lysosomes back to the nucleus where RHEB waits, restoring mTOR activity.

Provided by Perelman School of Medicine at the University of Pennsylvania