Shifting cellular energy metabolism may help treat cardiovascular disease

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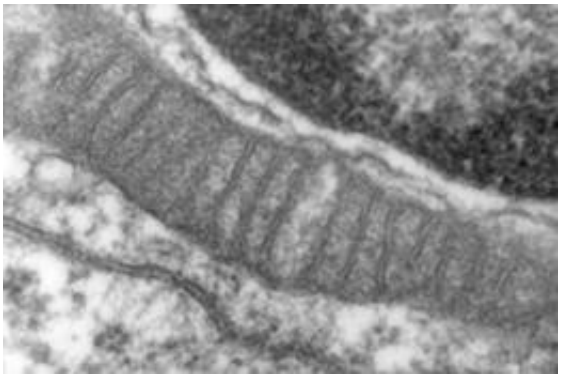

An over-the-counter drug interferes with the metabolic processes that take place in the mitochondrion (like the one pictured here) and could lead to a new way to treat heart attacks and strokes. Image courtesy of the Dartmouth Electron Microscope Facility, Dartmouth College

Drugs that target the way cells convert nutrients into energy could offer new approaches to treating a range of conditions including heart attack and stroke. Using a new way to screen for potential drugs, a team led by Massachusetts General Hospital (MGH) researchers has identified several FDA-approved agents, including an over-the-counter anti-nausea drug, that can shift cellular energy metabolism processes in animals. Their findings, being published online in *Nature Biotechnology,* may open the door to new therapeutic strategies for several serious health problems.

"Shifts in cells' energy production pathways take place naturally during development and in response to demanding activities - like sprinting versus long-distance running. They are also known to be involved in several disease states," explains Vamsi Mootha, MD, of the MGH Center for Human Genetic Research, who led the study. "We wanted to identify compounds that can safely induce this shift - those that have previously been discovered are too toxic - and investigate their therapeutic potential in animal models."

Normally cells convert nutrients into energy by relying on two cellular processes. One involves the uptake of sugars that are broken down in the cytoplasm into a molecule called lactate via a process called glycolysis, which quickly yields a small amount of ATP, the enzyme that provides cellular energy. Alternatively, sugars and proteins can be processed in cellular structures called mitochondria to release greater amounts of ATP through a more efficient process called cellular respiration.

In cancer cells and other rapidly proliferating cells, energy is produced predominantly by glycolysis, suggesting that a shift away from that mechanism might suppress tumor growth. Previous animal studies suggested that a reduction in mitochondrial respiration could mimic a process called ischemic preconditioning, in which brief episodes of ischemia - a reduction in blood flow - actually protect tissue against being damaged if its blood supply is later cut off completely.

To search for compounds that shift cells from respiration to glycolysis, Mootha's team devised a novel screening strategy. They cultured skin cells in two different nutrient environments - glucose, which provides energy through both glycolysis and respiration, or galactose, which forces cells to rely on mitochondrial respiration alone. A drug that redirects energy metabolism from respiration to glycolysis would stop growth in the galactose-cultured cells while having little effect on cells grown in glucose. Their initial screen of almost 3,700 compounds,

including nearly half of all FDA-approved drugs, identified several drugs known to inhibit cellular respiration on one end of the scale and several anti-cancer drugs that halt the growth of rapidly proliferating cells at the other, which verified the approach.

Because most agents known to mimic ischemic preconditioning in animal models are too toxic to use in human patients, the researchers were most interested in finding drugs that cause subtle metabolic shifts. The screen identified eight approved drugs that produced a less pronounced but still significant shift away from cellular respiration. One of those agents was meclizine, an over-the-counter drug used to treat nausea and vertigo - suggesting that it passes the blood-brain barrier - with few negative side effects.

To investigate meclizine's potential to prevent tissue damage in heart attack or stroke, Mootha's team collaborated with University of Rochester researchers who had developed rat models of heart attack damage and an MGH Pathology group with a mouse model of stroke damage. Blinded experiments using both animal models showed that pretreatment with meclizine dramatically reduced ischemic damage to cardiac cells in the heart attack model and to brain cells in the stroke model. They also found that meclizine's ischemia protective effects do not appear to involve its known mechanisms.

While the study results suggest that treatment with drugs like meclizine may someday be useful for reducing the damage associated with heart attack or stroke, Mootha stresses that much additional study is needed. "Before we can think about human studies, we need to do rigorous animal testing to determine optimal, safe dosing regimens and learn more about how this drug works," he says. He also notes that the drug-screening strategy developed by his team could help to identify previously unsuspected beneficial or detrimental effects of other approved drugs.

More information: Gohil et al. Nutrient-sensitized screening for drugs that shift energy metabolism from mitochondrial respiration to glycolysis. *Nature Biotechnology* DOI:10.1038/nbt.1606

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