Molecular alteration may be cause—not consequence—of heart failure

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Clinicians and scientists have long observed that cells in overstressed hearts have high levels of the simple sugar O-GlcNAc modifying thousands of proteins within cells. Now, researchers at Johns Hopkins

Medicine have found evidence in mouse experiments that these excess sugars could well be a cause, not merely a consequence or marker of heart failure.

Their research found that elevated levels of O-GlcNAc made mice more prone to heart failure, but lowering levels of O-GlcNAc restored the animals' risk of death and heart function to normal. Together, the investigators say, the new findings, described online in the April 27th issue of the journal *Circulation*, could offer a potentially new molecular target for therapies that prevent or stop human heart failure.

According to the Centers for Disease Control and Prevention, an estimated 6.2 million Americans have heart failure, a progressive condition in which the heart struggles and ultimately fails to pump enough blood and oxygen to support the body's organs. The ailment costs the U.S. an estimated $30.7 billion in hospitalizations, treatment and lost productivity. Other conditions, including high blood pressure, diabetes and obesity contribute to the development of heart failure.

"Heart failure is a huge problem around the world, and our experiments show we may be able to move the therapeutic needle in the right direction by manipulating levels of O-GlcNAc," says Priya Umapathi, M.D., assistant professor of medicine at the Johns Hopkins University School of Medicine and first author of the new paper.

Proteins within living cells can be modified with the addition of small chemical groups that coax the proteins to change their shape or function. Among those modifications is O-GlcNAcylation, the addition of the sugar molecule O-GlcNAc (O-linked N-acetylglucosamine). The modification is controlled by two other molecules: O-GlcNAc transferase (OGT), an enzyme that adds the sugars to proteins, and O-GlcNAcase (OGA), an enzyme that facilitates their removal.

Researchers have long known that proteins in the cells of people with heart failure have more O-GlcNAc than usual. But whether increased levels of the sugar were a cause or consequence of heart failure—or an attempt by the body to ward off heart failure—has been unclear.

"The field has been conflicted about whether O-GlcNAc in the heart is a good thing or a bad thing," says Umapathi.

In the new work, Umapathi and her colleagues genetically engineered mice with higher than usual levels of OGT or OGA in heart muscle cells. The animals with high OGT—and therefore more O-GlcNAc in these cells—developed severe heart failure. Their hearts began to weaken and pump less blood at just 6 weeks old. By 25 weeks of age, more than half of all mice with high OGT had died, while no control animals with normal levels of OGT had died.

"These mice developed really stunning heart failure," says Umapathi. "Similar to many patients with cardiomyopathy, the mice developed enlarged hearts, abnormal electrical rhythms and died very early."

Animals with high OGA—and therefore lower than usual O-GlcNAc in their heart cells—remained healthy, however, and showed no signs of heart failure, even when challenged with an operation that constricts one of the heart's blood vessels.

To test whether high levels of O-GlcNAc could be reversed to help prevent end-stage heart failure, the researchers next cross-bred the two strains of mice, engineering animals to have both high OGT and OGA levels.

These animals no longer developed heart failure or died early, presumably because while OGT led them to add excessive O-GlcNAc sugars to proteins in the heart cells, the high levels of OGA reversed that

excessive modification. That observation, the researchers say, suggests that drugs targeting the O-GlcNAc pathway could help prevent heart failure.

"Most existing heart failure therapies—including beta-blockers, diuretics and ACE inhibitors—target the same few molecular pathways," says Mark Anderson, M.D., Ph.D., professor and director of the Department of Medicine at Johns Hopkins University School of Medicine and an author of the new paper. "O-GlcNAc represents a completely new pathway that hasn't been targeted with therapeutics before, so that's really exciting."

In additional experiments, the team studied which proteins in heart cells were being modified with the addition of O-GlcNAc. Further studies along these same lines could reveal exactly why the sugars are so important and could possibly identify other molecules involved in heart failure.

"Now that we have these beautiful models to manipulate O-GlcNAc levels in the heart, we can start to get a much better understanding of how this modification plays a role in different subtypes of heart failure," says Natasha Zachara, Ph.D., associate professor of biological chemistry at the Institute for Basic Biomedical Sciences at Johns Hopkins University School of Medicine and a lead author of the new work.

More information: Priya Umapathi et al. Excessive O -GlcNAcylation Causes Heart Failure and Sudden Death, *Circulation* (2021). DOI: 10.1161/CIRCULATIONAHA.120.051911

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