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Gene therapy may aid failing hearts

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In an animal study, researchers at the University of Washington show that it was possible to use gene therapy to boost heart muscle function. The finding suggests that it might be possible to use this approach to treat patients whose hearts have been weakened by heart attacks and other heart conditions.

Led by University of Washington (UW) Professor and Vice Chair of Bioengineering Michael Regnier and Dr. Chuck Murry, director of the Center for Cardiovascular Biology and co-director of the Institute for Stem Cell and Regenerative Medicine at UW, the study appears online today in the journal *Proceedings of the National Academy of Sciences* (*PNAS*).

Normally, muscle contraction is powered by a molecule, the nucleotide called Adenosine-5'-triphosphate (ATP). Other naturally occurring nucleotides can also power muscle contraction, but, in most cases, they have proven to be less effective than ATP.

In an earlier study of isolated muscle, however, Regnier, Murry and colleagues had found that one naturally occurring molecule, called 2 deoxy-ATP (dATP), was actually more effective than ATP in powering muscle contraction, increasing both the speed and force of the contraction, at least over the short-term.

In the new *PNAS* study, the researchers wanted to see whether this effect could be sustained. To do this, they used genetic engineering to create a strain of mice whose cells produced higher-than-normal levels of an

enzyme called Ribonucleotide Reductase, which converts the precursor of ATP, adenosine-5'-diphosphate or ADP, to dADP, which, in turn, is rapidly converted to dATP.

"This fundamental discovery, that dATP can act as a 'super-fuel' for the contractile machinery of the heart, or myofilaments, opens up the possibility to treat a variety of heart failure conditions," Regnier said. "An exciting aspect of this study and our ongoing work is that a relatively small increase in dATP in the heart cells has a big effect on heart performance."

The researchers found that increased production of the enzyme Ribonucleotide Reductase increased the concentration of dATP within heart cells approximately tenfold, and even though this level was still less than one to two percent of the cell's total pool of ATP, the increase led to a sustained improvement in heart muscle function, with the genetically engineered hearts contracting more quickly and with greater force.

"It looks as though we may have stumbled on an important pathway that nature uses to regulate heart contractility," Murry added. "The same pathway that heart cells use to make the building blocks for DNA during embryonic growth makes dATP to supercharge contraction when the adult heart is mechanically stressed."

Importantly, the elevated dATP effect was achieved without imposing additional metabolic demands on the cells, suggesting the modification would not harm the cell's functioning over the long-term.

The finding, the authors write, suggest that treatments that elevate dATP levels in heart cells may prove to be an effective treatment for heart failure.

Provided by University of Washington