Faulty cell membrane repair causes heart disease

July 3 2007

During vigorous exercise, heart muscle cells take a beating. In fact, some of those cells rupture, and if not for a repair process capable of resealing cell membranes, those cells would die and cause heart damage (cardiomyopathy).

Researchers at the University of Iowa Roy J. and Lucille A. Carver College of Medicine have discovered a specific repair mechanism in heart muscle and identified a protein called dysferlin that is critical for resealing heart muscle cell membranes.

The study, led by UI researcher and Howard Hughes Medical Institute investigator Kevin Campbell, Ph.D., also shows that loss of dysferlin causes cardiomyopathy in mice. Furthermore, heart damage in these mice is exaggerated by vigorous exercise or by inherent muscle weakness caused by a muscular dystrophy defect. The results are published in the July 1 issue of the *Journal of Clinical Investigation*.

Active tissues, like a beating heart or contracting muscle, need mechanisms to repair the inevitable cell membrane tears caused by physical stress and strain. In 2003, Campbell and his colleagues identified dysferlin as a key protein in this vital repair mechanism in skeletal muscle. In humans, dysferlin deficiency -- which leads to faulty muscle membrane repair -- causes three types of muscular dystrophy.

The new study expands knowledge of dysferlin function, showing that dysferlin-mediated membrane repair is also important in heart muscle

cells and suggests that inadequate membrane repair can also lead to cardiomyopathy.

"If we could boost this repair mechanism, it might be possible to slow cardiac and skeletal muscle damage in muscular dystrophy patients," said Campbell who also holds the Roy J. Carver Biomedical Research Chair in Molecular Physiology and is head of the department and a UI professor of neurology.

The UI team initially found that young mice that lacked dysferlin showed no heart damage, which is consistent with what is seen in humans with dysferlin mutations. However, a case study describing late-onset cardiomyopathy in a Japanese patient with a dysferlin deficiency prompted the UI team to look at the mice as they aged.

They found that the mice started to develop cardiomyopathy at about one year of age (middle aged for a mouse). The team also found that exercise exaggerated the stress-induced injury in these mice, suggesting that inadequate membrane repair led to cardiomyopathy.

The research team also bred mice that lacked both dysferlin and the protein dystrophin, which is missing in patients with Duchenne muscular dystrophy. These "double knockout" mice had early onset cardiomyopathy, which was much more severe than in mice with either of the single mutations. The results suggest that dysferlin might provide some protection against heart damage in Duchenne patients, at least at a young age, by delaying the onset of cardiomyopathy.

"We hope these findings will stimulate clinicians to look at the cardiac health of muscular dystrophy patients and the overall muscle health of patients with cardiomyopathy," Campbell said.

Source: University of Iowa