Inhibiting CaMKII enzyme activity could lead to new therapies for heart disease

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University of Iowa researchers have previously shown that an enzyme called CaM kinase II plays a pivotal role in the death of heart cells following a heart attack or other conditions that damage or stress heart muscle. Loss of beating heart cells is generally permanent and leads to heart failure, a serious, debilitating condition that affects 5.8 million people in the United States.

Now the UI team, led by Mark Anderson, M.D., Ph.D., professor and head of internal medicine at the UI Carver College of Medicine, has honed in on how CaM kinase II triggers heart cell death following heart damage, showing that the action takes place in the cells' energy-producing mitochondria. In animal tests, the team reports that blocking the enzyme can prevent heart cells from dying, and protects the animals from heart failure.

Mitochondrial are the cells' batteries, generating the energy cells need to work. In heart cells, energy produced by these small cellular components fuels each heartbeat. However, when the heart is stressed, for example during a heart attack, the mitochondria become leaky and non-functional, which triggers cell death and heart failure.

"We found that activity of the CaM kinase II enzyme in mitochondria promotes cell death when the heart is stressed," says Mei-ling Joiner, Ph.D., UI assistant professor of internal medicine and lead author of the study, which was published online Oct. 10 in the journal *Nature*. "The findings might help us advance treatment of heart diseases and reduce

mortality after a heart attack."

The new study shows that activated CaM kinase II promotes leakiness of mitochondria and increases heart muscle damage by allowing too much calcium to enter mitochondria. Specifically, the UI team found that CaM kinase II regulates calcium entry into mitochondria by modifying a special mitochondrial calcium channel. Too much enzyme activity increased the amount of calcium flowing into mitochondria, and this calcium overload triggers cell death.

Using genetically modified mice, the team also showed that inhibiting CaM kinase II activity in mitochondria prevented the calcium overloading, reduced mitochondrial disruption, and protected the mice from heart cell death during heart attack.

These findings provide insight into molecular mechanisms for mitochondrial function and suggest that inhibiting the CaM kinase II enzyme in mitochondria could lead to new and more effective therapies for common forms of heart disease.

"Because mitochondria also play important roles in other diseases in brain and skeletal muscle, for example, our findings could also have broad implications for understanding and treating non-cardiac diseases," says Anderson, who also is director of the UI Cardiovascular Research Center.

Provided by University of Iowa