Enzyme weakens the heart

February 17 2009

An enzyme makes the mouse heart prone to chronic cardiac insufficiency - if it is suppressed, the heart remains strong despite increased stress. Cardiologists at the Internal Medicine Clinic at Heidelberg University Hospital in cooperation with scientists at the University of Texas Southwestern Medical Center at Dallas and Göttingen University Hospital have now explained this key mechanism in a mouse model and thus discovered a promising approach for the systematic prevention of chronic cardiac insufficiency. The study has now been published online before print in the prestigious journal *Proceedings of the National Academy of Sciences*.

Long-term high pressure and stenoses of the valves or aorta make the heart work harder. When it compensates by excessive muscle growth (cardiac hypertrophy), the pump function is affected - rhythm disorders or heart failure can be the result. Other risk factors are overweight and age - more than 40 percent of people over age 70 suffer from cardiac muscle hypertrophy.

Despite progress in medication, around 95,000 people in Germany die annually from the consequences of chronic cardiac insufficiency. "It is essential to find the molecules that are key to the development of cardiac insufficiency in order to develop new, more efficient treatment" states Dr. Johannes Backs, head of a research group in the Department of Cardiology, Angiology, and Pneumonology (Director Prof. Dr. med. Hugo A. Katus) at Heidelberg University Hospital.

Enzyme activates stress response and hypertrophy of

the heart

A key molecule for cardiac hypertrophy brought on by stress is the naturally occurring enzyme CaMKII delta (Calcium/Calmodulin-dependent kinase II delta). Dr. Backs' international research team proved this in genetically modified mice that could no longer produce this enzyme by surgically obstructing the main aorta to put the heart under greater stress and thus simulate permanent high blood pressure or valve stenosis in humans. The anticipated enlargement of the heart was very slight - the animals were protected.

"With these mice, we succeeded for the first time in specifically suppressing the CaMKII delta enzyme and clarifying its function in detail," said Dr. Backs. CaMKII delta has a direct effect on the cells' stress response. If it is missing, certain information in cell DNA is not accessed that is normally activated by stress, leading to hypertrophy of the heart. "There was still some slight enlargement of the heart, but presumably not enough to cause cardiac insufficiency," said Dr. Backs. Under normal conditions, the genetically modified mice are inconspicuous - their hearts function and react normally.

The function of CaMKII delta as an intermediate of the heart's stress response is a possible approach for effective therapy - the Heidelberg researchers anticipate that agents that block only this function of the enzyme would prevent the heart muscle from reacting to overload. Other functions of CaMKII delta should not be affected in order to avoid harmful side effects.

More information: Backs J, Backs T, Neef S, Kreusser MM, Lehmann LH, Patrick DM, Grueter CE, Qi X, Richardson JA, Hill JA, Katus HA, Bassel-Duby R, Maier LS, Olson EN. The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. *Proc Natl Acad Sci USA*. 2009 Jan 28. [Epub ahead of

print]

Source: University Hospital Heidelberg