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Researchers Pinpoint Genetic Cause of Heart Failure

Howard Hughes Medical Institute researchers have discovered how an inherited disorder triggers heart failure by disrupting the flow of calcium in heart muscle cells.

The researchers say that the finding could lead to targeted treatment for dilated cardiomyopathy, a disorder that causes the heart to become enlarged to the point where it can no longer pump blood efficiently. Although the discovery was made during studies of an inherited form of heart failure, the researchers suggest that this molecular defect may help explain other forms of heart failure - an emerging epidemic that affects 4.7 million Americans and costs \$17.8 billion annually.

In an article published in the February 28, 2003, issue of the journal *Science*, HHMI investigators Christine E. Seidman and Jonathan G. Seidman and their colleagues showed that a defect in the gene that encodes the protein phospholamban could cause dilated cardiomyopathy in humans. The Seidmans collaborated with scientists from Harvard Medical School, Brigham and Women's Hospital in Boston, the University of Toronto and the University of Cincinnati.

There are two basic forms of cardiomyopathies—disorders that affect the contractile ability of the heart. Hypertrophic cardiomyopathy causes thickening of the left ventricular wall, reducing its pumping ability. Dilated cardiomyopathy involves a stretching of the left ventricle, which reduces the heart's pumping strength. In either case, the inherited heart defects often cause early death. When underlying mutations, such as those observed in cardiomyopathies, are coupled with coronary artery disease, the results can be disastrous, say the researchers.

“Before our work, it was thought that calcium dysregulation might be involved in dilated cardiomyopathy, but it was uncertain whether this was contributing to myocyte dysfunction (i.e., an inciting event) or a secondary consequence, and that is a big difference,” said Christine Seidman.

The heart muscle is triggered to contract and relax by a mechanism in which calcium is released from a reservoir into the muscle cell, or myocyte, and

then rapidly pumped back into the reservoir, called the sarcoplasmic reticulum. According to Christine Seidman, phospholamban is a key regulatory molecule in the calcium reuptake pump.

In the process of studying the calcium regulation machinery, the Seidmans and their colleagues discovered that a sample group of people with inherited dilated cardiomyopathy—which often proves lethal in a person's 20s or 30s—showed a subtle mutation in the DNA sequence of the gene for phospholamban.

To explore whether this mutation could cause the disease Joachim Schmitt, a fellow in the Seidman lab, created a transgenic mouse with the corresponding phospholamban genetic defect. Analyses of the mutant transgenic mouse was facilitated by the previous work of co-author Evangelia G. Kranias of the University of Cincinnati. She had produced a transgenic mouse expressing normal (wildtype) phospholamban with normal cardiac structure and function and excellent survival.

“Substituting only one amino acid in phospholamban produced profound changes in cardiac function, causing a premature death of the mice with evidence of heart failure that recapitulates what we saw in our human families,” said Christine Seidman.

Further studies using cell cultures as well as tissue from affected people revealed in detail how the abnormal phospholamban disrupts the calcium pump in heart muscle cells. Specifically, the scientists found that the mutant form effectively “traps” a key enzyme necessary for the function of the normal phospholamban protein. Normal phospholamban is found in individuals with dilated cardiomyopathy, since they usually possess only one abnormal copy of the phospholamban gene.

The Seidmans and their colleagues found that affected individuals would suffer a chronic malfunction of calcium regulation in their heart muscle, which ultimately would lead to heart failure.

Previously known inherited defects underlying dilated cardiomyopathy affected muscle proteins, said Christine Seidman. However, the latest findings by the Seidmans and their colleagues suggest a second major mechanism.

“We believe these findings point to defects in this recycling of calcium—which do not allow the myocyte to fully relax. These can lead to profoundly devastating consequences,” she said. More generally, she said, the discovery hints that there may be more mechanisms of heart failure that are yet to be discovered.

“This finding provides evidence that all heart failure is unlikely to occur by the same pathogenic mechanism,” she said. “Unfortunately there are many

ways a heart can die.” However, these different etiologies may trigger the same signals; calcium dysregulation appears to be one of the important signals that causes myocyte death. According to Christine Seidman, such findings will likely have important implications for treatment.

“Our treatment of heart failure is, in this day and age, relatively non-specific,” she said. “The kind of molecular dissection of the cause of heart failure that we have done leads us to ask whether—if we can restore normal calcium cycling in this type of defect—can we prevent heart failure? The hope is that the answer will be yes.

“There are pieces of this puzzle that are starting to come together to fit a profile of a group of patients who we think would very much benefit from modulating calcium homeostasis in heart cells,” said Christine Seidman.

Additional research might well reveal that defects in calcium cycling could underlie some forms of hypertrophic cardiomyopathy, which are believed to be a very different type of failure in the contractile apparatus, said Christine Seidman.

A major route for further research, Seidman said, will be to follow the effects of mutant phospholamban “downstream” in the cell machinery to discover how that defect ultimately leads to the death of the myocyte. That type of search could lead to significant drug targets for treating heart failure in general, she said. “While these inherited cardiomyopathies are rare disorders, I think they teach us so much about the biology of the system that is relevant to a broader population,” said Seidman.