Protein changes in heart strengthen link between Alzheimer's disease and chronic heart failure

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A team of U.S., Canadian and Italian scientists led by researchers at Johns Hopkins report evidence from studies in animals and humans supporting a link between Alzheimer's disease and chronic heart failure, two of the 10 leading causes of death in the United States.

The international team of biochemists and cardiologists say they have identified three changes in the chemical make-up of a key structural protein, called desmin, in heart muscle cells in dogs. The changes led to the formation of debris-like protein clusters, or amyloid-like oligomers containing desmin, in heart muscle, similar to the amyloid plaques seen in the brain tissue of Alzheimer's patients. The protein alterations, which were reversed by surgically repairing the heart, occurred at the onset of heart failure. Further experiments by the Hopkins scientists found the same chemical modifications to desmin in the heart muscle in four people already diagnosed with the disease.

Misshaped desmin proteins and amyloid-like debris had been previously reported in 2005 in mice genetically altered to develop chronic heart failure, providing the first biological link between the two chronic diseases. Studies since have also reported desmin changes in failing animal hearts, but none detailed what the chemical changes were or how they might affect organ function.

Researchers say their latest analysis, to be presented Nov. 15 at the

American Heart Association's (AHA) annual Scientific Sessions in Orlando, is believed to be the first to tie common underlying structural changes in desmin to malformations observed in the heart as it weakens, strains to pump blood and starts to fail. Their results are also believed to be the first to suggest that toxic, desmin-like amyloids could form in response to stress placed on the heart.

"Our study leads us to believe that desmin plays a key role in heart failure," says lead study investigator and protein biochemist Giulio Agnetti, Ph.D. "Now we have a chemical target to research further and help us investigate what could be the underlying biological cause of heart failure and if it is like Alzheimer's, an amyloid-related disease."

"Just as significantly, our study raises the prospect of testing new treatment options for heart failure by moving beyond treating symptoms of the disease and getting to the root of the matter, preventing these desmin amyloids from forming and impairing heart function from the start," says Agnetti, a postdoctoral research fellow at both the Johns Hopkins University School of Medicine and its Heart and Vascular Institute, and the University of Bologna and its National Institute for Cardiovascular Research, in Italy. Symptoms of heart failure may include fatigue, shortness of breath and enlargement of the heart.

Agnetti's work has been recognized at the heart meeting, where he is a finalist for the inaugural Functional Genomics and Translational Biology Council's Young Investigator Award.

The team's latest investigation began with an analysis of proteins contained in heart tissue samples collected from a group of dogs whose hearts had been surgically altered to beat irregularly, become stressed and fail. Additional tissue samples were taken from another group of healthy controls.

Researchers compared these samples, looking for structural and chemical changes in desmin, which is found in all heart muscle cells and is a key component of the intermediate filaments that make up the scaffolding, or muscle cell support structure. They say this is the same muscle structure that becomes disorganized in heart failure.

The team's analysis yielded at least three chemical differences in each desmin protein in response to heart failure. Further tests showed that phosphate molecules had attached at two spots within the protein's structure. They also found accumulating amyloid-like debris, containing desmin, in the damaged heart tissue.

When researchers performed surgery restoring the dogs' heart pumping function to normal, they found phosphorylated sites mostly reverted to normal. The amlyoid-like oligomers also began to disappear. Tissue samples from four people with heart failure showed similar desmin modifications.

Senior study investigator Jennifer Van Eyk, Ph.D., says that it is "not surprising" these changes in the so-called "scaffolding" structure of the heart can produce toxic debris. "But what is most interesting about our findings is that we have shown that these chemical changes and debris are related to impaired heart function, which, ultimately, may explain how and why the heart can fail," says Van Eyk, a Johns Hopkins professor and director of Hopkins' NHLBI Proteomics Group and the Proteomics Center at Johns Hopkins Bayview Medical Center, where the protein analysis took place.

Researchers next plan to analyze each of the desmin modifications to determine the subsequent biological impact of each chemical change.

Agnetti points out that the team's protein analysis was only made possible in the last 15 years, and with the development of technologies

for detailed chemical analysis, such mass spectrometry and gel electrophoresis. Previously, he says, scientists had mostly focused on genetic changes and their relationship to disease, as opposed to disease-causing alterations to proteins that occur after proteins are made.

Source: Johns Hopkins Medical Institutions