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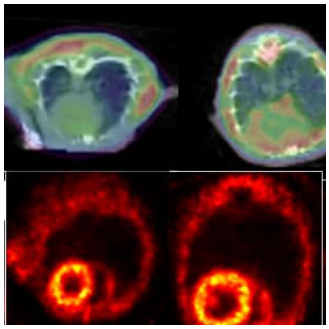
Heart failure: the Alzheimer's disease of the heart?



Desmin is a protein found in the cell's "skeleton," or supporting structure, and is known as intermediate filaments. New Johns Hopkins-led research shows desmin protein clumps appear to accumulate in the diseased hearts of mice and people with heart failure. The mechanism is similar to how protein clumps build up in the brain in people with some neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, according to research published in the journal Circulation Research.

"From a molecular standpoint there's not a unified, clear mechanism for why the heart goes into failure," says Giulio Agnetti, PhD, assistant professor of medicine at the Johns Hopkins University School of Medicine and University of Bologna. "But by figuring out this mechanism, we may be able to devise better treatments and diagnostic tools."

Current drugs used to treat heart failure — such as those that lower blood pressure by relaxing blood vessels — reduce stress on the heart and symptoms associated with heart failure without necessarily fixing the underlying cause. Once the heart fails to pump, the only treatment in the end is a heart transplant.

In a previous study (2014), Agnetti's team found that the protein desmin accumulates in clumps called amyloid in the hearts of dogs with heart failure. Why desmin clumps in diseased heart cells isn't known, Agnetti says.

To see if desmin protein clumps are also found in human heart failure, the researchers studied the proteins from heart tissue biopsies from people with or without heart failure. They used a fluorescent antibody commonly used in Alzheimer's disease research and a new fluorescent stain for amyloid developed by Agnetti to visualise and quantify the desmin protein clumps. They observed twice as many desmin clumps in heart failure patients than those without heart failure.

The team used a common mouse model of heart failure to look for desmin clumps. In this model, the aorta — the main artery coming from the heart — is surgically constricted, which noticeably raises pressure and stress, and causes heart failure. After four weeks of pressure on the aorta, the mice develop symptoms of heart failure such as an enlarged heart and lung congestion. Desmin amyloid was more than doubled in the heart failure mice when using the same antibody and staining techniques used for the human tissue samples.

Then the researchers treated proteins from the mice hearts with epigallocatechin gallate (EGCG) — a chemical from green tea known to break up amyloid. The treatment cut by half the amount of protein clumps.

"Interestingly, green tea has already been demonstrated to curb the incidence of cardiovascular disease as well as improve cognitive impairment in Alzheimer's models, though the mechanism for such action is unclear," notes Agnetti. "EGCG's ability to 'de-clump' these sticky proteins could be one of green tea's healthy effects. Knowing how this chemical works could open new avenues for designing a new class of drugs that target protein clumping."

Agnetti learned from Richard O'Brien, MD, PhD, a former Johns Hopkins neuroscientist now at Duke University, that positron emission tomography (PET) is used to detect protein clumps in the brains of Alzheimer's and Parkinson's disease patients and can detect the clumps in certain genetic heart conditions that cause excessive protein clump formation. Following O'Brien's advice, the researchers tested if they could use this noninvasive technique to detect desmin clumps in mice with heart failure. Healthy and heart failure mice were injected with Amyvid, a radioactive dye that allows the researchers to see the protein clumps by PET. The heart failure mice had 13 percent more of the Amyvid taken up in their hearts than the healthy mice.

"PET imaging of protein clumps may be eventually used in patients to identify structural changes in the heart as the disease progresses, and this information likely holds prognostic value," says Peter Rainer, MD, PhD, a former postdoctoral fellow at Johns Hopkins who is now at the Medical University of Graz in Austria. "It could be used as a nice measure of the effect of an intervention to halt or reverse disease progression."

In future experiments, Agnetti's team plans to confirm its results in more human tissue samples. The team also hope to identify a drug or small molecule to prevent desmin from forming clumps.

Source: Circulation Research
Image Credit: Circulation Research

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