Cellular pathway of genetic heart disease similar to neurodegenerative disease

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Research on a genetic heart disease has uncovered a new and unexpected mechanism for heart failure. This landmark discovery found a correlation between the clumping of RNA-binding proteins—long linked to neurodegenerative disease—and the aggregates of protein found in the heart tissue of patients with RBM20 dilated cardiomyopathy.

Dilated cardiomyopathy is a disease of the heart muscle that makes it harder for the heart to pump blood to the rest of the body. A decade ago, Timothy Olson, M.D., a pediatric cardiologist at Mayo Clinic, traced the disease to a genetic mutation in a gene called RBM20. Unlike most heart disease, this form of cardiomyopathy can affect patients as early as young adulthood, and they are at particularly high risk for sudden cardiac death.

For the past decade, heart failure in RBM20 cardiomyopathy was attributed to abnormalities in the splicing of genes for proteins that help the heart contract. However, the new discovery finds another way that mutant RBM20 damages heart muscle cells: through accumulation of pathological ribonucleoprotein granules, affecting everything in the cells and leading to a new form of disease.

"It's important to realize that there are kids and young adults that have heart failure because of this exact mutation," says Tim Nelson, M.D., Ph.D., director of Mayo Clinic's Todd and Karen Wanek Family Program for Hypoplastic Left Heart Syndrome and lead author of the study. "We have taken these findings back into the lab and developed cell cultures to test new therapeutics. The future of this research is focused on moving discoveries out of the lab and into clinical trials to make new therapies available to our patients. This research is a very important catalytic step to do that."

Through gene editing technology, Dr. Nelson's team produced the first large animal model displaying all the typical clinical signs and symptoms of human heart failure: a pig born with the human gene for RBM20 dilated cardiomyopathy. This model allowed them to study development of the heart disease in the animal in a matter of months. It takes 20 years or more for the disease to progress in humans.

A simple staining test performed on the pig heart tissue samples discovered clumps full of RNA-binding protein. Archived tissue samples from Dr. Olson's RBM20 dilated cardiomyopathy human patient tissue confirmed this discovery. They were likewise flooded with the same protein granules. This supports a new concept that beyond splicing caused by the gene mutation, RBM20 is an RNA-binding protein granule disease similar to diseases like Lou Gehrig's disease, or amyotrophic lateral sclerosis, and Alzheimer's disease.

"To my knowledge, this overload of protein granules in cells has only previously been seen in the brain or spinal cord, and some very rare skeletal muscle diseases. Now we have found it in the heart, a large organ that is much more accessible to study than spinal neurons or brain tissue. Most importantly, we can study and develop therapies to prevent the buildup of these toxic granules at the beginning of life instead of waiting 50 years or more for degenerative disease to appear clinically. This is a huge advantage that should accelerate drug discovery in ribonucleoprotein granule degenerative diseases of the heart and nervous system," says Jay Schneider, M.D., Ph.D., a Mayo Clinic cardiologist and first author of the study.

Provided by Mayo Clinic