New study uncovers mechanisms underlying how diabetes damages the heart

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Lead author Mugé Kuyumcu-Martinez, Ph.D. Credit: The University of Texas Medical Branch at Galveston

Cardiac complications are the number one cause of death among diabetics. Now a team of scientists has uncovered a molecular mechanism involved in a common form of heart damage found in people with diabetes.

A research team from The University of Texas Medical Branch at Galveston in collaboration with Baylor College of Medicine, University of California San Diego and the University of Texas at Dallas have published their findings the journal *Cell Reports*.

People with diabetes have a two to five time higher risk of developing cardiovascular diseases. For decades physicians have noticed unhealthy changes in the hearts of diabetics called diabetic cardiomyopathy, which is a disorder of the heart muscle that can lead to heart failure.

The molecular mechanisms responsible for this cardiac disorder are poorly understood, although they are key to revealing new targets for the discovery of better treatments and development of more accurate diagnostics.

RNA provides the blueprint for making the protein building blocks of cells. The RNA is cut or spliced to generate mRNA used to build proteins. RNA splicing mistakes are associated with many human diseases because they lead to production of the wrong or harmful proteins.

The research team has previously shown that splicing is incorrectly regulated and levels of the splicing regulator RBFOX2 are elevated in diabetic heart tissue. The current study sought to further investigate how RBFOX2 regulation contributes to splicing defects seen in diabetic hearts and the consequences of splicing changes on cardiac function.

The UTMB-led study found that RBFOX2 binds to 73 percent of the RNA that are mis-spliced in diabetic heart tissues. This alternative splicing was found to impair normal gene expression patterns in the heart, especially genes important for molecular metabolism, programmed cell death, protein trafficking and calcium handling in heart muscle tissue. Calcium balance is important in regulating a heartbeat.

"We discovered that RBFOX2 function is disrupted in diabetic hearts before cardiac complications are noticeable and RBFOX2 dysregulation contributes to abnormal calcium signaling in the heart," said N. Muge Kuyumcu-Martinez, lead author and UTMB assistant professor in the department of biochemistry and molecular biology. "Identifying RBFOX2 as an important contributor to diabetic complications and learning how it is dysregulated may allow us to develop new tools to diagnose, prevent or treat diabetic cardiomyopathy in the future."

Provided by University of Texas Medical Branch at Galveston