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Researchers ID key drivers of heart complications in sickle cell anemia

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Patients with sickle cell anemia (SCA) develop heart complications and nearly a quarter die a sudden death. Now, researchers have linked malfunctioning molecular pathways to specific heart anomalies in SCA that result from progressive fibrosis and result in sudden death.

In a study published online this week by *PNAS* (*Proceedings of the National Academy of Sciences*), researchers at Cincinnati Children's Hospital Medical Center report their findings open a path to earlier non-invasive diagnosis and development of new targeted therapies to help SCA patients live longer with better quality of life

The researchers used a mouse model of SCA to identify a unique "restrictive cardiomyopathy" that is superimposed on the anemia-associated heart enlargement. They also found upregulated gene expression that fuels heart fibrosis and harmful electrophysiological changes.

"Sickle Cell Anemia is associated with significant morbidity and mortality, including a high incidence of unexplained sudden death in young adults," said Punam Malik, MD, senior author and director of the Comprehensive Sickle Cell Program at Cincinnati Children's. "Our findings may provide a unifying cardiac pathophysiology that explains reported cardiac abnormalities and sudden death seen in humans with SCA."

SCA is an inherited disease initially triggered by a mutation of the β-

globin gene. It causes blood cells to lose their round donut-like shape and acquire a sharp sickled shape. The sickled cells get stuck and clog in the circulatory system, creating a high risk for infection and leading to organ damage.

The study - a broad collaboration between researchers in the Cancer and Blood Diseases Institute and the Heart Institute at Cincinnati Children's - used mice bred to have SCA mimicking the human version of the disease.

The SCA mice underwent serial comprehensive cardiac analysis, including the detailed cardiac imaging (MRI), electrocardiography, microscopic cross-section analysis of heart tissues (histopathology and electron microscopy). The researchers also conducted transcriptome analysis, which provided a blueprint of messenger RNA molecules expressed in the genes of mouse heart tissues. They compared the SCA mice to mice with chronic anemia to find pathologies specific to sickle cell anemia.

Transcriptome analyses identified upregulated genes that cause increased oxidation, hypoxia and fibrosis in heart tissues. It also showed a down regulation of genes associated with electrophysiological function. The researchers observed these traits in SCA mice shortly before a significant number of the animals experienced sudden death.

Using a variety of genetic knockout mice, researchers continue to study the molecular mechanisms and pathways that trigger heart fibrosis in SCA. The project is a collaboration including Cincinnati Children's colleagues, Charles Quinn, MD, Theodosia A. Kalfa, MD, PhD (Division of Hematology), and Jeffrey Towbin, Jeanne James, MD, and Michael Taylor MD (Heart Institute). Malik said identification of these pathways will allow development of new targeted therapies to treat cardiac dysfunction in people with SCA.

The extensive non-invasive cardiac imaging techniques used successfully in the current study have prompted Quinn, Taylor and Niss to launch a clinical trial to proactively test these early diagnostic techniques on people with SCA. Enrollment for that study has just concluded, Malik said. Earlier detection of widespread heart fibrosis with MRI would allow earlier medical intervention while the disease process is potentially reversible.

"It is incredibly exciting to see that this work has inspired clinical trials and other research studies," said Nihal Bakeer, MD, study first author, a former hematology/oncology fellow in Malik's lab and now a pediatric hematologist at the Indiana Hemophilia and Thrombosis Center in Indianapolis. "Our goal has always been one and one only: find the underling pathobiology of cardiac complications in sickle cell anemia and help find new diagnostics and therapeutics to decrease the morbidity and rate of sudden cardiac death in young adults with SCA."

More information: Nihal Bakeer et al, Sickle cell anemia mice develop a unique cardiomyopathy with restrictive physiology, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1600311113

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