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Study identifies a developmental cause of cardiac hypertrophy

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Investigators at Beth Israel Deaconess Medical Center (BIDMC) have identified a developmental cause of adult-onset cardiac hypertrophy, a dangerous thickening of the heart muscle that can lead to heart failure and death. Reported online in *The Journal of Clinical Investigation*, the new findings could lead to targeted therapies for this condition.

"Genetic mutations that alter signaling pathways involved in cardiac development have been implicated in approximately 30 percent of birth defects associated with congenital heart disease," explained Maria Kontaridis, PhD, Interim Director of Basic Cardiovascular Research in the CardioVascular Institute at BIDMC and Assistant Professor of Medicine at Harvard Medical School. "In this study, we wanted to determine whether these same genetic mutations can also lead to the development of cardiac hypertrophy in adults."

Work in the Kontaridis lab focuses on a cluster of genetic diseases known as RASopathies, which impact the Ras/MAPK cell signaling pathway and affect the growth and differentiation of cells. One of these diseases, Noonan Syndrome with Multiple Lentigines (NSML), is a rare condition caused primarily by mutations in the gene PTPN11. NSML has multiple phenotypic characteristics, including short stature, growth retardation, and craniofacial abnormalities, but the most prevalent defects affect the heart, the most common of which is cardiac hypertrophy.

By creating NSML mice that expressed the PTPN11 mutation, the

scientists were able to gain important insights into what causes congenital heart disease and how these defects lead to hypertrophy.

"In this study, we observed that there were significant developmental abnormalities in hearts affected by NSML," explained Kontaridis. "We wanted to figure out if the adult-onset cardiac hypertrophy we observed might be caused by abnormal regulation of one or more of the critical cell populations necessary for growth and development of the heart."

Cardiac development consists of a sequential order of events that are controlled by intercellular communication between three critical cell populations, which become the heart's endocardium, myocardium and neural crest regions. Carefully orchestrated cross-talk between these cell populations culminates in a fully functional heart. Multiple cell signaling pathways regulate these complex developmental events, but when these pathways are disrupted, communication breaks down, leading to various cardiac defects.

"Our experiments unexpectedly revealed that hypertrophy was caused by abnormal cell signaling mechanisms originating from developing endocardium—not the myocardium, as had been long assumed," said Kontaridis.

Experiments with mice expressing the genetic mutation only in the cells destined to give rise to the endocardium showed that as these mice aged, they developed hypertrophic cardiomyopathy. Mice with mutations in the myocardial- or neural crest- regions did not show signs of associated hypertrophy, definitively identifying the endocardium as the source of hypertrophy in NSML.

"This was the first time we were able to trace the cause of an adult-onset hypertrophic disease to abnormal development, and specifically to a disruption in critical endocardial to myocardial cell 'crosstalk,'"

explained Kontaridis.

"These findings not only tell us that there are developmental components to NSML that we can potentially target therapeutically, but also suggest that we can start to think about what the signaling differences may be between this RASopathy and other RASopathy disorders that cause similar but different cardiac defects," said Kontaridis. "More important, we can consider these same approaches when thinking about treating other, more common, congenital hypertrophy disorders."

Provided by Beth Israel Deaconess Medical Center

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