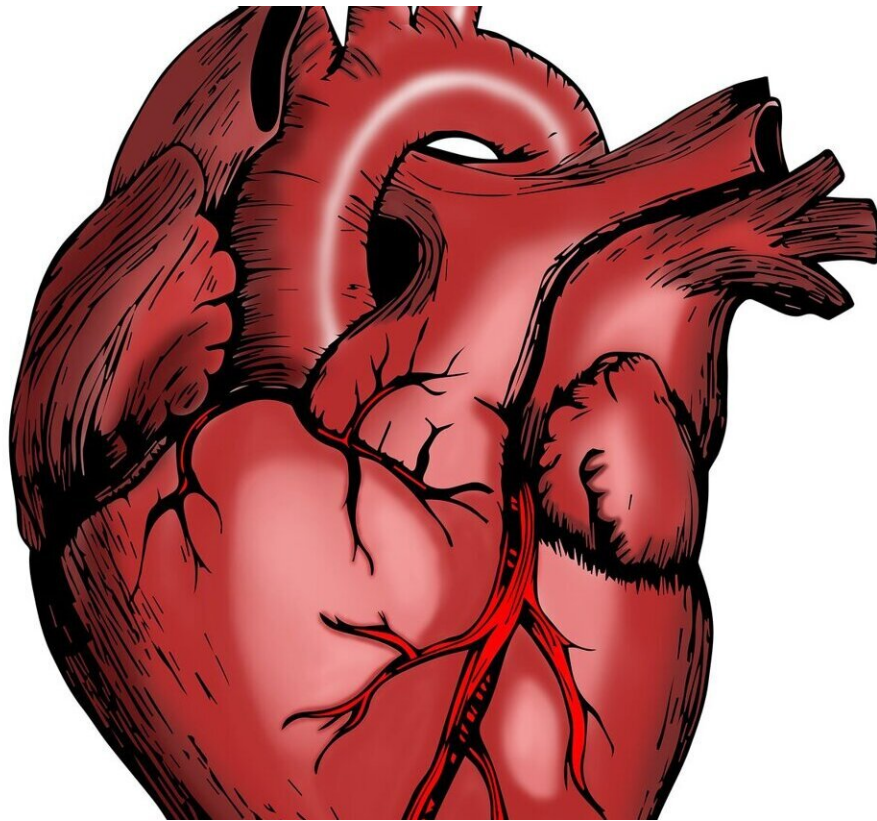


# Study finds two protein pathways downregulated in postnatal heart

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In work published today in *Stem Cell Reports*, researchers from the University of Minnesota Medical School discovered two signaling pathways that are downregulated in human hearts after birth. These

pathways, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)–AKT, lead to maturation of heart cells, allowing them to adapt functionally to their postnatal role. The researchers showed that manipulating these pathways enabled better outcomes in experiments to generate cardiac myocytes, the beating cells of the heart, in vitro from pluripotent stem cells.

Heart disease is one of the leading causes of death worldwide, partially because the adult human heart does not have any heart stem cells allowing it to regenerate after damage. Induced [pluripotent stem cells](#), which are undifferentiated human stem cells derived by reprogramming of adult cells and typically cells from skin tissue, can be made to differentiate into [cardiac myocytes](#) in vitro, but they preferentially make immature versions of these cells. This essentially makes fetal-type cells rather than post-natal cardiomyocytes. The inability to generate mature cardiomyocytes has hindered the development of cell therapy for [heart disease](#) as well as the generation of cells for the in vitro study of cardiac physiology and toxicology.

"The last decade has seen an explosion in research to produce human cardiac myocytes from pluripotent stem cells," said Bayardo Garay, a graduate student in the Medical Scientist Training Program. "Our study advances these efforts by providing a practical way to generate cells that are relevant to [human disease](#)."

To discover these two pathways, the investigators mined previously published genomic data on cardiomyocytes from different stages of development. "Maturation of stem cell-derived somatic cells in a dish is difficult to achieve, but is critical for the generation of human in vitro models of health and disease," said Brenda Ogle, Ph.D., Professor and Head of the Department of Biomedical Engineering and director of the Stem Cell Institute. "This work cleverly utilizes existing data to identify novel pathways that control cardiomyocyte maturation and that can be

easily manipulated with small molecules to accelerate cardiomyocyte maturation."

Researchers conclude that suppression of the MAPK and PI3K–AKT pathways on in vitro-derived human cardiomyocytes for only five days results in enhanced maturity in many domains. According to the study's corresponding author, Rita Perlingeiro, Ph.D., of the Cardiology Division/Department of Medicine, "this multidisciplinary work is the fruit of the university's investment in collaborative science, and brings the [cells](#) we can produce in the lab significantly closer to being clinically relevant to cardiac disease in humans."

**More information:** Bayardo I. Garay et al, Dual inhibition of MAPK and PI3K/AKT pathways enhances maturation of human iPSC-derived cardiomyocytes, *Stem Cell Reports* (2022). [DOI: 10.1016/j.stemcr.2022.07.003](#)

Provided by University of Minnesota Medical School

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