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Researchers develop method to advance maturation of human pluripotent stem cell-derived heart cells

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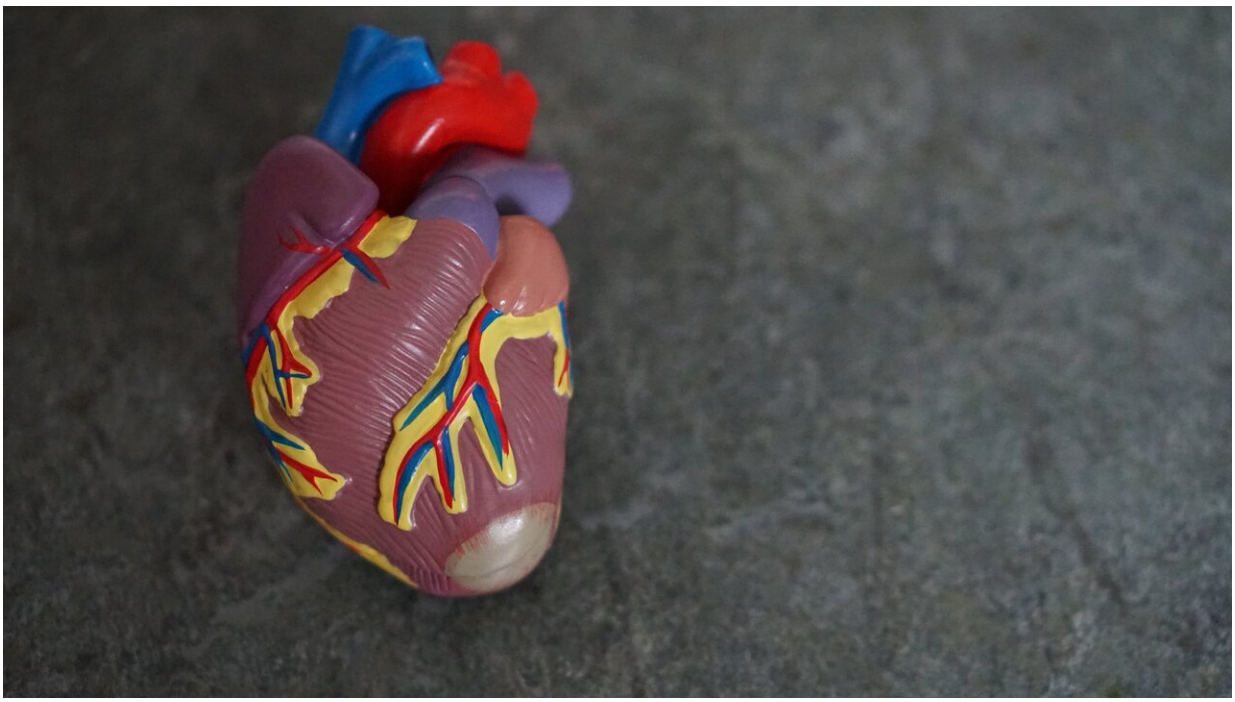

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A Mount Sinai-led team has developed a reproducible and scalable method to advance maturation of human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs)—cells that support heart muscle contraction, generated in the lab from human stem cell lines—which

researchers say will improve approaches for disease modeling, regenerative therapies, and drug testing. A study reporting this new protocol was published in the April 7 print edition of the journal *Cell Stem Cell*.

Mount Sinai researchers investigated multiple metabolic modifications in hPSC-CMs. The research team also identified the role of the protein known as peroxisome proliferator activated receptor delta (PPARd) in inducing what is referred to as the metabolic switch in the lab-generated heart muscle cells. This metabolic switch is a critical part of the maturation process of the heart.

"This work will create exciting opportunities to further assess human heart biology through multi-disciplinary approaches incorporating developmental biology, transcriptomics, contractile measurements and drug testing," said senior author Nicole C. Dubois, Ph.D., Associate Professor of Cell, Developmental and Regenerative Biology at the Black Family Stem Cell Institute and The Mindich Child Health and Development Institute at the Icahn School of Medicine at Mount Sinai. "Our findings provide a new avenue to generate mature hPSC-CMs for disease modeling and regenerative therapy. We are moving a step closer to understanding how to leverage our knowledge of human development to improved access to mature human cell types."

In the study, the researchers activated different signaling pathways *in vitro* to replicate the metabolic changes that would occur during heart development in the organism. They found that PPARd induces the metabolic switch from glycolysis to fatty acid oxidation in the lab setting, thus influencing whether heart muscle cells generate energy from glucose or fatty acids. While the signaling effects of the protein peroxisome proliferator activated receptor alpha (PPARa) are the most active in heart muscle cells, the researchers said PPARd signaling has a separate and important role in efficiently activating the gene regulatory

networks, increasing the quantity and organization of the organelles involved in energy production, and augmenting the fatty acid oxidation process. The activation of signaling regulated by PPARd can further enhance heart muscle cell size and organization, and improve contractility, all hallmarks of heart maturation.

The research team also investigated the effects of lactate exposure, where heart muscle cells are able to survive on lactate in the absence of glucose. This is frequently used to enrich hPSC-CMs. The researchers found that this method can induce an independent mechanism of cardiac maturation, and when combined with PPARd, it enhances oxidative metabolism, allowing for efficient energy generation from both carbohydrates and fatty acids. This study allowed for a detailed analysis into the long-term effects of a commonly used protocol in the heart muscle field.

In collaboration with the Ma'ayan lab at Mount Sinai, the group has generated a comprehensive and publicly accessible dataset which details the transcriptomic changes observed by the Mount Sinai-led team. This dataset allows researchers studying either PPAR-regulated signaling or lactate selection to rapidly assess future targets for research or drug testing.

More information: PPARdelta activation induces metabolic and contractile maturation of human pluripotent stem-cell-derived cardiomyocytes, *Cell Stem Cell* (2022). doi.org/10.1016/j.stem.2022.02.011

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