Study elucidates mechanism behind cardiac fibrosis, opening way for new heart failure treatments

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Aortic Pressure Gradients and B-mode speckle tracking on transgenic mice. Credit: Nature Cardiovascular Research (2024). DOI: 10.1038/s44161-024-00502-3

Cardiovascular disease often culminates in heart failure, a hallmark of
which is fibrosis, a form of tissue scarring. Cardiac fibrosis initially repairs damaged heart tissue, but it can quickly become excessive and pathological. Identifying the mechanisms behind fibrosis is a focal point in cardiovascular research, and now scientists at the Lewis Katz School of Medicine at Temple University have discovered a critical genetic mechanism driving the process—and they have identified a novel target for reversing it.

"In pathological fibrosis, resident fibroblasts in the heart that are activated by tissue injury differentiate into myofibroblasts that then produce and secrete excessive extracellular matrix," explained John W. Elrod, Ph.D., Director of the Aging + Cardiovascular Discovery Center (ACDC) and Professor of Cardiovascular Sciences at the Katz School of Medicine, and senior investigator on the new study.

"Fibroblast activation often depends on transforming growth factor-β (TGFβ), and we now show for the first time that TGFβ increases the enzyme ATP-citrate lyase (ACLY), which localizes to the cell nucleus and interacts at specific sites on genes to epigenetically drive and maintain fibrosis."

Dr. Elrod's team further found that inhibition of ACLY prevents myofibroblast formation and activation of epigenetic sites. The discovery marks ACLY as a novel therapeutic target for the reversal of fibrosis. The team described their findings in a paper published online in the journal Nature Cardiovascular Research.

The new work builds on previous observations from Dr. Elrod's laboratory, particularly their prior discovery of a signaling pathway that promotes myofibroblast formation via histone demethylation. Histone demethylation is an epigenetic modification involved in gene transcription and related processes that regulate the flow of genetic information in cells. The team's earlier research also demonstrated that
inhibiting a metabolic pathway known as glutaminolysis can reverse myofibroblast-mediated fibrosis in an epigenetic-dependent fashion.

ACLY is a key component of the latest research by Dr. Elrod and colleagues, owing to the link between glutaminolysis, metabolite levels, and acetyl-CoA biosynthesis. ACLY also is known to sustain histone acetylation, which influences processes that determine cell fate. In the new study, Dr. Elrod's team, led by MD/Ph.D. graduate student Michael P. Lazaropoulos, set out to better understand the involvement of ACLY and, more specifically, the role of histone acetylation in regulating the fate of myofibroblasts.

Nuclear ACLY activity is essential to TGFβ-dependent myofibroblast activation.
In initial experiments carried out in cardiac fibroblasts isolated from mice, the researchers demonstrated that ACLY is necessary for myofibroblast differentiation and that its inhibition reverses the pro-fibrotic phenotype of myofibroblasts, reverting the cells to a less pathogenic state.

Employing a novel genetic system that enabled simultaneous gene deletion and protein tracking, they then showed that ACLY translocates to the cell nucleus, where it interacts with a transcription factor known as SMAD. Aided by SMAD, ACLY is directed to locations within the genome where its involvement in histone acetylation facilitates fibrosis.

"We found that ACLY binding to SMAD allows ACLY to localize to specific genetic loci, where it then locks in genetic programming that promotes myofibroblast formation and a fibrotic phenotype," Dr. Elrod explained.

Dr. Elrod's team further showed that ACLY inhibition reverses myofibroblast fate, enabling cells to change back to a non-disease phenotype. This was demonstrated in mouse cardiac fibroblasts and in cardiac fibroblasts isolated from human heart failure patients. ACLY was inhibited experimentally in two ways, including by a pharmacological intervention and by a genetic disruption.

"Because of these observations, we can confidently say that epigenetic mechanisms involving acetylation are essential to maintaining the fibrotic process in heart cells," Dr. Elrod said. "We also now have a target—ACLY—to reverse fibrosis, based on our studies in animal cells.
and cells from human patients."

Dr. Elrod hopes next to advance the translational impact of the new findings by investigating pharmacological agents capable of inhibiting ACLY. "One of the agents we used in our experiments has been investigated in clinical trials for other applications," he noted. In addition to exploring therapeutic avenues, his team also plans on expanding their findings to other diseases involving pathological fibrosis.

**More information:** Michael P. Lazaropoulos et al, Nuclear ATP-citrate lyase regulates chromatin-dependent activation and maintenance of the myofibroblast gene program, *Nature Cardiovascular Research* (2024). [DOI: 10.1038/s44161-024-00502-3](https://doi.org/10.1038/s44161-024-00502-3)

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