A change of heart? Cellular reprogramming reverses fibrosis after heart attack

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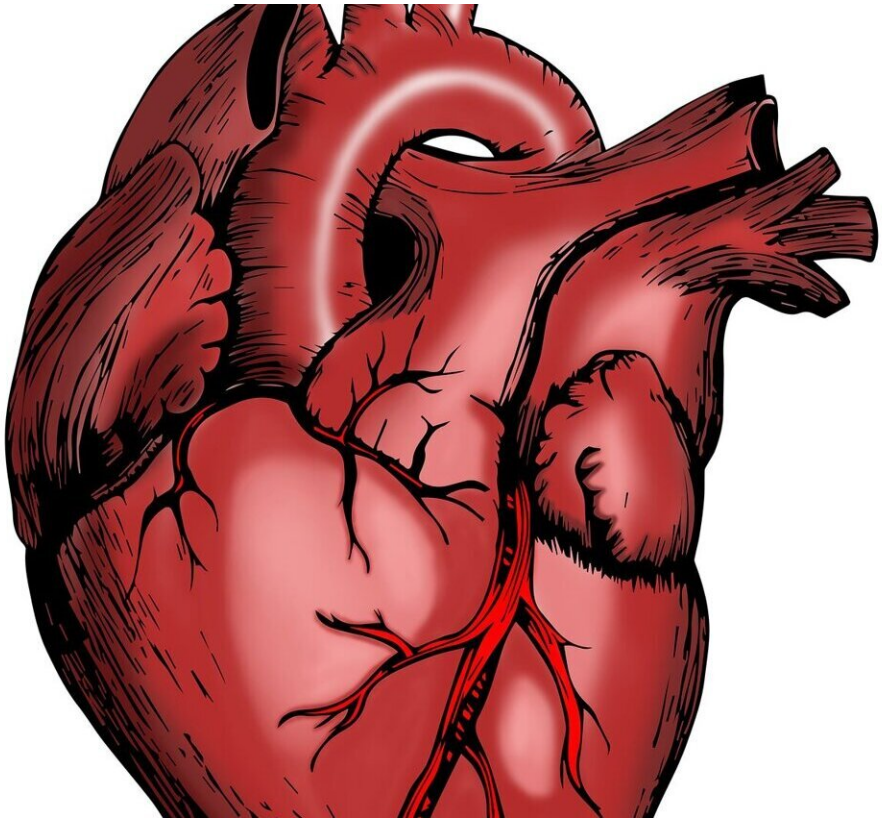

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Researchers from Japan reveal that they may just have found a way to repair cardiac damage in patients suffering from chronic heart attack and heart failure.

In a study published in *Circulation*, researchers from the University of Tsukuba have shown that changing heart cell programming by tweaking the expression of a few key genes can actually reverse the lasting damage caused by heart attacks.

Adult heart cells have very limited ability to form new heart tissue, so when the heart muscle is damaged by a heart attack, the damaged areas are filled in with inflexible scar tissue. The presence of scar tissue impairs heart function and leads to arrhythmias, progressive heart failure and eventual death.

"Previous studies have shown that reprogramming cardiac fibroblasts (CFs), the cell type that generates scar tissue, into cardiomyocytes (CMs), or normal heart muscle cells, can improve cardiac function in the context of acute myocardial infarction," says Professor Masaki Ieda, the senior author of the study. "However, it was unclear whether cardiac reprogramming could restore function in a damaged heart with established scars."

To explore this possibility, the researchers created a mouse model in which treatment with a medication called tamoxifen would activate the overexpression of cardiac transcription factors, including a gene called Mef2c/Gata4/Tbx5/Hand2 (MGTH), to reprogram CFs into CMs. They then induced heart attacks in the mice and, one month later, treated the mice with tamoxifen to activate the cell-type change and determine its effect on the heart.

"The results were very clear," states Professor Ieda. "In these mice, cardiac reprogramming converted ~2% of resident CFs into CMs, significantly improved myocardial contraction, and reduced fibrosis."

Detailed genetic analysis showed that overexpression of MGTH activated the rebuilding of heart muscle and suppressed scar tissue

formation and inflammation. Importantly, this approach not only prevented the formation of additional scar tissue, but also reversed the formation of established scar tissue.

"Our findings show that cardiac reprogramming can repair the lasting damage caused by heart attack by regenerating heart muscle and reducing harmful fibrosis," explains Professor Ieda.

Given that there are few effective clinical therapies available for patients who have experienced a heart attack, this direct cardiac reprogramming approach could be a promising new treatment. Regenerating heart tissue and reversing scarring could not only improve heart function in these patients, but also decrease the risk of death from heart failure. These results open a promising avenue of research to actualize this treatment for patients.

The article, "Direct reprogramming improves cardiac function and reverses fibrosis in chronic myocardial infarction," was published in *Circulation*.

More information: Hidenori Tani et al, Direct Reprogramming Improves Cardiac Function and Reverses Fibrosis in Chronic Myocardial Infarction, *Circulation* (2022). DOI: 10.1161/CIRCULATIONAHA.121.058655

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