REGENERATIVE MEDICINE

TREE-based gene therapy boosts cardiac repair in mice

Yan, R., Cigliola, V. et al. *Cell Stem Cell* **30**, 96–111 (2023)

Myocardial infarction (MI) is a leading cause of death worldwide due to the inability of the adult human heart to regenerate after injury. As a result, many researchers are investigating the possibility of using approaches such as gene therapy to improve the heart's regenerative capacity. In a new study published in *Cell Stem Cell*, Ken Poss and colleagues describe a new gene-therapy strategy based on the use of short DNA sequences isolated from zebrafish to target mammalian hearts after MI and deliver pro-regenerative factors.

The capacity for cardiac regeneration differs between species, being high in teleost fish, and almost negligible in mammals after the neonatal period. In a 2016 study, Poss and colleagues identified small regulatory elements involved in the tissue regeneration program of the zebrafish. They showed that these genomic sequences, which they termed tissue regeneration enhancer elements (TREEs), could induce expression of their target genes at injury sites, and reduce gene expression as regeneration concludes. The investigators also demonstrated that TREE-based systems could be used to spatiotemporally target gene expression to injury sites in transgenic zebrafish and improve regenerative responses.

Here, Poss and colleagues utilized an adeno-associated virus (AAV)-based approach to deliver TREE-based systems to mice. They showed that zebrafish TREE constructs could direct the expression of a reporter gene (EGFP) to the MI border zone in injured murine cardiac tissue when delivered pre- or post-MI. EGFP expression was prevalent in the MI border zone, with little or no expression detected in distal areas or uninjured hearts, opening up the possibility of safe, targeted gene therapy in injured tissues. TREEs were further validated in a pig model of ischemia-reperfusion MI, where reporter gene expression was also detected in the injury border zone.

Next, the investigators designed AAV vectors in which TREE was used to direct the expression of yes-associated protein 1 (YAP) with an activating mutation – a version of the protein previously shown to promote cardiomyocyte proliferation in mice – in injured cardiac mouse tissues. TREE-based YAP delivery boosted indicators of cardiac regeneration and improved heart function after MI.

Altogether these results show that zebrafish TREEs have broad cross-species effects and that TREE-based systems can be delivered noninvasively to target gene expression to cardiac injury sites in mammals. "Our study provides a foundation for new gene-therapy approaches to improve tissue repair in disease settings," explain the investigators in their report.

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