Intervening during scar process could help cardiac patients, reviewers say

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Literal heartbreak, from illness or injury, triggers the body's natural healing mechanisms. The result of such mending is often a scar. It's a patch that works, but fibrotic scar tissue replaces healthy heart muscle, a problem that has led scientists across the world to ponder ways to modify the wound-healing process for the benefit of patients.

An international team of researchers from the Virginia Tech Carilion Research Institute and the Universities of Frankfurt and Freiberg in Germany recently published a review paper online in *Nature Reviews Drug Discovery* - one of the highest ranked journals in medical research - that summarizes the potential therapeutic promise of targeting the non-muscle cells in the heart responsible for cardiac scarring. The study is now online and will appear in print in August.

"After disease or injury, the adult mammalian heart repairs by forming a scar, while other classes of vertebrates such as amphibians and fish can regenerate injured cardiac tissue," said Rob Gourdie, the director of the Virginia Tech Carilion Research Institute's Center for Heart and Regenerative Medicine and an author of the paper. "Understanding the molecular difference between scarring and regeneration might help us develop treatments for heart disease in humans."

Annually, more than 600,000 Americans are hospitalized or die from their first heart attack. Of the more than half that survive, 280,000 people will have at least one more coronary event. According the American Heart Association, the annual financial burden of heart

disease is $180 billion.

"Heart disease is the leading cause of sickness and death in the developed world," Gourdie said. "The central problem in heart disease is loss of cardiac muscle and its replacement with fibrotic non-muscle tissue."

Fibroblasts, the cells responsible for connecting cardiac muscle, make up the fibrotic tissue. Fibroblasts support the walls of the heart in health, but they can thicken and scar in disease, hindering the heart's ability to contract effectively and pump blood throughout the body, including to the heart muscle itself and the brain.

"Utilizing the natural reparative processes of fibroblasts to modify properties of the forming cardiac scar is quietly emerging as an exciting therapeutic avenue," said Gourdie, who is also a professor at the Virginia Tech-Wake Forest University School of Biomedical Engineering and Sciences and a professor of emergency medicine at the Virginia Tech Carilion School of Medicine.

In a related vein, some scientists are attempting to use sophisticated gene therapies to reprogram fibroblasts into different types of adult cells, such as a muscle cells, providing another path to a future way to treat heart disease.

Fibroblasts were once thought to simply be the glue holding together cardiac tissue, but now researchers are discovering the complex and active roles these cells play in maintaining the structure and operation of the heart.

In a healthy heart, fibroblasts are actually the main type of cell that forms and maintains the connective tissue. The fibroblasts secrete molecules that comprise the extracellular matrix, which acts as

scaffolding for the entire heart.

"The concept that fibroblasts link together to form a cardiac sub-system of equal importance to the network of cardiac muscle cells should inform our approach to targeting or even using the connective cells in therapies for heart disease," Gourdie said.

Equally significant, Gourdie noted, is to fully understand the mechanisms underlying communication between cardiac cells. Such knowledge could lead to the development of cell-specific therapeutic delivery systems, among other critical tools to strategically reprogram cell types.

"The topic reviewed in this paper is immensely important for evolving strategies to treat diseases that are routinely viewed as hopeless, from common ailments like advanced heart failure, to rare but deadly ones like muscular dystrophy," said Eduardo Marbán, the director of Cedars-Sinai Heart Institute. Marbán, who has both a medical degree and a doctorate, was not involved in this review.

A more complete understanding of how cells communicate during and after damage may eventually lead to therapeutic applications for a wide range of diseases and disorders. It's an admirable aim, and perhaps researchers can start to make a difference for patients now.

"In the meantime, the more modest goal of modifying scar tissue for patient benefit seems to be a useful tangible objective," Gourdie said. "Perhaps we can therapeutically nudge or re-engineer the scarring process to improve clinical outcomes for people with heart disease."

More information: Robert G. Gourdie et al. Novel therapeutic strategies targeting fibroblasts and fibrosis in heart disease, *Nature Reviews Drug Discovery* (2016). DOI: 10.1038/nrd.2016.89

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