Long Noncoding RNA Molecules May Be Targets for Cardiac Fibrosis

Research indicates that the majority of the noncoding genome is actively transcribed, generating thousands of small and long regulatory non-coding RNAs that play important roles in numerous cell types. Now investigators have provided a specific example of how 1 such regulatory noncoding RNA might be harnessed to improve cardiovascular health.

In a Science Translational Medicine article, a team led by scientists at the University of Lausanne Medical School in Switzerland report that a long noncoding RNA (lncRNA) called Wisper is highly abundant in cardiac fibroblasts, the culprits behind fibrotic scar formation, and that depleting the molecule can protect heart function and decrease scarring after myocardial infarction in mice. Experiments in both culture and mouse models of heart injury revealed that Wisper controls various molecules involved in proscarring pathways in cardiac fibroblasts.

When the investigators analyzed human tissue, they found a 57% identical lncRNA within the human genome, which they dubbed WISPER. Furthermore, in heart biopsy samples from human patients with aortic stenosis, WISPER levels correlated with fibrosis severity. Also, the lncRNAs effects on scarring were specific to cardiac cells and not fibroblasts from other tissue types. For example, both the heart and kidney develop severe fibrosis, but Wisper is only induced in the heart.

“For the first time, we have identified a therapeutic target that is highly specific to both the heart and fibroblasts within the heart, allowing the direct modulation of cardiac fibrosis with unprecedented specificity,” said coauthor Samir Ounzain, PhD.

Additional studies are needed to determine whether cardiac fibroblast-specific lncRNAs such as WISPER may be promising therapeutic targets for cardiac fibrosis and heart failure. Also, because it is possible to detect lncRNAs in human plasma, measuring circulating concentrations of molecules such as WISPER might provide a noninvasive means to monitor certain aspects of cardiovascular health.

“Cardiac fibrosis is now emerging as a critical process to tackle therapeutically, and sadly no current therapies exist. Our therapeutic target offers an unprecedented opportunity to tackle this issue in a highly specific manner,” said Dr. Ounzain.


Enhancing Mitochondrial Calcium Efflux: A Promising Treatment for Heart Disease

New research published in Nature shows for the first time that mitochondrial calcium overload is a key contributor to myocyte death in the heart after myocardial infarction and also a driver of heart failure development and progression. Calcium signaling in mitochondria is critical for numerous cellular processes, such as energy production, but its role in cardiovascular health and disease is unclear. To search for clues, a team led by John Elrod, PhD, from Temple...
University in Philadelphia has been studying the main pathway by which calcium exits the mitochondria—the mitochondrial sodium–calcium exchanger (NCLX)—in the heart.

The scientists used different genetic strategies to either delete the NCLX gene or overexpress NCLX specifically in the heart cells of adult mice. Studying these models revealed that mitochondrial calcium exchange is critical for cardiac function because loss of the efflux pathway resulted in calcium overload of the mitochondria and rampant cell death in the heart, leading to heart failure and sudden death of the animals. Enhancement of the efflux pathway (through overexpression of NCLX) was sufficient to reduce cell death during simulated heart attacks and also delayed the progression of heart failure after myocardial infarction.

The next step is to uncover more details about the control of NCLX in the heart. “The goal is to sufficiently understand its regulation so that we can develop therapeutic strategies to increase NCLX function or activity,” said Dr. Elrod. “Given the prevalence of calcium dysregulation and mitochondrial dysfunction in numerous disease states—heart failure, neurodegeneration, stroke, heart attack, the list goes on—we see modulating mitochondrial calcium exchange as an exciting clinical target.”


Protein Restores Heart Regeneration in Mice

Investigators from the Weizmann Institute of Science in Israel have discovered that a molecule in the extracellular matrix of newborn hearts promotes regeneration and repair after heart damage. The molecule, termed Agrin, is expressed during embryonic development but is no longer produced after birth. Agrin was already known for its effects on the communication from nerve to muscle in the neuromuscular junction during embryogenesis.

“When injected into adult hearts of mice that underwent myocardial infarction, Agrin appears to ‘unlock’ a regenerative process that enables the repair of the heart muscle,” said Eldad Tzahor, PhD, senior author of the Nature study. The treatment significantly reduced scar tissue, which was replaced by living heart tissue.

In vitro experiments indicated that Agrin promotes the division of cardiomyocytes through a mechanism that involves the disassembly of the dystrophin glycoprotein complex, which has both mechanical stabilizing and signaling roles for cardiac and skeletal muscle cells and their surroundings.

In addition to promoting cardiomyocyte renewal, Agrin may also affect inflammatory and immune responses to a heart attack, as well as pathways involved in suppressing fibrosis. The molecule likely triggers processes that continue long after it has disappeared. Agrin is retained in the heart for 3 days, but its regenerative effect occurs 3 to 5 weeks after injury.

“These findings have highlighted a role for the extracellular matrix in both directing heart growth and promoting regeneration, and this insight may help in the design of novel treatments for heart disease in humans,” said Prof. Tzahor.


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Tracy Hampton

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