

Study provides new insights into the role of aging in heart failure

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A team led by Massachusetts General Hospital (MGH) investigators has

found that activity of an important signaling pathway increases with aging and with heart failure. In their report published in *Science Translational Medicine*, they describe evidence from both humans and animal models that increased activin type II receptor (ActRII) activity correlates with worsening heart failure and that inhibiting ActRII can improve cardiac function in mouse models.

"Age has long been recognized as one of the major, if not the dominant, risk factor for [heart disease](#), but why is not well known," says Jason Roh, MD, of the Corrigan Minehan Heart Center at MGH, lead author of the report. "Our findings suggest that the ActRII pathway plays a major role in the intersection between aging and heart disease and that inhibiting it could offer much-needed new treatment strategies for [heart failure](#), a deadly disease that is also the number one cause of hospitalization for older adults."

The ActRII pathway is a complex one in which multiple circulating proteins bind to ActRII receptors, eliciting [molecular signals](#) important for functions ranging from muscle growth to reproduction. Its potential role in aging and heart failure has been controversial, since levels of some ActRII ligands—molecules that bind to the receptor—have been found to decrease with aging, while others increase. The MGH-led team looked at levels of the major ActRII ligands and other biomarkers of overall pathway activation and found evidence in both [human patients](#) and mouse models of heart failure that ActRII activity increases in aging and heart failure.

Additional experiments found that levels of the signaling molecule activin A were three times higher in aged mice compared to younger mice and that increasing circulating activin A levels led to cardiac dysfunction in young mice. Conversely, ActRII inhibition improved cardiac function in several mouse models of heart failure. The investigators also found that increased ActRII signaling leads to the

breakdown of SERCA2a, a critical protein involved in the regulation of [cardiac function](#), which is known to decline in both aging and heart failure.

"Previous studies have shown that increasing SERCA2a levels can improve the function of the failing heart," says Roh, an instructor in Medicine at Harvard Medical School (HMS). "Based on our findings, we believe that over-activation of ActRII signaling leads to increased breakdown of SERCA2a in cardiac muscle and that inhibiting ActRII may offer a new strategy for increasing SERCA2a protein levels in the failing heart." In fact, by using several ActRII inhibitors that are currently being tested in humans for other indications, the investigators found that inhibiting this pathway in animal models of heart failure dramatically increased the function of the failing heart.

Senior and corresponding author Anthony Rosenzweig, MD, chief of the MGH Division of Cardiology, says, "It is becoming increasingly clear that the ActRII pathway is involved in many of the chronic diseases associated with aging—such as heart failure, muscle loss, and neurovascular diseases. The results of this study need to be validated in larger animal models before being tested in human heart failure; and since the ActRII pathway is so complex, we need to develop ways of rigorously determining how the various components change in the context of aging and disease."

He adds, "Even though we have some treatments for heart failure, the overall prognosis is poor for many patients, and the number of patients we are seeing with heart failure is increasing rapidly due to the ageing of our population. So finding new approaches to treating [heart](#) failure has important public health implications for the future." Rosenzweig is the Evelyn and James Jenks and Paul Dudley White Professor of Medicine in the Field of Cardiology at HMS.

More information: J.D. Roh et al., "Activin type II receptor signaling in cardiac aging and heart failure," *Science Translational Medicine* (2019). [stm.sciencemag.org/lookup/doi/ ... scitranslmed.aau8680](https://stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.aau8680)

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