CARDIOVASCULAR DISEASE

ActRII takes centre stage in heart failure

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With ageing populations worldwide, the prevalence of heart failure (HF) is increasing while prognosis remains poor. New research presents the activin type II receptor (ActRII) as a catabolic link between ageing and HF and shows that inhibition of this receptor improves cardiac function in mouse models.

Previous studies have provided conflicting results on the role of ActRII signalling in HF pathophysiology. The receptor has several endogenous ligands — including activin A, growth and differentiation factor 8 (GDF8) and GDF11 — which can exist in various forms with different biological activity, hampering efforts to study overall pathway activity.

FSTL3 is upregulated by the major ActRII ligands and is itself a downstream regulator of ActRII activity. In the current study, Roh et al. measured serum levels of FSTL3 as a proxy indicator of ActRII activity.

In a plasma proteomics analysis of 899 individuals from the Framingham Heart Study, circulating FSTL3 levels increased with ageing. In a separate cohort of 50 adults, plasma levels of FSTL3 and activins correlated with worsening HF. Moreover, frail individuals (defined by slow walk speed and weak handgrip) had higher FSTL3. These findings suggested that activin-driven ActRII signalling increases with ageing and HF.

Next, the authors examined ActRII signalling in mouse models. In aged (28-month-old) C57BL/6 mice, an established model of cardiac ageing, circulating activin A concentrations were threefold higher than in 4-month-old mice. Cardiac FSTL3 expression was also higher in the aged mice. In a transverse aortic constriction (TAC) model of left ventricular pressure overload, plasma levels of activin A, cardiac FSTL3 expression and ActRII activity were elevated compared with controls.

To directly assess the effects of increased ActRII signalling, Roh et al. injected young mice with recombinant adenoviral vectors encoding activin A (Ad.activin A). The intervention increased ActRII signalling compared with controls, as indicated by phosphorylation of SMAD3 (a downstream target of ActRII signalling), and impaired cardiac function. Similar effects on cardiac function were observed in aged mice treated with recombinant GDF11.

Next, the researchers examined the effects of inhibiting ActRII signalling. They used an ActRII-targeted monoclonal antibody called bimagrumab, which has struggled in mid-stage clinical testing for muscle-wasting diseases but remains in phase II trials for type 2 diabetes.

Subcutaneous injection of a murinized version of bimagrumab in aged mice blocked cardiac ActRII signalling, reduced pulmonary congestion and improved left ventricular systolic function. In a transgenic mouse model of dilated cardiomyopathy, weekly injections of bimagrumab significantly improved left ventricular fractional shortening.

Further, in a more severe model of systolic HF induced by TAC, treatment with bimagrumab substantially improved systolic cardiac function, even when initiated after fractional shortening had declined to 45% of baseline. The treatment also attenuated pathological gene expression profiles and improved survival.

The authors next sought to determine whether the beneficial effects of bimagrumab were mediated at the level of the cardiomyocyte. They generated cardiomyocyte-specific knockouts of ActRII subtype B and found these mice to be substantially protected from systolic dysfunction after TAC, suggesting an important part for cardiomyocyte ActRII in pathophysiological signalling.

Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a) is a key Ca^{2+} pump within cardiomyocytes that has a central role in regulating excitation–contraction coupling. Roh et al. found that cardiac levels of SERCA2a protein were reduced in mice treated with GDF11. Moreover, Ad.activin A-treated mice had reduced cardiac SERCA2a levels in association with impairments to cardiomyocyte function and Ca^{2+} cycling. Conversely, bimagrumab treatment increased SERCA2a protein in aged mice and TAC models. Evidence in rat ventricular myocytes suggested activin–ActRII signalling might increase proteasomal degradation of SERCA2a.

Further studies on the potential of ActRII as a therapeutic target in HF are warranted, and the researchers say they are currently in discussions with pharmaceutical companies that make inhibitors of the pathway to explore the possibility of moving the current research into clinical trials in HF.

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