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THE CARDIAC ENHANCER RNA CHHEAF PRESERVES HEART FUNCTION DURING STRESS ADAPTATION VIA RTN4-DEPENDENT AUTOPHAGY

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Cardiac hypertrophy is an adaptive response to pressure overload that can progress to heart failure, yet the epigenetic mechanisms coordinating this transition remain incompletely understood [1]. Here we identify a cardiomyocyte-specific long non-coding RNA, Chheaf, as a key regulator of the early stress response. Chheaf is rapidly induced in adult cardiomyocytes following pressure overload and is functionally conserved in humans. Loss of Chheaf in mice accelerates cardiac dysfunction after transverse aortic constriction, accompanied by reduced expression of the anti-hypertrophic gene Rtn4 (Nogo-A) and impaired autophagy [2].
Mechanistically, Chheaf is a chromatin-associated enhancer RNA required to maintain active histone marks at the Chheaf–Rtn4 locus and to sustain Rtn4 transcription in response to stress. We show that Nkx2.5 directly activates Chheaf transcription, while Nkx2.5, and Gata4 cooperate at the Rtn4 locus to drive its expression. Chheaf interacts with Nkx2.5 and Gata4 and enhances their transcriptional activity, facilitating enhancer–promoter communication and promoting Rtn4 induction.
Together, our findings define a cardiomyocyte-specific Nkx2.5–Chheaf–Gata4 regulatory axis that controls enhancer-dependent activation of Rtn4 and protective autophagy during early cardiac hypertrophy. These results uncover a previously unrecognized lncRNA-mediated mechanism of cardiac stress adaptation and identify Chheaf as a potential therapeutic target in heart disease.

References

1. T. Thum, G. Condorelli, Long noncoding RNAs and microRNAs in cardiovascular pathophysiology. Circ Res 116, 751-762 (2015).
2. L. Sasset et al., Nogo-A reduces ceramide de novo biosynthesis to protect from heart failure. Cardiovasc Res 119, 506-519 (2023).