Dissecting the role of CNOT6L deadenylase in pressure overload-induced cardiac fibrosis

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Heart failure is a leading cause of death in developed countries. The role of mRNA regulation in the pathology of heart failure remains elusive. CCR4-NOT complex is a multi-subunit protein complex constituting exonuclease-mediated degradation of poly(A) tails of mRNA, a process called deadenylation. We had previously elucidated that CNOT3, a scaffold subunit of the CCR4-NOT complex, is a crucial regulator of heart function (*Cell* 2010, *Science Signaling* 2018). Here we analyzed the roles of deadenylase subunit in heart failure. After 2 weeks of transverse aortic constriction (TAC)-induced pressure overload, expression of CNOT6L deadenylase subunit was markedly upregulated in the hearts. Loss of CNOT6L significantly decreased cardiac contractility and enhanced fibrosis at 2 weeks after TAC. Analyses with transcriptome and CCR4-NOT RIP elucidated that CNOT6L targets mRNA of the GeneX, which stimulates tissue fibrosis. Double knockout of GeneX and CNOT6L improved cardiac fibrosis and dysfunction in single CNOT6 knockout mice. Our ongoing analyses are further elucidating cellular mechanisms for CNOT6L - GeneX axis in heart failure. Thus, CNOT6L deadenylase contributes to prevent progression of heart failure by suppressing expression of fibrotic geneX, implicating a potential therapeutic strategy of targeting mRNA deadenylation.