**Title: CELF1 Downregulates Cx43 mRNA in Dilated Cardiomyopathy**

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy. One of

the causes of mortality in DCM patients is arrhythmia-related death. Under pathological

conditions, reduced Cx43 expression is a hallmark of the transition from adaptive or compensatory stage to decompensation and heart failure. The regulatory mechanism controls the transition leading to reduced Cx43 expression is largely unknown, in particular the regulation at the posttranscriptional level. We showed that CELF1, a nuclear RNA-binding protein implicated in the cardiac pathogenesis of myotonic dystrophy, mediated Cx43 mRNA degradation. CELF1 bound to Cx43 RNA and interacted with an exoribonuclease RRP6 in an RNA-independent and nucleus specific manner. Increased CELF1 expression accompanied with RRP6 upregulation and downregulation of CELF1 mediated target genes including Cx43 was detected in mouse models of DCM including myocardial infarction (MI). Importantly, using a heart-specific Celf1 knockout mouse model we showed that Celf1 depletion in infarcted heart ameliorated the contractility dysfunction and preserved Cx43 mRNA level. The results not only demonstrate a pathogenic role for CELF1 in contributing to the Cx43 mRNA degradation during heart failure, also suggest increased CELF1 expression may be a common feature of DCM and CELF1 might be a potential therapeutic target in both acute and chronic heart failure.

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