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Title: EIF4G2 MEDIATES SPECIFIC MRNA TRANSLATIONAL CONTROL OF CARDIAC FIBROSIS

Abstract:
RNA-binding proteins mediate translational control of gene expression during TGFβ-driven fibrotic response in cardiac fibroblasts. Among them, eukaryotic translation initiation factor eIF4G2, a homolog of the canonical translation initiation factor eIF4G1, is crucial to facilitate an alternate form of mRNA translation upon various stresses. However, the role and mechanism of eIF4G2 in translation that eventually entail cardiac fibrosis remains poorly understood. Here, we show an increment of eIF4G2 protein in the hearts of human dilated cardiomyopathy patients and mice with myocardial infarction. eIF4G2 protein but not the mRNA level increases in TGFb-treated human and mouse cardiac fibroblasts. Upon eIF4G2 knockdown, the downregulated genes are more prominent in translational regulation than mRNA level changes and highly enriched in focal adhesion and extracellular matrix receptor interaction pathways as revealed by RNA-seq and polysome-seq analyses. We also show that eIF4G2 knockdown reduces the proliferation, migration, and collagen secretion of TGFb-treated cardiac fibroblast by downregulating the myofibroblast markers, including a-SMA and COL1A1 proteins, instead of mRNA level. When Eif4g2 is genetically knocked out in myofibroblasts in an inducible and conditional mouse model, a less severe cardiac fibrosis is evident in both myocardial-infarcted and isoproterenol-induced cardiac remodeling murine hearts, thus precludes cardiac dysfunction. Taken together, our work offers an imperative perspective of translational control-promoted cardiac fibrosis and provides mechanistic insights into eIF4G2 function in cardiac remodeling, facilitating the future development of novel anti-fibrotic therapy for the treatment of heart disease.