ABSTRACT

RBM10 is a well-known RNA binding protein involved in the regulation of alternative splicing and associated with various disease states. We have shown a splicing-independent function of RBM10 that regulates heart failure. This study reveals a new function of RBM10 phosphorylation by proto-oncogene cSrc that enables anti-hypertrophy gene program and controls cardiac hypertrophy. We confirm RBM10 phosphorylation at the three-tyrosine residues (Y81, Y500, and Y971) by cSrc in vitro and in the cell. We show that RBM10 phosphorylation is induced in cellular hypertrophy and animal heart model of cardiac hypertrophy and regulates target mRNA expression and 3′-end formation. Inhibition of cSrc kinase or mutation of the three-tyrosine phosphorylation sites to phenylalanine accentuates myocyte hypertrophy, and results in advancement and an early attainment of hypertrophy in the heart. RBM10 is down regulated in the hypertrophic myocyte and that its re-expression reverses cellular and molecular changes in the myocyte. However, in the absence of phosphorylation (cSrc inhibition or phospho-deficient mutation), restoration of endogenous RBM10 level in the hypertrophic heart or ectopic re-expression in vitro failed to reverse cardiomyocyte hypertrophy. Mechanistically, loss of RBM10 phosphorylation inhibits its nuclear localisation and interaction with Star-PAP compromising anti-hypertrophy gene expression. Thus, our study establishes that cSrc-mediated RBM10 phosphorylation arbitrates anti-hypertrophy gene program and controls cardiac hypertrophy. We also report a new functional regulation of RBM10 by phosphorylation that is poised to control heart failure.