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THE MAMMALIAN STE20-LIKE KINASE 2 (MST2), A CENTRAL MODULATOR OF THE HIPPO PATHWAY, MODULATES STRESS-INDUCED CARDIAC HYPERTROPHY

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Because of its key role in the development of heart failure, cardiac hypertrophy becomes one of the main focuses of current research. The Hippo signalling pathway has recently moved to centre stage in this field because of it plays major role in cardiomyocyte proliferation and regeneration of the embryonic and newborn heart. However, its role in remodelling of the adult heart is less clear. Here we use an integrative biology approach incorporating molecular, cellular, *in vivo* animal model and translational bench to bedside research to characterise the role of mammalian STE20-like kinase 2 (Mst2), one of the two mammalian orthologs of Drosophila *hippo,* in cardiac hypertrophy.

Mice with genetic ablation of Mst2 gene ($Mst2^{-/-}$) exhibited a significant reduction of hypertrophy in response to transverse aortic constriction (TAC): heart weight/tibia length ratio after 2 weeks TAC: $Mst2^{-/-}$, 7.32 mg/mm vs wild type (WT), 8.35 mg/mm, n=8, $P<0.05$. $Mst2^{-/-}$ mice showed a significant reduction of cardiac fibrosis, lower expression of hypertrophic markers (BNP and ANP) and better contractility (end systolic elastance) compared to

WT following TAC. Consistently, $Mst2^{-/-}$ mice showed reduce hypertrophy and fibrosis following chronic infusion with Angiotensin II. Interestingly, no alteration of cardiomyocyte proliferation was observed either basally or after TAC as indicated by phospho-Histone H3 staining. Mechanistically, we found that Mst2 interacted with Raf1 and activated the pro-hypertrophic Raf1-ERK1/2 pathway in cardiomyocytes. Mutation in the kinase domain of Mst2 (K56R mutation) abolished the ability to activate Raf1-ERK1/2 pathway. However, activation of the canonical downstream effectors of the Hippo pathway (LATS and YAP) were not affected by Mst2 ablation. Clinical implication of this finding was revealed as our initial genetic study in mitral valve prolapse patients showed an association between a polymorphism in the human Mst2 gene (+214G/A) and adverse cardiac remodelling: patients with homozygous G allele had larger LVmass than patients with GA or AA allele ($n=62$, $P<0.05$). Using cellular model we found that the polymorphism in patients with higher remodelling (+214GG) directed higher gene expression.

Our data shows that Mst2 regulates cardiac hypertrophy by modulating the Raf1-ERK1/2 pathway. It also provides evidence that Mst2 may play a major role in left ventricular remodelling in human heart disease, thereby revealing a potentially new therapeutic target.