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ANGIOTENSIN II TYPE 1 RECEPTOR MEDIATED CARDIOMYOCYTE AUTOPHAGY INDUCED BY MECHANICAL STRESS THROUGH P38 MAPK

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¹Li Lin, ²Yunzeng Zou. ¹Shanghai East Hospital; ²Zhongshan Hospital, Fudan University

Objectives This study is designated to investigate the mechanism involved in the mechanical stress induced-cardiomyocyte autophagy.

Methods We investigated the role of angiotensin II type 1 (AT1) receptor and mitogen-activated protein kinase (MAPK) in mechanical stress-induced autophagic response in cardiomyocytes. LC3b, a marker of autophagy, was detected by western blot analysis. In addition, mice were subjected to transverse aortic constriction (TAC) for 4 weeks to test the effect of autophagy.

Results After mechanical stretch stimulation (48 h), neonatal cardiomyocytes expressed hypertrophic responses and remarkable up-regulation of LC3b. While losartan, an AT1 receptor antagonist, not only attenuated cardiac hypertrophy but also abrogated up-regulation of LC3b induced by mechanical stresses. And treatment with PD123319, the AT2 receptor antagonist, did not reverse mechanical stress-induced autophagy. We also investigated the change of activity of MAPK pathway in the autophagy induced by mechanical stress. We found that the phosphorylation of ERK, JNK and p38 were significantly increased after stimulation compared with Control group. The increase of LC3b was significantly blocked by SB 203580, a p38 MAPK inhibitor. However, treatment with PD98059, an ERK inhibitor, or SP600125, a JNK inhibitor, did not abrogate the mechanical stress-induced autophagy. AT1 mediated autophagic and hypertrophic responses were also assessed in vivo. The expression of LC3b in left ventricular cardiomyocyte increased significantly in TAC-operated mice compared with that in sham-operated mice. And losartan significantly inhibited the up-regulation of LC3b induced by chronic pressure overload. Moreover, losartan also ameliorated cardiac remodelling and dysfunction induced by TAC after 4 weeks.

Conclusions The results indicate that autophagy in cardiomyocytes induced by mechanical stress is AT1 receptor-dependent, and is through p38 MAPK signal pathway.