Role of Autophagy in Cardiac Hypertrophy: An Insight into Use of Autophagy-Targeted Drugs

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Objective / Purpose: Cardiovascular diseases (CVD) are the leading cause of death in the world. The percentage of deaths due to CVD is equivalent to that due to cancer, COPD, diabetes and other non communicable diseases put together. Hypertension ranks among the first risk factors for CVD. Sustained hemodynamic load imposed by hypertension on the heart leads to cardiac remodeling. Hypertrophy is the first and foremost element in cardiac remodelling. Hypertrophy, even though an adaptive mechanism initially, leads to heart failure in the long run. Hence prevention of hypertrophy is a major therapeutic target. Autophagy is a cellular homeostatic process that involves lysosome-dependent turnover of organelles as well as proteins. Alterations in autophagy may occur in cardiac pathologies. Efforts to target autophagy selectively in the cardiac cells may be a logical step towards development of novel therapeutic strategies for the prevention of hypertrophy and thereby heart failure. In this backdrop, the main objective of the study was to determine the regulation of autophagy in hypertrophy using known inhibitors and activators of autophagy. Another objective is to test the effect of selected natural compounds on autophagy and determine the end outcome on hypertrophy.

Material and Methods: Hypertrophy was induced by exposing H9c2 cell lines (rat embryonic cardiomyoblasts) to β-adrenergic receptor agonist, isoproterenol (ISO). Evaluation of hypertrophy was carried out by analyzing the size of the cells using phase contrast microscopy and flow cytometry. Autophagy was assessed by confocal microscopy and flow cytometry utilizing a novel autophagy-specific dye. Rapamycin (RAP) and chloroquine (CHL) were used as activator and inhibitor of autophagy respectively. LC3B and LAMP2 protein markers of autophagy were detected by immunofluorescence microscopy and immunophenotyping. Lysosomal activity was also measured.

Results: ISO stimulation induced hypertrophying (27% increase in cell size) in H9c2 cell line. Autophagy was found to be significantly lower in ISO- stimulated cells when compared to control. RAP showed a heightened induction of autophagy in the cells. Surprisingly, in ISO+RAP cotreatment group, there was a robust induction of autophagy which was significantly higher than that of other groups. CHL and ISO+ CHL groups showed negligible autophagy when compared to other groups. In ISO+RAP, the heightened autophagy induction well correlated with increased hypertrophying of the cells ($p \leq 0.05$). There was a proportional increase in granularity with increase in cell size as well. Lysosomal activity was significantly higher for ISO even though it demonstrated lower autophagic activity. In addition, increased autophagic activity correlated with increased lysosomal activity in ISO + RAP group. LC3B puncta was significantly higher in ISO+CHL indicating inhibition of LC3 turnover. Increased autophagy (26.5% increase) could be associated with exacerbation of hypertrophy (120% increase) as cellular hypertrophy was found to increase significantly in ISO+RAP group. Chloroquine, being an autophagy inhibitor, reduced autophagy and also reduced (52%) the percentage of hypertrophied cells. Thus it is inferred that by inhibiting autophagy, it is possible to attenuate hypertrophy, even though further investigations have to be done to establish the findings.

Conclusion / Discussion: Reduction of cardiac hypertrophy as a strategy for prevention of cardiac failure is a fairly novel area as till recently; regression of cardiac hypertrophy was not attempted as it was considered to be an adaptive change. In view of the fact that therapeutic option for cardiac failure is limited, it is appropriate to prevent the progression of cardiac hypertrophy to failure. The current study is aimed to target autophagy in cardiac hypertrophy which will hopefully provide an insight into a potential therapeutic strategy. Moreover, studies are aimed to test the effect of selected natural compounds on autophagy and observe the end outcome on hypertrophy. With the thrust given on the use of natural products and herbal medicines and the absence of scientific records in line with modern medicine, research in this direction will have a great impact on the acceptance of traditional medicine as well. I sincerely hope that the Herbal and Alternative Medicine Conference 2017 will provide a platform for suggestions regarding natural products that can be used in the current study and prospects for future collaborations.

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