Index No. 223/18/Life Sc./26

Thesis Title: The Role of Developmental Regulatory Factors YAP1 and FOXM1 and Associated Molecular Signaling in the Induction of Cardiomyocyte Hypertrophy and Fibrosis in Rodent Diabetic Cardiomyopathy Model

ABSTRACT

Cardiovascular diseases (CVDs) are currently the leading cause of increasing morbidity and mortality worldwide. Among the different types of CVDs, cardiomyocyte hypertrophy deteriorates the functional ability of heart leading to increased risk of heart failure. At the tissue level, cardiac hypertrophy is characterized by thickening of ventricular wall, increased myocardial fibrosis and impaired cardiac contractility. The underlying cause of cardiomyocyte hypertrophy often involves genetics, hypertension, coronary artery disease, inflammation, oxidative stress etc. Metabolic disease such as diabetes is currently a major health burden which is also associated with the development of various cardiac diseases. While different medications are being used against diabetic cardiomyopathy, the role of specific molecular players in the disease pathogenesis seek further research in-depth that may help in identification of novel therapeutic targets in future. This study primarily aims to understand the transcriptional regulation of FOXM1 upon high glucose stress in cardiac cells both *in vitro* and *in vivo*. *yap1* and *foxm1*, two important genes expressed during early developmental period, were found to be upregulated in hyperglycemic condition. Inhibition of these molecules in the high glucose condition with specific inhibitors resulted in significant amelioration of cardiomyocyte hypertrophy and fibrosis. YAP1 has been observed to upregulate AKT activation followed by subsequent GSK3β inhibition that in turn upregulates FOXM1 expression leading to exacerbated hypertrophy. In the hyperglycemic cells, activated YAP1 also modulated renin angiotensin system (RAS) through upregulation of angiotensin converting enzyme (ACE) and downregulating its homolog molecule angiotensin converting enzyme2 (ACE2). Moreover, YAP1-dependent increased expression of ACE and ACE2 has been observed to be mediated through *β-catenin* overexpression in cardiomyocyte and cardiac fibroblast *in vitro*. Activated ACE induced epithelial to mesenchymal transition (EMT) - mediated pro-fibrotic remodeling *via* upregulated TGF-β-SMAD2/3 pathway. In nutshell, the study demonstrates the role of YAP1 in cardiomyocyte hypertrophy and fibrosis by FOXM1 and ACE respectively in high glucose stress condition.

Arunima Mondal
12/3/24

Arunima Sengupta
12/3/24

Dr. Arunima Sengupta
UGC – Assistant Professor
Dept. of Life science and Bio-technology
JADAVPUR UNIVERSITY, KOLKATA