# ABSTRACT


**Understanding the mechanism of cardiac gene remodelling via PPAR α signalling in cardiac hypertrophy**

Cardiac hypertrophy is a compensatory response to pressure-overload induced heart and is characterised by an increase in cardiomyocyte size. Prolonged hypertrophy becomes maladaptive and triggers significant pathological changes at both cellular and molecular levels. Cardiac hypertrophy is accompanied by down regulation of PPAR α that result in metabolic reprogramming. PPAR α is critical for mitochondrial biogenesis and fatty acid oxidation and reduction in fatty acid β oxidation further leads to cardiac dysfunction. Down regulation of PPARα therefore worsens the hypertrophic state. Yet, the role of PPAR α in adaptive phase of stress-induced cardiomyocytes is mostly unknown. To understand the role of PPAR α signalling in cardiac remodelling during cardiac hypertrophy, PPAR α $^{-/-}$ mice was used. PPAR α $^{-/-}$ mice exhibited significantly compromised hemodynamics as observed via echocardiography but an unexpected down regulation of apoptotic markers. Critical apoptotic marker like PTEN was also noticeably reduced along with several other apoptotic markers like p53, cCaspase9. This reduction in apoptotic markers was accompanied by an upsurge in autophagy markers. The autophagy markers like Atg3, Atg5, Atg7, Beclin1 and LC3 A/B were up regulated in PPAR α $^{-/-}$ mice. Significant increase in autophagosomes in Neonatal Rat Ventricular Myocytes (NRVMs) further confirmed this increase in autophagy. The data therefore revealed the role of PPARα signalling in this cardiac remodelling where an adaptive switch towards autophagy is observed in stress-induced cardiomyocytes in the absence of PPAR α. To further investigate this phenomenon, differential expression of miRNA in PPAR α $^{-/-}$ mice was studied. Role of miRNA has been majorly explored in cardiac hypertrophy but the biological relevance of the differentially expressed miRNA with the PPAR α signalling in hypertrophied condition is yet to be explored. Analysis of miRNA profile revealed differential expression of specific miRNAs like mmu-miR-3102-5p; mmu-miR-30a-5p; mmu-miR-30c-5p; mmu-miR-466i-5p that are involved in negative regulation of intrinsic apoptotic signalling pathway. Therefore the data revealed that the altered expression of miRNAs in the absence of PPAR α resulted in inhibition of apoptosis suggesting a critical role of this transcription factor in regulating the adaptive switch. Overall this study highlights the significance of PPAR α in regulating the cardiac remodelling in hypertrophy.