Topic: Heart Failure (Basic), Molecular Cardiology**The GATA4 Acetylation Site Plays a Key Role in the Development of Cardiomyocyte Hypertrophy**

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Introduction

The zinc finger protein GATA4 is a transcription factor that associates with the intrinsic histone acetyltransferase p300 and regulates myocardial transcriptional activity in response to hypertrophic stimuli. It is known that GATA1, another member of the GATA transcription family, forms a homo-dimer and regulates transcriptional activity. However, whether GATA4 forms a homo-dimer, and what its relationship is to hypertrophic responses, are still unknown.

Methods and Results

GST pull-down assay demonstrated that GATA4 dimerisation required the GATA4 acetylation site from residues 308-326. Overexpression of a mutant containing a 3xGATA4 acetylation site (3xG4D) both prevented p300-induced GATA4 dimerisation and inhibited p300/GATA4-induced ANF and ET-1 promoter activity without inhibiting

GATA4 acetylation. In cardiomyocytes, the overexpression of 3xG4D inhibited phenylephrine-induced cardiomyocyte hypertrophy. To perform a crystal structure analysis, a recombinant GATA4 fragment, including an acetylation site with a GST tag, was purified with GS4B beads. The GST tag was cleaved using HRV3C protease and applied to an anion-exchange column followed by a size-exclusion column. Crystallisation was performed using a commercial kit to screen crystallisation conditions and then optimise them. X-ray diffraction data was collected with the BL-17A beamline at Photon Factory.

Conclusions

These results suggest that the dimerisation of GATA4 is involved in hypertrophic responses in cardiomyocytes. This finding may contribute to the development of new heart failure drugs. ■