Topic: Heart Failure (Basic), Molecular Cardiology**TBL1 Suppresses Cardiomyocyte Hypertrophy by Regulating the Interaction Between HDAC3 and GATA4**

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Keywords: Cardiac hypertrophy, heart failure, HDAC3, novel pharmacological therapy, p300 acetylation of GATA4, transducin beta like protein 1, GATA4-binding protein, cardiomyocytes, atrial natriuretic peptide, endothelin-1, HEK293T cells

Citation: *European Cardiology Review* 2018;**13**(2):126. **DOI:** <https://doi.org/10.15420/ecr.2018.13.2.PO7>

Cardiac hypertrophy is a risk factor for the development of heart failure. To elucidate underlying molecular mechanism is necessary for the development of novel pharmacological therapy targeting to pathological cardiac hypertrophy. We have previously reported that the acetylation of GATA4 by p300 is essential for cardiomyocyte hypertrophy and heart failure.

In the present study, we have identified transducin beta like protein 1 (TBL1) as a novel GATA4-binding protein by tandem affinity purification and mass spectrometry analyses. Overexpression of TBL1 significantly repressed p300/GATA4-induced activations of atrial natriuretic peptide (ANP) and endothelin-1 (ET-1) promoters in HEK293T cells. Furthermore, overexpression of TBL1 significantly inhibited phenylephrine- (PE) induced hypertrophic responses,

including an increase in the cell size and the transcriptional activation of ANP and ET-1 promoters in primary cultured cardiomyocyte. Conversely, knockdown of TBL1 by RNAi increased PE-induced mRNA expression of ANP and BNP. TBL1 repressed p300-induced acetylation of GATA4 and enhanced the binding between HDAC3 and GATA4. The treatment with RGFP966, a specific inhibitor of HDAC3, rescued the TBL1- mediated inhibition of hypertrophic responses in cultured cardiomyocytes.

Finally, the interaction of TBL1 with HDAC3 decreased by treatment with PE in cardiomyocytes. These findings have demonstrated that TBL1 suppresses p300/GATA4-dependent gene transcription and cardiomyocyte hypertrophy by regulating the interaction between HDAC3 and GATA4. ■