Understanding Cardiac Physiological Hypertrophy in a LncRNA Way

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Exercise training has been recognized as an effective way for maintaining cardiovascular health and attenuates cardiovascular diseases. Exercise training can induce cardiac physiological hypertrophy, which is distinct from pathological hypertrophy. Uncovering the underlying pathways responsible for physiological hypertrophy can help develop novel therapeutics for cardiovascular diseases [1].

In a recent study by Gao et al., the authors used long noncoding RNA (lncRNA) microarrays to identify lncRNA expression changes associated with cardiac physiological hypertrophy induced by swimming [2]. Although the role of lncRNAs in different cardiac pathologies has been reported [3, 4], their functional role in exercise-induced physiological hypertrophy is not well understood. The authors found that lncRNA FR236703 was significantly induced in the left ventricle of mice that had undergone swimming. FR236703 expression was higher in the heart compared to other tissues and it was specifically increased in cardiomyocytes but not in cardiac fibroblasts after exercise. Thus, FR236703 was named cardiac physiological hypertrophy-associated regulator (CPhar). In neonatal mouse cardiomyocytes, CPhar overexpression promoted hypertrophy, proliferation, and reduced apoptosis induced by oxygen glucose deprivation/reperfusion (OGD/R). In vivo, CPhar was necessary for swimming-induced physiological hypertrophy. When investigating the mechanism, the authors found that CPhar's neighbor gene, *Cyp2u1*, was not regulated by CPhar, thus excluding cis-regulation. Based on the microarray data, lncRNA-transcription factor correlation analysis and functional validation, activating transcription factor 7 (ATF7) was identified as a key downstream effector of CPhar. Furthermore, DEAD-box helicase 17 (DDX17) was found to bind CPhar to regulate

ATF7 by sequestering CCAAT/enhancer-binding protein β (C/EBP β). Finally, overexpression of CPhar using adeno-associated virus type 9 (AAV9) prevented cardiac remodeling and dysfunction induced by myocardial ischemia/reperfusion injury in mice.

This intriguing study provides novel insights into the mechanisms mediating exercise-induced physiological hypertrophy. First, it reports a new lncRNA that controls physiological hypertrophy. Second, a transcription factor ATF7 was identified as a downstream effector of CPhar. Interestingly, knockdown of ATF7 promoted hypertrophy, proliferation, and reduced apoptosis induced by OGD/R, whereas ATF7 overexpression reversed the effects of CPhar in cardiomyocytes. To the best of knowledge, this is the first description of ATF7's function in the heart. Third, the study shows that CPhar is responsible for the interaction between DDX17 and C/EBP β , which then regulate ATF7 in the heart. This study adds another layer of complexity to gene regulation by lncRNA, expanding the role of lncRNAs beyond the regulation of target mRNA expression and degradation. It shows that lncRNAs can regulate the availability or subcellular localization of transcription factors by interacting with different binding partners.

The study also opens new avenues that warrant further investigation. The therapeutic effects of CPhar overexpression need to be explored further in established heart failure models. In addition, lncRNAs can also be detected in the circulation and may be used as biomarkers [5]. It remains to be determined whether circulating CPhar would be increased after exercise training and whether it may have a paracrine effect.

Together, the study of Gao et al. provides valuable insights into the molecular mechanism of exercise-induced physiological cardiac hypertrophy. Increasing CPhar may have translational potential and may pave the way for new therapeutic approaches for heart diseases.

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