

## **MAP Kinase Phosphatase-5 Regulates Cardiac Adaption to Endurance Exercise**

JAIME A. PERALES, KISUK MIN

Metabolic, Nutrition and Exercise Research Laboratory; Department of Kinesiology;  
University of Texas at El Paso; El Paso, TX

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*Advisor / Mentor: Dr. Min, Kisuk (kmin@utep.edu)*

### **ABSTRACT**

Endurance exercise induces a beneficial effect on the cardiovascular system and promotes cardio protection against heart disease. It has been established that the mitogen-activated protein kinases (MAPKs) promote the improvement of cardiac function in response to endurance exercise. However, molecular mechanisms of how MAPK signaling pathways regulate cardiac adaptation to endurance exercise remain unclear. The MAPKs are inactivated by MAP kinase phosphatases (MKPs) through direct dephosphorylation. Recently, growing evidence suggests the importance of MKP-5 signaling mechanisms in physiological and pathological processes. Previously, we have demonstrated that MKP-5-deficient skeletal muscle exhibits improved regenerative myogenesis in response to injury and mice lacking the expression of MKP-5 ameliorate dystrophic muscle disease. However, the role of MKP-5 has not been explored in cardiac muscle. **PURPOSE:** This study aims to understand how MKP-5 regulates cardiac adaptation to endurance exercise. **METHODS:** Wild type mice and MKP-5-deficient mice were subjected to endurance exercise at 70~75% VO<sub>2</sub>max: treadmill running at 15 m/min, 0% grade, 60 min/day, and 5 consecutive days. After 5 days of endurance exercise, we performed a progressive exercise stress test. Endurance exercise capacity was determined by a graded increase in treadmill speed (2~6 m/min every 5 min) to the point of exhaustion and then running distance was measured. **RESULTS:** Our findings revealed that MKP-5-deficient mice exhibit 3-fold increased endurance exercise capacity as compared with wild type mice ( $p < 0.0001$ ). We also found that MKP-5 gene expression is dramatically downregulated by 81% in cardiac muscle following endurance exercise as compared to non-exercised mice ( $p < 0.005$ ). **CONCLUSION:** Our study demonstrates that MKP-5 plays a central role in cardiac adaptation to endurance exercise. It suggests that MKP-5 may serve as a pivotal regulator for MAPKs in cardiac adaptation to endurance exercise.