

# A transcription cofactor that alters our muscle cells during exercise

By Caitlin Hanlon

Pick up almost any magazine at a grocery store, and chances are the benefits of exercise will be lauded on the cover. While the health, aesthetic and mental benefits of exercise often are discussed in the popular press, the cellular changes that happen to the muscle itself are glossed over. We know that exercise promotes changes in muscle as it adapts to an increased workload, and in a recent issue of the **Journal of Lipid Research**, researchers identified a transcription cofactor that links exercise to specific changes in muscle cell phospholipids.

Phospholipids surround our cells, providing structure and protection in the membranes. They consist of a hydrophilic head group and hydrophobic long chain hydrocarbon tails. Variations between head groups, hydrocarbon chain lengths and hydrocarbon saturation lead to many different subtypes of phospholipids. Each type of phospholipid lends different characteristics to the membrane it resides in. For example, some phospholipids promote membrane curvature or flexibility, while others are necessary to retain specific proteins. Previous work has demonstrated that a transcription cofactor known as PGC1 $\alpha$ , or peroxisome proliferator-activity receptor  $\gamma$  coactivator 1 $\alpha$ , is upregulated in response to exercise and that exercise alters muscle phospholipid composition. In their article, Nanami Senoo and others from the University of Shizuoka in Japan describe a study that investigated whether the exercise-induced changes in phospholipid composition of muscle are dependent upon PGC1 $\alpha$ .

The authors began by examining

mouse skeletal muscle as it overexpressed PGC1 $\alpha$ . Two types of lower hind leg muscle were isolated from the mice — the extensor digitorum longus, or EDL, which is a glycolytic or fast-twitch muscle, and the soleus, an oxidative or slow-twitch muscle. The researchers extracted lipids from these muscles and analyzed them by type and amount via liquid chromatography/mass spectrometry analysis and thin-layer chromatography analysis. The authors noticed changes in the phospholipid composition in both muscle types. Specifically, they found that overexpression of PGC1 $\alpha$  caused the fast-twitch EDL muscle to have a phospholipid profile that resembled the slow-twitch soleus. The authors then examined specifically which phospholipids were changing with PGC1 $\alpha$  overexpression. In the EDL, many types of phosphatidylcholine, or PC, and phosphatidylethanolamine, or PE, two specific phospholipids found in the membrane, were upregulated, but one specific isoform (18:0/22:6) of both was quite significantly increased. They observed a similar change in the soleus, although the baseline levels of these phospholipids already were increased in this type of muscle.

The next step was to determine if these specific phospholipids increased in response to exercise. The researchers separated the mice into a sedentary group and a group that had access to an exercise wheel. Interestingly, in the EDL, exercise alone mimicked the effects of overexpression of PGC1 $\alpha$ , as both types of phospholipids increased. The authors then asked the most intriguing question of the study: Are these changes caused by PGC1 $\alpha$ ? In mice that lacked PGC1 $\alpha$ , the

increases in PC (18:0/22:6) and PE (18:0/22:6) after exercise were completely absent.

This work is the first to show that exercise induces a change in muscle phospholipids via increased PGC1 $\alpha$  activity. More broadly, this finding demonstrates that exercise itself causes fast-twitch muscles to adopt some characteristics of the more endurance-oriented slow-twitch muscles.

Because PGC1 $\alpha$  is a nuclear receptor or transcription coactivator involved in regulating the transcriptional activity of genes, it is unlikely to affect the composition of membrane phospholipids directly due to its primary role in the nucleus. With this in mind, the authors tried to identify the pathways or enzymes that may be responsible for the changes in PC and PE. Although the expression of some enzymes that are involved early in the fatty acid synthesis pathway increased with PGC1 $\alpha$  over-expression, the expression of enzymes that specifically make PC and PE did not. Therefore, the exact mechanism of how PGC1 $\alpha$  is translating exercise into changes in cell membranes remains unknown.

Uncovering the pathways that govern PGC1 $\alpha$  activity may have important therapeutic implications for diseases that affect muscle function, such as muscular dystrophy. In fact, PGC1 $\alpha$  can lessen the effects of muscular dystrophy in mouse models, but it remains to be investigated if this improvement can be attributed to changes in muscle phospholipid composition.



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