Exercise and skeletal muscle gene expression: molecular mechanisms

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Skeletal muscle adaptations to exercise can be explained in part by transient changes in gene expression. Such changes in gene expression correspond to enhanced expression of selected proteins, which in turn improve skeletal muscle function and performance[1]. A single bout of exercise is sufficient to enhance the expression of many genes. To examine the underlying mechanisms mediating exercise-induced gene expression, we have focussed on the regulation of the myocyte enhancer factor 2 (MEF2), a transcription factor required for the expression of many exercise responsive genes in skeletal muscle. MEF2 regulation during muscle cell differentiation is well characterised, however little is known of its regulation during exercise. Following exercise in humans, histone deacetylase 5 (HDAC5), a MEF2 transcriptional repressor, is dissociated from MEF2 and is exported from the nucleus[2]. While this event is dependent on HDAC5 phosphorylation, the putative upstream kinase, the calcium/calmodulin dependent protein kinase IV (CaMKIV), is not present in the nuclei of human skeletal muscle. However, a potential kinase could be the AMP activated protein kinase (AMPK), which is activated by exercise, shares similar substrate specificities with CaMKIV and translocates to the nucleus in response to exercise[3]. *In vitro* phosphorylation assays reveal that AMPK can phosphorylate HDAC5. In addition, the PPAR γ coactivator 1 (PGC1) associates with MEF2 during exercise, presumably to recruit transcriptional cofactors possessing histone acetyltransferase (HAT) activity. While these events are sufficient to initiate MEF2 dependent transcription, the rate of transcription increases following MEF2 phosphorylation, which is thought to be mediated by the p38 mitogen activated protein kinase (MAPK). Exercise increases nuclear p38 phosphorylation, the association of p38 with MEF2 and p38 sequence specific phosphorylation of MEF2. These molecular events describe the complex regulation of a transcription factor required for the expression of many exercise responsive genes and therefore could describe the molecular mechanisms mediating skeletal muscle adaptations to exercise. Full elucidation of these mechanisms could be important in understanding skeletal muscle function and performance.

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