TIME-COURSE OF TRANSCRIPTOMIC RESPONSES IN SKELETAL MUSCLE DURING RECOVERY FROM ENDURANCE EXERCISE INDICATES PROLONGED MUSCULAR INFLAMMATION

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Introduction

Re-programming of gene expression is fundamental for skeletal muscle adaptations in response to endurance exercise. Although inflammatory responses in muscle following muscle-damaging exercise can persist for days, there is a paucity of global gene expression data beyond 48 hours following exercise. This study aimed to investigate the changes in the transcriptome of skeletal muscle until 96 hours after an endurance exercise trial (EXTRI; one hour of cycling followed by one hour of running). Data on the transcriptome of circulating neutrophils from participants in the current study indicated that the neutrophil transcriptional activity was related to the muscle-damaging component of the EXTRI (Neubauer et al. 2013, *J Appl Physiol*.). We hypothesised that the muscular transcriptome would particularly reflect interactions between muscle and infiltrating leukocytes.

Methods

Eight healthy, endurance-trained, male individuals participated. Skeletal muscle samples were taken one week before the EXTRI, 3, 48, and 96 hours post-EXTRI. RNA was extracted from muscle tissue. Differential gene expression was evaluated using Illumina microarrays, and validated with q-PCR. Gene set enrichment analysis identified functionally related gene sets chosen from the Molecular Signatures Database.

Results

Significantly (FWER *p*-value<0.05) up-regulated gene sets included groups of genes related with leukocyte migration, immune and chaperone activation (3 hours post-EXTRI), and chemokine signalling (96 hours post-EXTRI). Significantly ($P<0.05$) up-regulated, q-PCR-validated genes in the muscle included the leukocyte-specific transcripts CD18 and CD68 (both of which increased 96 hours post-EXTRI), chemokine (C-C-motif) ligand 2 (CCL2), and heme oxygenase (HMOX1; both of which increased 3 and 96 hours post-EXTRI). The pre- to 48 hour post-EXTRI gene expression fold-change of the macrophage-specific CD68 gene in the muscle correlated with plasma myoglobin changes ($r=0.85$; $P<0.01$).

Conclusions

The current data indicate that many of the coordinated gene expression responses in skeletal muscle, particularly at 96 hours post-EXTRI, were related with exercise-induced muscle damage, and the subsequent accumulation of muscle leukocytes. The substantial transcriptional activity 96 h post-EXTRI was strongly associated with inflammatory and immune responses, and suggests that muscular recovery, from a transcriptional perspective, is incomplete 96 hours after exercise.