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Autor(es): Neubauer, Oliver; Broadbent, James; Sampson, Dayle; Sabapathy, Surendran; Haseler, Luke; Wagner, Karl-Heinz; Bulmer, Andrew; Peake, Jonathan

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NOVEL TIME-COURSE RELATED LINKAGES OF SKELETAL MUSCLE GENE NETWORKS WITH BLOOD INFLAMMATION AND MUSCLE DAMAGE MARKERS FOLLOWING ENDURANCE EXERCISE

Oliver Neubauer¹; James Broadbent¹; Dayle Sampson¹; Surendran Sabapathy²; Luke Haseler²; Karl-Heinz Wagner³; Andrew Bulmer²; Jonathan Peake¹

KEY WORDS: Muscle recovery, systemic inflammatory response, blood biomarker panels

INTRODUCTION

Network biology is an important new frontier in physiology that enables us, for example, to understand whether functional gene networks in tissues are related to clinically accessible blood markers⁽²⁾. We previously analyzed the muscle and blood neutrophil transcriptomes in trained men at 3, 48 and 96 h after 2 h cycling and running^(4,5). By applying weighted gene co-expression analysis (WGCNA)⁽³⁾, an advanced network-driven method, to these data, we identified muscle gene networks that are co-expressed in neutrophils and correlated with inflammation markers⁽¹⁾. Expanding on these results, we specifically examined time-course related correlations of muscle gene networks with exercise-induced changes in blood leukocyte counts, cytokines, high-sensitive C-reactive protein (hsCRP) and muscle damage markers.

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METHODS

WGCNA was performed to construct and analyze muscle gene co-expression networks based on data from pre- to 3 h, pre- to 48 h, and pre- to 96 h post-exercise. Relationships

¹ Queensland University of Technology, Australia.

² Griffith University, Australia.

³ University of Vienna, Austria.

[✉]mail: oliver.neubauer@qut.edu.au

of the time-course related gene networks with blood variables were quantified by using the networks' eigengenes⁽³⁾.

RESULTS

The strongest correlations were identified between blood leukocyte counts, muscle damage markers, cytokine and hsCRP concentrations, and an acetylation- and mitochondria-related muscle gene network that was preserved from pre- to 3 h post-exercise. We also identified 5307 correlations ($P < 0.05$) between blood variables and individual network genes including heat shock protein-encoding genes and nuclear factor interleukin 3 regulated. Furthermore, blood leukocyte counts, interleukin-6, hsCRP and plasma CK activity strongly correlated with a muscle network that was enriched with immune-related genes and preserved until 96 h post-exercise. 290 correlations ($P < 0.05$) were identified between blood variables and individual genes of this latter network including the M1 macrophage 'marker gene' CD68, biglycan (BGN) and NCK-associated protein 1-like (NCKAP1L). BGN and NCKAP1L have specific roles in muscle-immune interactions and immune cell migration.

DISCUSSION

The linkages of blood variables with muscle gene networks might reflect different phases of muscle recovery. These findings provide tentative evidence in support of the notion that a panel of predictive blood biomarkers may potentially help us to assess changes in the muscle, such as occurring during muscle recovery and remodeling following exercise. Such a biomarker panel may consist of more traditional physiological/biochemical/immunological variables combined with multi-gene biomarkers associated with a blood leukocyte/neutrophil gene network⁽¹⁾.

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