Genetic regulation of myofiber hypertrophy?

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ABSTRACT

Introduction. Progressive, resistance exercise training (RT) induces skeletal muscle hypertrophy, increases strength, power, and quality of muscle, and is potentially the most promising method to regenerate and re-grow muscle in populations suffering from involuntary atrophy. However, we have previously shown that there is a large degree of intersubject variability for myofiber hypertrophy in response to RT with adults having no response [-16μm2 (mean myofiber growth), Non], a modest response (1111μm2, Mod), or an extreme hypertrophic response (2475μm2, Xtr). Underlying mechanisms for this differential growth response are largely unknown. Therefore, the **purpose** of this study was to determine whether differences in the skeletal muscle transcriptome exist among the three response clusters, prior to 16 weeks of RT. **Methods.** mRNA was isolated from muscle biopsies taken from the vastus lateralis of 44 previously clustered men and women (aged 19-75y). Agilent 4X44K single color genechips were used to determine differences in skeletal muscle gene expression among the three response clusters. Ingenuity Pathways Analysis (IPA) and available Gene Ontology were used for functional annotation of differentially expressed genes and identification of informative genes that may instigate the observed myofiber growth phenotypes. **Results.** After removing genes with low signal intensities and normalizing the data, we identified substantial differences in the transcript profile among the response clusters with the most notable differences between the Xtr- and Non-responders. 8026 differentially expressed genes were identified between Xtr vs. Non, 2463 between Xtr vs. Mod, and 1294 between Mod vs. Non. There were 1632 genes with expression specific to the Xtr (i.e. differences existed between Xtr vs. Non and Mod, but not between the Non vs. Mod) and 617 genes with expression specific to the Non. Functional classification, with IPA, identified *Skeletal Muscle System Development and Function (SMSDF)* as a top functional category containing a significant number of differentially expressed genes ($p<0.05$) in all three comparisons. SMSDF was also a top five functional category for the genes specific to both Xtr and Non ($p<0.05$). Within the broad *SMSDF* category, IPA defined sub-categories of functional annotation, which allowed us to further interpret the differentially expressed genes. We have highlighted several genes that primarily had expression specific to the Xtr or had increased expression from Non to Mod to Xtr. Highlighted genes are involved with *satellite cell activation and function (*SOX8, HGF, PAX7), *differentiation* (MYOD1, MYOG, APOE, TRIO, MSTN)*, skeletal muscle growth* (DGKZ, ESR1, OXT, OXTR, UCN2, GREB1)*, modulation of inflammation and fuel utilization* (PYY)*,* and *improved function* (TFAM, UCN2, CRHR1, CRHR2)*.* Additionally, there was a decrease in expression (Xtr vs. Non) for several genes involved with *modulation of inflammation and fuel utilization* (AEBP1, NFKB1, CD36, AIF1). **Discussion.** These results indicate that differences in gene expression do exist among the response clusters prior to mechanically induced hypertrophy and that the Xtr-responders were “primed” to respond. We identified several genes and signaling pathways that may promote or inhibit muscle growth and thus, initiate the three observed hypertrophic response phenotypes. Results from this study enabled us to identify distinctive molecular pathways, particularly between the Xtr- and Non-responders, for development of targeted interventions. Further research is necessary to determine which of these genes or networks of genes truly distinguish load mediated hypertrophy potential.