Prediction of transcription factors regulating contractile activity-induced gene expression in skeletal muscle

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Skeletal muscle tissue makes up more than a third of the human body mass playing a key role in fat and carbohydrate metabolism; maintenance of normal/increased level of diurnal physical activity provides effective protection against various metabolic disorders. Therefore, investigation of the molecular mechanisms underlying skeletal muscle gene expression to physical exercise is of fundamental importance. We aimed to predict transcription factors (TFs) regulating transcriptomic response to an exercise in human skeletal muscle using the position of transcription start sites (TSSs) and individual promoter regions surrounding each TSS.

Biopsies from the vastus lateralis muscle were taken prior to, 1 h, 3 h, and 6 h after an aerobic exercise in 10 males. The exact TSSs were identified using the cap analysis of gene expression. The individual promoters were identified using the open chromatin position (obtained in myotubes) and the density of various TFs binding sites (15982 human ChIP-seq experiments; the GTRD database).

The position of TSSs and individual promoters (with length from hundred to 2000 b.p.) were identified for ~12000 genes. The position weight matrix method showed that the individual promoters work better for prediction of TFs than promoters with "standard" length. Finally, using unsupervised clustering we identified 20 groups of co-expressed exercise-induced genes and predict TFs for each cluster: several well-investigated TFs (Ca2+-dependent and early response TFs, regulators of fat and carbohydrate metabolism, etc.), as well as TFs with unknown role in the regulation of skeletal muscle gene expression (zinc fingers, etc.).

A robust approach to prediction of TFs using the position of TSSs and individual promoters was developed. The method can be used to study the dynamics of TFs activation in co-expressed genes in human skeletal muscle subjected to various physiological and pharmacological stressors.