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Effect of aging, chronic inflammation and long-term physical disability on human skeletal muscle transcriptome

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Motivation and Aim: At normal physical activity, skeletal muscle tissue plays a key role in the carbohydrate and fat metabolism of the organism and has a positive effect on the functioning of other tissues and organs. Aging is associated with complex changes, including decrease in physical activity, mass and functionality of skeletal muscles (insulin sensitivity, muscular endurance and strength), and with the development of various diseases, often leading to the chronic inflammation. The aim of our study was to investigate effect of aging, chronic inflammation and long-term physical disability on human skeletal muscle transcriptome.

Methods and Algorithms: Transcriptomic profile of skeletal muscle of elderly patients with primary knee/hip arthrosis (OP, n = 35, 72(66–83) years old, body mass index (BMI) 30(21–43) kg/m^2) was compared with that of young healthy volunteers (YH, n = 10, 35(25–43) years old, BMI 22.5 (18.9–29.4) kg/m^2). To identify the role of chronic inflammation and long-term physical disability in gene expression changes, YH was compared with a group of young patients with primary arthrosis (YP, n = 7, 39(26–45) years old, BMI 25.8(25.4–30.9) kg/m^2). To evaluate the effect of age, the YP and OP groups were compared. Tissue samples from *m. vastus lateralis* were collected in patients before joint replacement surgery, in healthy people – using needle biopsy. Then single-end RNA sequencing (75 nucleotides, 66 million reads/sample) was performed. Differentially expressed genes were evaluated using DESeq2 with a cutoff criteria: fold change > 1.5 and $P_{adj} < 0.05$.

Results: Physical score (Short form survey SF-12) did not differ between the groups of patients and was significantly lower than in YH. Inflammatory markers (blood leukocyte and neutrophil levels) were comparable between OP and YP, but significantly greater than in YH. In the OP group, compared with YH, metabolic disorders were observed: an increase in fasting blood glucose and insulin levels, as well as an increase in BMI.

In old people (comparison OP vs. YH) up-regulated genes (2529) were associated with inflammatory response, extracellular matrix reorganization and lipid metabolism; down-regulated genes (1007 genes) mainly encoded mitochondrial proteins and carbohydrate metabolism regulators. In young patients (comparison of YP vs. YH) up-regulated genes (2107) were associated with inflammation and biogenesis of the extracellular matrix, and down-regulated genes (558) mainly encoded mitochondrial proteins, and were associated with G protein signaling. These changes were comparable (but less pronounced) with those in OP vs. YH. Age-related changes in gene expression in patients (OP vs. YP) are less than in previous comparisons: a decrease (536) and an increase

(299) in gene expression are associated with the regulation of the inflammatory response, and down-regulated genes are associated with angiogenesis and G-proteins signaling.
Conclusion: In old patients with primary arthrosis, there are marked changes in the transcriptome of skeletal muscles (OP vs. YH). Most of these changes were found in young patients with arthrosis and long-term physical disability compared with young healthy people (YP vs. YH). This suggests that inflammation and decreased physical activity (induced by long-term physical disability) are key factors inducing age-dependent changes in skeletal muscle transcriptome.
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