How to escape from muscle atrophy: whole-genome analysis of gene expression in edible dormouse (*Glis glis*) during immobilization

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In the course of evolution, animals have developed various mechanisms of resistance to extreme environmental conditions (e.g. heat, cold, drought, lack of food). One of the remarkable adaptive ways to survive these adverse conditions in mammalians is hibernation when animals decrease their metabolic rate and demonstrate physical inactivity for prolonged periods of time (6-8 months).

For the long time, classic model animals for hibernation mechanisms investigation were ground squirrels, bears, hamsters and marmots. However, as the completely new model can be considered the edible dormouse (*Glis glis*), a small arboreal rodent who has extremely high average life longevity (9 year) and prolonged periods of hibernation (for 8 months).

To identify common molecular pathways of the protective musculoskeletal adaptation and genome structure in hibernator edible dormouse, we conducted whole-genome analysis of mRNA expression using Illumina HiSeq platform in muscle (m. soleus) and lumbar spinal cord samples. We examined two groups of the dormice: normal animals and animals immobilized for two weeks in laboratory, so that animals could not move, but successfully prevented muscle atrophy processes. Transcriptome was assembled de novo and further analyzed for differential expression of transcripts using CLC Genomics Workbench 7.5.1.

In transcriptome of examined animals 48 010 sequences were determined. We identified 296 genes differentially expressed in soleus muscle and 251 genes differentially expressed in lumbar spinal cord (Fold change ≥ 3) in the animal subjected to hypokinesia. In

addition, we determined top-30 highly expressed transcripts and top-25 differentially overexpressed and under-expressed transcripts.

Some transcripts demonstrated the significant changes in expression of muscle proteins taking part in contractile system. Surprisingly, some isoforms of actin significantly 15 times overexpressed and some isoforms of myosin heavy chains 3-9 times overexpressed, while titin, nebulin, myoglobin and troponin proteins showed no significant changes in their expression. Analysis of transcriptome data in lumbar spinal cord revealed overexpressing of neogenin (5 times), which is involved in myogenesis. Remarkably, disuse muscle atrophy markers MuRF1 and MAFbx demonstrated low expression values.

In addition, we tested some genes involved in DNA repair and DNA damage signaling. Most of these transcripts revealed no changes of their expression in both m. soleus and lumbar spinal cord.

Because of edible dormice have relatively high life longevity we tested some genes, which play the key role in aging mechanisms (IGF1, GHR, mTOR-signaling). Interestingly, PI3-kinase, which is activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology, differentially overexpressed in m. soleus showed high level of gene expression alteration in immobilized animals.

At this stage of the analysis of transcriptome data, we can conclude that edible dormouse (*Glis glis*) does not develop atrophic processes in muscle during physical inactivity. It is likely the significant increase in the expression level of neogenin and some isoforms of actin and myosin is an important step in the prevention of skeletal muscle atrophy in these animals.

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