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Skeletal muscle atrophy occurs in catabolic conditions, such as aging, inactivity, and undernutrition, leading to the decrease of physical activity and frailty. Thus, maintaining muscle mass and function is necessary for promoting health and improving quality of life. However, the effective therapeutic agents for muscle atrophy have not yet been established, since the molecular mechanism underlying muscle atrophy is poorly understood. We previously generated FOXO1 transgenic mice (FOXO1-Tg) with skeletal muscle-specific overexpression of FOXO1 and demonstrated that FOXO1 is the important factor in causing muscle atrophy. Therefore, understanding FOXO1 functions will be the basis for the development of therapeutic agents for muscle atrophy. Here, we generated FOXOs deficient mice in skeletal muscle (FOXO1,3a,4$^{-/-}$) and comprehensively analyzed the changes of gene expression profiles in skeletal muscle of FOXO1-Tg and FOXO1,3a,4$^{-/-}$.

The purpose of this study was to clarify the molecular mechanism of muscle atrophy caused by FOXO1 during skeletal muscle atrophy. Prior to our study, it was unclear whether there are other factors involved in the FOXO-induced muscle atrophy. Using both FOXO1-Tg and FOXO1,3a,4$^{-/-}$ mice, we uncovered several novel FOXO1 target genes and identified the intermediary factor linking FOXO1 and muscle proteolysis. In addition, we uncovered the previously unknown regulatory mechanism to activate FOXO1 target genes. Also, FOXO1 inactivated positive regulator of protein synthesis with the induction of several inhibitory genes, which emerged as the novel anti-anabolic function of FOXO1 in skeletal muscle. This study sheds light on the novel molecular mechanism underlying muscle atrophy.

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FOXO1 cooperates with C/EBPδ and ATF4 to regulate skeletal muscle atrophy transcriptional program during fasting

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