Effect of TRB3 on Skeletal Muscle Mass Regulation and Exercise-induced Adaptation

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Skeletal muscle, which composes over 40% of body mass, is responsible for daily locomotion and energy metabolism. It is a malleable tissue that can adapt its structure and function in response to internal and external environmental stimuli. Changing muscle mass and energy substrate utilization is a common skeletal muscle adaptation in response to various pathological conditions, including type 2 diabetes and obesity. Failure to maintain skeletal muscle mass and function has been correlated with increasing morbidity and mortality, as well as poor quality of life. Hence, maintenance of skeletal muscle integrity is a recommended strategy in achieving better quality of life. TRB3 is a pseudokinase that is known to negatively regulate Akt phosphorylation, a key protein kinase in regulating protein turnover and energy metabolism in skeletal muscle. Although TRB3 is found in skeletal muscle and its expression is associated with Akt signaling, no previous studies have elucidated the effects of TRB3 on skeletal muscle mass regulation. The purpose of this dissertation was to determine the role of TRB3 in skeletal muscle mass regulation and exercise-induced adaptation. We hypothesized that TRB3 expression would regulate protein turnover by regulating Akt and its downstream proteins, mTOR and FOXO, at the basal state and under atrophic conditions. We also expected TRB3 expression to blunt exercise-induced skeletal muscle adaptation. In Aim 1, we tested whether TRB3 expression in mouse skeletal muscle regulated protein turnover through the Akt/mTOR/FOXO pathway at the basal state. We found that skeletal muscle protein turnover was regulated by TRB3 expression. In Aim 2, we examined whether TRB3 expression in mouse skeletal muscle affected food deprivation (FD)-induced skeletal muscle atrophy. We observed that muscle-specific TRB3 overexpression worsened FD-induced atrophy via increasing proteolysis systems, while TRB3 knockout prevented the atrophy by preserving protein synthesis. In Aim 3, we tested whether
TRB3 expression was involved in exercise-induced skeletal muscle adaptation. Here, we found that muscle specific TRB3 overexpression blunted the benefits of exercise training in glucose uptake and mitochondrial adaptation. These findings provide evidence that TRB3 is a potential target to improve skeletal muscle integrity and quality in both healthy conditions and atrophic conditions.