Novel players in the regulation of muscle mass, strength, and regeneration.

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Chronic unresolved inflammation is an important player in the etiology of metabolic diseases such as obesity and diabetes. Constantly elevated pro-inflammatory cytokines and immune cell infiltration in skeletal muscle, liver, and adipose tissue can be observed in the early stages of metabolic disease and greatly contribute to the development of insulin resistance and muscle atrophy, among other effects. On the other hand, select cytokine secretion and immune cell recruitment is fundamental for tissue adaptation, remodeling, and regeneration. Thus, identifying tissue regulators of adaptive immune cell recruitment could help develop tools to improve metabolism, tissue function, and whole-body insulin sensitivity. We have identified in skeletal muscle a previously uncharacterized protein as a novel Tissue Remodeler and Activator of INflammation, which we have called TRAIN. TRAIN expression is increased in skeletal muscle of mouse models of genetic- and diet-induced obesity and highly correlated with the mRNA levels of pro-inflammatory cytokines and immune cell markers. AAV-mediated TRAIN delivery to muscle improves exercise performance, whereas skeletal muscle-specific TRAIN knockout mice show compromised recovery in a model of disuse-induced muscle atrophy and compensatory hypertrophy. TRAIN's biological activity seems to depend, at least in part, on its ability to bind specific RNAs (such as miRNAs). This work identifies TRAIN as a novel RNA-binding protein involved in the regulation of tissue remodeling, immune cell recruitment, and regeneration.