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Multiple injuries (polytrauma) result in skeletal muscle wasting and insulin resistance

Polytrauma is a combination of injuries that occur over a short period of time (simultaneously or within minutes of each other). These injuries can include burn, fracture, hemorrhage, trauma to the extremities, or penetrating trauma to the gastrointestinal (GI) tract. Polytrauma is common in modern warfare, especially since the introduction of improvised explosive devices (IEDs). Polytrauma can also occur in the civilian population through automobile/mass transit accidents, industrial accidents and terrorist attacks. Multiple, simultaneous, minor injuries (polytrauma) have worse outcomes than a more severe single injury. Advances in emergency response strategies have increased initial survival following polytrauma, but later complications (multiple organ failure, metabolic dysfunction, severe infection) result in high mortality.

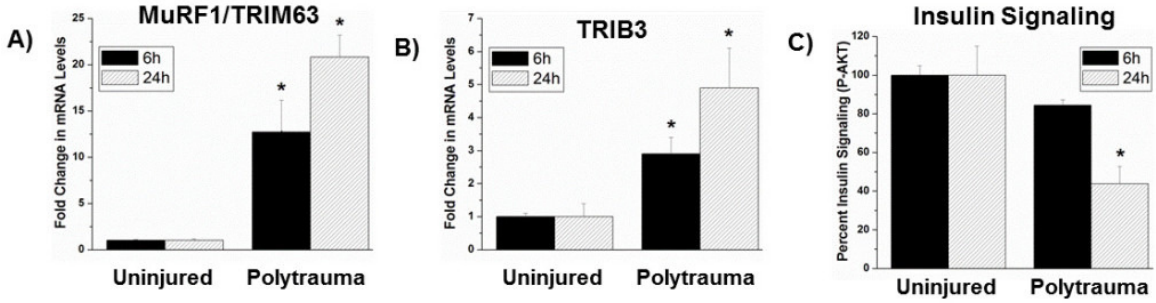

Fig. 1. Atrogene and TRIB3 mRNA levels increase, insulin signaling decreases following polytrauma. A) Increased skeletal muscle mRNA levels of MuRF1/TRIM63 at 6h and 24h following polytrauma. B) Increased skeletal muscle TRIB3 mRNA levels at 6h and 24h following polytrauma C) Reduced skeletal muscle insulin-inducible AKT phosphorylation/activation 24h following polytrauma. The data are presented as the mean ± standard error of the mean, n = 3-6 animals per group. * = $p < 0.05$ versus the uninjured group at the same timepoint.

We have developed a model of polytrauma in rats which combines burn injury, soft tissue trauma and penetrating injury to the GI tract. Rats were fully anesthetized and subjected to 15-20% total body surface area scald burn on the back in combination with a surgery and puncture of the lower GI tract (cecal ligation and puncture). Our study used four treatment groups; a uninjured group, burn injury alone, GI trauma alone, and burn plus GI trauma (polytrauma). Our previous studies have revealed that either single injury alone, are highly survivable, with 80-90% survival. However, when these two injuries are combined (polytrauma), there is dramatically decreased survival (~30% survival).

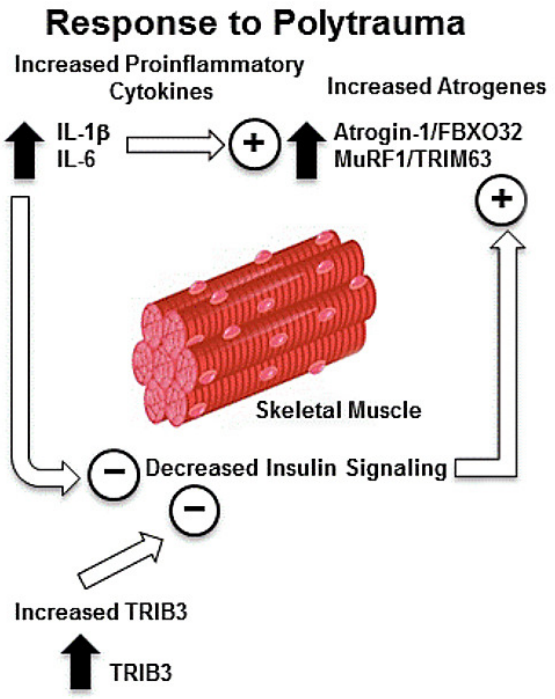

Fig. 2. The effects of polytrauma on skeletal muscle. Skeletal muscle proinflammatory cytokines (IL-1β and IL-6) increase following polytrauma which likely contributes to the decrease of skeletal muscle insulin-inducible signaling. Increased TRIB3 may also contribute to the decrease of insulin signaling. Both increased proinflammatory cytokines and decreased insulin signaling contribute to the increased expression of the atrogenes (Atrogin-1/FBXO32 and MuRF1/TRIM63) resulting in an enhanced rate of muscle protein degradation and muscle mass loss following polytrauma.

Injury is known to induce a catabolic state with muscle wasting (loss of muscle) and resistance to anabolic hormones (hormones that promote muscle growth and prevent muscle loss). Thus, we determined the effects of polytrauma on skeletal muscle. At both 6 and 24 hours following injury there was increased mRNA levels of IL-1β and IL-6, two proinflammatory cytokines, indicating an inflammatory state in skeletal muscle following polytrauma. Simultaneously, there was increased expression of two atrogenes, Atrogin-1 and MuRF-1 (Fig. 1A). These two proteins play a crucial role in the ubiquitin proteasome pathway which breaks down skeletal muscle proteins leading to muscle wasting and atrophy. There was also an increase in Tribbles homolog 3 (TRIB3) mRNA levels following polytrauma (Fig. 1B); a protein associated with the insulin resistant state in Type 2 Diabetic patients and in animal models of Type 2 Diabetes. To our knowledge this is the first report of increased TRIB3 expression following injury. In addition, there was development of an insulin resistant state in skeletal muscle following polytrauma. We observed reduced insulin activation of both the insulin receptor and an insulin-signaling pathway protein (AKT) downstream from the insulin receptor following polytrauma (Fig. 1C). Lastly, following polytrauma there were reduced total protein levels of the insulin receptor as well as insulin receptor substrate-1, another crucial protein in the insulin signaling pathway.

These studies demonstrate deleterious effects of polytrauma in skeletal muscle tissue, summarized in (Fig. 2), which is remote from the sites of injury and will contribute to the complex whole-body immune and metabolic dysfunction following combined injuries. Understanding the effects of polytrauma on skeletal muscle can result in improved treatment strategies to improve patient outcomes following complex injuries.

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Publication

Skeletal Muscle Atrogene Expression and Insulin Resistance in a Rat Model of Polytrauma
Akscyn RM, Franklin JL, Gavrikova TA, Messina JL.
Physiol Rep. 2016 Feb