TACSM Abstract

ROS-Mediated Localization of Caveolin-3 in the Sarcolemma During Short-term Mechanical Unloading

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ABSTRACT

The dystroglycan complex (DGC) is a latticework of cell membrane proteins that provide a mechanical link to the cytoskeleton and initiate cell signaling that provides integrity, regulates protein turnover, stimulates growth, etc. Caveolin-3 has been identified as a muscle-specific isoform of the caveolin family of proteins, and in skeletal muscle, caveolin-3 is localized in caveolae within the sarcolemma. Evidence from Duchenne and Limb-Girdle Muscular Dystrophies suggests the involvement of caveolin-3 and reactive oxygen species (ROS) in the disruption of the DGC and thus myopathy. We examined ROS as upstream activators of caveolin-3 sarcolemmal localization in skeletal muscle during disuse atrophy. EUK-134, a catalytic mimetic of superoxide dismutase (SOD) and catalase that degrades superoxide and hydrogen peroxide, was administered to hindlimb unloaded, fully mature rats, 24 hours prior to and during 54 hours of mechanical unloading. We observed that disuse-induced ROS production, using 4-hydroxynonenal as a marker, was accompanied by elevated localization of caveolin-3 in the sarcolemma and fiber atrophy in the unloaded group. In contrast, the unloaded+EUK-134 treatment group resulted in less caveolin-3 localization at the sarcolemma, attenuation of oxidative stress, and mitigation of muscle fiber atrophy. These results suggest that the increased sarcolemmal localization of caveolin-3 following mechanical unloading is redox dependent. Our findings imply that ROS play an important role in the early signaling events of mechanical unloading that elicit muscle atrophy. Our data also offer the prospect that targeted antioxidants such as the EUK family of drugs could have therapeutic potential during inactivity or other forms of myopathy.