Lipid hydroperoxides promote sarcopenia through carbonyl stress.

Abstract

Reactive oxygen species (ROS) accumulation is a cardinal feature of skeletal muscle atrophy. ROS refers to a collection of radical molecules whose cellular signals are vast, and it is unclear which downstream consequences of ROS are responsible for the loss of muscle mass and strength. Here, we show that lipid hydroperoxides (LOOH) are increased with age and disuse, and the accumulation of LOOH by deletion of glutathione peroxidase 4 (GPx4) is sufficient to augment muscle atrophy. LOOH promoted atrophy in a lysosomal-dependent, proteasomal-independent manner. In young and old mice, genetic and pharmacological neutralization of LOOH or their secondary reactive lipid aldehydes robustly prevented muscle atrophy and weakness, indicating that LOOH-derived carbonyl stress mediates age- and disuse-induced muscle dysfunction. Our findings provide novel insights for the role of LOOH in sarcopenia including a therapeutic implication by pharmacological suppression.