



AGE-RELATED DISRUPTION OF REDOX-REGULATED SIGNALLING FOLLOWING CONTRACTILE ACTIVITY IN SKELETAL MUSCLE

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Specific skeletal muscle adaptations to contractile activity appear to be modulated by redox signaling, primarily through reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2). While all early research assumed that ROS were deleterious by-products generated in muscle during exercise, subsequent studies established their roles as signaling molecules involved in a variety of key processes including mitochondrial biogenesis, stress responses, and metabolic regulation. Superoxide can potentially be generated through several pathways in contracting skeletal muscle, but most data now indicate that activation of NADPH oxidase 2 plays a key role (1, 2). Nox2-generated superoxide is rapidly converted to H_2O_2 which acts to activate a series of adaptive signalling pathways. Despite clear evidence that H_2O_2 is generated in muscle during contractions and that some key adaptations can be inhibited by high dose antioxidants, a major challenge in elucidating redox-regulated mechanisms in muscle has been the disparity between physiological intracellular H_2O_2 levels and the higher concentrations typically used in *in vitro* studies to activate redox-sensitive signalling pathways (3). This has led to development of the concept of redox relays, in

which thiol peroxidases, particularly 2-Cys peroxiredoxins (Prdxs), act as intermediates by reacting with H_2O_2 and transferring oxidizing equivalents to downstream proteins (4). Our recent findings demonstrate that low levels of H_2O_2 , or electrically-stimulated contractions rapidly oxidize Prdx1, Prdx2, and Prdx3 in mouse muscle fibres (5). Subsequent transcriptomic analysis of human skeletal muscle myotubes confirmed that Prdx2 is essential for upregulating mitochondrial genes in response to H_2O_2 or contraction (6). With ageing, skeletal muscle exhibits attenuated adaptations to exercise and impaired redox signalling with elevated mitochondrial H_2O_2 generation (7). Using an ageing mouse model, we observed diminished Prdx2 oxidation during contractile activity suggesting disruption of redox signalling (5). Thus, it appears that impaired muscle redox signalling may contribute to the poor responses to contractile activity seen during ageing that are a factor in age-related loss of muscle mass and function. Our findings emphasize the importance of redox homeostasis (not merely ROS suppression) in maintaining muscle health and the need to identify specific redox sensitive pathways and proteins affected by ageing.

Keywords: peroxiredoxins, hydrogen peroxide, superoxide, NADPH oxidase.