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Interplay between mitochondrial reactive oxygen species, oxidative stress, and hypoxic adaptation in FSHD: metabolic stress as a potential therapeutic target

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Oxidative damage characterizes FSHD, and recent evidence suggests metabolic dysfunction and perturbed hypoxia signalling as potential pathomechanisms. Here, we pinpoint the kinetic involvement of altered mitochondrial ROS metabolism and impaired mitochondrial function in the aetiology of oxidative stress in FSHD. Transcriptomic analysis in FSHD muscle biopsies reveals pathway enrichment for mitochondrial complex I assembly, oxidative stress response, and hypoxia signalling. Elevated mitochondrial ROS levels correlate with increased steady-state mitochondrial membrane potential in FSHD myogenic cells. DUX4 triggers mitochondrial membrane polarisation prior to oxidative stress generation and apoptosis, and affects mitochondrial health through lipid peroxidation. We identify complex I as the primary target for DUX4-induced mitochondrial dysfunction, with strong correlation between complex I-linked respiration and cellular oxygenation/hypoxia signalling in environmental hypoxia. Thus, FSHD myogenesis is uniquely susceptible to hypoxia-induced oxidative stress as a consequence of metabolic mis-adaptation. Mitochondria-targeted antioxidants rescue FSHD pathology more effectively than conventional antioxidants, highlighting the central involvement of disturbed mitochondrial ROS metabolism. Summarizing, this work provides a pathomechanistic model where DUX4-induced changes in oxidative metabolism impair muscle function, amplified when metabolic adaptation to varying O2 tension is required.