The stress-responsive NDRG2 protein alters the redox state in C2C12 myoblasts and is protective against hydrogen peroxide-induced oxidative stress

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How cells respond to different stresses is vital to maintain cellular homeostasis and cell survival. Maintenance of the cellular redox state is necessary for normal proliferation, differentiation and apoptosis of many cell types including skeletal muscle cells. The N-myc downstream-regulated gene 2 (NDRG2) gene contributes to the control of myoblast growth and differentiation where its suppression reduces myoblast proliferation and results in premature cell cycle exiting, impairing differentiation (Foletta *et al.*, 2009). In addition, NDRG2 is responsive to a variety of cell stresses in skeletal muscle. Its expression increases under catabolic conditions including glucocorticoid treatment, hypoxia and following endurance exercise; whereas, its expression is reduced in response to hypertrophic resistance training and following treatment with anabolic agents such as insulin and testosterone (Foletta *et al.*, 2009, 2013). The physiological outcomes of NDRG2's responses to these different stresses, however, are not well understood or whether changes in NDRG2 levels affect the cellular redox state in skeletal muscle cells. Here, we investigated the role of NDRG2 in the control of the cellular redox state in proliferating C2C12 myoblasts. Suppression of NDRG2 caused increased reactive oxygen species (ROS) levels, mitochondrial membrane potential and cellular respiration. Furthermore, increased oxidation of glutathione was measured in conjunction with elevated mRNA expression of the glutathione peroxidase 3, peroxiredoxin 5 and NADPH oxidase 4; enzymes that are all linked to the control of cellular hydrogen peroxide levels. Despite the elevated ROS and altered redox state, no enhanced cell death was observed, and in fact, reduced caspase 3/7 activities were measured. In addition, NDRG2 overexpression was performed and found protective against hydrogen peroxide-induced oxidative stress where its increased expression enhanced cell viability, and reduced endoplasmic reticulum stress and apoptosis. These data suggest that NDRG2 has positive benefits for maintaining cellular homeostasis in response to stress and that a key process through which it does this involves the control of the cellular redox state.

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