

The Impact of Mitochondria in Muscle Cell Tolerance Induction

Genevieve Abd, PhD¹, Agata M. Parsons, DMV¹, Haiying Pan, MS¹, Yong Li, MD, PhD²

¹ Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI, USA.

²Department of Orthopaedic Surgery, and Biomedical Engineering, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI, USA. Email: yong.li@med.wmich.edu

DISCLOSURES: Dr. Li is one of the executive editors for Journal of Cellular Biochemistry (JCB), all other author have no COI.

INTRODUCTION: Cell transplantation has tremendous potential as a therapeutic in cases of extensive damage to skeletal muscle tissue as well as muscle related disorders such as muscular dystrophy. Treatment success is measured by the ability of donor cell survival to overcome rejection after implantation. We detected hypoxic or cobalt chloride (CoCl₂) pretreatment of muscle cells can trigger an adaptive response called hypoxia-induced tolerance which markedly increases the ability of these cells to survive, leading to enhanced therapeutic effects in muscle regeneration. This likely is due to up-regulation of hypoxia-inducible factor-1alpha (HIF-1α) which promotes angiogenesis and influences mitochondrial oxidative metabolism. Mitochondria plays a key role in cellular responses to internal and external stressors. As such, we hypothesize that mitochondria play an important role in hypoxia-induced tolerance acquisition in muscle cells.

METHODS: *Hypoxia:* C2C12 (myoblast cell line) and MuSCs cells were cultured in either 5% oxygen (hypoxia) or 21% oxygen (control). After 12, 24 and 48 hours protein was isolated and western blot was performed for XIAP, Bcl-2 and OXPHOS respiratory complex subunits. *Chemical Stimulation:* C2C12 cells were cultured in 0 μM (Ctl), 25 and 50 μM CoCl₂. After 6-, 12- and 24-hours western blot were performed for XIAP and Bcl-2.

RESULTS SECTION: Those apoptotic inhibitors, such as XIAP and Bcl2 expression increased following hypoxia treatment. Similarly, CoCl₂ stimulation led to increased expression of XIAP and Bcl-2 (**Fig. 1**). Mitochondrial complex I and III protein were significantly decreased in hypoxia treated C2C12 myoblasts (**Fig. 2**).

DISCUSSION: These findings suggest that hypoxia and CoCl₂ encourage the development of mitochondrial pro-survival proteins, which may benefit cell survival and increase the effectiveness of muscle cell transplantation. The investigation into altered respiration is suggested by altered levels of respiratory complex proteins.

SIGNIFICANCE/CLINICAL RELEVANCE: Understanding the mechanism causing cellular tolerance in muscle cells, such as myoblasts and MuSCs, will have great significance and application in cell therapies aimed at treating muscle injury or dystrophy disorders.

ACKNOWLEDGEMENTS: This project was funded by the WMed Pilot Research Project Support Program.

IMAGES AND TABLES:

