CHRD 2022: Abstract & Poster Submission Form

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Presenter Status

- ○ Undergraduate Students
- ○ Masters Student
- ◉ PhD Student
- ○ Post-Doctoral Fellows
- ○ Residents
- ○ Non-Trainee

Research Category

- ◉ Basic Science
- ○ Clinical
- ○ Community Health / Policy

Role in the project

- ☑ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Title

Tuning Muscle Energy Homeostasis: The Role of Nix in Muscle Metabolism

Background

Early in diabetes, skeletal muscle ceases to respond to insulin signalling and as the disease progresses, the positive effects from muscle on whole body metabolism during exercise are diminished. The protein Nix is a central signalling protein in muscle metabolism that can regulate insulin signaling, mitochondrial turnover, and muscle growth and development.

Objective

The objective of this research is to answer the questions: What aspects of muscle metabolism is Nix critical for, and what are the effects on muscle and whole-body metabolism in the absence of Nix?

Methods

To determine the effect of Nix, muscle-specific deletion of Nix in mice was achieved using Cre-lox recombination and used in a series of histological, biochemical, and physiological tests. To assess cellular mechanisms, a cell culture model of C2C12 myotubes was coupled with fluorescent microscopy.

Results

Deletion of Nix in muscle caused the appearance of ragged red fibers (N=3, $p<0.001$), a diagnostic marker of accumulated dysfunctional mitochondria, which was confirmed by electron microscopy. In the cellular model, we observed that depleting Nix levels resulted in impaired mitochondrial clearance which supports the phenotypes observed in vivo. Array-based analysis of kinase activity (kinomics) indicated that Nix-knockout mice could have deficiencies in activity of enzymes in aerobic respiration. Lastly, physiological tests showed that Nix-knockout mice had reduced exercise endurance, increased CO_2 output during treadmill running suggesting greater reliance on anaerobic respiration, and impaired glucose tolerance.

Conclusion

Together these data provide evidence that deletion of Nix results in impaired clearance of dysfunctional mitochondrial, decreased exercise tolerance, and diminished ability to regulate blood glucose levels. In conclusion, Nix plays no small role in muscle metabolism through the mitochondria, and the absence of Nix results in multi-faceted disruption muscle metabolism including systems important to the development (ie. insulin resistance) and management (ie. exercise) of type 2 diabetes.

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Authors

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