ABSTRACT SUBMISSION FORM

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SEX + GENDER

Exploring the role of sex and gender on health research

CHRD
CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

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Title
Tuning Muscle Energy Homeostasis: The Role of Nix in Mitophagy and Adaptation

Background
Exercise is instrumental in reversing derangements to muscle metabolism, such as insulin-resistance during type 2 diabetes. Mitochondrial quality control is important for efficient use of metabolic fuel, but the mechanism remains unclear. We observed that deletion of the gene Nix, a regulator of mitochondrial clearance (mitophagy) and calcium signals, in muscle caused the accumulation of dysfunctional mitochondria in mice.

Objective
The objective is to determine the role of Nix in regulating mitophagy and muscle adaption in relation to muscle metabolism.

Methods
To determine the effect of Nix, the muscle-specific deletion of Nix in mice was achieved using Cre-lox recombination and human skeletal actin-Cre. To assess the mechanism of Nix, a cell culture model of C2C12 myotubes were stimulated with electrical pulses to induce contraction (1hr) then fluorescent microscopy or biochemical assays were performed.

Results
Deletion of Nix in the muscle of mice caused the appearance of ragged red fibers only in males (N=3, $p<0.001$). This phenotype is a diagnostic marker of myopathy caused by accumulation of dysfunctional mitochondria. Myotubes that underwent contractile activity increased expression of Nix (~1.9-fold, $p<0.05$) and increased mitophagy markers (P62, ~5-fold, $p<0.05$; LC3A-II, ~4-fold, $p<0.05$). The increase in mitophagy was cross-validated with a fluorescent mitophagy indicator (~1.4-fold, $p<0.05$); however, when Nix protein levels were reduced by sh-RNAs, the effect was blocked ($p<0.05$) implicating Nix as a mitophagy regulator. Additionally, nuclear calcium accumulation increased in response to contractile activity (~2-fold, $p<0.05$) and this response was blocked by partial loss of Nix ($p<0.05$). Nix regulates

calcium-dependent transcription factors, activating NFATc3 (~3-fold, p,0.05) and deactivating HDAC5 (~0.5-fold, p-value) which target adaptive gene expression (myoglobin, ~4-fold, p<0.05).

Conclusion
Together these data show that Nix regulates both mitophagy and adaptive gene expression in muscle, both of which are important components of metabolism and are known to be disrupted during the onset of diabetes.

Theme:
Basic Science

Do you have a table/figure to upload?
No

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
PhD Student

What was your role in the project?
All of the above - Design, perform experiments, analyze data, and write abstract

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