CHRD 2024: Abstract Submission Form

Presenter Name
Nicholas Klassen

Presenter Status
Undergraduate Students

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Diagnostic potential and functional effects of circulating extracellular vesicles in patients with MELAS

Background
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a mitochondrial disorder characterised by progressive muscular and neurological symptoms. MELAS manifests during early childhood, is difficult to diagnose, and has no known cure. Extracellular vesicles (EVs) are lipid-delimited nanoparticles secreted from cells containing biological cargo.

Objective
Here, we investigated the potential of EVs as diagnostic biomarkers of MELAS, and their functional effects on mitochondrial respiration in skeletal muscle myotubes.

Methods
Blood was collected from consented patients with a confirmed MELAS diagnosis (N=9), along with age- and sex-matched healthy controls (under REB# HS25169 [H2021:341]). Plasma was separated, small EVs isolated via size-exclusion chromatography, and characterised by size, concentration, and zeta potential using tunable resistive pulse sensing (Izon). Protein yield was determined by microBCA, and expression of EV-subtype markers quantified by immunoblotting. Oxygen consumption rates (OCR) were measured (Agilent XFe24) in myotubes treated with freshly isolated MELAS-EVs or control-EVs from 33µl plasma (once/day, for 2 consecutive days, 3 technical replicates/subject). Data were analysed using paired t-tests .

Results
Plasma EV concentration (particles/ml) increased by 1.96-fold ($p=0.0273$, N=9), concomitant with a 45.8% decrease in total protein yield per EV (µg/particle, $p=0.0117$, N=9) in MELAS vs. control, with no significant differences in average EV size and zeta potential between groups. Protein expression of small-EV markers TSG101 decreased by 49.8% ($p=0.0118$, N=8), CD63 decreased by 64.5% ($p=0.0001$, N=9), and flotillin-1 increased by 1.90-fold ($p=0.0245$, N=9) in MELAS. Basal OCR was reduced by 12.8% ($p=0.0315$, N=9), with no difference in maximal OCR, in myotubes treated with MELAS-EVs.

Conclusion
Patients with MELAS had higher plasma EV concentration, with less protein yield/EV, and a remarkably differential expression of small-EV protein markers. MELAS-EVs reduced basal OCR in myotubes. EVs appear to be a promising biomarker for MELAS, and circulating EVs in this population may be perpetuating metabolic dysfunction systemically.

Do you have a table/figure to upload?
No

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