Presenting Author Name
Nicholas Klassen

Presenting Author Category
PhD Student

Research Category
Basic Science

Abstract Title
Age- and sex-dependent changes in biological characteristics and functional effects of plasma-derived extracellular vesicles from patients with MELAS

Background
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome is a genetic disorder characterised by progressive neuromuscular and other multisystemic signs and symptoms. MELAS manifests during childhood, can be difficult to diagnose, and has no cure. Extracellular vesicles (EVs) are lipid-delimited nanoparticles secreted from cells containing biological cargo, with demonstrated efficacy as biomarkers.

Objective
Previously we found plasma-derived EVs from MELAS patients (MELAS-EVs) were biochemically distinct and reduced oxygen consumption rates (OCR) in myocytes. Here, we performed a secondary analysis of data to identify any sex- and age-specific effects in these variables.

Methods
Plasma-derived EVs were isolated from MELAS patients, and age- and sex-matched healthy controls (n=9). EV biophysical characteristics, protein expression and double-stranded (ds)DNA content were measured. OCR were assessed in myotubes treated with control-EVs or MELAS-EVs (once/day, 2 days). Results were stratified by age (<25 years, n=6; >25 years, n=3) and sex (female n=6; male n=3). Data were checked for normality, and analysed using paired Student's t-tests or Wilcoxon tests.

Results
Younger MELAS patients (<25 years) had a 1.42-fold increase in plasma-EV concentration (p=0.0191), 50.7% lower EV-protein yield (p=0.0156), and a 67.1% lower expression of small-EV protein CD63 (p=<0.0001) vs. age-matched controls. In males, EV-dsDNA increased 2.02-fold (p=0.0027), small-EV protein TSG101 decreased by 68.6% (p=0.0337), and CD63 expression reduced by 73.8% (p=0.0007) vs. sex-matched controls. In females, EV-dsDNA was 29.2% lower (p=0.0920), EV-protein yield decreased by 51.5%, (p=0.0368), and small-EV protein flotillin-1 was 2.03-fold higher (p=0.0462) than sex-matched controls. Lastly, a 10.6% decrease (p=0.0292) in basal OCR in myotubes treated with MELAS-EVs from females vs. sex-matched controls was observed.

Conclusion
EVs may serve as a promising biomarker for MELAS due to observed biophysical differences. These differences are more pronounced in younger patients, which could facilitate earlier diagnosis. Sex-specific differences in EV composition and functional effects are striking, and warrant further investigation.

Authors

Name	Role	Profession
Nicholas Klassen	Presenting Author	Graduate
Tamiris de Fatima de Goebel de Souza	Co Author	Post Doctoral Fellow
Patience O. Obi	Co Author	Graduate
Berkay Özerkliğ	Co Author	Graduate
Tiana Tiede	Co Author	Undergraduate
Abhay Srivastava	Co Author	Post Doctoral Fellow
Christopher Pascoe	Co Author	Associate Professor
Samantha Marin	Co Author	Medical Doctor
Sanjiv Dhingra	Co Author	Full Professor
Cheryl Rockman-Greenberg	Co Author	Full Professor
Ayesha Saleem	Supervisor	Assistant Professor