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

Energy deficits and reduced mitochondrial capacity: cause of the extra-skeletal features of hypophosphatasia?

Background

Hypophosphatasia (HPP) is an inherited disorder of skeletal mineralization primarily affecting bones and teeth. HPP is characterized by low circulating levels of tissue non-specific alkaline phosphatase (TNSALP). Mutations in the ALPL gene encoding TNSALP cause HPP. Patients with HPP also have numerous debilitating extra-skeletal manifestations including fatigue, muscle weakness, bone and joint pain, CNS deficits and seizures. Evidence is accumulating that TNSALP is important for regulating mitochondrial energy metabolism.

Objective

To investigate if mitochondrial energy deficits may be the root cause of the extra-skeletal features in HPP.

Methods

We tested this hypothesis in iPSC-lines from 3 patients with childhood-onset HPP due to compound heterozygous ALPL gene mutations (c.571G>A [p.Glu191Lys] and c.1001G>A [p.Gly334Asp]). Peripheral blood mononuclear cells were reprogrammed into induced pluripotent stem cells (iPSCs). These iPSCs were evaluated for pluripotency, trilineage differentiation and chromosomal abnormalities. Mitochondrial function was assessed by comparing cellular lactate dehydrogenase (LDH) and ATP levels along with mitochondrial respiration using Seahorse between the patient and control iPSC lines.

Results

We generated 3 HPP patient-specific iPSC lines. The ALPL mutations were confirmed. No chromosomal abnormalities were detected. These lines were positive for pluripotency markers. These lines could differentiate into endodermal, mesodermal and ectodermal cell lineages. We observed that the HPP iPSC cell lines were stressed and were significantly energy deficient as indicated by elevated LDH levels and lower cellular ATP levels respectively. Further, significantly reduced mitochondrial respiration was observed in the HPP iPSCs compared to controls.

Conclusion

We successfully established HPP patient-specific iPSC cell line models and report the first demonstration of energy deficits and reduced mitochondrial capacity in iPSCs derived from patients with HPP. Mitochondrial dysfunction could be the basis for the extra-skeletal phenotypes of HPP and is a promising target for potential new adjuvant interventions in addition to recently approved enzyme replacement therapy.

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Authors

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