Abstract for half-time review

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Title: Mitochondrial disorders in children - development of a diagnostic tool

Background
Mitochondrial disorders affect cell survival and function. Symptoms can present early in life as severe illness where the infant deteriorates, or later as seizures, liver failure, heart failure or muscle weakness. For doctors faced with a critically ill or unhealthy child it is often difficult to rule out or to confirm mitochondrial disease as the reason for the patient’s illness. The conventional clinical investigation at Skåne University Hospital usually requires patient transportation to Gothenburg or Stockholm for muscle biopsy. A possible alternative is the use of freshly isolated mitochondria-containing blood cells for diagnosis of mitochondrial disease.

Aims and methods
The first aim of this project was to establish methodology for assessment of mitochondrial function using high-resolution respirometry in intact and permeabilized platelets cells and apply these methods on different reference cohorts. This was done by collecting and analysing blood samples from adults, and children undergoing a simple operation, and from
newborn children (umbilical cord blood). Further, we studied the impact of storage of samples at different temperatures and times.

A second aim was to apply our developed diagnostic methods on children with symptoms where there was suspicion of mitochondrial disease. The clinical data from patient with suspected mitochondrial disease were collected and comparison of other methods (mitochondrial analysis of muscle biopsy and full clinical workup) was done. With this data the aim was to assess the value of platelet respirometry as a complement to the existing clinical routines to diagnose mitochondrial disease.

As the third aim we will compare the use of platelets with white blood cells as a diagnostic tools. In this study, which includes a total of 318 patients and controls, we will directly compare platelet and white blood cell respiration from the same sample for each person, as well as with muscle tissue in a subgroup of healthy persons.

The fourth aim of this thesis project will be to simulate mitochondrial disease in healthy blood cells and specifically study which parameters or ratios of parameters that are most sensitive to particular mitochondrial inhibition. The results could be used to fine-tune our respiration analysis protocol. Further, samples will be submitted for metabolomics analyses with the aim to determine the metabolomic profile of defined mitochondrial complex inhibition.

**Preliminary results**
The results from aim 1 and aim 2 have been published (see below).
For aim 3 all data have been retrieved and is now being analysed by the group.
For aim 4 initial method development for titration of the various inhibitors have been executed and feasibility samples have been sent for metabolomic analyses.

**Significance**
Oxygen consumption measurement in blood cells, can be of aid in diagnosing mitochondrial disease in pediatric patients. Respirometry is a fast method with low invasiveness. In combination with other clinical parameters and tests it can increase the diagnostic yield, and can be a adjunct tool for diagnosis of mitochondrial disease.

**Papers for the PhD thesis:**