Do mitochondria play a role in ME/CFS?

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ME/CFS Awareness Week May 10th 2016
Mitochondrial dysfunction associates with many chronic diseases.

- Parkinson’s disease
- Aging
- Hepatobiology & In vitro toxicity
- Cardiovascular
- Obesity/Diabetes
- Cancer

Cause? Consequence? Viable treatment option?
What do mitochondria do?

Make “cellular” energy from carbohydrates, fats and proteins

70 Kg per day!

“300mg for every heart beat!”

“36 ATP molecules are produced from one molecule of glucose with mitochondria working but only 2 ATP are produced if mitochondria completely fail”

Resting metabolic rates Kcal Kg$^{-1}$ d$^{-1}$ (Ellia 1992)

- Brain: 240
- Liver: 200
- Heart/kidneys: 440
- Muscle: 13
- Adipose tissue: 4.5
- Residual organs & tissue: 12
>70 polypeptides

Nuclear DNA

13 polypeptides

MtDNA

Matrix

ADP

ATP

Inner membrane

O$_2^-$

CI

CII

CIII

CIV

e$^-$
Mitochondria more fascinating facts

Mitochondria are also involved in:

- The synthesis of many building blocks (i.e. DNA & lipids for membranes.)
- Regulating cellular processes (i.e. insulin secretion, immunity, intracellular signalling)
- Cellular reducing power (NADH, NADPH) required by many enzymes.

Mitochondrial quality control: mitophagy

Mitochondria = red, Autophagosomes = green

Matt Daniels
The 5 main symptoms of ME/CFS

• Reduction or impairment in ability to carry out normal daily activities, accompanied by profound fatigue.
• Post-exertional malaise (a dramatic worsening of symptoms after physical, cognitive or emotional effort).
• Unrefreshing sleep.
• Cognitive impairment.
• Orthostatic intolerance (symptoms worsen when a person stands upright and improve when a person lies back down)

Institute of Medicine report, Feb 2015
What is the cause of ME/CFS?

- Triggered by infection or viral illness?
- Evidence of epidemics.
- Stress, work overload?
- Immune system dysfunction?
- Genetic pre-disposition?
- Environmental factors (i.e. pesticides, toxins, anaethetics, recycled air on flights, etc)?
ATP levels are reduced in neutrophils from ME/CFS patients.

2-6 million per ml of blood. Live for around 24 hrs. Activated by pathogens. Role to fight infection.
What might reduced cellular/mitochondrial ATP mean for ME/CFS neutrophil function?

• The neutrophil mitochondria are damaged.
• The neutrophil mitochondria are fully functional but switched off.
• The neutrophils are dying/processing issues.
• Nothing wrong with the mitochondria a non-deconditioned control group was used for comparison.
Mitochondria are damaged

Mitochondrial disorders
Mitochondrial disorders: can affect any organ at any age

Caused by mutations in mtDNA or nuclear encoded genes affecting mitochondrial function (1/5000)

Muscle pathology

Proliferation of mitochondria

COX –ve fibres

Frequency of the most common mtDNA mutations in the general population is 1/200

Evidence for mtDNA variants associating with ME/CFS severity (disease modifiers?) (Billing-Ross (2016))
Mitochondrial function can be modified by the environment, viral infection and trauma.
High glucose switches off cancer cell mitochondria in cancer cell lines

Otto Warburg
High glucose switches off cancer cell mitochondria in cancer cell lines

Otto Warburg

Mitochondrial respiration

Glycolysis

Add glucose (30-60mins)
Omics approaches

Hypothesis/obsession
Omics approaches

**Genomics: big data**
DNA differences found by sequencing the whole genome (3 billion bases per person).


**Proteomics**
Looking at differences in all proteins (approx 20,000)

**Metabolomics**
Changes in cellular chemicals (i.e. ATP) in a disease or with treatment.
>17,000 metabolities

**Others**
Comparing metabolic differences in two cancer cell lines cultured on 5mM glucose (plasma levels) and galactose (no glucose) using metabolomics: Untargeted analysis

17,605 metabolites

Emma Newport & James McCullagh (Chemistry)
Brain death in the donor can cause kidneys to be damaged to the point they are no longer suitable for transplantation: how & why?
Brain death induces mitochondrial dysfunction in Kidneys: role of cytokines?

Proteomic analysis identified 1434 proteins
Viral infection may induce an immune response via mitochondria

- Altered mitochondrial morphology
- mtDNA fragmentation & release into the cell
- Activation of innate immunity pathways

Draft clinical study with a post exertional malaise component

Karl Morten & Joanna Poulton (Mitochondrial biology)
Helen Dawes (Exercise Physiology, Brookes)
Fiona Duxbury, Brian Angus and the Oxford ME/CFS clinical team
James McCullagh (Metabolomics, Chemistry)
Benedikt Kessler (Proteomics, TDI)
Berne Ferry (Clinical Immunology, NHS)

Collaborators: Betsy Keller (Ithica, Cornell)

<table>
<thead>
<tr>
<th>TABLE 1. Means and standard deviations for exercise performance variables by group and test.</th>
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<tbody>
<tr>
<td><strong>Test 1</strong></td>
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<tr>
<td></td>
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<tr>
<td>CFS</td>
</tr>
<tr>
<td>VO₂ peak*</td>
</tr>
<tr>
<td>26.23(4.92)</td>
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<tr>
<td>AT*</td>
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<tr>
<td>15.01(4.90)</td>
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<tr>
<td>HER (%)</td>
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<td>94.83(8.86)</td>
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<td>DUR (min)</td>
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<td>9.3(2.44)</td>
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<td>Controls</td>
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<td>20.47(1.80)</td>
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* ml/kg/min

VanNess (2007) 14 (2) 77
Oxford clinical study on ME/CFS (> 100 patients)

Key issues: Patient selection, suitability of neutrophils/monocytes for mitochondrial testing, selection of an appropriate control group

Tests on blood samples

- Mitochondrial function tests on neutrophil & monocyte fractions (Oxford)
- Proteomics: plasma & cell fractions (Oxford)
- Metabolomics: plasma & cell fractions (Oxford)
- Immune cell function (Oxford)
- Genomics: DNA sequencing (?)
Initial MEA funded pilot (5 months)

• Determine mitochondrial stability in neutrophils/monocytes. Develop robust testing criteria to assess whether cells have gone off!
• Use cell lines with established mitochondrial defects to develop a mitochondrial assessment protocol similar to the Acumen test.
Do we have all the right pieces yet?
Common SNP variants associated with type II diabetes: modifiers or causal?