Cellular and molecular assessment of mitochondrial function as a predictor of ageing phenotype in older PLWH

Matthew Hunt
3rd year PhD student, Newcastle University
10th International Workshop on HIV & Ageing
10/10/19
Public Health England (2018) – Progress towards ending the HIV epidemic in the United Kingdom
Mitochondria and nucleoside reverse transcriptase inhibitors (NRTIs) in skeletal muscle

Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy

Enrica Arnaudo, Marinos Dalakas, Sara Shanske, Carlos T. Moraes, Salvatore DiMauro, Eric A. Schon

Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations

Brendan A Payne, Ian J Wilson, Charlotte A Hateley, Rita Horvath, Mauro Santibanez-Koref, David C Samuels, D Ashley Price, & Patrick F Chinnery

VOLUME 43 | NUMBER 8 | AUGUST 2011 | NATURE GENETICS
Mitochondrial dysfunction in skeletal muscle

Mitochondrial dysfunction

Myofiber defects

Physiological decline

Frailty
Study aims

1. Investigate the extent of skeletal muscle mitochondrial dysfunction in older PLWH

2. Better understand the pathogenesis of sarcopenia and frailty in older PLWH

3. Identify any correlations between mitochondrial dysfunction and other muscle abnormalities in older PLWH
MAGMA Study

- 30 HIV+
- 15 HIV-
- ≥50 years old
- Male
- Skeletal muscle biopsies (TA)
- DXA scan (body composition)
- Short physical performance battery (SPPB)
Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV+ (n = 30)</th>
<th>HIV- (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 (54-65)</td>
<td>59 (52-69)</td>
</tr>
<tr>
<td>Race (white)</td>
<td>30 (100%)</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27 (25-28)</td>
<td>32 (28-37)</td>
</tr>
<tr>
<td>Months on ART</td>
<td>99 (74-158)</td>
<td>//</td>
</tr>
<tr>
<td>Months since diagnosis</td>
<td>189 (118-273)</td>
<td>//</td>
</tr>
<tr>
<td>Months with untreated HIV</td>
<td>70 (5-131)</td>
<td>//</td>
</tr>
<tr>
<td>CD4 (cells/ml)</td>
<td>637 (502-766)</td>
<td>//</td>
</tr>
<tr>
<td>Viral load (copies/ml)</td>
<td>55 (31-79)</td>
<td>//</td>
</tr>
</tbody>
</table>
## Frailty and physical function

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV+ (n = 30)</th>
<th>HIV- (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frailty status (FFP):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frail</td>
<td>4 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>15 (50%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Robust</td>
<td>11 (37%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td><strong>Physical performance (SPPB):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19 (63%)</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 (34%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Low</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Muscle function/sarcopenia status:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcopenia</td>
<td>5 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pre-sarcopenia</td>
<td>6 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normal</td>
<td>18 (60%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>34 (30-41)</td>
<td>35 (32-43)</td>
</tr>
</tbody>
</table>
Multiplex fluorescence immunohistochemistry

LAMININ
VDAC1
NDUFB8
MTCO1
OVERLAY

Laminin – myofiber boundary marker
VDAC1 – mitochondrial mass
NDUFB8 – complex I subunit
MTCO1 – complex IV subunit
Complex I and IV defects in PLWH
Lower proportion of regenerated myofibres in HIV+ individuals
HIV status does not affect fibre type proportions or fibre area
Intramyocellular lipid analysis (bodipy)

• Fluorescent alternative to oil red O
• Stains intramyocellular lipid
• Associated with insulin resistance and muscle pathology
No difference in IMCL accumulation
Which factors drive increased mitochondrial dysfunction in PLWH?

Factors include:

• Age
• HIV-related clinical characteristics
• ART regimens
• BMI
• Lifestyle factors (smoking etc.)

➢ CI defects associated with age (p=0.038, r= 0.31)
What are the consequences of mitochondrial dysfunction?

Factors include:

- Frailty status
- Sarcopenic status
- Physical activity
- Body composition

Cl defects associated with frailty
(p=0.037, r=0.102)
Conclusions

1. Data supports previous observations of increased prevalence of frailty and sarcopenia in older PLWH compared to matched HIV- individuals.

2. Older PLWH have higher levels of skeletal muscle mitochondrial dysfunction than HIV- individuals.

3. Skeletal muscle mitochondrial defects are associated with frailty.

4. However, these defects are not explained by exposure to any particular ART regimens.
Future questions to answer...

• What is driving the clear differences in mitochondrial function if ART isn’t involved?

• Is there an accelerated ageing phenotype that can be defined?
Acknowledgements

Supervisors

• Dr Brendan Payne
• Dr Amy Vincent
• Professor Sir Doug Turnbull

Mitochondrial research group

• Dr Angela Pyle
• Professor Robert Taylor
• Megan McNiff
• Aarabi Canagarajah
• Gavin Falkous
• Laura Bone

MAGMA/POPPY study

• Caroline Sabin (University College London)
• Alan Winston (Imperial College London)