Mitochondrial DNA damage in brain associated with HIV infection

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MtDNA depletion and HIV

Depletion of mtDNA content is well described in old NRTIs, which inhibit pol-γ in cells from blood, muscle and adipose tissue.

Lewis et al. (2003) Nat Rev Drug Discov 2(10)
Mitochondrial DNA mutations and HIV

- Increased mtDNA mutations are now described in HIV patients
  - Blood (PBMCs), muscle, peripheral neurons
  - Mainly linked to NRTI treatment
HIV and mtDNA in brain

- Mild cognitive impairment remains common in treated HIV patients but the pathophysiology is not fully understood.

- Changes in mitochondrial DNA in brain have been described in normal aging and age-related conditions.
Hypothesis

MtDNA content will be decreased and mtDNA mutations increased in the brain of HIV-infected patients
Methods

• Samples – Brain biobanks in US & UK, frontal cortex
  • Number of cases = 25; number of controls = 10
  • Excluded: brain opportunistic infections
• Neurocognitive testing done within ~6 months prior to date of death
• mtDNA Copy Number and Common Deletion mutation measured by multiplex qPCR
δ4977 mtDNA common deletion

Adapted from Chen et al. (2011) BMC Med Genet 12
MtDNA content
MtDNA content was lower in HIV-infected subjects compared with controls.

Mean ± SEM
Controls 706±68 copies/cell
HIV 364±39 copies/cell
No association between age at death and mtDNA copy number

Mean age HIV 47.7 y
Mean age controls 40.5 y
Pol-\(\gamma\) inhibiting NRTI exposure

D-drug Treatment

mtDNA copy number

Never (\(n=5\)) Past (\(n=10\)) Present (\(n=10\))

ddC, ddl, d4T
Low mtDNA content was significantly associated with low CD4 lymphocyte count.

\[ P = 0.0007 \]
\[ r = 0.65 \]

CD4 mean 92 cells/µL (range 2-791)
Uncontrolled viraemia associates with low mtDNA content

Mean ± SEM
Low VL 482±86 copies/cell
High VL 295±31 copies/cell
Neurocognitive impairment

HAD = HIV-associated dementia
MCMD = mild cognitive motor disorder
SNI = subclinical neuropsychological impairment
NN = neurocognitively normal
MtDNA deletions
CD mutation was significantly more prevalent in the brain of HIV-infected cases compared with controls.

Mean ± SEM
Control -3.21±0.15 copies/cell
HIV+ -2.87±0.07 copies/cell

P = 0.03
Common deletion levels and age at death

HIV, P=0.07, r=0.37
Control, P=0.76, r=0.11
Pol-γ inhibiting NRTI exposure

D-drug Treatment

![Box plot showing log10(CD549/mtDNA genome copy) for Never (n=5), Past (n=10), and Present (n=9) categories.]

ddC, ddl, d4T
Neurocognitive impairment

HAD = HIV-associated dementia
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Conclusions

• Brain from HIV-infected people shows an excess of mtDNA damage compared with uninfected controls
  • Reduced mtDNA content
  • Increase in the aging-associated mtDNA common deletion
• Changes not associated with NRTI exposure
  • Lower levels of drug in the CNS?
• A reduction in mtDNA content was associated with markers of HIV disease activity
  • Mitochondrially-mediated viral neurotoxicity?
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