NAD$^+$ supplementation and DNA repair as therapeutic strategies in Alzheimer’s disease

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Alzheimer’s disease (AD)
Alzheimer’s disease and DNA repair

DNA repair activity

Weissman et al, 2007, NAR
DNA polymerase $\beta$ in human brain

Inferior parietal lobule

Cerebellum

Polymerase $\beta^{+/-}$

Weissman et al, 2007, NAR
Sykora et al, 2015, NAR.
3xTgAD/Polβ°/− mice have many more similarities to human AD than 3xTgAD mice

- Synergistic loss of hippocampal volume
- Deficient neurogenesis
- Neuronal cell death
- Loss of synaptic plasticity
- Memory loss
- Higher similarity to human diseases
- Higher similarity to human AD
- Breakdown of mitochondrial bioenergetics
- Diabetes profile
- Deficient sense of smelling

Sykora et al NAR 2015
Misiak et al, Aging Cell 2016
NAD\(^+\) links DNA repair and mitophagy to mitochondrial maintenance

Genome maintenance
Mitochondrial homeostasis
Healthy aging

Fang EF et al., Nature Reviews MCB, 2016
Fang EF and Bohr VA, Autophagy, 2016
NAD⁺/NADH ratio is lower in AD mice and increases after NR treatment

Modified from Fang et al, 2016, Cell Metabolism.
Experimental Design

Nicotinamide Riboside (NR)

- Treatment
  - WT
  - Polβ
  - AD
  - AD/Polβ
  - NR
  - Veh

16-18 months

Behavior Tests
- Cognitive Tests
- Locomotor Tests
- Metabolic Tests
- Anxiety Tests
- Motor Tests

Mechanism
- Electrophysiology
- Biochemistry
- Immunostaining
- Microarray
- ...
NR improves learning and memory in 3xTgAD and 3xTgAD/Polβ+/− mice

Morris Water Maze test

Hou Y et al., PNAS, 2018
NR ameliorates cognition and memory deficiency in 3xTgAD and 3xTgAD/Polβ+/- mice

Object Recognition test

Y-maze

Hou Y et al., PNAS, 2018
Pathway analysis bases on gene expression changes

Hou Y et al., PNAS, 2018
NR improves synaptic function in long-term potentiation

Hou Y et al., PNAS, 2018
NR decreases neuroinflammation in 3xTgAD and 3xTgAD/Polβ\(^{+/-}\) mice.
NR decreases tau phosphorylation in 3xTgAD and 3xTgAD/Polβ+/− mice

Hou Y et al., PNAS, 2018
NR doesn’t decrease Aβ in 3xTgAD and 3xTgAD/Polβ+/− mice

Hou Y et al., PNAS, 2018
DNA damage was decreased after NR treatment in 3xTgAD and 3xTgAD/Polβ+/- mice

Hou Y et al., PNAS, 2018
Oxidative damage and mitochondrial ROS was decreased after NR treatment in AD human fibroblasts

Hou Y et al., PNAS, 2018
SIRT3 and SIRT6 levels are restored after NR treatment in 3xTgAD and 3xTgAD/Polβ+/− mice

Hou Y et al., PNAS, 2018
Summary

DNA Damage

PARP1

NAD^+

SIRT6

SIRT3

NR

↓

Neurogenesis

Neuronal dysfunction

Neuro-inflammation

Mitochondrial dysfunction

Alzheimer’s Disease

Hou Y et al., PNAS, 2018
Summary

- NAD⁺/NADH ratio decreases in Polβ⁺/⁻, 3xTgAD and 3xTgAD/Polβ⁺/⁻ mice and increases after NR treatment.
- NAD⁺ supplementation improves learning and memory.
- NAD⁺ supplementation dramatically improve long-term potentiation.
- NAD⁺ supplementation decreases neuroinflammation and tau phosphorylation but not Aβ in 3xTgAD and 3xTgAD/Polβ⁺/⁻ mice.
- DNA damage was decreased after NR treatment in 3xTgAD and 3xTgAD/Polβ⁺/⁻ mice.

*Red means NR has better effects in 3xTgAD/Polβ⁺/⁻ than 3xTgAD mice
Future plan

- Investigate neuroinflammatory mechanisms in Polβ deficiency or AD models. Investigate the ability of NR or mitophagy inducers to specifically inhibit neuroinflammation.
- Investigate the effects of mitophagy inducers on mitochondrial function in AD mice.
- Generate another way to determine the role of BER by deleting another BER gene in an AD mouse model.

Modified from Hou et al., Mechanisms of Ageing and Development, 2016
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