Title: Mechanisms of ageing and the linkages to Alzheimer's disease

Evandro Fei Fang, PhD (CUHK)
Associate Professor
University of Oslo and Akershus University Hospital, Norway

Abstract

Increased lifespan enables people to live longer, but not necessarily healthier lives[1, 2]. Ageing is arguably the highest risk factor for numerous human diseases, including Alzheimer's disease (AD); thus understanding the molecular mechanisms of human aging holds the promise of developing interventional and therapeutic strategies for many diseases simultaneously, promoting healthy longevity. Accumulation of damaged mitochondria is a hallmark of aging and age-related AD. However, the molecular mechanisms of impaired mitochondrial homeostasis and their relationship to AD are still elusive. Mitochondrial autophagy (mitophagy) is the cellular self-clearing process that removes damaged and superfluous mitochondria, and therefore plays a fundamental role in maintaining neuronal homeostasis and survival[1, 3, 4]. We hypothesise that age-susceptible defective mitophagy causes accumulation of damaged mitochondria, which in combination with the two AD-defining pathologies, Aβ plaques and tau tangles, further exacerbates AD onset and progression. Restoration of mitophagy, through pharmaceutical (e.g., NAD^+, passion fruit components, and urolithin A) and genetic approaches, forestalls pathology and cognitive decline in mouse models of AD and improves neuronal function in AD iPSC-derived neurons[5-7]. Additionally, artificial intelligence (AI) is now being used to propel drug screening, as well as being used for drug design specifically targeting AD and ageing pathways[8]. The Evandro Fang lab is now involved in several clinical trials looking into the use of NAD^+ precursors to treat AD and premature ageing diseases, among others[9].

Key References

1. Fang, E.F. *et al.* A research agenda for ageing in China in the 21st century (2nd edition): Focusing on basic and translational research, long-term care, policy and social networks. *Ageing Res Rev* **64**, 101174 (2020).
2. Fang, E.F. *et al.* A research agenda for aging in China in the 21st century. *Ageing Res Rev* **24**, 197-205 (2015).
3. Aman, Y. *et al.* Autophagy in healthy ageing and disease. *Nat Aging* **1**, 634-650 (2021).
4. Fang, E.F. *et al.* Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. *Cell* **157**, 882-896 (2014).
5. Fang, E.F. *et al.* Mitophagy inhibits amyloid-beta and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci* **22**, 401-412 (2019).
6. Lautrup, S., Sinclair, D.A., Mattson, M.P. & Fang, E.F. NAD(+) in Brain Aging and Neurodegenerative Disorders. *Cell Metab* **30**, 630-655 (2019).
7. Cao, S.Q., Aman, Y., Fang, E.F. & Tencomnao, T. P. edulis Extract Protects Against Amyloid-beta Toxicity in Alzheimer's Disease Models Through Maintenance of Mitochondrial Homeostasis via the FOXO3/DAF-16 Pathway. *Mol Neurobiol* (2022).
8. Xie, C. *et al.* Amelioration of Alzheimer's disease pathology by mitophagy inducers identified via machine learning and a cross-species workflow. *Nat Biomed Eng* (2022).
9. Reiten, O.K., Wilvang, M.A., Mitchell, S.J., Hu, Z. & Fang, E.F. Preclinical and clinical evidence of NAD(+) precursors in health, disease, and ageing. *Mech Ageing Dev*, 111567 (2021).

Biography (<500 words)

Evandro F. Fang is an Associate Professor on Molecular Gerontology at the University of Oslo (UiO) and the Akershus University Hospital, Norway, and his group are working on the molecular mechanisms of human ageing and age-predisposed neurodegeneration (https://evandrofanglab.com/). More specifically, the Fang laboratory is focusing on the molecular mechanisms behind how cells clear their damaged and aged mitochondria, a process termed “mitophagy”, as well as the roles of the NAD^+-mitophagy/autophagy axis in healthy ageing and AD inhibition. NAD^+ is a fundamental molecule in life and health and decreases in ageing and AD. Dr Fang is fascinated with and actively engaged in moving his laboratory findings to translational applications and is involved in 5 NAD^+-based clinical trials, with the overarching goal of establishing novel and safe biological approaches to promote longer and healthier human lives.

He has published over 100 papers in international peer-reviewed journals including papers in *Cell, Cell Metabolism, Nature Reviews MCB*, *Nature Neuroscience, Nature Ageing, and Nature Biomedical Engineering*. He has received several awards including the Butler-Williams Scholar on Aging 2016 by NIA (USA) and the 'Scientific Award to Young Scientist in the Natural Sciences for 2020 by The Royal Norwegian Society of Sciences and Letters (Norway). He sits/sat in the editorial board of several leading ageing journals, including as associate editor-in-chief (deputy editor) in Mechanisms of Ageing and Development (IF 5.5), Ageing Research Reviews (IF 11.8), NPJ Aging, and The Journal of Gerontology: Series a (Biological Sciences) (IF 6.5).

After finishing his PhD at the Chinese Universtiy of Hong Kong, he had a 6-year postdoc training with Prof. Vilhelm Bohr on molecular gerontology and Prof. Mark Mattson on neuronal resilience in Alzheimer’s disease at the National Institute on Ageing, Baltimore. He opened his lab in Oslo on 2 October 2017. He is the founding (co)coordinator of the Norwegian Centre on Healthy Ageing network (**NO-Age**, www.noage100.com), the Norwegian National anti-Alzheimer’s disease Network (**NO-AD**, www.noad100.com), and the Hong Kong-Nordic Research Network.