Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease Neuroinflammation affects Mitochondrial Function

Vic Shao-Chih Chiang

Received: 12 June 2021 Accepted: 30 June 2021 Published: 15 July 2021

Abstract

The mitochondria are the powerhouses of the body, which is paramount for the central nervous system given their high energy expenditure. This high dependence on the mitochondria renders mitochondrial dysfunctions to impair the central nervous system, as seen in neurodegenerative diseases. This article concentrates on the neurodgenerative disease, Alzheimer?s disease and the well-established neuroinflammation pathophysiology, from a mitochondrial perspective. I first focused on the energy production functions of the mitochondria, and the mitochondrial DNA, imperative for mitochondrial function. For instance in their aberrations in Alzheimer?s disease, and in vitro experiments with inflammatory markers that drove damages to the mitochondria DNA. Subsequently, I discussed about mitochondrial biogenesis using expression studies with correlated changes in Alzheimer?s disease and stem cells whereby mitochondria are critical regulators of their fate, pertinent to Alzheimer?s disease. Finally, I accentuated on emerging technologies that enable disentangling the abstruse nature of mitochondria, and some uprising areas of mitochondria research deserving attention from the lens of Alzheimer?s disease. Overall, there is a plausible link between Alzheimer?s disease, neuroinflammation, and mitochondrial mechanisms, but current studies are limited to causally address this question. I presented several improvements and strategies that could be taken to advance the understanding of this relationship in future studies.

Index terms—

Introduction itochondria are 0.5 -1.0 ?m cellular organelles that generate energy in the form of ATP 1 . By virtue of the high energy expenditure in the central nervous system, mitochondria pose exceptionally important roles 2 . Corresponding to their gravity, multiple neurodegenerative diseases exhibit mitochondrial dysfunction [3][4][5] . Alongside mitochondrial dysfunction, neurodegenerative diseases frequently accompany chronic inflammation within the brain [6][7][8] . Scholars termed this as "neuroinflammation" 9 and while this phenomenon serves a diverse range of purposes, it most fundamentally associates with the body's natural innate immune response to eliminate unwanted material and initiate repair 10 . Is there a relationship between neuroinflammation and mitochondrial function? Could neuroinflammation be the cause of mitochondrial dysfunction? To answer this, this article concentrates on sporadic Alzheimer's disease (AD) due to decades of research since the 1970s that supports a role of inflammation in AD pathophysiology [11][12][13][14] . AD is a disease that leads to progressive synaptic degeneration and neuronal death with ageing 15 .

In the US, researchers estimated the prevalence of AD to affect one in three elderlies 16 and ascribed to a financial burden estimated to be well over $200 billion 17 . This article aims to answer whether neuroinflammation may affect mitochondrial function in the context of AD in relation to three fundamental aspects of mitochondrial function: mitochondrial energy production, mitochondrial DNA, and mitochondrial biogenesis.

1 II.

2 Neuroinflammation may affect Mitochondrial Energy Production

Mitochondria is the critical site of energy production through the tricarboxylic acid cycle and oxidative phosphorylation (OXPHOS) during respiration 18 . In particular, OXPHOS generates a large amount of energy in the form of ATP by electron transfer from NADH and FADH2 in the electron transport chain 18 . Respiration and OXPHOS energy production are disrupted in AD (Table 2). Ageing studies were included in Table 2 to provide further insights since ageing is the greatest risk factor for neurodegeneration 19 . From this, OXPHOS and respiration appear to reduce with AD and ageing. In saying that, these studies deployed animal models, which deviates from human AD progression, ergo, researchers should attend to possible caveats of clinical translatability 20 . Aside from the differences reported, some of these animal studies have also provided results for other components of the electron transport chain. However, these failed to demonstrate any differences compared to the control. The failure of global changes in these components can create a selection bias where researchers make interpretations only on the OXPHOS components they selected to measure. Respiration is an objective measure for energy production. Therefore, future studies should include incorporating respiration as the primary outcome to reduce ambiguity in interpretation. Researchers can then further investigate these differences in respiration which specific components of the electron transport chain may drive this. Two reviews have summarized older studies that have consistently demonstrated that inflammatory cues affected respiration 21,22 . One study focused on how NO inhibits respiration in neurons due to NO restriction of complex I 21 . Another review concentrated on sepsis, which is the acute systemic inflammation from exposure to bacterial endotoxins (e.g., lipopolysaccharide LPS) 22 . It summarizes clinical, animal, and cellular studies and provides countenance to the view for reduced respiration, ATP/ADP ratio, and protein expression of OXPHOS complexes during sepsis 22 . Two other studies not covered in these reviews tendered supplementary support that inflammation does affect measurements relevant to mitochondrial energy production. The LPS treatment of murine macrophages (B6-MCL) and bone marrow-derived macrophages resulted in the complex IV gene and protein expression increase 23 . In tandem with this, another study espoused this relationship in the context of feeding different lipidbased diets to overweight subjects 24 . The comparing diets developed differences in pro-inflammatory proteins in the plasma, including IL1?, macrophage inflammatory protein 1?, and serum amyloid P 24 . Surprisingly, with the decrease in plasma inflammatory proteins, their microarray data showed down-regulation of various OXPHOS-related genes in the peripheral blood mononuclear cells of these subjects 24 . These studies present evidence that inflammation may affect mitochondrial energy production. Notwithstanding, their results displayed opposing views regarding how it perturbed mitochondrial energy production. On the grounds that these researchers did not undertake further experiments to disentangle the mechanisms for these observations, it is imperative to enunciate a more solid framework to construe the data. For example, reduced energy production may not always be inimical, such that it may reduce the amount of oxidative stress 24 . It would be context-dependent whether changes in mitochondrial energy production are deduced as beneficial or adverse. Likewise to the abovementioned, future studies should consider respiration as the primary outcome to reduce the indefiniteness of any speculations. In addition to that, by virtues of cell and tissue-specificity most probable for the effects of inflammation on mitochondrial energy production, future research in this domain specific for AD is warranted. Neuroinflammation likely affects mitochondrial energy production, but its existence in circumstances of neurodegeneration awaits discovery.

3 III.

4 Neuroinflammation may affect

Mitochondrial DNA Mitochondria possess DNA (mtDNA), and unlike nuclear DNA, it transcribes and replicates outside of the cell cycle 25 . Due to the mtDNA encoding for pivotal proteins for the mitochondria, any adverse changes to this DNA may subsequently develop the impaired mitochondrial function 25 . AD unerringly leads to changes in the mtDNA content and increases the number of mutations (Table 2). Single mitochondrion may contain multiple mtDNA, and single cells contain multiple mitochondria. The multiple mtDNA and mitochondria put the cells at risk of heteroplasmy, which refers to the presence of heterogeneous mtDNA within the same cell 26 . Mutations present in heterogeneous mtDNA may gain power through clonal expansion that can occur rapidly independent of the cell cycle 26 . Accumulation of adverse mtDNA mutations may compromise mitochondrial functions. Further to this, mtDNA changes appear to be site-specific 27 , henceforth future studies should demarcate the most vulnerable sites to determine therapeutic priorities. Only a paucity of studies exists which examines how inflammation may directly affect mtDNA. Researchers identified using TNF? and IL1? treatments in primary human chondrocytes to increase mtDNA breaks 28 . Germane to this alludes to a study utilizing primary murine peritoneal macrophages 29 . They observed LPS translocating mtDNA into the cytoplasm through unknown interactions with the cryopyrin inflammasome 29 . The authors speculated this as adverse on the grounds that the loss of mtDNA from the mitochondria could debilitate mitochondrial function 29 . These limited data are adjuvant to the notion that inflammation may affect mtDNA. However, substantially more studies are required to ascertain this effect, especially those relevant to the central nervous system. Major drawbacks with these studies lie in their insufficient exploration of the mtDNA. For example, future studies should recognize the importance of identifying heteroplasmy and specific types of mtDNA breaks or mutations that ensue with inflammation. MtDNA demonstrated the possibility to be affected by neuroinflammation, but whether this is present in the central nervous system remains to be explored.

5 IV.

6 Neuroinflammation may affect Mitochondrial Biogenesis

Mitochondria are constantly undergoing turnover to replace damaged mitochondria with functional counterparts 18 . The process of generating new mitochondria is termed ”mitochondrial biogenesis” 18. Disruptions to this process may affect the number of mitochondria available to carry out paramount cellular functions. The homeostasis of mitochondrial biogenesis appeared to be disturbed in AD (Table 3), evident in the overall reduction of gene and protein expression related to mitochondrial biogenesis. However, this trend contrasts with this study 30 , where researchers found mitochondrial biogenesis to increase in AD. This study experimented with primary hippocampal neurons derived from the Tg2576 AD mice model in comparison to those that originated from wild-type mice 30 . They further subjected these neurons to oxidative stress to exacerbating neurodegeneration 30 . Based on their bromodeoxyuridine labelling, they unearthed an increase in mitochondrial biogenesis 30 . Their explanation for this contingent finding was the mtDNA of these neurons had a reduced half-life, which reciprocally stimulated additional mitochondrial biogenesis 30 . From this, I hypothesize that impairments in mtDNA may precede dysfunctional mitochondrial biogenesis. The initial compensation to counteract detrimental effects from impaired mtDNA through intensifying mitochondrial biogenesis may also become dysfunctional at later stages of AD. Could neuroinflammation affect mitochondrial biogenesis? We can take clues from hypoxia studies as NO is generated 31 . Mice subjected to hypoxia had increased gene expression of PGC1?, NRF1, and TFAM within their brains 31 . Additionally, with the observed strengthening of mitochondrial density in their brains, researchers inferred that mitochondrial biogenesis augmented 31 . This effect was known to be directed by NO since changes in mitochondrial biogenesis were absent in neuronal and endothelial NO synthase gene-deficient mice 31 . Other studies of the central nervous system detected simultaneous changes in inflammation and mitochondrial biogenesis (? plasma chemokine ligand 11 protein, ? PGC1? protein 32 ; â??”brain NF?B, chemokine ligand 11 genes, ? PGC1?, NRF1, TFAM 33). However, the researchers did not further correlate these variables in these studies. Several other studies likewise support the notion that inflammation affects mitochondrial biogenesis, albeit not in the central nervous system. A good illustration exemplifies in a study that treated human cardiac AC16 cells with TNF? 34 . This experiment resulted in the downregulation of PGC1? protein expression 34 . Furthermore, LPS treatment of human gingival fibroblasts diminished protein expressions of PGC1? and TFAM 35 . Another example was the human knee chondrocyte study carried out by 36 that found IL1? treatment to reduce protein levels of PGC1?, TFAM, NRF1, and NRF2. From these studies, it can be asserted that neuroinflammation affects mitochondrial biogenesis. However, it remains equivocal whether mitochondrial biogenesis is increased or decreased with inflammation. It is imperative to consider the inflammatory mediators utilised in these studies as their effects on mitochondrial biogenesis may be distinct from each other. Neuroinflammation involves a plethora of inflammatory mediators, and therefore, the synergistic or antagonistic effects on mitochondrial biogenesis from different combinations require to be elucidated. In vivo AD studies of chronic inflammation are similarly sine qua non to address the drawbacks of existing studies on inflammation and mitochondrial biogenesis. Neuroinflammation affects mitochondrial biogenesis, but elaborate substantiation in in vivo AD studies awaits.

V.

7 Neuroinflammation and Mitochondria in the Context of Stem Cells

Memory is impaired in AD patients, which correlates with hippocampal degeneration, a site imperative for adult neurogenesis (reviewed in 37). Supporting clinical evidence espouse abated neurogenesis in AD patients (reviewed in 37). In several rodent studies, amelioration of the AD sequalae oftentimes accompanies rescued neurogenesis (reviewed in 37). For example, in an immunotherapy study, the successful delivery of antibody therapeutics across the blood-brain barrier promoted hippocampal neurogenesis 38 . Another study enabling better causal inference, directly administered mesenchymal stem cells, which can differentiate into neuronal-like cells, demonstrated reversal of aberrant signalling pathways related to AD in vitro 39 and in 3x Tg-AD mice model 40 . Given that the mitochondria are key signalling organelles for stem cell fate (reviewed in 41), it is highly plausible that the observed changes in AD symptomatology may mediate through the mitochondria. For instance, stem cell fates may be controlled through the mitochondria by generating reactive oxygenspecies (ROS), influencing bioenergetics, as well as mitochondrial dynamics (reviewed in 41). Particularly relevant to AD are neural stem cells and ample evidence likewise buttress mitochondrial regulation through affecting their proliferation, daughter cells, and transcriptional changes especially through mitochondria metabolism (reviewed in 42). Several of the mitochondrial components involved have been mentioned above to be altered by neuroinflammation. For instance, ROS increases neural stem cell self-renewal 43 and with correlative evidence, scholars have postulated

NLRP3 inflammasome to modify mitochondrial ROS production 44 . Mitofusin-2 is a pivotal component in mitochondrial dynamics, and essential for the differentiation of induced pluripotent stem cells into cortical neurons 45 . Recently, transgenic mice overexpressing mitofusin-2 demonstrated its critical roles in response to LPS-induced neuroinflammation ??6 . In essence, I hypothesize the mitochondria to mediate the effects of stem cell changes in AD through neuroinflammation mechanisms, which require vindication with mechanistic in vivo studies.

8 Technology to Study Neuroinflammation effects on Mitochondria

In order to rigorously obtain scientifically valid data to answer the plethora of experimental questions described throughout this review, the methodology deployed is the perforce consideration factor. Methods for studying the mitochondria has advanced dramatically over the past few decades from studying their morphology and metabolism to their physical properties. First, the three-dimensional ultrastructure of the mitochondria requires resolution through electron microscopy (reviewed in 47). However, traditional methods of manual segmentation of mitochondria imaging in electron micrographs become rate-limiting in the contemporary data-driven era (reviewed in 47). Therefore a recent study utilized machine learning in the form of a recurrent neural network to enable automated detection and segmentation of the electron micrographed mitochondria 47 . To conduct analysis beyond visualization, isolating the mitochondria is a pivotal method for detailed molecular examination. Several methods exist for this purpose that has varying success with regards to the number of mitochondria retained and preservation of membrane integrity (reviewed in 48). One study compared between three different methods, and ferreted out there was no superiority of one method, but each method harboured different strengths, either having a higher yield of mitochondrial protein and mtDNA copy numbers, higher activity retained in the isolated mitochondria or better membrane integrity 48 . Ergo, researchers were recommended to carefully assess which methods most suit them depending on the purpose of their research. As mentioned previously, mitochondrial ROS has tremendous implications in Alzheimer's disease. There have been endeavours of measuring mitochondrial ROS using redox-active probes, but these were limited due to the probe oxidation by several ROS (reviewed in 49). One study implemented an electron paramagnetic resonance approach that enabled overcoming this hurdle to identify specific ROS generated 49 . Another challenge with ROS is their short lifetimes and high reactivity (reviewed in 50).One recent solution employed relaxometry from field magnetometry achieved quantum sensing of ROS at the mitochondrial resolution 50 . A myriad of methods is commensurately materializing to understand the physics associated with mitochondria. To name a few, an emission probe was developed to monitor mitochondrial viscosity, cardinal for understanding damaged mitochondria 51 , as well as a molecular thermometer to measure the temperature in mitochondria, which impart information on cellular inflammation 52 . Above all, we are at a time where exciting avenues of mitochondria research could be sought through the advancements in vanguard methods to dissect the wonders of the mitochondria.

9 VII.

10 Future Directions

Beyond the AD topics discussed in the review in the context of mitochondria and neuroinflammation, a myriad of emanating areas of the mitochondria require to be unearthed for their potential in AD pathophysiology. For example, the TCA cycle in the mitochondria generate metabolites for epigenetic mechanisms, yet it was only recently discovered the exigent impact of mitochondria on epigenetics (reviewed in 53). Epigenetics is similarly infiltrated in AD pathophysiology in the realm of DNA methylation, histone modifications and non-coding RNAs (reviewed in 54). Another area that is beginning to recognize mitochondria as new players is firing rate homeostasis that stabilizes neural circuit function by maintaining firing rate distribution among neurons 55 . The authors laid out cogent arguments for the mitochondria as part of this homeostatic machinery using robust theoretical frameworks 55 . Vis-à-vis AD, indeed several studies endorsed the claim of an impaired firing homeostatic control in AD. These studies were conglomerated in two articles led by Inna Slutsky whereby a dysregulated integrated homeostatic network may drive causations in AD progression at its early stages (reviewed in 56 ; reviewed in 57). The final uprising area in mitochondria research I want to accentuate is gut microbiota. In one study through trans-kingdom network analysis, mitochondria in the liver exhibited improved metabolism through metabolites derived from the Lactobacillus genus 58 . Another study leveraged blood and faecal samples found correlations between mitochondriarelated inflammation with the Lachnospiraceae family, amongst other findings 59 . This intersects with the role of gut microbiota in AD pathogenesis, that have already garnered a gargantuan amount of attention in the past decade (reviewed 60). There are an abound of approaches that strive to implement these insights into AD treatments such as using faecal microbial transplants (reviewed in 60). In saying that, the efficacy and safety of these treatments remain to be conclusively grasped, and understanding the role of mitochondria in their effects is crucial for this endeavour. As can be seen, a variety of novel areas in mitochondria research are being developed. The intersection of these areas of epigenetics, firing rate homeostasis, and gut microbiota with AD, indicate ripeness of exploring these in the crossover between AD, neuroinflammation, and mitochondria. mitochondria have a reduced capacity to carry out energy production.

In addition, increased mutations in their mitochondrial DNA could impair the transcription of components for mitochondrial function. These are in conjunction with disturbed homeostasis of molecular components required for mitochondrial biogenesis. Altogether, these may be culprits for altered stem cell fates that goads AD pathophysiology. This article answers whether the neuroinflammation in AD may be responsible for the observed mitochondrial dysfunction. However, I raised more questions than answers due to the limited amount of data available and the substantial amount of research still required. Although limited, existing data supports neuroinflammation to affect mitochondrial energy production, mitochondrial DNA, and mitochondrial biogenesis. To answer this question conclusively, we need future in vivo central nervous system studies in the context of AD, using the emerging technologies I described. These studies should generate primary outcomes that minimize the possibility of any ambiguity in interpretation. Other measurements taken must spread in breadth and depth to correspond to mitochondrial dysfunction data in AD patients. In tandem with these, researchers must account for the complexity of neuroinflammation demands in their experimental design, and emphasize the potential of emerging areas in epigenetics, firing rate homeostasis, and gut microbiota. AD is a highly prevalent disease that contributes to an immense societal burden. Understanding how the underlying neuroinflammation contributes to AD could help develop novel or improved strategies to combat this.

11 VIII.

12 Conclusion

13 Conflict of interest

The author declares no conflict of interest. [1]

1

Study Sample	Sample Type	Changes in OXPHOS / respiration (methodology of assessment)	Reference
Male Wistar Rats (20 months)	Hippocampus		61
Female triple transgenic AD mice (3xTg-AD) (3 months)	Hippocampus		62
Male Wistar rats (30 months)	Cortex		63
Male Wistar rats (24 months)	Brain		64
APPswe/PS1dE9 mice (3 months)	Hippocampus		65
Female Wistar rats (24 months)	Hippocampus, cortex, cerebellum, brainstem		66
NMRI-mice (24 months)	Frontal brain region		

Figure 1: Table 1 :

---

[1] Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease

2

Study Sample	Sample Type	Changes in mitochondrial DNA (methodology of assessment)	References
yrs) AD patients (76.3	neurons pyramidal Hippocampal		68
Caucasian male (67 -89 yrs)	Putamen		69
Male Fischer 344 rats (26 months old)	Frontal cortex		70
AD patients (56 -86 yrs)	Different brain sections		27
AD patients (59 -93 yrs)	Frontal cortex		71
AD patients (65 -90 yrs)	Blood		72

qPCR, quantitative real-time polymerase chain reaction

Figure 2: Table 2 :

3

Study sample	Sample type	Changes in mitochondrial biogenesis	Method of assessment	Reference
Male Fischer 344 rats (24 -28 months)	Livers	â??” nuclear Nrf2 protein expression	Western blotting	73
AD patients	Hippocampus	â??” PGC1? gene expression	Microarray & qPCR	74
Female Wistar rats (24 months)	heart, lung, liver	â??” intracellular NAD+ & substrate -regulates PGC1?) NAD;NADH ratio (sirtuin 1	Thiazolyl blue assay microcyclcing	75
AD Mice model (Tg2576 line)	Primary hippocampal with rotenone & neurons (treated H_2O_2)	? mitochondrial biogenesis	BrdU labeling	30
AD patients (65 - 91 yrs)	Hippocampus	â??” protein expression of PGC1?, NRF1/2 & TFAM	Western blotting	76
AD Mice model (APPswe/PS1dE9)	Brain	â??” PGC1? gene expression	qPCR	

[Note: 65Bromodeoxyuridine, BrdU; mitochondrial transcription factor A, TFAM; nicotinamide adenine dinucleotide, NAD; nuclear respiratory factor, NRF; peroxisome proliferated-activated receptor gamma co-activator one alpha, PGC1?; quantitative real-time polymerase chain reaction, qPCR A © 2021 Global Journals]

Figure 3: Table 3 :

[Mol Neurobiol ()] , *Mol Neurobiol* 2012. 46 p. .

[Bauerfeld ()] , C P Bauerfeld . 2012. 4 p. .

[Babcock et al. ()] 'Adult Hippocampal Neurogenesis in Aging and Alzheimer's Disease'. K R Babcock , J S Page , J R Fallon , A E Webb . *Stem Cell* 2021. 16 p. .

[Braidy ()] 'Age related changes in NAD+ metabolism oxidative stress and Sirt1 activity in wistar rats'. N Braidy . *PLoS One6* 2011.

[Picca ()] *Age-and calorie restriction-related changes in rat brain mitochondrial DNA and TFAM binding*, A Picca . 2013. 35 p. .

[Frenzel et al. ()] 'Ageing alters the supramolecular architecture of OxPhos complexes in rat brain cortex'. M Frenzel , H Rommelspacher , M D Sugawa , N A Dencher . *Exp Gerontol* 2010. 45 p. .

[Niccoli and Partridge ()] 'Ageing as a risk factor for disease'. T Niccoli , L Partridge . *Curr Biol* 2012. 22 p. .

[Coskun et al. ()] 'Alzheimer's brains harbor somatic mtDNA controlregion mutations that suppress mitochondrial transcription and replication'. P E Coskun , M F Beal , D C Wallace . *Proc Natl Acad Sci* 2004. p. .

[Frere and Slutsky ()] 'Alzheimer's Disease: From Firing Instability to Homeostasis Network Collapse'. S Frere , I Slutsky . *Neuron* 2018. 97 p. .

[Lee and Han ()] 'An update of animal models of Alzheimer disease with a reevaluation of plaque depositions'. J E Lee , P L Han . *Exp Neurobiol* 2013. 22 p. .

[Calkins and Reddy ()] 'Assessment of newly synthesized mitochondrial DNA using BrdU labeling in primary neurons from Alzheimer's disease mice: Implications for impaired mitochondrial biogenesis and synaptic damage'. M J Calkins , P H Reddy . *Biochim Biophys Acta* 2011. 1812 p. .

[Liu ()] 'Automatic Reconstruction of Mitochondria and Endoplasmic Reticulum in Electron Microscopy Volumes by Deep Learning'. J Liu . *Front. Neurosci* 2020. 14 p. .

[Nakahira ()] 'Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome'. K Nakahira . *Nat Immunol* 2011. 12 p. .

[Dubey ()] 'Clinically approved IVIg delivered to the hippocampus with focused ultrasound promotes neurogenesis in a model of Alzheimer's disease'. S Dubey . *Proc. Natl. Acad. Sci. U. S. A* 2020. 117 p. .

[Azimzadeh ()] 'Comparison of three methods for mitochondria isolation from the human liver cell line (HepG2)'. P Azimzadeh . *Gastroenterol. Hepatol. from Bed to* 2016. 9 p. .

[Dijk ()] 'Consumption of a high monounsaturated fat diet reduces oxidative phosphorylation gene expression in peripheral blood mononuclear cells of abdominally overweight men and women'. V Dijk . *J Nutr* 2012. 142 p. .

[Minati et al. ()] 'Current concepts in Alzheimer's disease: a multidisciplinary review'. L Minati , T Edginton , M G Bruzzone , G Giaccone . *Am J Alzheimers Dis Other Demen* 2009. 24 p. .

[Petrosillo et al. ()] 'Decline in cytochrome c oxidase activity in rat-brain mitochondria with aging. Role peroxidized cardiolipin Benef. Eff. melatonin'. G Petrosillo , D Benedictis , M , F Paradies , G . *J Bioenerg Biomembr* 2013. 45 p. .

[Suh ()] 'Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid'. J H Suh . *Proc Natl Acad Sci* 2004. p. .

[Cheng ()] 'Detection of mitochondriagenerated reactive oxygen species in cells using multiple probes and methods: Potentials, pitfalls, and the future'. G Cheng . *J. Biol. Chem* 2018. 293 p. .

[Pedrós ()] 'Early alterations in energy metabolism in the hippocampus of APPswe/PS1dE9 mouse model of Alzheimer's disease'. I Pedrós . *Biochim Biophys Acta* 2014. 1842 p. .

[Burns and Swerdlow ()] 'Effect of highintensity exercise on aged mouse brain mitochondria, neurogenesis, and inflammation'. E , L Burns , J M Swerdlow , RH . *Neurobiol Aging* 2014. 35 p. .

[Schaffer et al.] *Effects of polyphenols on brain ageing and Alzheimer's focus on mitochondria*, S Schaffer , H Asseburg , S Kuntz , W E Muller , G P Eckert .

[Safiulina and Kaasik ()] 'Energetic and dynamic: how mitochondria meet neuronal energy demands'. D Safiulina , A Kaasik . *PLoS Biol11* 2013.

[Xiao et al. ()] 'Epigenetics: Recent Advances and Its Role in the Treatment of Alzheimer's Disease'. X Xiao , X Liu , B Jiao . *Front. Neurol* 2020. 11 p. .

[Brookmeyer et al. ()] 'Forecasting the global burden of Alzheimer's disease'. R Brookmeyer , E Johnson , K Ziegler-Graham , H M Arrighi . *Alzheimers Dement* 2007. 3 p. .

[Hurd et al. ()] 'Future Monetary Costs of Dementia in the United States under Alternative Dementia Prevalence Scenarios'. M D Hurd , P Martorell , K Langa . *J Popul Ageing* 2015. 8 p. .

[Liu et al. ()] 'Gut Microbiota and Dysbiosis in Alzheimer's Disease: Implications for Pathogenesis and Treatment'. S Liu , J Gao , M Zhu , K Liu , H L Zhang . *Mol. Neurobiol* 2020. 57 p. .

[Navarro ()] 'Hippocampal mitochondrial dysfunction in rat aging'. A Navarro . *Am J Physiol Regul Integr Comp Physiol* 2008. 294 p. .

[Ishii and Haga ()] 'Identification of components of immunoglobulins in senile plaques by means of fluorescent antibody technique'. T Ishii , S Haga . *Acta* 1975. 32 p. .

[Styr and Slutsky ()] 'Imbalance between firing homeostasis and synaptic plasticity drives earlyphase Alzheimer's disease'. B Styr , I Slutsky . *Nat. Neurosci* 2018. 21 p. .

[Sheng ()] 'Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease'. B Sheng . *J Neurochem* 2012. 120 p. .

[Wyss-Coray ()] 'Inflammation in Alzheimer disease: driving force, bystander or beneficial response'. T Wyss-Coray . *Nat Med* 2006. 12 p. .

[Neves ()] 'Intravenous administration of mesenchymal stem cells reduces Tau phosphorylation and inflammation in the 3xTg-AD mouse model of Alzheimer's disease'. A F Neves . *Exp. Neurol* 2021. 341 p. 113706.

[Coto ()] *Late-onset Alzheimer's Dis. is Assoc. with mitochondrial DNA 7028*, E Coto . 2011. p. .

[Bullón ()] 'Lipophilic antioxidants prevent lipopolysaccharide-induced mitochondrial dysfunction through mitochondrial biogenesis improvement'. P Bullón . *Pharmacol Res* 2015. 91 p. .

[Bettcher and Kramer ()] 'Longitudinal inflammation, cognitive decline, and Alzheimer's disease: a mini-review'. B M Bettcher , J H Kramer . *Clin Pharmacol Ther* 2014. 96 p. .

[Braidy ()] 'Mapping NAD(+) metabolism in the brain of ageing Wistar rats: potential targets for influencing brain senescence'. N Braidy . *Biogerontology* 2014. 15 p. .

[Farahzadi et al. ()] 'Mesenchymal Stem Cells Could Be Considered as a Candidate for Further Studies in Cell-Based Therapy of Alzheimer's Disease via Targeting the Signaling Pathways'. R Farahzadi , E Fathi , I Vietor . *ACS Chem. Neurosci* 2020. 11 p. .

[Fang et al. ()] 'Mfn2 is required for mitochondrial development and synapse formation in human induced pluripotent stem cells/hiPSC derived cortical neurons'. D Fang , S Yan , Q Yu , D Chen , S S Yan . *Sci. Rep* 2016. 6 p. .

[Chakrabarty and Chandel ()] 'Mitochondria as Signaling Organelles Control Mammalian Stem Cell Fate'. R P Chakrabarty , N S Chandel . *Cell Stem Cell* 2021. 28 p. .

[Santos ()] 'Mitochondria signaling to the epigenome: A novel role for an old organelle. Free Radic'. J H Santos . *Biol. Med* 2021. 170 p. .

[Chaturvedi and Beal ()] 'Mitochondria targeted therapeutic approaches in Parkinson's and Huntington's diseases'. R K Chaturvedi , M F Beal . *Mol Cell Neurosci* 2013. 55 p. .

[Huang et al. ()] 'Mitochondria-Anchored Molecular Thermometer Quantitatively Monitoring Cellular Inflammations'. Z Huang , N Li , X Zhang , Y Xiao . *Anal. Chem* 2021. 93 p. .

[Ruggiero et al. ()] 'Mitochondria: new players in homeostatic regulation of firing rate set points'. A Ruggiero , M Katsenelson , I Slutsky . *Trends Neurosci.xx* 2021.

[Yao ()] 'Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease'. J Yao . *Proc Natl Acad Sci* 2009. p. .

[Wang et al. ()] 'Mitochondrial biogenesis is impaired in osteoarthritis chondrocytes but reversible via peroxisome proliferator-activated receptor ? coactivator 1?'. Y Wang , X Zhao , M Lotz , R Terkeltaub , R Liubryan . *Arthritis Rheumatol* 2015. 67 p. .

[Kim ()] 'Mitochondrial DNA damage is involved in apoptosis caused by pro-inflammatory cytokines in human OA chondrocytes'. J Kim . *Osteoarthr. Cartil* 2010. 18 p. .

[Krishnan ()] 'Mitochondrial DNA deletions cause the biochemical defect observed in Alzheimer's disease'. K J Krishnan . *Neurobiol Aging* 2012. 33 p. .

[Phillips et al. ()] 'Mitochondrial DNA deletions in Alzheimer's brains: a review'. N R Phillips , J W Simpkins , R K Roby . *Alzheimers Dement* 2014. 10 p. .

[Su et al. ()] 'Mitochondrial dysfunction and neurodegeneration in multiple sclerosis'. K Su , D Bourdette , M Forte . *Front Physiol* 2013. 4 p. 169.

[Yin et al. ()] 'Mitochondrial energy metabolism and redox signaling in brain aging and neurodegeneration'. F Yin , A Boveris , E Cadenas . *Antioxid Redox Signal* 2014. 20 p. .

[Ellwardt and Zipp ()] 'Molecular mechanisms linking neuroinflammation and neurodegeneration in MS'. E Ellwardt , F Zipp . *Exp Neurol* 2014. 262 p. .

[Boche and Nicoll ()] 'Neuroinflammation in ageing and in neurodegenerative disease'. D Boche , J A Nicoll . *Neuropathol Appl Neurobiol* 2013. 39 p. .

[Heneka ()] 'Neuroinflammation in Alzheimer's disease'. M T Heneka . *Lancet Neurol* 2015. 14 p. .

[Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease] *Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease*,

[Lyman et al. ()] 'Neuroinflammation: the role and consequences'. M Lyman , D G Lloyd , X Ji , M P Vizcaychipi , D Ma . *Neurosci Res* 2014. 79 p. .

[Gersch"utz ()] 'Neuron-specific mitochondrial DNA deletion levels in sporadic Alzheimer's disease'. A Gersch"utz . *Curr Alzheimer Res* 2013. 10 p. .

[Torres et al. ()] 'Neuronal mitochondria modulation of LPS-induced neuroinflammation'. M Torres , S Liu , J Wang , X . *Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease 46. Harland*, 2020. 40 p. .

[Brown and Borutaite ()] 'Nitric oxide inhibition of mitochondrial respiration and its role in cell death'. G C Brown , V Borutaite . *Free Radic Biol Med* 2002. 33 p. .

[Afshordel ()] 'Omega-3 polyunsaturated fatty acids improve mitochondrial dysfunction in brain aging–impact of Bcl-2 and NPD-1 like metabolites'. S Afshordel . *Prostaglandins Leukot Essent Fat* 2015. 92 p. .

[Wilkins ()] 'Oxaloacetate activates brain mitochondrial biogenesis, enhances the insulin pathway, reduces inflammation and stimulates neurogenesis'. H M Wilkins . *Hum Mol Genet* 2014. 23 p. .

[Nolan et al. ()] 'Parkinson's disease in the nuclear age of neuroinflammation'. Y M Nolan , A M Sullivan , A Toulouse . *Trends Mol Med* 2013. 19 p. .

[Qin ()] 'PGC-1alpha expression decreases in the Alzheimer disease brain as a function of dementia'. W Qin . *Arch Neurol* 2009. 66 p. .

[Belle ()] 'Proliferative neural stem cells have high endogenous ROS levels that regulate self-renewal and neurogenesis in a PI3K/Aktdependant manner'. Le Belle , JE . *Cell Stem Cell* 2011. 8 p. .

[Nie ()] 'Quantum monitoring of cellular metabolic activities in single mitochondria'. L Nie . *Sci. Adv* 2021. 7 p. .

[Fan ()] 'Real-time monitoring mitochondrial viscosity during mitophagy using a mitochondriaimmobilized near-infrared aggregation-induced emission probe'. L Fan . *Anal. Chem* 2021. 93 p. .

[Cherry and Piantadosi ()] 'Regulation of mitochondrial biogenesis and its intersection with inflammatory responses'. A D Cherry , C A Piantadosi . *Antioxid Redox Signal* 2015. 22 p. .

[Iwata and Vanderhaeghen ()] 'Regulatory roles of mitochondria and metabolism in neurogenesis'. R Iwata , P Vanderhaeghen . *Curr. Opin. Neurobiol* 2021. 69 p. .

[Selfridge et al. ()] 'Role of mitochondrial homeostasis and dynamics in Alzheimer's disease'. J E Selfridge , E , L Lu , J Swerdlow , RH . *Neurobiol Dis* 2013. 51 p. .

[Williams et al. ()] 'Somatic mtDNA mutation spectra in the aging human putamen'. S L Williams , D C Mash , S Z"uchner , C T Moraes . *PLoS Genet9* 2013.

[Kalaria ()] 'The immunopathology of Alzheimer's disease and some related disorders'. R N Kalaria . *Brain* 1993. 3 p. .

[Alvarez-Guardia ()] 'The p65 subunit of NF-kappaB binds to PGC-1alpha, linking inflammation and metabolic disturbances in cardiac cells'. D Alvarez-Guardia . *Cardiovasc Res* 2010. 87 p. .

[Wei et al. ()] 'The potential role of the NLRP3 inflammasome activation as a link between mitochondria ROS generation and neuroinflammation in postoperative cognitive dysfunction'. P Wei , F Yang , Q Zheng , W Tang , J Li . *Front. Cell. Neurosci* 2019. 13 p. .

[Lagouge and Larsson ()] 'The role of mitochondrial DNA mutations and free radicals in disease and ageing'. M Lagouge , N G Larsson . *J Intern Med* 2013. 273 p. .

[Gutsaeva ()] 'Transient hypoxia stimulates mitochondrial biogenesis in brain subcortex by a neuronal nitric oxide synthase-dependent mechanism'. D R Gutsaeva . *J Neurosci* 2008. 28 p. .

[Rodrigues ()] 'Transkingdom interactions between Lactobacilli and hepatic mitochondria attenuate western diet-induced diabetes'. R R Rodrigues . *Nat. Commun* 2021. 12 p. .

[Mach ()] 'Understanding the Holobiont: Crosstalk Between Gut Microbiota and Mitochondria During Long Exercise in Horse'. N Mach . *Front. Mol. Biosci* 2021. 8 p. .