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Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease

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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.

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Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease

Neuroinflammation affects Mitochondrial Function

Vic Shao-Chih Chiang

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.

I. Introduction

Mitochondria are 0.5 – 1.0 μm 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[3–5]. Alongside mitochondrial dysfunction, neurodegenerative diseases frequently accompany chronic inflammation within the brain[6–8]. 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 [11–14]. 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.

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II. 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 lipid-based diets to overweight subjects[24]. The comparing diets developed differences in pro-inflammatory proteins in the plasma, including IL1β, macrophage inflammatory protein 1α, 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.

III. 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 TNFα and IL1β 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.

IV. 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 PGC1α, 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, ↑ PGC1α protein[32]; ↓brain NFκB, chemokine ligand 11 genes, ↑ PGC1α, 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 TNFα[34]. This experiment resulted in the down-regulation of PGC1α protein expression[34]. Furthermore, LPS treatment of human gingival fibroblasts diminished protein expressions of PGC1α and TFAM[35]. Another example was the human knee chondrocyte study carried out by [36] that found IL1β treatment to reduce protein levels of PGC1α, 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. 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 [46]. 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.

VI. 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.

VII. 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 mitochondria-related 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.

VIII. Conclusion

Sporadic Alzheimer's disease is under a chronic state of neuroinflammation. Simultaneously, AD patients exhibit signs of mitochondrial dysfunction. Their

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.

Conflict of interest

The author declares no conflict of interest.

Table 1: Changes in mitochondrial OXPHOS and respiration in Alzheimer's disease and ageing

Study Sample	Sample Type	Changes in OXPHOS / respiration (methodology of assessment)	Reference
Male Wistar Rats (20 months)	Hippocampus	□ ↓ state 3 respiration (initiated with ADP) (Clark electrode) □ ↓ Complex I & IV activity (spectrophotometry)	61
Female triple transgenic AD mice (3xTg-AD) (3 months)	Hippocampus	□ ↓ mitochondrial respiration (Clark electrode) □ ↓ mitochondrial respiration (Seahorse XF-24 metabolic flux)	62
Male Wistar rats (30 months)	Cortex	□ ↓ATP synthase (1D-SDS gel) □ ↓ Complex I (1D BN-gel & 2D SDS-gel)	63
Male Wistar rats (24 months)	Brain	□ ↓ Complex I activity (mitochondrial particles)	64
APPswe/PS1dE9 mice (3 months)	Hippocampus	□ ↓ state 3 respiration (initiated with ADP) (Clark electrode) □ ↓ Complex I, II, III, IV (Western blotting)	65
Female Wistar rats (24 months)	Hippocampus, cortex, cerebellum, brainstem	□ ↓ Complex I, II, III, IV activity (spectrophotometry)	66
NMRI-mice (24 months)	Frontal brain region	□ ↓ Complex I, II, IV activity (respirometer) □ ↓ ATP levels (bioluminescence)	67

Table 2: Changes in mitochondrial DNA in Alzheimer's disease and ageing

Study Sample	Sample Type	Changes in mitochondrial DNA (methodology of assessment)	References
AD patients (76.3 yrs)	Hippocampal pyramidal neurons	□ ↑total mtDNA deletions (qPCR N4:N1) □ ↑ size & ↑ number of mtDNA deletion break points (long extension PCR) □ ↑ "common" & "major arc" mtDNA deletions (Sequencing) □ ↑ single nucleotide variants (Sequencing)	68
Caucasian male (67 - 89 yrs)	Putamen	□ ↑ m.3243A>G tRNA mutation (Sequencing) □ ↑ clonal ~50bp deletions in the control region (Sequencing)	69
Male Fischer 344 rats (26 months old)	Frontal cortex	□ 25% ↓ in mtDNA content (qPCR D-loop: β-actin) □ 37% ↑ in 4.8kb deletions (qPCR 4.8kb deleted region: D-loop)	70
AD patients (56 - 86 yrs)	Different brain sections	□ ↑ mtDNA deletion in cerebellar granule cells > pyramidal cells (qPCR N4:N1)	27
AD patients (59 - 93 yrs)	Frontal cortex	□ ↓ mtDNA content (qPCR ND2: 18S rRNA) □ ↑ heteroplasmy (Sequencing) □ ↑ T414G mutation (PNA-clamping PCR)	71
AD patients (65 - 90 yrs)	Blood	□ ↑ heteroplasmy (sequencing & PCR)	72

qPCR, quantitative real-time polymerase chain reaction

Table 3: Changes in mitochondrial biogenesis in Alzheimer's disease and ageing.

Study sample	Sample type	Changes in mitochondrial biogenesis	Method of assessment	Reference
Male Fischer 344 rats (24 - 28 months)	Livers	↓ nuclear Nrf2 protein expression	Western blotting	73
AD patients	Hippocampus	↓ PGC1α gene expression	Microarray & qPCR	74
Female Wistar rats (24 months)	heart, lung, liver	↓ intracellular NAD+ & NAD;NADH ratio (sirtuin 1 substrate – regulates PGC1α)	Thiazolyl blue microcyclcing assay	75
AD Mice model (Tg2576 line)	Primary hippocampal neurons (treated with rotenone & H_2O_2)	↑ mitochondrial biogenesis	BrdU labeling	30
AD patients (65 - 91 yrs)	Hippocampus	↓ protein expression of PGC1α, NRF1/2 & TFAM	Western blotting	76
AD Mice model (APPswe/PS1dE9)	Brain	↓ PGC1α gene expression	qPCR	65

Bromodeoxyuridine, BrdU; mitochondrial transcription factor A, TFAM; nicotinamide adenine dinucleotide, NAD; nuclear respiratory factor, NRF; peroxisome proliferated-activated receptor gamma co-activator one alpha, PGC1α; quantitative real-time polymerase chain reaction, qPCR

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