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Commentary

Mitochondrial Manipulation and the Quest for Alzheimer's Treatments

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Alzheimer's disease (AD) implies the presence of progressive cognitive decline to the point an individual cannot manage their daily affairs (dementia), in conjunction with intraneuronal accumulations of tau protein (tangles) in defined cortical regions and extracellular cortical accumulations of beta amyloid protein (Aβ plaques). Our ability to define AD does not mean we fully understand it; AD definitions themselves continue to evolve and disagreements over its causes remain (Swerdlow, 2007). All agree, though, that better treatments are needed. It is this need the study of Zhang et al. (published in this issue of *EBioMedicine*) sought to address (Zhang et al., in press). Members of this group previously reported a tricyclic pyrone compound, CP2, ameliorated Aβ toxicity in a cell culture setting, reduced fibrillary and non-fibrillar Aβ species in an AD transgenic mouse model, and in fact directly bound Aβ (Zhang et al., in press). Observations reported in the current study by Zhang, Trushina, and colleagues, though, indicate that this compound's biological effects transcend its ability to directly bind Aβ.

Through a series of elegant experiments, it was deduced that CP2 competitively occupies the flavin mononucleotide (FMN) redox site within complex I, a respiratory chain holoenzyme on the mitochondrial inner membrane, thereby inhibiting its function. Unlike other complex I inhibitors, CP2-mediated complex I inhibition does not seem to induce oxidative stress or inflammation, perhaps by limiting the initial entry of NADH-donated electrons into the complex. While CP2 lowers respiratory chain oxygen consumption it also concomitantly increases respiratory coupling, a measure of how efficiently the respiratory chain converts electron energy to ATP. It creates a mild energy stress, which appears to activate AMP kinase (AMPK), a protein that monitors and responds to cell energy states, promotes cell resiliency under stress conditions, and inhibits the glycogen synthase kinase 3β (GSK3β) enzyme that enhances tau phosphorylation. Other changes observed in CP2-treated mice or neuronal cultures from mice that express a mutated human amyloid precursor protein (APP) transgene, a mutated human presenilin 1 (PS1) transgene, or both included reduced tau phosphorylation, improved axon transport, increased brain derived neurotrophic factor (BDNF) levels, altered APP processing, reduced plaque burden, and perhaps most importantly preserved behavioral function. Presumably, these effects represent downstream consequences of CP2-altered respiratory chain function, CP2 binding to Aβ, or both.

This study has implications for the field of aging research. Mitochondria and energy metabolism influence aging, but this is not a straightforward relationship. Intact mitochondrial function and enhancing respiration promote healthy aging and longevity in at least some models (Trifunovic et al., 2004; Schulz et al., 2007). Consistent with other reports, though, the Zhang et al. data argue inhibiting respiration can also benefit healthspan as CP2-treated mice in general seemed to age better, with fecundity preserved until later ages, than untreated mice. The Zhang et al. data are also consistent with the emerging recognition that energy stress, as opposed to energy bounty, confers lifespan and healthspan benefits (Munkacsy and Rea, 2014) and may underlie some reported benefits of caloric restriction and physical exercise. The paradoxical ability of energy stress to promote health and survival may arise through an activation of mitochondria-associated stress responses (Durieux et al., 2011).

The Zhang et al. study also provides insight into an increasingly recognized mitochondria-APP-Aβ nexus. APP and Aβ reportedly localize to mitochondria, and may affect mitochondrial function, but mitochondrial function also modifies APP processing (Swerdlow, 2012). This latter phenomenon raises the possibility that CP2-mediated reductions in fibrillary Aβ deposition reflect altered mitochondrial function, as opposed to a direct consequence of Aβ-binding. Of potential relevance to this possibility is the study of Fukui et al. (2007), which found preventing complex IV holoenzyme assembly, thereby limiting respiration, also reduced Aβ deposition in APP/PS1 transgenic mice.

To date, numerous attempts to treat AD by removing Aβ, interfering with Aβ aggregation steps, or directly altering APP have failed in human

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clinical trials. This could reflect limitations of the specific tested interventions, trial design, or the amyloid cascade hypothesis, and has promoted interest in alternative treatment strategies. One alternative approach focuses on manipulations of mitochondria and energy metabolism, both of which are altered in the brains of AD patients (Swerdlow, 2014). CP2 certainly qualifies as an interesting mitochondrial and bioenergetic medicine agent. By interfering with cell ATP production and changing NAD+/NADH ratios the effects of CP2 extend beyond its inhibition of complex I. In the Zhang et al. study examples of this manifested through a variety of demonstrated effects such as AMPK activation, reduced tau phosphorylation, and altered APP processing but no doubt many downstream consequences remain to be shown.

Preclinical success in AD transgenic mouse models does not imply that successful translation to human subjects will occur. Overexpressing mutant human transgenes in mice may poorly model the disorder or disorders that characterize the vast majority of AD patients. This study also assumed a "prevention" strategy, as CP2 was started before histologic or pathologic changes developed in the mice; preventing and treating AD may require different approaches. Regardless, the study by Zhang et al. justifies testing CP2 in human AD subjects. If AD is indeed driven by Aβ, CP2 could impact the disease through direct effects on that protein. Perhaps of greater interest, if altered APP homeostasis and Aβ accumulation represent downstream consequences of mitochondrial dysfunction and compromised brain bioenergetics (Swerdlow et al., 2014), CP2 may impact the disease by acting on the possible upstream causes of altered APP homeostasis and Aβ accumulation.

Author Contribution

RHS was the sole contributor to this paper.

Conflicts of Interest

RHS declared that he has no conflicts of interest.

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