Balancing mitochondrial dynamics in Alzheimer's disease

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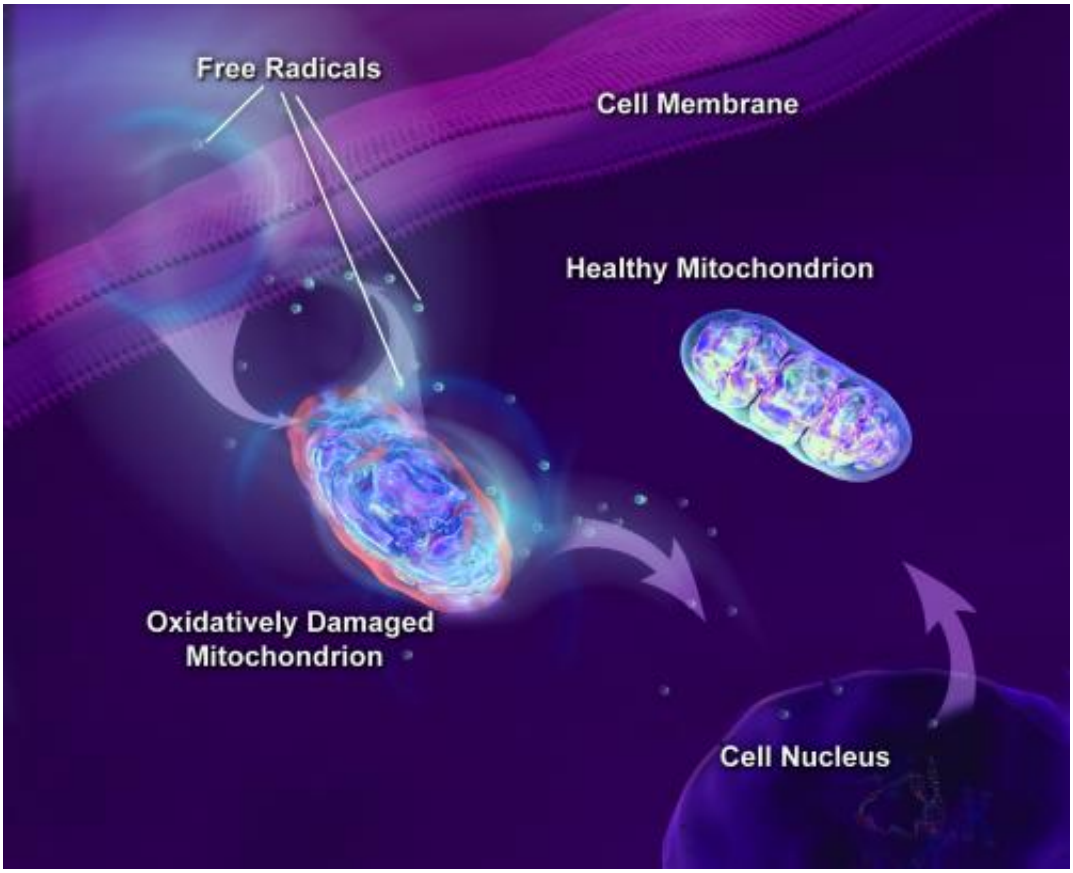

Healthy and damaged mitochondria in Alzheimer's disease. Credit: nia.nih.gov

(Medical Xpress)—Many diseases are multifactorial and can not be understood by simple molecular associations alone. Alzheimer's disease (AD)is associated with toxic transformations in two classes of

protein,amyloid beta and tau, but they do not explain the full underlying pathology. On the cellular scale, much of the real-time morphological changes in neurons can be attributed to their underlying mitochondrial dynamics—namely fission, fusion, and the motions between these events. Last year, researchers from Harvard Medical School made the intriguing discovery that alterations in tau could lead to a doubling in the length of mitochondria. This week, they published a review article in *Trends in Neuroscience*, in which they seek to explain the primary features of AD in terms of mitochondrial dynamics.

Together with a collaborator from the Queensland Brain Institute, the Harvard researchers arrive at the conclusion that, like many other neurological diseases, AD is fundamentally an energy problem. While some proteins, like APOE-ε4 can predispose one to AD, point defects in individual proteins can not account for AD in the same way that a single alteration in hemoglobin leads to sickle cell disease. Attempts to assign casual relations to the complex interactions of tau or amyloid, with hundreds of other proteins inside neurons have frequently served to cloud, rather than simplify the AD story.

In years gone by, it was possible to publish a paper about how phosphorylation at certain sites on proteins, like tau, could lead to any number of downstream events. Tau is one of many proteins that control the assembly and stability of microtubules, critical structures that are among those compromised in AD. The problem now, is that we know tau comes in so many flavors—it is a big family of different isoforms with different properties depending on how they are processed. As far as simple phosphorylation, tau has been found to have 79 potential sites, with at least 30 of them normally phosphorylated.

A welcome simplification to this situation of compounding molecular complexity, is that many pathways converge onto convenient pre-existing packets of time, space, and predictable molecular structure—the

mitochondria. As opposed to massive cell-wide molecular accounting, describing a few sub-cellular morphological features may be a more tractable approach not only to capture disease etiology, but perhaps to treat it.

To this end, the researchers apply existing knowledge regarding some of the molecular players in AD, to a few of the well-established control points in mitochondrial dynamics. State transitions between fission and fusion are, at the moment at least, characterized by only a small handful of proteins. This simple formula might be prescribed as the following: molecular pathway locally effects the organelle dynamics, then, the dynamic behavior of organelle accounts for the disease. The imposition of this middleman can potentially simplify much of the vast body of fact and conjecture associated with the disease.

The elongation of mitochondria by tau can be caused by increasing fusion, decreasing fission, or both. One function of tau is to stabilize F-actin networks which prevents a key fission protein from ever reaching the mitochondria. Elongated mitochondria do not necessarily cause AD. In fact, amyloid beta, which is concentrated inside mitochondria, has been shown to cause increased fission and decreased fusion. When the balance between fission and fusion is pushed too far in either direction, the result is bad news for neurons. If there are defects in the transport of mitochondria, as seems to be the case in many neurological diseases, their redistribution is unable to compensate for this loss of balance.

Specific disease-associated isoforms and phosphorylation states of tau can lead to AD through the loss of mitochondria in axons. In studies of AD tissue, mitochondria have been found to be preferentially redistributed to the soma. These selective localizations can take place quickly, and are therefore difficult to quantify except by live videomicroscopy. In synapses, the mitochondria have been observed to be longer lived, and to play a more critical role in calcium regulation

then those elsewhere. Disruption in the normal handling of calcium has been attributed to many aspects of AD, particularly synaptic pathology.

The canonical dogma that action potentials lead to vesicle fusion and transmitter release exclusively through the entry of extracellular calcium has recently been enhanced with the understanding that mitochondria contribute significantly to the synaptic calcium cycle. While mitochondria clearly do not depolarize as rapidly as whole spiking cells,(generally when mitochondria are depolarized there is some problem) their calcium transporters operate quickly to mop up and redistribute calcium. To say that mitochondria might single-handedly initiate vesicle fusion, or for that matter minipotentials or full-blown spikes, would await future experimental corroboration.

Countless scores of papers over the years have attempted to make sense of the myriad synaptic pathways underlying memory and LTP. They might be better understood when mitochondria are viewed as the primary authors of synaptic vesicle release probability, and by implication, "spontaneous" release (vesicle fusion in the absence of a spike). As in disease states, specific pathways, structures and organelles have significant roles to play in many aspects of brain function—but causally relating the motions and dynamics of mitochondria to these phenomena now gives the broadest interpretive power.

More information: Why size matters – balancing mitochondrial dynamics in Alzheimer's disease, Authors: Brian DuBoff, Mel Feany, Jürgen Götz, *Trends in Neurosciences,* Volume 36, Issue 6, 325-335, 12 April 2013. DOI: 10.1016/j.tins.2013.03.002

Abstract
Once perceived as solitary structures, mitochondria are now recognized as highly dynamic, interconnected organelles. The tight control of their fusion and fission, a process termed 'mitochondrial dynamics', is crucial

for neurons, given their unique architecture and special energy and calcium-buffering requirements at the synapse. Interestingly, in Alzheimer's disease (AD), a condition initiated at the synapse, mitochondrial dynamics are severely impaired. Of the two proteins implicated in AD pathogenesis, amyloid-β (Aβ) and TAU, only the impact of Aβ on mitochondrial dynamics has been studied in detail. We highlight recent findings that TAU exerts a determinative effect in the regulation of mitochondrial dynamics, and therefore neuronal function. In this process, the GTPase DRP1 has emerged as a key target of both Aβ and TAU.