

Researchers link high calcium levels in mitochondria to neuronal death in Alzheimer's disease

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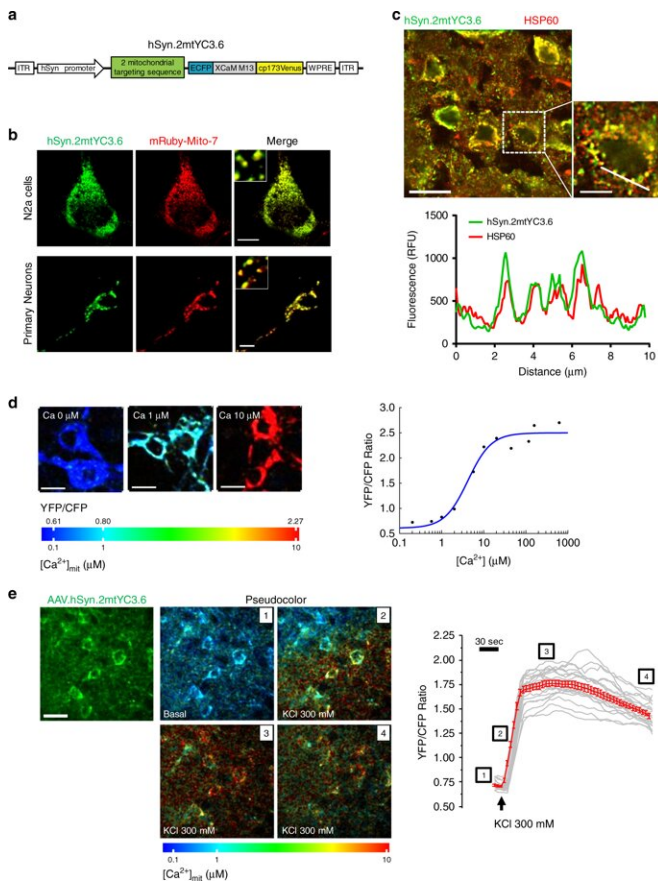


Fig. 1: hSyn.2mtYC3.6 targets neuronal mitochondria and is functional in vivo. Credit: *Nature Communications* (2020). DOI: 10.1038/s41467-020-16074-2

For the first time, using a mouse model of Alzheimer's disease, scientists have documented a link between raised levels of calcium in mitochondria and neuronal death in the living brain. This relationship was previously documented in cell culture, but seeing this phenomenon in living mice makes it more likely that this occurs in people also and could point to a new target for Alzheimer's disease.

"We were able to show mitochondrial calcium dysregulation in the neurons of living mice with Alzheimer's-like symptoms using cutting edge live imaging techniques," says the lead author of the paper, Maria Calvo-Rodriguez, Ph.D. The senior author is Brian J. Bacskai, Ph.D. They are both from the Department of Neurology at Massachusetts General Hospital.

Their collaborators included researchers from Harvard School of Public Health and the School of Medicine at Instituto de Investigacion Biomedica de Cadiz (INIBICA) in Spain. This study was recently published in *Nature Communications*.

One of the defining hallmarks of Alzheimer's [disease](#) is the deposition of amyloid beta (A β) plaques and loss of neurons. The accumulation of A β has long been thought to be a trigger of the disease, but the exact means by which neurons die in Alzheimer's remain a mystery, and the A β theory has become controversial because so many drug candidates targeting A β have failed in clinical trials.

One of the effects of A β plaques is that they cause high calcium ion (Ca $^{2+}$) levels in the [brain cells](#). There is also evidence that, at least in cell culture, exposure to A β can raise Ca $^{2+}$ levels within [mitochondria](#) and lead to neuronal death. Mitochondria influence Ca $^{2+}$ signaling inside neurons through the "mitochondrial calcium uniporter" that takes up Ca $^{2+}$ into mitochondria. The investigation of this mechanism in living mice has been hampered by the lack of technologies sensitive enough to directly assess Ca $^{2+}$ levels in mitochondria in the living brain.

To explore the relationship between Ca $^{2+}$, mitochondria and neuronal death, Calvo-Rodriguez and her colleagues combined multiphoton-microscopy with a ratiometric Ca $^{2+}$ indicator

targeted to mitochondria to assess Ca^{2+} levels. They applied these technologies to examine the neurons of a transgenic mouse model of Alzheimer's disease that develops amyloid plaques similar to those from human patients.

Their studies demonstrate that increased mitochondrial Ca^{2+} levels are associated with plaque deposition and [neuronal death](#) in this model, indicating that abnormal Ca^{2+} levels in mitochondria could play a role in neuronal cell death in Alzheimer's disease.

Additionally, they observed that when soluble A β is applied to the healthy mouse brain Ca^{2+} concentration in mitochondria increases. That process can be prevented by blockage of the mitochondrial calcium uniporter with a drug. Soluble A β is a type of A β similar to that in the human Alzheimer's brain.

"High calcium levels in the mitochondria cause [oxidative stress](#), and the death of neurons via apoptosis," says Calvo-Rodriguez. "We propose that by blocking the neuronal mitochondrial calcium uniporter we can prevent cell death and impact disease progression." Their work suggests targeting calcium entry to the mitochondria could be a promising new therapeutic approach in Alzheimer's disease.

More information: Maria Calvo-Rodriguez et al. Increased mitochondrial calcium levels associated with neuronal death in a mouse model of Alzheimer's disease, *Nature Communications* (2020). DOI: [10.1038/s41467-020-16074-2](https://doi.org/10.1038/s41467-020-16074-2)

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