eIF2α links mitochondrial dysfunction to dendritic degeneration

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Although mitochondrial dysfunction has been associated with dendritic pathology in many neuronal types, how mitochondrial impairment causes the vulnerability of neuronal subtypes remains unknown. In this issue, Tsuyama et al. (2017. *J. Cell Biol.* https://doi.org/10.1083/jcb.201604065) identify eIF2α phosphorylation as a critical regulator of mitochondrial dysfunction-mediated selective dendritic loss in *Drosophila* neurons.

Type-specific dendrite morphology is a hallmark of the neuron and has important functional implications required for neuronal circuit formation. Although changes in dendritic complexity occur in various neurological disorders or during normal aging (Kulkarni and Firestein, 2012), the cellular mechanisms underlying dendritic sustainability remain unclear. Mitochondria are vital organelles present in all eukaryotic cells. In addition to generating ATP, mitochondria function actively in the buffering of intracellular calcium, the regulation of redox signaling, and the mechanisms of programmed cell death. Mitochondria exist as tubules of variable size that fuse and divide in a dynamic network. In nerve cells, individual mitochondria can move purposefully within axons and dendrites, thus allowing them to satisfy local energy demands including the generation of action potentials and synaptic potentials (Cheng et al., 2010). Mitochondria dynamically redistribute into dendritic protrusions in response to synaptic excitation and correlate with synaptogenesis and spine formation. The dendritic distribution of mitochondria appears to be an essential and limiting factor for synapse density and plasticity (Li et al., 2004). Therefore, mitochondrial function has been proposed to be a key determinant for both the generation and the maintenance of the neuronal architecture essential for brain information processing (MacAskill and Kittler, 2010; Sheng and Cai, 2012). Notably, mitochondrial malfunction in neurons has long been appreciated in the pathogenesis of prominent neurodegenerative diseases including Alzheimer's, Parkinson's and Huntington's diseases, and in the neurological phenotypes in rare diseases caused by mutations in mitochondrial genes (Schon and Manfredi, 2003). However, how dysfunctional mitochondria cause neuronal demise in selective types of neurons and the impact of mitochondria on neuronal subtype-specific pathologies in diseases are poorly understood. In this issue, Tsuyama et al. identify eIF2α phosphorylation as a critical regulator of mitochondrial dysfunction-mediated selective dendritic loss in *Drosophila* class IV neurons.

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Drosophila dendritic arborization (da) sensory neurons that develop stereotyped dendritic arbors provide a suitable system in which to study dendritic morphologies and related pathology. The patterns of dendritic branching of da neurons have been characterized and, based on branching morphology, are grouped into four distinct classes (I–IV; Grueber et al., 2002). Using this unique neuronal model system, Tsuyama et al. (2017) first studied whether disturbance of mitochondrial function influenced dendritic morphology in da neurons from class I to IV subtypes. Prel is a mitochondrial protein that facilitates transfer of phosphatidic acid between the mitochondrial inner and outer membrane. The group previously reported that overexpression or knockdown of prel impaired mitochondrial oxidative phosphorylation (OXPHOS) (Tsubouchi et al., 2009). In this study, Tsuyama et al. (2017) found that either overexpression or knockout of prel disrupted mitochondrial function by induction of mitochondrial fragmentation and caused a significantly greater shortening of class IV dendritic arbors, relative to other types of da neurons, suggesting a selective neuronal vulnerability. Interestingly, in contrast to the idea that ATP metabolism is required for the dendrite morphogenesis, Tsuyama et al. (2017) reported a lack of correlation between ATP levels and dendritic defects in the class IV neurons. To understand the possible mechanism behind this, the authors examined the dependency on glycolysis for ATP production, as glycolysis produces the bulk of ATP and is often up-regulated in neurons with OXPHOS impairment (Eid et al., 2008). Using several inhibitors of ATP production pathways, Tsuyama et al. (2017) showed that enhanced glucose utilization by increased reliance on glycolysis may help maintain the ATP levels. The findings reveal a novel mechanistic switch in da neurons, which may compensate for mitochondrial impairment and related changes in energy consumption.

How is the compensatory activation of glycolysis regulated in da neurons upon mitochondrial functional disturbance? Under conditions of metabolic stress, glycolysis activation is controlled by the energy stress pathway. Thus, Tsuyama et al. (2017) decided to examine whether expression of modulators of mitochondrial stress pathways can reverse dendritic loss in the class IV neurons. They found that dPPP1R15, a protein that inhibits eIF2α phosphorylation, restored dendritic shortening in class IV neurons induced by prel overexpression. Moreover, in their genetic models, the neuronal phenotype was partially

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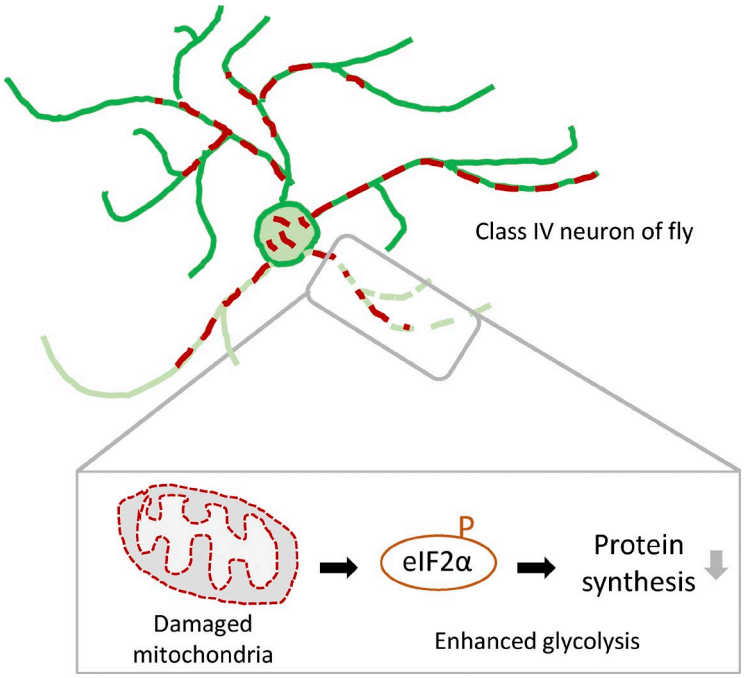

Figure 1. **Schematic illustration of the signaling pathway of mitochondria-mediated dendritic loss.** Mitochondria are impaired in dendritic terminals under stress conditions. Mitochondrial malfunction induces eIF2α phosphorylation that subsequently results into protein translational inhibition in the dendrites of class IV neurons. As a result, the activation of glycolysis is enhanced, which alters growth and stability of class IV dendritic arbors, leading to dendritic loss.

reversed by knockout of PERK, an eIFa2a kinase, supporting their observation that eIF2α phosphorylation contributes to the dendrite phenotypes. In addition, treatment with a series of mitochondrial inhibitors that impair either OXPHOS or mitochondrial membrane integrity all induced eIF2α phosphorylation, further indicating that mitochondrial stress is able to induce eIF2α phosphorylation.

eIF2α is a subunit of the eukaryotic initiation factor 2 and its active form promotes general protein translational initiation by stabilizing the 43S preinitiation complex (Wek et al., 2006). Upon diverse environmental stresses, including mitochondrial dysfunction, eIF2α is phosphorylated at a conserved serine residue by eIF2α kinases, and this phosphorylation blocks general translation in the cytoplasm (Wek et al., 2006). Does mitochondrial dysregulation trigger eIF2α phosphorylation-mediated translational inhibition? To address this question, Tsuyama et al. (2017) evaluated de novo protein synthesis in da neurons at single-cell resolution. Their studies showed that prel overexpression in class IV neurons suppressed protein synthesis, which was reversed by dPPP1R15 coexpression. Moreover, the suppression of protein translation was stronger in class IV neurons than other neuronal classes. These lines of evidence provide insight into the selective vulnerability of class IV neurons to mitochondrial dysfunction. The findings therefore support the authors' hypothesis that chronic mitochondrial malfunction leads to induction of stress signaling, which alters growth and stability of class IV dendritic arbors, resulting in dendritic loss (Fig. 1).

In this study, Tsuyama et al. (2017) mainly overexpressed prel to induce mitochondrial impairment in da neurons. Is the dendritic phenotype specific to prel pathway or is it in fact responsive to a wide range of mitochondrial stressors? To answer this question, Tsuyama et al. (2017) extended their findings to other mitochondrial dysfunction models induced by either overexpression or loss-of-function of mitochondrial proteins such as OPA1 (a mitochondrial fusion protein), Ttm50 (a component of the mitochondrial protein translocator complex TIM23), TFAM (a mitochondrial transcriptional factor that binds to mitochondrial DNA), or CoVa (a subunit Va of the respiratory complex IV). They found that all of these genetic manipulations caused increased eIF2α phosphorylation and resulted in a shortening of class IV neuronal dendrites. As was the case with pre1 manipulations, this effect was partially rescued by coexpression of PPP1R15. Therefore, increased eIF2α phosphorylation might be a common mediator of dendritic loss resulting from mitochondrial disturbance.

Altogether, these findings begin to shed light on how mitochondrial signals can elicit alterations in the structure of neuronal subtypes, ultimately leading to neuronal degeneration. The findings also raise several important questions that remain to be investigated. For example, ER stress elevates eIF2α phosphorylation and prel has been reported to induce unfolded protein response and mitochondrial OXPHOS impairment. How do the ER and the mitochondria cross talk to induce the dendritic vulnerability? In addition, Tsuyama et al. (2017) relied exclusively on the fly model system. Do the molecular events described here similarly occur in mammalian neurons? Is the eIF2α phosphorylation-mediated dendritic loss associated with neuronal or behavioral phenotypes in vivo? Additionally, the authors determined mitochondrial fragmentation to indicate mitochondrial damage. Are other elements of mitochondrial function compromised under stress conditions? Finally, what specific mitochondrial impairment triggers eIF2α phosphorylation? Answering these questions will help elucidate the underlying mechanisms and may enhance our understanding of the role of mitochondrial signals in the regulation of dendritic physiology and neuronal pathology.

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References

Cheng, A., Y. Hou, and M.P. Mattson. 2010. Mitochondria and neuroplasticity. *ASN Neuro.* 2:e00045. http://dx.doi.org/10.1042/AN20100019

Eid, T., A. Ghosh, Y. Wang, H. Beckström, H.P. Zaveri, T.S. Lee, J.C. Lai, G.H. Malthankar-Phatak, and N.C. de Lanerolle. 2008. Recurrent seizures and brain pathology after inhibition of glutamine synthetase in the hippocampus in rats. *Brain.* 131:2061–2070. http://dx.doi.org/10.1093/brain/awn133

Grueber, W.B., L.Y. Jan, and Y.N. Jan. 2002. Tiling of the *Drosophila* epidermis by multidendritic sensory neurons. *Development.* 129:2867–2878.

Kulkarni, V.A., and B.L. Firestein. 2012. The dendritic tree and brain disorders. *Mol. Cell. Neurosci.* 50:10–20. http://dx.doi.org/10.1016/j.mcn.2012.03.005

Li, Z., K. Okamoto, Y. Hayashi, and M. Sheng. 2004. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. *Cell.* 119:873–887. http://dx.doi.org/10.1016/j.cell.2004.11.003

MacAskill, A.F., and J.T. Kittler. 2010. Control of mitochondrial transport and localization in neurons. *Trends Cell Biol.* 20:102–112. http://dx.doi.org/10.1016/j.tcb.2009.11.002

Schon, E.A., and G. Manfredi. 2003. Neuronal degeneration and mitochondrial dysfunction. *J. Clin. Invest.* 111:303–312. http://dx.doi.org/10.1172/JCI200317741

Sheng, Z.H., and Q. Cai. 2012. Mitochondrial transport in neurons: Impact on synaptic homeostasis and neurodegeneration. *Nat. Rev. Neurosci.* 13:77–93.

Tsubouchi, A., T. Tsuyama, M. Fujioka, H. Kohda, K. Okamoto-Furuta, T. Aigaki, and T. Uemura. 2009. Mitochondrial protein Preli-like is required for development of dendritic arbors and prevents their regression in the *Drosophila* sensory nervous system. *Development.* 136:3757–3766. http://dx.doi.org/10.1242/dev.042135

Tsuyama, T., A. Tsubouchi, T. Usui, H. Imamura, and T. Uemura. 2017. Mitochondrial dysfunction induces dendritic loss via eIF2α phosphorylation. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201604065

Wek, R.C., H.Y. Jiang, and T.G. Anthony. 2006. Coping with stress: eIF2 kinases and translational control. *Biochem. Soc. Trans.* 34:7–11. http://dx.doi.org/10.1042/BST0340007