MITOPHAGY

Enhanced brain mitophagy slows systemic aging

Compromised clearance of dysfunctional mitochondria, through the process of mitophagy, has garnered attention as an essential contributor to aging and neurodegeneration. Schmid and colleagues[1] reveal that genetic enhancement of mitophagy via neuronal overexpression of BNIP3 alleviates brain aging and prolongs healthspan in fruit flies.

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During aging, our brain function deteriorates, with consequences such as cognitive decline, memory and learning impairments and disrupted motor coordination, and the risk of neurodegenerative disorders such as Alzheimer's disease increases. One of the essential hallmarks underlying brain aging is mitochondrial dysfunction[2,3]. Mechanistically, cellular accumulation of damaged mitochondria might be caused by the impairment of two main recycling systems: the ubiquitin–proteasome system that recognizes and eliminates unwanted proteins, and mitochondrial autophagy (mitophagy), which specifically engulfs and degrades the whole mitochondrion. Age-dependent deterioration in mitophagic capacity results in derailed mitochondrial homeostasis, leading to frailty, disease and shortened healthspan[4,5]. However, it is incompletely understood how enhancing neuronal mitophagy affects brain and systemic aging. A study by Schmid et al. in *Nature Aging*[1] shows that neuron-specific overexpression of BCL2 interacting protein 3 (BNIP3) — a protein that participates in mitophagy and apoptosis — improves brain mitochondrial homeostasis and brain health in fruit flies. Additionally, it prolongs overall organismal health with age in a non-autonomous manner (Fig. 1).

In brief, mitophagy is a multistep process that is initiated through the engulfment of damaged or dysfunctional mitochondria by a phagophore, creating a mitophagosome. The mitophagosome fuses with an acidic lysosome, enabling degradation and intracellular recycling of the cargo. BNIP3 is a multifunctional protein that is localized to the outer membrane of the mitochondria, where it can act as either a proapoptotic protein or a mitophagy receptor. BNIP3 participates in the nucleation and elongation steps of mitophagy[5] ensuring the recruitment of the phagophore to the mitochondrion by binding to the autophagosome protein, microtubule-associated proteins 1A/1B light chain 3B (Atg8A (known as LC3 in humans))[6,7].

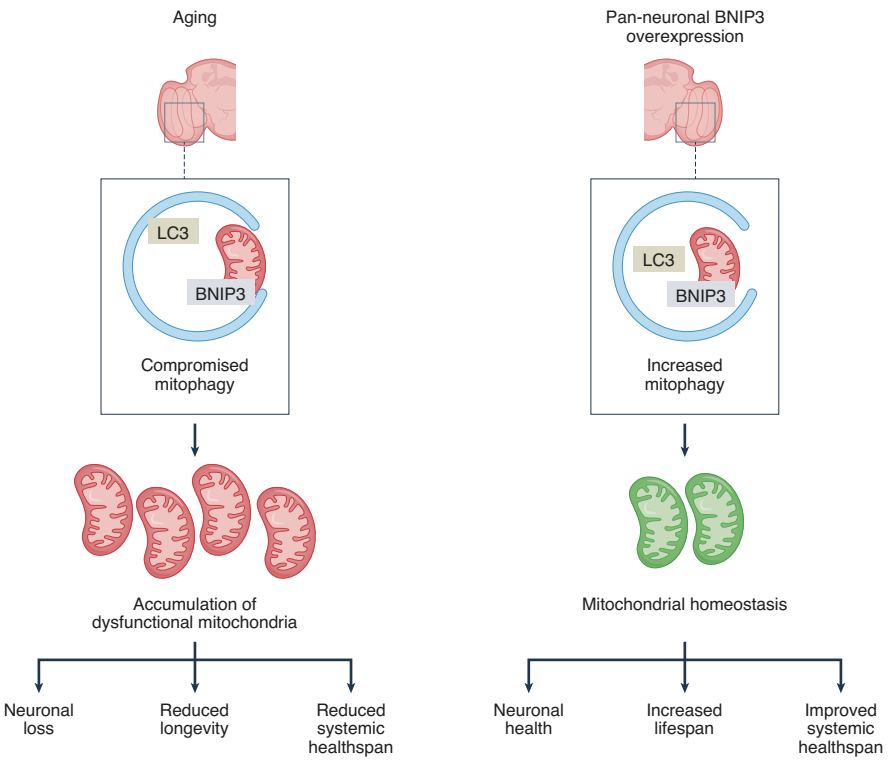

Fig. 1 | Neuronal overexpression of BNIP3 delays systemic aging via mitophagy induction in fruit flies. Left, Aging leads to an accumulation of dysfunctional mitochondria in the brain, probably contributing to neuronal loss, and reduced lifespan and healthspan (such as reduced motor and muscle function, and impaired intestinal homeostasis) in *Drosophila melanogaster*. Right, Pan-neuronal overexpression of human BNIP3 using the UAS-Gene-Switch system and the elav-Gene-Switch driver restores neuronal mitophagy. This results in improved mitochondrial homeostasis in the neurons, and maintenance of neuronal health. Moreover, pan-neuronal BNIP3 overexpression also increases lifespan and healthspan parameters (such as activity, motor function, muscle function, intestinal stem cell function and intestinal barrier function), which normally decrease with age.

Furthermore, BNIP3 binds to the central mitophagy protein PTEN-induced kinase 1 (Pink1), blocking its clearance and promoting mitophagy induction[8].

In their study, Schmid et al.[1] first convincingly showed an accumulation of mitochondria in the optic lope of the brain from wild-type old (30 days), as compared to young (10 days), flies. Moreover, they showed that mitochondria in the brains of the aged flies are dysfunctional, as measured by decreased membrane potential and increased oxidative stress. By triggering pan-neuronal overexpression of BNIP3 through use of the UAS-Gene-Switch system with a neuron-specific driver (elav) in the aged flies, they induced mitophagy — which restored mitochondrial homeostasis to the level of young wild-type flies. When knocking down Autophagy-related 1

(Atg1 (known as ULK1 in humans)) simultaneously with pan-neuronal BNIP3 overexpression, the induction of mitophagy and thus mitochondrial homeostasis was lost; this demonstrates that the effect of BNIP3 is dependent on the autophagy and/or mitophagy machinery. Furthermore, BNIP3 overexpression counteracts neuronal loss during aging.

Further, the authors demonstrate that neuronal overexpression of BNIP3 also counteracts systemic aging. They show that pan-neuronal BNIP3 overexpression extends lifespan and prolongs several parameters of healthspan, including improved motor and muscle function, higher intestinal homeostasis and enhanced stem cell function. Through overexpression of BNIP3 in the neurons, mitochondrial homeostasis is maintained during aging via mitophagy induction in the muscle cells and in the enterocytes of the gut. The beneficial effects of neuronal BNIP3 overexpression are lost when knocking down Atg1 in parallel to BNIP3 overexpression — again demonstrating that the positive effects of BNIP3 depend on neuronal autophagy and/or mitophagy. Importantly, overexpression of BNIP3 ubiquitously, or in muscle or intestinal cells, does not show benefits for either longevity or healthspan, which indicates a pivotal and unique role for neuronal mitophagy in maintaining healthspan and extending lifespan. One limitation of the findings is the lack of validation in vertebrates. Future directions of research should aim at validating the regulatory role of neuronal BNIP3 in both mice and human cells. It would be of great interest to evaluate brain-region or cell-type specificity of BNIP3 overexpression or activation in both mice and human stem-cell-derived neurons or glia cells. By evaluating the genetic or pharmacological activation of BNIP3 in both wild type and disease models (such as models of Alzheimer's disease), potential clinical translations of BNIP3 as a biomarker for disease or a target to delay aging and/or neurodegeneration in humans could be evaluated.

This study points to neuronal mitophagy as a systemic regulator of mitochondrial homeostasis and adds to evidence pointing to mitochondrial dysfunction as a master regulator of aging. Future studies are needed to evaluate the mechanisms that control BNIP3-mediated coordination of mitophagy and apoptosis in both animal models and humans, and how we can specifically induce neuronal BNIP3 as a therapeutic intervention against brain aging and common neurodegenerative diseases, such as Alzheimer's disease. ❐

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Competing interests

E.F.F. has a CRADA arrangement with ChromaDex (USA) and is consultant to Aladdin Healthcare Technologies (UK and Germany), the Vancouver Dementia Prevention Centre (Canada), Intellectual Labs (Norway) and MindRank AI (China).