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Does Autophagy Promote Longevity? It Depends.

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Zhou et al. challenge the well-known beneficial effect of autophagy in promoting longevity. Evidence presented demonstrate that autophagy induction coupled with increased mitochondrial permeability is detrimental to organismal health in both the nematode *Caenorhabditis elegans* and mammals.

According to historians, the orchestrated removal of solid waste dates back to the 1st century AD in ancient Rome, where a specialized police service known as *vigiles* provided community oversight for garbage disposal. A cleaning mechanism also occurs at a micro-level in every eukaryotic cell, known as autophagy. This evolutionary conserved process constantly eliminates and recycles waste products in the cells, playing a major role in coordinating cellular homeostasis, as well as influencing organismal health and longevity (Madeo et al., 2010; Ryter et al., 2013). Compromised autophagic capability is associated with premature aging (Kang et al., 2007), while induced autophagy has been shown to confer a prolongevity effect in different model organisms (Eisenberg et al., 2009; Simonsen et al., 2008). But is the induction of autophagy always beneficial, or are there context-dependent mechanisms to determine its benefits on organismal health? In this issue of *Cell*, Zhou et. al (2019) report that mitochondrial permeability determines the impact of autophagy on lifespan in *C. elegans* and on reperfusion injury in mouse liver.

It was known previously that mutations in mTOR complex 2 (mTORC2) component Rictor (*rict-1)* and its downstream effector, the serum/glucocorticoid regulated kinase 1 (*sgk-1*) shorten lifespan in *C. elegans* (Soukas et al., 2009). Surprisingly, these short-lived *sgk-1* and *rict-1* mutants induce autophagy, which raises the question whether the increased autophagy flux is still beneficial in the context of mTORC2 reduction. The authors find RNAi-mediated knockdown in the *sgk-1* and the *rict-1* mutants rescues the shortened lifespans to wild-type levels, and these effects are restricted to the intestinal action of autophagy. These new findings strongly argue for a previously unknown harmful role of autophagy induction.

To decipher the underlying molecular mechanism, Zhou et al. conduct an unbiased mass-spectrometry analysis searching for interacting proteins of SGK-1 and identify a group of regulators involved in the mitochondrial permeability transition pore (mPTP), including voltage-dependent anion channel (VDAC). Transient or prolonged mPTP opening is detrimental and has been reported to be involved in calcium signaling or apoptotic and necrotic cell death, respectively (Kwong et al., 2015). The authors hypothesize that mPTP opening and increased mitochondrial permeability are responsible for lifespan shortening in both the *sgk-1* and the *rict-1* mutants. Supporting this notion, RNAi knockdown of mPTP regulators rescues lifespan shortening in the *sgk-1* and the *rict-1* mutants. Importantly, the authors further discover that SGK-1 directly phosphorylates and interacts with VDAC-1, which regulates the degradation of VDAC-1 via the proteasomal pathway in *C. elegans* and mammals. Like the *sgk-1* and the *rict-1* mutants, overexpression of *vdac-1* transcriptionally upregulates autophagy genes and leads to lifespan reduction in *C. elegans*, which can be rescued by inhibition of autophagy. Together, these results discover the novel function of mTORC2 permeability, confirm SGK-1 as a key regulator of mitochondrial homeostasis through controlling VDAC1 abundance, and reveal the detrimental effect of autophagy induction in the context of increased mitochondrial permeability.

Strikingly, this mechanism regarding increased mitochondrial permeability can be generalized and applicable to other longevity mechanisms and reperfusion injury. The authors find that *vdac-1* overexpression suppresses the longevity effects caused by caloric restriction (*eat-2* mutants), germline deficiency (*glp-1* mutants), or mitochondrial reduction (*frh-1* and *nuo-6* RNAi). In contrast, inactivation of insulin/insulin growth factor (IGF)-1 receptor/*daf-2* reduces *vdac-1* levels and can still extend lifespan upon *vdac-1* overexpression. Therefore, the induction of autophagy by these longevity regimens is only beneficial when mPTP remains closed and mitochondrial permeability is low. Furthermore, the authors have generated mice lacking *Sgk1* in liver ($Sgk1^{LKO}$) or *Sgk1*, *Sgk2*, and *Sgk3* in liver (*SgkTKO)* that show increased mPTP opening, autophagy flux, and VDAC1 protein levels. These knockout mice also exhibit increased sensitivity to hepatic ischemia/reperfusion injury, which is evident by the induction of serum alanine transaminase and serum aspartate transaminase. The authors use cyclosporine A to pharmacologically inhibit mPTP opening and confirm its protective effect against hepatic ischemia/reperfusion injury in the *SgkTKO* mice. This work supports the previous preclinical and clinical application of mPTP inhibitors in reducing ischemia/reperfusion

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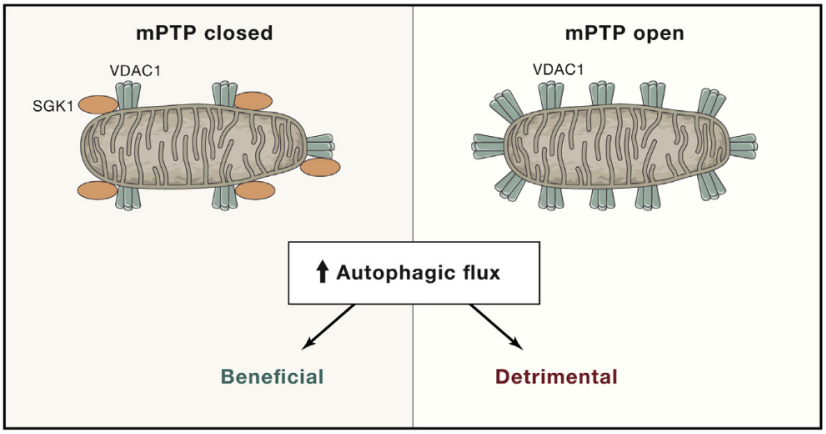

Figure 1. The Effect of Autophagic Flux on Organism Health Is Determined by Mitochondrial Permeability

Mitochondrial permeability transition pore (mPTP) is tightly associated with mitochondrial permeability. The serum/glucocorticoid regulated kinase 1 (SGK1) binds to the voltage-dependent anion channel (VDAC1) of mPTP to positively regulate its degradation. In the absence of SGK1, the accumulation of VDAC1 facilitates mPTP open and increases mitochondrial permeability, leading to detrimental effects associated with increased autophagic flux. Therefore, increased autophagic flux can be either detrimental or beneficial based on facilitated mPTP opening or mPTP closure, respectively.

Context matters; like Gregory Bateson said, "Without context, words and actions have no meaning at all." Accordingly, without context, autophagy cannot be judged good or bad. This exciting work by Zhou et. al now assigns mitochondrial permeability as a crucial determinant for the effect of autophagy (Figure 1) and demonstrates the importance of understanding this context dependence in longevity regulation and hepatic injury prevention. They also discover mTORC2 as a key regulator of mitochondrial permeability to set this context for autophagy. mPTP is a large multi-protein complex whose molecular composition is still under investigations. For future studies, it would be interesting to characterize whether and how mPTP structural components and/or post-translational modification undergo significant changes during aging and how these changes affect mitochondrial permeability. In addition, mPTP and mitochondrial permeability may exhibit tissue specificity in different organisms, and it would be vital to understand their interactions with autophagy flux in a tissue-specific manner. Furthermore, future studies to identify additional mechanisms regulating mitochondrial permeability and characterize their mechanistic link with autophagy might open new avenues to promote healthy aging and prevent age-related diseases.

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