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Spotlight

Self-Digestion for Lifespan Extension: Enhanced Autophagy Delays Aging

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By systemically boosting autophagy with a knockin mutation that prevents binding of beclin 1 to BCL2, Fernández et al. (2018) demonstrate that enhanced autophagy prolongs lifespan in mammals.

Autophagy, a term coined by Christian de Duve and derived from the Greek meaning of "to eat self," orchestrates the delivery of cytosolic components to the lysosome for degradation and subsequent recycling. This process enables cells to survive during periods of nutrient deprivation by mobilizing endogenous macromolecules, and it also supports the clearance of protein aggregates and damaged subcellular structures to avoid proteotoxic stress and maintain homeostasis. BECN1/beclin 1 (the mammalian ortholog of Atg6) was among the first genes identified to promote autophagy in mammals (Liang et al., 1999). Beclin 1 is an essential component of the class III PI3K autophagy-initiation complex, which, under the proper cellular signaling cues, sets off a cascade of events resulting in phagophore formation, cargo loading to autophagosomes, and finally fusion with and degradation by the lysosome. In a recent study published in *Nature*, Fernández et al. utilized a mouse model containing a knockin (KI) mutation in beclin 1 (F121A) that prevents the binding of beclin 1 to its negative regulator BCL2 (Rocchi et al., 2017), resulting in constitutive activation of autophagy. The systemic increase in basal autophagic flux notably increased lifespan and decreased incidence of age-related pathologies (Fernández et al., 2018) (Figure 1).

The connection between autophagy and aging has been well established in model organisms such as yeast, worms and flies. In these organisms, defects in autophagy-related genes decrease survival and also reduce lifespan extension caused by autophagy-inducing treatments such as caloric restriction, rapamycin, and spermidine (Rubinsztein et al., 2011). However, it has not been possible to assess the impact of whole-body loss of critical autophagy genes on lifespan in mammals, as loss of such genes results in embryonic or neonatal lethality. Autophagy generally declines with age, and this decline can be circumvented by caloric restriction and rapamycin. Although these treatments prolong lifespan in mice (Rubinsztein et al., 2011), it is unclear whether the autophagy induction elicited by these regimens is solely responsible for the observed increase in mammalian lifespan.

Fernández et al. lay this debate to rest by demonstrating that specific activation of autophagy through a mutation in beclin 1 prolongs median survival by approximately 12% in both male and female mice. The enhanced autophagic flux observed with the F121A BECN1 mutation also alleviated age-related pathology in the kidneys and heart, evidenced by decreased renal and cardiac cellular damage and decreased fibrosis (Fernández et al., 2018). To further strengthen the conclusion that autophagy combats aging, Fernández et al. investigated whether autophagy induction can rescue the phenotypes associated with klotho hypomorphism, a murine model of premature aging (Kuro-o et al., 1997). Remarkably, constitutive activation of autophagy by beclin 1 mutation almost completely rescued the premature lethality and growth retardation of klotho-hypomorphic mice, suggesting that autophagy induction may be able to offset genetic predispositions to premature aging.

Other consequences of aging include declined metabolic fitness and propensity toward neurodegenerative diseases. In mice overexpressing Atg5, enhanced autophagy and lifespan extension were observed along with improvements in metabolic outcomes such as insulin sensitivity (Pyo et al., 2013). The improvement in metabolic phenotypes was accompanied by body weight reduction in the Atg5 transgenic mice. As F121A BECN1 mice also appeared leaner (Fernández et al., 2018), it would be interesting to examine if metabolic capacity was additionally enhanced. Another study utilizing the same F121A BECN1 KI mouse revealed that autophagy-mediated clearance of amyloid plaques results in improved cognitive function and prolonged survival in murine models of Alzheimer's disease (Rocchi et al., 2017). Taken together, these findings provide substantial evidence that sustained autophagy activation can prolong lifespan and improve pathologies associated with aging.

Fernández et al. also investigated the association between autophagy enhancement and aging-induced spontaneous cancers. Studies examining the dependence of cancer on autophagy have been conflicting, with disruption of autophagy causing tumor regression, tumor growth, or no effect, depending on the cancer model utilized and time of intervention (Levy et al., 2017). Beclin 1 has previously been identified as a haploinsufficient tumor suppressor (Liang et al., 1999), and monoallelic deficiency of beclin 1 increases spontaneous tumor formation (Qu et al., 2003). Fernández et al. expand upon these findings by demonstrating that constitutive activation of beclin 1 decreases the incidence of spontaneous age-related cancers, including both lymphomas and solid tumors. Furthermore, a recent report by the same group details reductions in tumorigenesis in a HER2-driven mouse

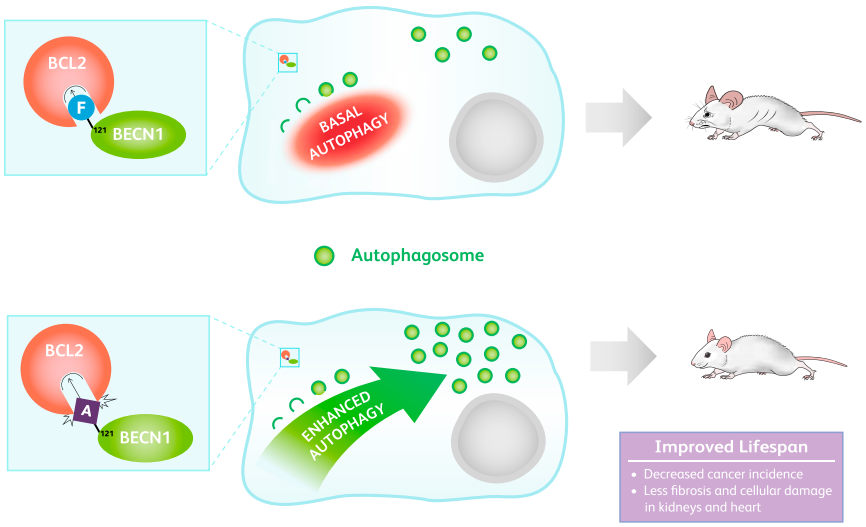

Figure 1. Autophagy Induction via Beclin 1 Mutation Prolongs Lifespan
Top: Wild-type beclin 1 (BECN1) binds its negative regulator, BCL2. With the proper signaling cues, autophagosome formation is permitted and basal cellular autophagy is maintained. Mice age normally and eventually succumb to age-related diseases. Bottom: Constitutively active BECN1 is generated by mutating phenylalanine 121 to alanine. BECN1 is unable to bind BCL2, resulting in enhanced autophagosome formation and increased autophagic flux. Mice expressing the F121A mutation have decreased incidence of age-related pathology and prolonged lifespan.

model of breast cancer upon disruption of beclin 1/BCL2 binding (Vega-Rubín-de-Celis et al., 2018). Collectively, these findings suggest that chronic activation of autophagy may be a strategy to delay or prevent the onset of tumorigenesis.

Whether systemic activation of autophagy is required from birth or if autophagy induction later in life would have similar lifespan- and healthspan-promoting effects remains to be addressed. By generating mice with inducible expression of BECN1 F121A, it could be determined whether intervention with autophagy enhancers could delay or even reverse the progression of age-related pathologies such as cancer, neurodegeneration, and metabolic decline. Furthermore, the authors note that the F121A BECN1 mutation partially alleviated but did not completely rescue age-associated decline in autophagic capacity (Fernández et al., 2018). Thus, if alternative interventions were identified that fully restored autophagic flux to levels observed in younger mammals, perhaps even longer extensions in lifespan could be achieved. These studies would provide further rationale for the development of specific autophagy-inducing compounds with the intent of prolonging lifespan and preventing or alleviating age-related diseases. Taken with recent findings predicting that mortality risk in humans plateaus once individuals surpass 100 years of age (Barbi et al., 2018), the report by Fernández et al. raises the exciting possibility that significant increases in human lifespan are just over the horizon.

DECLARATION OF INTERESTS

M.D.A. and C.H.E. are employees and shareholders of Pfizer.

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