News and Commentary

Linking calorie restriction to longevity through sirtuins and autophagy: any role for TOR

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In this issue of Cell Death & Disease, Morselli et al. described that calorie restriction (CR) and resveratrol activate autophagy through sirtuin-1 and, most importantly, autophagy is required for the life extending effect of CR (Figure 1a). This paper touches upon three hot topics, entering into three debated fields. Let us discuss this in a broader context. In almost all species from yeast to primates, CR increases both median and maximal lifespan. Still the topic remains highly controversial. Why? As I recently analyzed, the antiaging effect of CR rules out the most intuitive theory of aging (see for reference, Blagosklonny1). According to the current dogma, aging is caused by lifelong accumulation of molecular damage. This damage is not repaired completely because energetic resources are limited in the wild.2 This must predict that the fewer the resources (CR), the less resources could be spend for repair (and the faster aging). Yet we know that CR slows down aging. To reconcile this fact with the theory, it was suggested that an organism allocates more resources to fight aging during famine or CR, in order to live longer and to reproduce later,2 even though aging does not limit lifespan in the wild. This suggestion leads to unfathomable paradoxes, forcing us to reconsider the origin of aging.1 In fact, recent discoveries reveal that aging is genetically regulated.3 For example, inhibition of TOR (target of rapamyin) or activation of sirtuins prolongs lifespan. And CR both deactivates TOR and activates sirtuins. But here is a second debate: which is indispensable for prolonged lifespan by CR, inhibiting TOR or activating sirtuins?

On one hand, it was shown that CR slows down aging through TOR.4,5 On the other hand, it was shown that CR and resveratrol activate sirtuins, thus extending lifespan.6,7 Let us start the discussion with TOR. The TOR intracellular signal-transduction pathway is conserved in eukaryotes from yeast to mammals.8 In mammals, TOR (known as mTOR) integrates signals (nutrients, hormones, growth factors, stressors) through a complex signaling network. Nutrients also increase levels of insulin, which additionally activates mTOR. TOR increases protein synthesis and inhibits autophagy, driving cellular mass growth.9,10 TOR also activates cellular functions, ranging from the bone absorption by osteoclasts and the contractility in smooth muscle cells to insulin secretion by β-cells of the pancreas and lipoprotein synthesis in liver.11 Finally, cellular hyperactivation causes a feedback signal resistance. For example, mTOR by activating S6 kinase causes insulin resistance. All these cellular alterations can be linked to organismal aging and age-related diseases such as benign and malignant tumors, cardiac hypertrophy, osteoporosis, metabolic syndrome, atherosclerosis, hypertension, neurodegeneration and age-related macular degeneration.11 Like in yeast,9 serum starvation and rapamycin suppress mammalian cell senescence.12 Finally, rapamycin extends lifespan in mice.13

Similarly, there is a strong case that NAD(+)-dependent deacetylases, called sirtuins, such as SIRT1 and Sir2 are involved in aging and age-related diseases.6,7 Evidence has emerged that sirtuins and mTOR are involved in the same longevity pathway.14 Importantly, resveratrol, an activator of sirtuins, antagonizes the mTOR/S6K pathway.15,16 Therefore, two notions that CR prolongs lifespan either by activating sirtuins or by deactivating TOR are complementary: CR deactivates the mTOR pathway in part by activating SIRT1 (Figure 1b).

In addition, sirtuins and TOR have opposing effects on autophagy independently from each other. As shown by Morselli et al. (this issue), sirtuin-1 was not required for the induction of autophagy by rapamycin. And, vice versa, sirtuin-1 can deacetylate essential autophagic modulators, such as ATG5 and ATG7, inducing autophagy. In addition to independent effects on common targets (such as autophagy), sirtuins may antagonize the TOR/S6K pathway.15,16 Therefore, two notions that CR prolongs lifespan either by activating sirtuins or by deactivating TOR are complementary: CR deactivates the mTOR pathway in part by activating SIRT1 (Figure 1b).

And here is a third debated question: what is the significance of autophagy in longevity. Is autophagy required for life extension by CR? Would it be sufficient to upregulate...
autophagy only (without either activating sirtuins or inhibiting TOR) in order to live longer? Could lifespan be increased without activating autophagy? At least for worms and flies, the answer to the first question seems to be yes, whereas the answer to two other questions is still unclear.

As shown by Kroemer and co-workers (this issue), resveratrol and dietary restriction only prolonged the lifespan of autophagy-proficient nematodes, whereas these beneficial effects on longevity were abolished by the knockdown of the essential autophagic modulator Beclin-1. Taken together with similar results in the literature, this indicates that autophagy is a very significant component for life extension. However, autophagy is such a fundamental cellular function that its inhibition would shorten lifespan, regardless of its role in the aging process. This would obfuscate determining its role in aging.

Although, the induction of autophagy increases lifespan in Drosophila, Atg1, a gene that stimulates autophagy, also inhibits the TOR pathway.17 The activation of autophagy in turn inhibits TOR.17 Is autophagy the only longevity mechanism? Although longevity pathways converge on autophagy, they converge on autophagy through TOR and sirtuins. Other effects of TOR inhibition may be essential for longevity. From this point of view, inhibition autophagy is one (but not the only one) end point of TOR-driven aging (Figure 1b). For example, rapamycin inhibits polyglutamine aggregation independently of autophagy by reducing protein synthesis.18 Inhibition of translation is sufficient to extend lifespan in Caenorhabditis elegans (see for reference6). Although the antiaging effect of CR can be linked to autophagy,19 autophagy is not sufficient for lifespan extension.19

Roughly speaking, autophagy is a degradation of intracellular components in lysosomes. The lysosomal theory of aging (the ‘garbage’ accumulation theory of aging) was formulated a half century ago. This theory explains some features of aging such as accumulation of lipofuscin and in part neurodegenerative diseases. Insufficient autophagy is linked to some other diseases and conditions.20 Still lysosomal insufficiency cannot explain other attributes of aging such as menopause and insulin-resistance, just to name a few.

There are some other difficult questions faced by lysosomal theory of aging. Why would autophagy fail in all species from yeast to man? Is autophagy such a neglected cellular function that causes aging universally? Is there an inherent problem with autophagy that could not be solved by nature? Or perhaps autophagy is one of the ‘tips of the iceberg’ of something else. This underlying process is neither failure of maintenance nor random damage but a calorie-dependent quasi-program, an aimless continuation of the developmental growth.11 The nutrient-sensing pathways are essential for growth and development. Their inhibition or knockout is lethal in early development. This is an example of antagonistic pleiotropy. The nutrient-sensing and growth promoting network is beneficial and essential early in life but drives aging later in life. As development and growth are universal features of life, aging is universal too. But now we can suppress aging pharmacologically.

Preferably, an antiaging drug should not directly interfere with autophagy but rather should act upstream (e.g., sirtuins and TOR), in order to inhibit the cause of aging and all its manifestations. I mention rapamycin as an example. One may argue that TOR-deficient mutant animals have growth and other defects. But unlike genetic knockout, pharmacological inhibition of mTOR with rapamycin could be (and should be) performed in aging individuals, thus avoiding inhibition of mTOR during growth and development. (Why would we think about prevention of aging in infants?) Also, there is no need to inhibit mTOR completely and at low doses rapamycin may have no side effects, because even at high doses its side effects are minimal. Upstream activators of autophagy, such as rapamycin, resveratrol and metformine are well-tolerated drugs.21 In contrast, there is no drug that directly activate autophagy in mammalian cells and even if there were, such a chemical might have both on-target and off-target side effects.

**Conflict of interest**

The authors declare no conflict of interest.

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1. Blagosklonny MV. mTOR-driven aging: speeding car without brakes. Cell Cycle 2009; 8: 4055–4059.
2. Kirkwood TB, Shanley DP. Food restriction, evolution and ageing. Mech Ageing Dev 2005; 125: 1011–1016.
3. Guarente L, Kenyon C. Genetic pathways that regulate ageing in model organisms. Nature 2000; 408: 255–262.
4. Kapahi P, Zid BM, Harper T, Koslover D, Sapin V, Benzer S. Regulation of lifespan in Drosophila by modulation of genes in the TOR signaling pathway. Curr Biol 2004; 14: 885–890.
5. Kaeberlein M, Powers III RW, Steffen KK, Westman EA, Hu D, Dang N et al. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. Science 2005; 310: 1119–1123.
6. Cohen HY, Miller C, Bitterman KJ, Wall NR, Hekking B, Kessler B et al. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 2004; 305: 390–392.
7. Wood JD, Ro Gina B, La ve S, Howitz K, Helfand SL, Tatar M et al. Sirtuin activators mimic caloric restriction and delay aging in metazoans. Nature 2004; 430: 666–669.
8. Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell 2006; 124: 471–484.
9. Hands SL, Proud CG, Wytenbach A. mTOR’s role in ageing: protein synthesis or autophagy? Aging 2009; 1: 586–597.
10. Blagosklonny MV, Hall MN. Growth and aging: a common molecular mechanism. Aging 2009; 1: 357–362.
11. Blagosklonny MV. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle 2006; 5: 2087–2102.

12. Demidenko ZN, Zubova SG, Bukreeva EI, Pospelov VA, Pospelova TV, Blagosklonny MV. Rapamycin decelerates cellular senescence. Cell Cycle 2009; 8: 1888–1895.

13. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K et al. Rapamycin fed late in life extends lifespan in genetically heterogenous mice. Nature 2009; 460: 392–396.

14. Medvedik O, Lamming DW, Kim KD, Sinclair DA. MSN2 and MSN4 link calorie restriction and TOR to Sir2n-mediated lifespan extension in Saccharomyces cerevisiae. PLoS Biol 2007; 5: e261.

15. Demidenko ZN, Blagosklonny MV. At concentrations that inhibit mTOR, resveratrol suppresses cellular senescence. Cell Cycle 2009; 8: 1901–1904.

16. Armour SM, Baur JA, Hsieh SN, Land-Bracha A, Thomas SM, Sinclair DA. Inhibition of mammalian S6 kinase by resveratrol suppresses autophagy. Aging 2009; 1: 515–528.

17. Chang YY, Juhasz G, Goraksha-Hicks P, Ansham AM, Malin DR, Mufer JK et al. Nutrient-dependent regulation of autophagy through the target of rapamycin pathway. Biochem Soc Trans 2009; 37 (Part 1): 232–236.

18. King MA, Hands S, Hafiz F, Mizushima N, Tolkovsky AM, Wytenbach A. Rapamycin inhibits polyglutamine aggregation independently of autophagy by reducing protein synthesis. Mol Pharmacol 2008; 73: 1052–1063.

19. Hansen M, Chandra A, Mitic LL, Onken B, Driscoll M, Kenyon CR. A role for autophagy in the extension of lifespan by dietary restriction in C. elegans. PLoS Genet 2008; 4: e24.

20. Huang J, Klionsky DJ. Autophagy and human disease. Cell Cycle 2007; 6: 1837–1849.

21. Blagosklonny MV. Validation of anti-aging drugs by treating age-related diseases. Aging 2009; 1: 281–288.

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