3. mTOR pathways in aging

Karthikeyani Chellappa, Joseph A. Baur

Mammalian/mechanistic target of rapamycin (mTOR) is the catalytic subunit of two distinct protein kinase complexes that coordinate nutrient and growth factor signaling with downstream anabolic processes. Although mTOR signaling has been extensively studied with respect to cancer and immunology, it has been appreciated only in the past decade that this pathway can have a profound influence on longevity in laboratory organisms. Determining the nature of the downstream effects that are responsible for changes in lifespan, and whether they might be relevant to human health, is an active area of investigation. Herein, we review recent findings and discuss the evidence in support of potential mechanisms to account for increased longevity in organisms with reduced mTOR signaling.

Introduction to mTOR signaling

Mechanistic/mammalian target of rapamycin (mTOR) is a serine/threonine kinase that is highly conserved in eukaryotes spanning from yeast to plants, worms, flies, mice, and humans. mTOR is the catalytic subunit for two functionally distinct protein complexes, termed mTORC1 and mTORC2. These complexes vary in their protein constituents, sensitivity to rapamycin, upstream activating signals/input and downstream functional consequences/output (**Figure 1**, reviewed in Ref. 1).

The mTOR catalytic subunit, mLST8/GβL, Deptor, Tti1, and Tel2 are core components that are common to both the complexes. mTORC1 further contains PRAS40 and Raptor, whereas mTORC2 contains Rictor, mSin1 and Protor1/2. Acute treatment with rapamycin, a growth-inhibitory macrolide, is sufficient to inhibit the kinase activity of mTORC1. In contrast, chronic rapamycin exposure is required to inhibit mTORC2 through a mechanism that involves physical disruption of the complex. Disruption of mTORC2 has been observed in some, but not all, cultured cell lines *in vitro* and multiple tissues *in vivo* [2,3]. mTORC1 positively regulates multiple anabolic processes, including protein, lipid and nucleic acid synthesis, organelle biogenesis and metabolism in response to diverse external cues including nutrients, growth factors, stress, energy status, oxygen and amino acids. Conversely, inhibition of mTORC1 slows cell growth and stimulates autophagy, in large part by relieving inhibitory phosphorylations of the upstream autophagy inducers ULK1 and ATG13 [4,5]. Numerous targets have been identified for mTORC1 and a complete listing is

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mTOR pathways in aging
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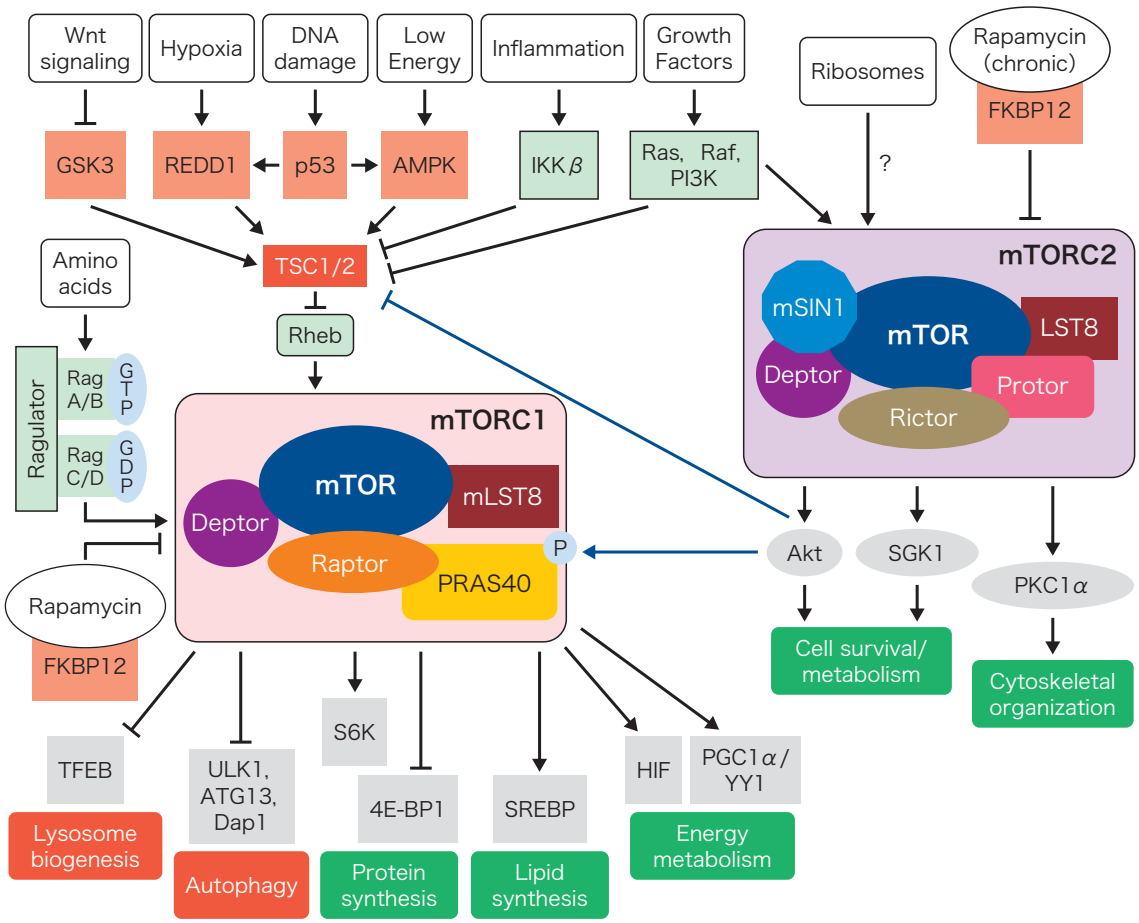

Figure 1 The mTOR signaling cascade

The mTOR signaling pathway comprises two distinct complexes, mTORC1 and mTORC2. mTORC1 modulates protein synthesis, lipid synthesis, metabolism and autophagy in response to plethora of environmental cues including growth factors, nutrients, energy status, hypoxia, Wnt signaling and DNA damage. mTORC2 is activated by growth factors and ribosomes to regulate cell survival, metabolism and cytoskeletal organization.

beyond the scope of this review. However, it is worth noting that the two best-known substrates, S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein (4E-BP) play key roles in the regulation of protein translation, and have each been independently implicated in the control of lifespan. mTORC2, the less-studied of the two mTOR complexes, is regulated by growth factors and ribosome association, and in turn, regulates AGC subfamily kinases, including AKT, SGK1 and protein kinase c α (PKC α). Through these substrates, and likely more that have yet to be revealed, mTORC2 influences cytoskeletal organization, cell survival, and metabolism, including playing a key role in the insulin signaling cascade (Figure 1).

1 Genetic evidence linking reduced mTOR signaling to longevity

The first evidence for a role of the mTOR pathway in aging was reported by Vellai and colleagues, who found that in *Caenorhabditis elegans*, loss of *let-363* (TOR) increased mean life span by 2.5-fold (mean life span of 10 vs. 25 days in WT and TOR deficient worms, respectively) [6]. This effect was independent of *daf-16*, a FOXO family transcription factor that was already known to be required for the long life spans of worms with mutations in the insulin signaling pathway. Similarly, loss of the TORC1 substrate *rsks-1* (S6K)

extended life span in a number of studies [7,8], and heterozygous mutation of the TORC1 subunit *daf-15* (Raptor) was shown to extend both mean and maximum life span in *C. elegans* [9]. Puzzlingly, the effect of *daf-15* loss was reported to be dependent on *daf-16*, in contrast to the *daf-16*-independent effect of *let-363* deletion. A resolution to this apparent contradiction was provided by the discovery that TORC2 disruption (due to *rict-1*/Rictor loss) can also extend lifespan in *C. elegans* [10]. Indeed, a subsequent study established that knockdown of multiple proteins that are specifically required for the TORC1 pathway during adulthood (*raga-1*, *ragc-1*, *rheb-1*, *daf-15*) extended life span in *daf-16*-dependent manner, whereas lifespan extension by TORC2 disruption was independent of *daf-16* [11]. Since deletion of *let-363* disrupts the activity of both complexes, it was proposed that lifespan extension occurs via the TORC2 pathway even in the absence of *daf-16*. In addition, the authors demonstrated that lifespan extension by either TOR complex in worms requires an intact SKN-1/Nrf2 pathway, and provide evidence that the effect of *rict-1* loss on life span is sensitive to diet, temperature, and/or the timing and degree of *rict-1* deficiency. Interestingly, knockdown of *sgk-1*, a substrate of TORC2, has been reported to extend life span in worms [12], providing a potential clue as to the mechanism of action. However, a complete null allele for *sgk-1* shortens lifespan, and a gain of function mutant lengthens life, suggesting that *sgk-1* actually promotes longevity [13]. The same study shows that deletion of another TORC2 substrate, *akt-1/akt-2*, extends life, providing an alternative mechanism by which TORC2 loss might be beneficial. Finally, *pkc-2*/PKC α, a third TORC2 substrate, is required for cold-induced lifespan extension in *C. elegans* [14]. Thus, multiple substrates of TORC2 may be involved in lifespan regulation, but only *akt-1/akt-2* appear positioned to cause a beneficial effect when TORC2 is lost. Taken together, these studies provide strong evidence that both TOR complexes regulate life span in *C. elegans*.

In yeast, unbiased longevity screens have revealed that deletion of *TOR1* or *SCH9*, the *Akt/S6K* homolog, increases both replicative and chronological life spans [15,16]. In flies, overexpression of negative regulators of TOR signaling, dTSC1 and dTSC2, or dominant negative mutants of dTOR and dS6K increases life span [17]. Further, constitutive activation of 4E-BP (mimicking the loss of TORC1-dependent inhibition) also extends lifespan, whereas deletion of 4E-BP reduces longevity [18,19]. Data on the influence of TORC2 on lifespan in yeast and flies are not yet available.

Deciphering the role of mTOR pathway in mammalian aging by genetic manipulation has been hindered by the pivotal requirements of both complexes for normal development. Deletion of the mTORC1 substrate *S6K1* has been shown to extend the lifespan of female mice by ~19% [20]. Recently, we found that *mTOR*$^{+/-}$, *mLST8*$^{+/-}$ exhibit a selective decrease in the activity of mTORC1 with apparently preserved mTORC2 activity, and that females of this strain have an approximately 14% increase in mean lifespan [2]. The reasons for this gender discrepancy in both models remain unclear. Although several additional studies have suggested intriguing associations between mTORC1 signaling and lifespan in mammals, including humans [21], the above studies are, to our knowledge, the only reports of longevity following genetic manipulations designed to altered mTOR signaling in mammals. Notably, disruption of mTORC2 signaling via deletion of *Rictor* in the liver or brain, or inducibly in the whole body after bypassing development, have all been reported to cause detrimental phenotypes that would be predictive of a shortened lifespan (e.g. Ref. 2, 22, 23). Therefore, a role for mTOR signaling in longevity appears to be conserved in mammals, but our understanding of the mechanisms involved remains very primitive.

2 Pharmacological evidence linking reduced mTOR signaling to longevity

Rapamycin extends life across a variety of species and is arguably the compound with the strongest experimental support for an effect on longevity in mammals [24]. Studies to date have demonstrated significant extensions of lifespans in budding yeast (replicative and chronological), fission yeast (chronological), *C. elegans*, male and female *Drosophila*, and male and female mice of several strains. Importantly, rapamycin extends maximum lifespan in mice, as opposed to other interventions such as aspirin or exercise, which increase mean, but not maximum lifespan (i.e. tend to "square" the survival curve).

Caffeine has gained attention in recent years based on human epidemiological data suggesting that chronic consumption of coffee and/or tea ameliorates the age-associated decline in cognitive function and diseases including myocardial infarction, diabetes, and

Alzheimer's and Parkinson's diseases, and may extend life span [25]. Caffeine increases life span in fission and budding yeast, as well as worms [26–28]. Interestingly, caffeine treatment specifically inhibits TORC1, and at least in yeast, this appears to be the mechanism for life span extension. However, caffeine clearly has other effects in humans, and has been shown to decrease life span in fruit flies at high doses [29,30], and in a mouse model of amyotrophic lateral sclerosis [31], as well as induce cardiovascular disease in rats [32]. It remains to be seen whether caffeine will hold up as a bona fide mTOR inhibitor in mammals, and whether the net effect on longevity will be positive.

3 Does inhibition of mTOR by rapamycin mimic DR?

Given the central roles of the mTOR complexes in coordinating nutrient and growth factor responses, it is interesting to consider whether their inhibition might constitute a strategy for mimicking the beneficial effects of dietary restriction (DR). Indeed, deletion of *TOR1* or its substrate *SCH9* in yeast extends life to a similar degree as DR, and there is no additive effect, suggesting that the two interventions act in the same pathway [15]. Similarly TOR inhibition does not further increase the life span of *eat-2* mutant worms, a genetic model of DR [7]. In *Drosophila*, DR induces expression of 4E-BP, an inhibitor of translation that is phosphorylated and inhibited by TORC1 [19]. Flies that lack 4E-BP are short-lived and have a greatly diminished response to DR, suggesting that DR acts by relieving TORC1-dependent repression of 4E-BP. On the other hand, rapamycin has been found to extend life to a greater degree than DR in flies, hinting that direct mTOR inhibition might engage additional mechanisms. In mammals to date, greater lifespan extensions have been reported for DR than for genetic or pharmacological inhibition of mTOR signaling. However, the dosing for rapamycin (both frequency and amount) has yet to be optimized. Moreover, epistasis experiments have not been performed in mammals using any strategy for mTOR inhibition, making it unclear whether there is potential for additive benefits.

From a metabolic standpoint, lifespan extension by mTOR inhibition does not seem to be coupled to the same improvements in insulin sensitivity and cardiovascular risk factors that characterize DR. Female mice lacking S6K1 have increased longevity, improved insulin sensitivity, reduced body weight, and decreased adiposity, reminiscent of DR [20]. Yet female mice that are heterozygous for mTOR and mLST8 (empirically determined to have ~50% mTORC1 activity with nearly normal mTORC2) display a similar lifespan extension with no detectable changes in insulin sensitivity or body weight [2]. Moreover, rapamycin-treated mice are glucose-intolerant and hyperlipidemic, despite the longer life spans of both genders (**Figure 2**).

Several additional pieces of evidence point to distinct mechanisms of action for rapamycin and DR. DR, but not rapamycin, delays disease onset and extends survival in the H46R/H48Q mouse model of amyotrophic lateral sclerosis [33]. Conversely, rapamycin was recently shown to extend lifespan in $Rb1^{+/-}$ mice, which are prone to neuroendocrine tumors and are not protected by DR [34]. Furthermore, it is clear that DR has a stronger effect when begun early in life, and that the benefits are diminished by one year of age, whereas initiating rapamycin treatment at 20 months of age conferred nearly the same benefit as beginning at 9 months. These observations lend support to the conclusion that while rapamycin and DR may have some overlapping features, their *in vivo* effects are far from identical (**Table 1**).

4 Does reducing mTOR signaling slow aging?

A crucial question to ask for any intervention that prolongs life is whether it actually slows aging, and thus would be expected to confer improved health and quality of life, or whether it acts more specifically on one or a few causes of death, and thus runs the risk of prolonging a period of infirmity at the end of life. Two major studies have recently attempted to address this question for rapamycin. Despite the somewhat opposing conclusions reached by the authors, it is clear from both studies that rapamycin causes a subset of traits to appear more "youthful" in aged animals, while other traits are unaffected.

In the first study examining the effects of rapamycin on aging phenotypes, Wilkinson et al. examined changes in multiple tissues as well as the loss of spontaneous locomotor activity in aging HET3 mice fed dietary rapamycin from 9 months of age [35]. The majority of these phenotypes showed at least a partial reversal with rapamycin treatment, leading the authors to conclude that the drug does indeed reverse some aspects of the aging process, rather than simply

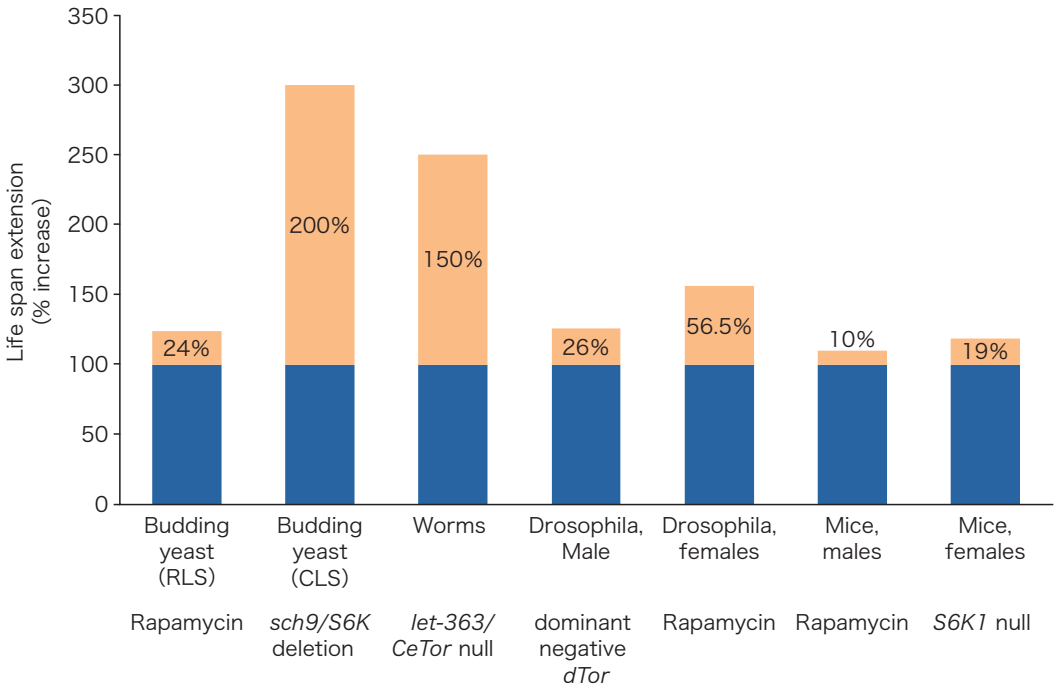

Figure 2 Largest life span extensions obtained in model organisms by manipulating the mTOR pathway

Inhibiting the mTOR pathway, either by genetic or pharmacological means, increases life span in *Saccharomyces cerevisiae* [45) 46)], *Caenorhabditis elegans* [6)], *Drosophila melanogaster* [17) 47)] and *Mus musculus* [20) 35)].

delaying death from cancer. These findings are in line with a number of other reports investigating individual age-related phenotypes, such as hematopoietic stem cell function, cardiac hypertrophy, and neurodegeneration [24)].

In a second, larger study, Neff et al. evaluated more than 150 phenotypes in male C57BL/6J mice treated with rapamycin for one year starting at three different ages, 4 months, 16 months, or 28 months [36)]. A unique aspect of this study was the follow-up of certain phenotypes in young animals (6 month-old mice that had been treated for 3 months) to determine whether rapamycin was truly preventing age-related changes, or instead, having age-independent effects. In line with previous studies, rapamycin opposed the effects of aging on a number of key functional measures, although it was notable that this applied to only ~10% of the phenotypes that were studied. Intriguingly, most of rapamycin's effects were also observed in young animals, leading the authors to conclude that the drug acts mainly independently from the aging process.

While it is clear that rapamycin-treated mice are not immune to the effects of aging, it is equally clear that this inhibitor of mTOR signaling does more than simply prevent death. Determining whether strategies that target mTOR signaling will be able to provide a better quality of life, aside from any effects on the quantity of life, in humans will be a key goal for future studies.

5 Possible mechanisms for lifespan extension by mTOR inhibition

1) Cancer

Anti-cancer effects clearly contribute to lifespan extension by rapamycin, but whether this reflects a direct effect on tumors or the slowing of something more fundamental to aging remains uncertain [1) 24)]. Data on causes of death are not available for other models of inhibited mTOR function in rodents. Although there are a few interesting trends in the data from rapamycin-treated mice, such as the exchange of lung carcinomas for liver cancers, end of life pathology is, on the whole, quite similar to that of

Table 1 Some effects of dietary restriction vs. mTOR inhibition by rapamycin in mammals

	Dietary Restriction	Ref.	Rapamycin	Ref.
Lifespan	↑↑	48–50	↑	51
Cancer	↓↓	52	↓	53
Glucose tolerance	↑↑	54	↓	55
Cholesterol/TG	↓	56	↑	57
Body weight	↓↓	49, 50	↓	58
Adiposity	↓↓	59	↓	55, 60, 61
Mitochondria	↑	62	⇔	63, 64
Autophagy	↑	54	↑	54
Metabolic rate	↓ ?	65	↓ (female), ⇔ (male)	36, 66
Respiratory exchange ratio	↓ (overall), ↑ (post-feeding)	67	⇔, possibly ↑ in aged	36
Body temperature	↓	65	⇔	36
Glomerulosclerosis	↓	68	⇔ (nephrotoxic ?)	36
Stem cell function	↑	69, 70	↑	70, 71

Double arrows indicate a stronger effect for one intervention vs. the other. ⇔ : no change, ? : unclear or conflicted results

untreated controls. Therefore, the existing data do not support prevention of a specific cancer or degenerative disorder as the explanation for life extension. Numerous studies have demonstrated improvements in age-related phenotypes with rapamycin treatment, which might be expected to lead to an improved quality of life, but thus far, cancer is the only direct cause of death in WT mice that can be definitively stated to be delayed.

Importantly, prevention of cancer cannot account for lifespan extension in yeast, worms, or flies with inhibited mTOR signaling. Improved longevity in these species strongly suggests that mTOR plays a more fundamental role in the aging process. It is also notable that rapamycin has therapeutic effects in rodent models of neurodegeneration and cardiac hypertrophy – conditions that do not generally affect WT mice, but do cause mortality in aging humans.

2) Translation inhibition

mTORC1 is a positive regulator of translation, and it has been speculated that inhibition of this pathway might improve protein quality via increased translational fidelity or availability of cofactors that ensure proper folding and post-translational modification [37]. Indeed, genetic interventions that slow translation extend life in yeast, worms, and flies to a similar extent as inhibiting TORC1 signaling [19) 20)]. However, inhibition of TORC1 and direct inhibition of translation can have additive effects on lifespan in worms, and recent studies have shown that neither rapamycin nor S6K1 deletion significantly diminishes overall translation in mice [38]. Instead, recent studies have suggested that inhibition of the TORC1 pathway might bias translation toward specific subsets of transcripts that could promote longevity [24]. This is an area that clearly warrants further attention in mammals.

3) Autophagy

Autophagy is a process by which cells recycle proteins and organelles to generate raw materials and energy, and remove accumulated damage. Aging associated with a decline in autophagy in rodents and possibly in humans [39) 40)] and an increase in autophagy is one of the most prominent effects of mTORC1 inhibition. It is interesting to note that interventions known to increase lifespan in worms including DR, reduced insulin signaling, reduced TOR signaling, germline removal, and reduced mitochondrial respiration converge on autophagy [41]. Zhang and Cuervo showed that maintaining youthful levels of autophagy in aged livers (via expression of LAMP-2A) was sufficient to clear damaged proteins and restore organ function [72]. Nevertheless, induction of autophagy alone is gener-

ally not sufficient to extend life in invertebrates, despite the fact that it is required for life span extension by other means.

Alvers et al. reported that CLS extension following rapamycin treatment was abolished in autophagy deficient strains [42]. Similarly, the autophagy gene *ATG16* was required for extension of yeast CLS in a *tor1* mutant strain [43]. In addition, rapamycin treatment induces autophagy to clear toxic protein aggregates and improve neurological functions in mouse model of Huntington disease [44]. However, it remains to be established whether improved autophagy is solely or partially responsible for longevity and improved age-associated phenotype observed in mice following mTOR inhibition.

4) Other mechanisms

There are a number of additional mechanisms by which mTOR signaling might influence longevity in mammals. Inhibition of mTOR signaling has complex effects on the immune system that may affect disease resistance and inflammatory status in aging individuals. Active mTORC1 signaling can impair pluripotency in stem cells, and overstimulation of this pathway appears to occur naturally in aging mice. Intriguingly, the effects of aging on hematopoietic stem cells are rapidly reversed by treatment with rapamycin. Studies in worms suggest that disruption of either mTOR complex extends life in part via induction of SKN-1/Nrf2-dependent stress-response mechanisms, and the corresponding pathways are induced by rapamycin treatment in mice, suggesting that they could also contribute to the extension of mammalian life span [11].

Conclusion

The mTORC1, and possibly mTORC2, pathways play a conserved role in the regulation of longevity across species. Pharmacological inhibition of these pathways may be a viable approach to prevent or delay age-related diseases, as evidenced by the growing body of literature on the effects of rapamycin in rodents. Despite extensive study, the precise mechanisms accounting for the beneficial effects of mTOR inhibition remain uncertain, and should be a high priority for future research. Understanding the molecular events downstream of mTOR signaling may lead to new therapeutic approaches and offer basic insights into the nature of the underlying aging process.

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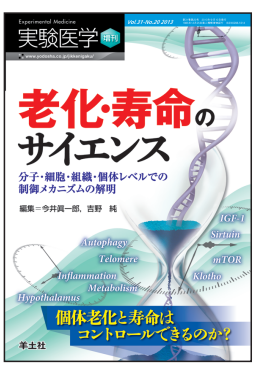

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