Published in final edited form as:
Aging Cell. 2011 April ; 10(2): 185–190. doi:10.1111/j.1474-9726.2010.00665.x.

Hot Topics in Aging Research: Protein Translation and TOR Signaling, 2010

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Summary

In this, the fourth installment of our annual Hot Topics review on mRNA translation and aging, we have decided to expand our scope to include recent findings related to the role of TOR signaling in aging. As new data emerge, it is clear that TOR signaling acts upstream of mRNA translation, as well as a variety of other cellular processes, to modulate longevity and healthspan in evolutionarily diverse species. This Hot Topics review will cover important new findings in this area that have occurred over the past year. These include the demonstration that the TOR substrate ribosomal S6 kinase modulates longevity in mammals, the potential for TOR inhibitors as therapeutic treatments for Alzheimer's disease, and further studies emphasizing the importance of differential translation of specific mRNAs for healthy aging and enhanced longevity.

Keywords

TORC1; mTOR; S6K1; rapamycin; longevity; dietary restriction; mRNA translation; ribosome

Introduction

The target of rapamycin (TOR) kinase first gained recognition as an important player in the biology of aging from experiments performed in yeast and invertebrate model organisms (Stanfel *et al.* 2009). These studies reported that genetic inhibition of TOR complex 1 (TORC1) activity was sufficient to increase life span in yeast, nematodes, and fruit flies, suggesting that inhibition of TOR signaling is a key mechanism by which dietary restriction (DR) slows aging in these species (Vellai *et al.* 2003; Jia *et al.* 2004; Kapahi *et al.* 2004; Kaeberlein *et al.* 2005). Several subsequent studies have further strengthened this model, identifying potential mechanisms by which TOR signaling modulates both life span and healthspan, the period of time that individuals remain healthy, across a broad evolutionary spectrum (Kapahi *et al.* 2010).

The TORC1 complex influences a variety of cellular processes through both direct and indirect means (Wullschleger *et al.* 2006; Evans *et al.* 2010). TORC1 is known to promote global mRNA translation and ribosome synthesis by direct phosphorylation of the ribosomal S6 kinase (S6K1 in mice) and eukaryotic initiation factor 4E (eIF4E) binding proteins (4E-

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BP). TORC1 also negatively regulates macroautophagy, the lysosomal degradation pathway. Thus, two important consequences of TORC1 inhibition are down-regulation of mRNA translation and up-regulation of autophagy, both of which have been implicated in longevity control downstream of DR and TORC1 in non-mammalian species(Mehta *et al.* 2010; Vellai & Takacs-Vellai 2010). In addition, TORC1 signaling interacts with a variety of additional longevity pathways, including the insulin-like signaling pathway, the hypoxic response transcription factor, Gcn4 in yeast, and sirtuins.

As studies in non-mammalian models have continued to flesh out details about pathways that modulate longevity, there has been growing interest in the potential for pharmacological manipulation of these pathways to promote health and longevity in people. TORC1 is, fortunately, amenable to such an approach, with several specific inhibitors of TORC1, structurally based on the compound rapamycin, already known and in use both clinically and for basic research purposes(Kaeberlein 2010). Spurred on by the longevity data from non-mammalian models and indications that rapamycin may be therapeutic against certain forms of cancer, the National Institute on Aging Interventions Testing Program initiated longevity studies in genetically heterogeneous mice fed a diet supplemented with rapamycin. The striking result of this trial, published in the middle of 2009, was that supplementation with rapamycin beginning at 600 days of age was sufficient to significantly increase life span in both male and female mice(Harrison *et al.* 2009). This finding established inhibition of TOR signaling as the first intervention other than DR known to modulate aging in yeast, nematodes, fruit flies, and mice(Kaeberlein & Kennedy 2009).

S6K1 and Mammalian Aging

Soon after the ITP publication showing life span extension from rapamycin in mice, a second report further validated the importance of this pathway in mammalian aging. In this study, Selman et al. (Selman *et al.* 2009) showed that mice lacking *S6K1*, encoding one of two mammalian S6 kinases, have significantly increased life span. Similar to inhibition of TORC1, prior studies in yeast, nematodes, and fruit flies had shown that mutation of *S6K1* functional orthologs could increase life span in those organisms(Fabrizio *et al.* 2001; Kapahi *et al.* 2004; Kaeberlein *et al.* 2005; Hansen *et al.* 2007; Pan *et al.* 2007). Thus, Selman et al. not only independently verified the importance of TORC1 in mammalian aging, but also established a second component of this pathway as a longevity factor conserved from yeast to mice (Kaeberlein & Kapahi 2009).

There are a few additional noteworthy aspects of the study by Selman et al. For example, the *S6K1* knockout was examined in the commonly used C57BL/6 background, an inbred background that differs substantially from the 4-way outcross background used by the ITP for testing rapamycin. The demonstration that TORC1 signaling modulates longevity in two genetically distinct backgrounds provides important validation for the general role of this pathway in mammalian aging. Also, the effect of *S6K1* knockout on life span was only apparent in female animals, whose median life span was extended by 19%. Male $S6K1^{-/-}$ mice, in contrast, had a life span that was not significantly different from control animals. This observation parallels the trend observed with rapamycin feeding in the ITP study, where life span extension was more prominent in females, although significant in both sexes (Harrison *et al.* 2009). The mechanisms underlying this gender difference are unclear at this time, but will be important to understand, particularly if pharmacological intervention in this pathway ever becomes widely used in people.

Importantly, Selman et al. provided evidence for activation of the adenosine monophosphate (AMP)–activated protein kinase (AMPK) in the life span extension from S6K1 knockout. AMPK is an important sensor of cellular energy status that has been previously implicated

in *C. elegans* aging(Apfeld *et al.* 2004; Curtis *et al.* 2006; Greer & Brunet 2009). Selman et al. observed that loss of *S6K1* results in gene expression changes consistent with activation of AMPK in mice, and showed that life span extension from mutation of the *C. elegans S6K1*ortholog *rsks-1* is suppressed by mutation of the AMPK homolog *aak-2*. The mechanistic basis for activation of AMPK by reduced S6 kinase activity is unknown, and it remains unclear whether this represents a direct or indirect effect of S6 kinase deficiency. It is also unknown (1) whether rapamycin activates AMP kinase and (2) whether this activation is important for life span extension. Since chronic exposure to rapamycin results in reduced S6 kinase activation, S6K activation may be one component of life span extension by the TORC1 inhibitor.

AMPK can function as a negative regulator of TORC1 activity via phosphorylation of the TORC1 inhibitor Tsc2 or the TORC1 component, Raptor (Inoki *et al.* 2003; Shaw 2009; Gwinn *et al.* 2010). Thus, activation of AMPK in response to S6 kinase deficiency is likely to result in concomitant inhibition of TORC1. It may be the case, therefore, that AMPK activation under conditions where S6 kinase activity is reduced is an important mechanism for regulating overall TORC1 activity in order to prevent an imbalance among the various downstream components of TORC1 signaling.

S6 kinase orthologs play important roles in promoting global mRNA translation downstream of TORC1 in non-mammalian organisms. S6 kinase mutants show a reduction in cell and body size, decreased mRNA translation, and reduced protein synthesis in yeast, nematodes, and fruit flies (Montagne *et al.* 1999; Jorgensen *et al.* 2002; Pan *et al.* 2007; Steffen *et al.* 2008). Interestingly, the small body size and reduced fecundity of *rsks-1* mutants in *C. elegans* is suppressed by mutation of *aak-2* (Selman *et al.* 2009). This unexpected observation suggests that the inhibition of mRNA translation from mutation of S6 kinase is dependent on AMPK. Potential mechanisms for such regulation remain a mystery, but are clearly important given the strong connection between mRNA translation and aging in different species. It also remains unclear whether *S6K1*$^{-/-}$ mice or mice treated with rapamycin show significant defects in global mRNA translation. *S6K1*$^{-/-}$mice are substantially smaller than animals with normal S6 kinase activity; however, this phenotype may result from a lack of S6K1during development and not be correlated with reduction of global mRNA translation (Pende *et al.* 2000; Um *et al.* 2004). It will be important for future studies to quantify mRNA translation and protein synthesis in a variety of tissue types from whole body and conditional *S6K1*$^{-/-}$animals.

New insights into longevity control via reduced mRNA translation

The effort to understand life span extension mediated by reduced mRNA translation at the mechanistic level has been a central theme of prior entries in this Hot Topics series on mRNA translation (Kaeberlein & Kennedy 2007; Kaeberlein & Kennedy 2008; Kennedy & Kaeberlein 2009). At the most fundamental level, it remains unclear to what extent, if any, global reduction in mRNA translation contributes to increased life span or healthspan. In contrast, there are clear examples where changes in translation of specific mRNAs are thought to play a causal role. Two cases, differential translation of Gcn4 in yeast and electron transport chain components in flies, have been described previously (Steffen *et al.* 2008; Zid *et al.* 2009). In both instances, structural features of the 5'-UTR of specific mRNAs underlie differential translation: the yeast *GCN4* 5' UTR contains translation-inhibiting upstream open reading frames that are less efficiently translated in these long-lived mutants, while fly mRNAs with relatively simple, short 5'-UTRs are preferentially translated during DR.

A new study in *C. elegans* suggests that similar mechanisms for differential control of mRNA translation may also be important for stress resistance and longevity downstream of the insulin-like signaling pathway (McColl *et al.* 2010). McColl and colleagues examined the mechanistic basis for enhanced thermotolerance of long-lived animals with reduced insulin-like signaling due to mutation of the insulin-like receptor *daf-2*. Resistance of *daf-2* animals to thermal stress was found to require continuous protein translation. Translation state array analysis was then used to show that several dozen mRNAs undergo differential translation in response to heat shock. One of the mRNAs that is more efficiently translated in *daf-2* mutants following heat shock, *C08H9.1*, codes for a putative lysosomal serine carboxypeptidase. RNAi-mediated knock-down of *C08H9.1* suppressed the thermotolerance of *daf-2* mutants, consistent with the idea that translational up-regulation of this mRNA is important for enhanced stress resistance associated with reduced insulin-like signaling. Interestingly, knockdown of *C08H9.1*expression also reduced the life span extension in *daf-2* mutants, without affecting the life span of wild type animals. Heat shock had a profound inhibitory effect on mRNA translation in both wild type and *daf-2* mutant animals, raising the possibility that similar mechanisms of differential translation control may be utilized in long-lived animals where translation is impaired and in response to stressful environmental conditions.

Two additional studies from *C. elegans* are noteworthy in that they have added information about potential factors acting downstream of TORC1 signaling and mRNA translation. In the first, Ching et al. (Ching *et al.* 2010) report that the translation initiation factor DRR-2 functions downstream of TORC1 in parallel to *rsks-1* to modulate life span. RNAi knock-down of *drr-2* had been previously shown to extend life span and enhance resistance to polyglutamine and amyloid beta toxicity, and genetic experiments suggested that DRR-2 functions downstream of dietary restriction (Hansen *et al.* 2005; Steinkraus *et al.* 2008). In the second study, Wang and colleagues (Wang *et al.* 2010) provide evidence for activation of the oxidative stress responsive transcription factor SKN-1 in long-lived mutants with reduced mRNA translation. Activation of SNK-1 has been previously shown to increase life span in *C. elegans*, and SKN-1 has been implicated in life span extension from reduced insulin-like signaling and DR (Bishop & Guarente 2007; Tullet *et al.* 2008). Wang et al. show that RNAi knock-down of *rsks-1*, as well as several translation initiation factors, results in enhanced SKN-1-dependent expression of known target genes (Wang *et al.* 2010). Interestingly, the life span extension from knock-down of these translation factors is reduced in *skn-1* mutant animals. The mechanism by which SKN-1 target genes are differentially regulated in response to translation inhibition, and whether such regulation is specific for life span-extending conditions is unknown. The authors note that “one intriguing possibility is that the SKN-1-dependent transcriptional response we have observed here is induced as a consequence of particular genes being translated preferentially”.

In addition to the nematode studies mentioned above, a new study in fruit flies has extended the organismal scope of life span extension from rapamycin (Bjedov *et al.* 2010). Flies treated with rapamycin exhibited enhanced longevity, similar to what has been previously observed in yeast and mice (Powers *et al.* 2006; Medvedik *et al.* 2007; Harrison *et al.* 2009). Life span extension from rapamycin in flies appears to involve both reduced mRNA translation and increased autophagy (Bjedov *et al.* 2010). Rapamycin failed to extend the life span of flies expressing an activated form of S6 kinase or flies with a null allele of 4E-BP. Likewise, RNAi knock-down of Atg5, which is required for autophagosome formation, prevented life span extension from rapamycin. Interestingly, life span extension from rapamycin in wild type flies occurred in the absence of AMPK activation, suggesting that direct inhibition of TORC1 with rapamycin results in a physiological state distinct from mutation of S6 kinase. Clearly further studies are needed to understand the degree to which TORC1 inhibition and reduced S6 kinase activity promote longevity by similar mechanisms.

Rapamycin and healthspan

The ITP report showing that rapamycin supplementation late in life can increase life span in mice has naturally led to much excitement in the field. Along with that excitement, however, important questions remain to be addressed. In particular, the fact that rapamycin is used clinically as an immunosuppressant has led to concerns about potential side effects which might, in principle, offset any pro-longevity or health benefits. As we have pointed out previously (Kaeberlein & Kennedy 2009; Kaeberlein 2010), however, the initial report provided no information regarding effects of rapamycin on immune function at the dose found to increase life span (Harrison *et al.* 2009).

A more recent study may indicate that, in contrast to the expected immunosuppressive effects, treating mice with rapamycin in old age can preserve immune function. Chen et al. (Chen *et al.* 2009) injected C57BL/6 mice with rapamycin at a dose of 4 mg per kilogram of body weight every other day for 6 weeks beginning at 22–24 weeks of age. This regimen was sufficient to extend life span, providing an important demonstration that rapamycin can promote longevity of middle-aged mice from a genetic background different than that used in the ITP study. In addition to enhanced survival, the authors found that rapamycin treatment also preserved the *in vivo* regenerative capacity of hematopoietic stem cells from aged animals. Further, when 26 month old mice were treated with rapamycin for 6 weeks, they showed enhanced resistance to infection with influenza virus. From these findings, a more likely scenario regarding rapamycin at doses that promote longevity may be that the immune response will be altered in a complex manner, promoting resistance to some foreign agents and sensitivity to others. Further studies related to rapamycin effects on a wider range of immune and infectious responses are underway.

Although rapamycin is clearly sufficient to extend life span in mice, the degree to which it retards the aging process remains to be determined. One way to assess this is to quantify the effects of TORC1 inhibition on several measures of healthspan. Adipose specific knockout of the TORC1 component raptor results in resistance to diet-induced obesity, as does whole body knockout of S6K1 (Um *et al.* 2004; Polak *et al.* 2008). Rapamycin analogs (also referred to as rapalogs) are used clinically for certain rare forms of cancer and may prove protective more broadly against a variety of cancer types (Stanfel *et al.* 2009). Thus far, however, it is unclear whether rapamycin blocks cancers or limits obesity at the concentrations used to extend life span, and both protective and deleterious effects have been reported in rapamycin-treated mice under conditions of overnutrition (Chang *et al.* 2009a; Chang *et al.* 2009b).

Two recent studies have suggested a potential benefit from rapamycin in mouse models of Alzheimer's disease. Spilman et al. (Spilman *et al.* 2010) utilized the PDAPP model of Alzheimer's disease. These mice accumulate amyloid beta peptide (Aβ) and show phenotypes similar to Alzheimer's disease, including hippocampal atrophy, synaptic deficits, and cognitive impairment (Hsia *et al.* 1999; Mucke *et al.* 2000; Galvan *et al.* 2006). Rapamycin fed to the PDAPP mice using the same protocol as was shown to extend life span in the ITP study (Harrison *et al.* 2009) resulted in a significant reduction in the accumulation of Aβ and prevention of the Alzheimer's-like cognitive defects. In addition to the impressive benefits from rapamycin in PDAPP mice, two effects of rapamycin noted in the control non-transgenic mice are noteworthy. First, food consumption was higher in the rapamycin treated animals than in untreated animals, yet body weights did not differ between groups. Second, there was a trend, although it did not reach statistical significance, toward improved learning and memory retention in the rapamycin-treated animals. These observations suggest that rapamycin may lead to altered metabolic and cognitive function in normal animals that merit further evaluation.

In the second study of rapamycin efficacy against Alzheimer's disease, Caccamo and colleagues (Caccamo *et al.* 2010) utilized a different mouse model, the 3xTg-AD mice. These mice are homozygous for the $PS1_{M146V}$ allele and express two different transgenes expressing human APP_{Swe} and human TauP301L(Oddo *et al.* 2003). By approximately 6 months, the brains of 3xTg-AD animals accumulate detectable Aβ deposits and somatodendritic phosphorylated Tau, which correlates with the onset of cognitive impairment. Caccamo et al. (Caccamo *et al.* 2010) observed that TORC1 activity is elevated in regions of the brain where Aβ deposits are present, as measured by S6 kinase phosphorylation, in 3xTg-AD animals as compared to non-transgenic controls. Feeding mice rapamycin suppressed this increase in TORC1 activity, reduced Aβ and Tau pathology, and rescued the learning and memory deficits of these mice. Interestingly, similar increases in TORC1 activity have been noted in brain regions from Alzheimer's disease patients (An *et al.* 2003; Onuki *et al.* 2004; Pei & Hugon 2008), further suggesting the possibility that rapamycin may prove therapeutic for re-calibrating TORC1 activity to normal levels during Alzheimer's disease progression.

Both of the studies described above implicated autophagy as a potential causal mechanism for the beneficial effects associated with rapamycin in mouse models of Alzheimer's disease (Caccamo *et al.* 2010; Spilman *et al.* 2010). Using a cell culture model, Caccamo et al. showed that inhibition of autophagy with the drug 3-methyladenine prevented the reduction in Aβ accumulation in response to treatment with rapamcyin. Spilman et al. observed that rapamycin feeding resulted in an increase in autophagy in PDAPP animals, but not in non-transgenic controls. This later observation is intriguing as it suggests the possibility that treatment with rapamycin at the doses associated with increased life span and improved function in Alzheimer's disease models may specifically enhance autophagy in response to proteotoxic stress without significantly increasing autophagy in otherwise healthy animals.

The beneficial effects of rapamycin in the brain may not be limited to Alzheimer's disease, as prior reports have indicated improvements in markers of pathology for models of Huntington's disease and Parkinson's disease (Santini *et al.* 2009; Malagelada *et al.* 2010; Rose *et al.* 2010). In contrast, high levels of rapamycin are known to impair learning and memory in mice (Garelick & Kennedy 2010). Two related models can explain why rapamycin can have beneficial effects under some conditions and detrimental effects under others. First, the dosage of rapamycin may be the critical determinant, with modest reduction of TORC1 activity beneficial and extreme reduction detrimental. Alternatively, TORC1 activity may be inappropriately elevated in a range of pathological conditions, and the benefits of rapamycin may derive from dialing TORC1 activity back to levels consistent with normal physiology.

Conclusion

Last year, we learned that reduced TORC1 function extends life span in mice, making this the first pathway with conserved effects on longevity from yeast to mammals. This year, two new extensions in this important field have been made. First, mice lacking S6K1 were also reported to be long-lived, initiating a process whereby downstream elements of the TORC1 pathway are tested to delineate mechanisms of enhanced longevity. One possibility is that multiple arms of the pathway downstream of TORC1 will be required for the life span effects, consistent with the hypothesis that single gene interventions in the TOR (and insulin/IGF-1) pathway may extend life span because they are at an important nexus, coordinating many processes linked to longevity. Will enhanced autophagy be sufficient to increase life span and healthspan in mammals? Or enhanced 4E-BP1 activity? It is likely that we will find out soon.

Secondly, continued discoveries of the benefits of rapamycin in the context of age-related diseases have emerged, supporting the concept that aging is a causal factor underlying many of these diseases that have a crippling effect on the quality of our later years. If this is the case, targeting aging itself may be a major new route to delay the onset of age-related disease, and, importantly, one that may lead to treatments that reach across boundaries, providing benefits against many diseases. Hopefully, rapamycin is a forerunner of many more agents and interventions that exploit the promise of this relatively new approach to disease.

Acknowledgments

Studies related to this topic are funded by NIH grants R01AG033373 and R01AG025549 to B.K.K. and by NIH grant R01AG031108 to M.K. M.K. is an Ellison Medical Foundation New Scholar in Aging.

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