TOR and ageing: a complex pathway for a complex process

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Studies in invertebrate model organisms have led to a wealth of knowledge concerning the ageing process. But which of these discoveries will apply to ageing in humans? Recently, an assessment of the degree of conservation of ageing pathways between two of the leading invertebrate model organisms, *Saccharomyces cerevisiae* and *Caenorhabditis elegans*, was completed. The results (i) quantitatively indicated that pathways were conserved between evolutionarily disparate invertebrate species and (ii) emphasized the importance of the TOR kinase pathway in ageing. With recent findings that deletion of the mTOR substrate S6K1 or exposure of mice to the mTOR inhibitor rapamycin result in lifespan extension, mTOR signalling has become a major focus of ageing research. Here, we address downstream targets of mTOR signalling and their possible links to ageing. We also briefly cover other ageing genes identified by comparing worms and yeast, addressing the likelihood that their mammalian counterparts will affect longevity.

**Keywords:** TOR; ageing; lifespan; longevity; rapamycin

1. INTRODUCTION

Most evolutionary biologists see ageing not as a programme, but rather as a series of events resulting in the functional decline of an individual after the pressures of natural selection have diminished. This view, if correct, necessitates a rethinking of classical approaches to understanding biology. We study development in flies, for instance, on the belief that fundamental aspects of the developmental process are programmed and thus conserved across disparate lineages. If ageing is not programmed, why should modulation of the mechanisms underlying functional decline be conserved? Nevertheless evidence has emerged that this is the case, and recent findings have quantitatively demonstrated that pathways modulating ageing are conserved between two organisms that diverged evolutionarily approximately 1.5 billion years ago: *Caenorhabditis elegans* (worms) and *Saccharomyces cerevisiae* (yeast) [1].

Prior to quantitation, evidence had already accumulated that orthologous genes could affect ageing in multiple organisms. The search for conserved ageing genes led first to the insulin/IGF-1 signal (IIS) transduction pathway. Reduced IIS signalling leads to lifespan extension in worms [2–5], flies [6] and mice [7]. Numerous studies have attempted to understand the downstream effectors of IIS signalling that are important for lifespan extension. We will only discuss the pathway in detail as it relates to TOR signalling, in part because a number of reviews of IIS signalling are available. Nevertheless, there are lessons to be learned from the more mature studies of IIS signalling, foremost of which is that lifespan extension by altered signalling through this pathway is likely to involve the coordinated action of several downstream responses that together place the organism in a state more conducive to successful ageing [8–10]. Some of these responses include altered metabolism, activation of stress response pathways and enhanced autophagy. At this point, there is no reason to think that ageing-related responses downstream of TOR signalling will be any less complex. This implies that if researchers are to follow downstream altered cell signalling pathways to understand the molecular pathology that drives ageing, a holistic approach that integrates relative contributions from several different molecular events driving ageing and a linked understanding of the contribution of different responses may ultimately prove necessary. Is there any avoiding systems biology as ageing research moves forward?

(a) The TOR pathway

In the comparison between yeast and worm ageing genes described above, 11 gene orthologue pairs were identified in which reduced expression led to lifespan extension in the yeast replicative lifespan assay (see below) and in worms [1]. Six of the 11 gene pairs, including the TOR kinase itself, could be...
linked to regulation of TOR pathway signalling and translation. In yeast, the TOR kinase is activated by nutrients, either in the form of amino acids or carbohydrates [11] and, when activated, promotes cell growth and proliferation (figure 1). In higher organisms, TOR kinase activation occurs in response to amino acids [12], glucose via the IIS pathway, signalling through other pathways including AMP kinase and MAP kinase, and in response to stress through the regulation of TSC1–TSC2 complex. TSC1/2 negatively regulates mTORC1 activity by converting Rheb into an inactive GDP-bound state. Growth factors promote several kinase activities such as Akt, Erk and Rsk, which phosphorylate TSC1/2 and inhibit its activities, thereby inducing the mTORC1 signalling pathway. On the other hand, stress such as hypoxia, energy deprivation, DNA damage and inflammation activate TSC1/2 and repress mTORC1 signalling. Amino-acid activation of mTORC1 is regulated by the Rag GTPase and is independent of TSC1/2. Rapamycin-insensitive mTORC2 controls actin organization, which is essential for cell shape determination. mTORC2 is also activated by growth factors but the detailed mechanism is unclear. Arrows indicate activation, whereas bars indicate repression.

In yeast, for example, inhibition of TOR signalling by rapamycin appears to affect the activity of hexose transporters, which lead to glucose entry and fermentation, and also the diauxic shift, a conversion from fermentation to respiration that occurs as cells deplete fermentable energy sources. These findings further underscore the intricate relationship that exists between TOR and energy consumption [11].

The central component of the TOR pathway, TOR kinase is encoded by two genes in yeast (TOR1 and TOR2) and one in other organisms relevant to this study (mTOR in mammals). TOR is essential for viability in organisms ranging from yeast to mammals (table 1); loss of TOR function results in embryonic lethality at the organism level and the growth inhibition of embryonic stem cells [18,19]. The kinase exists in two complexes, TORC1 and TORC2, which have different downstream targets. Among the proteins unique to TORC1 is Raptor, whereas Rictor...
Dietary restriction is invoked by multiple means in yeast [21], worms, flies, mice and, most importantly, humans? A major approach to answer this question is to attempt to determine the downstream components of both pathways or to what extent downstream components of both pathways may derive from a common ancestor evolutionarily is hinted at by the fact that yeast Sch9 is a protein unique to TORC2. Raptor and Rictor have both been linked to longevity, suggesting that both complexes may have age-specific functions [20]. TORC1 controls many events linked to ageing and will be the primary focus of this study. TORC2 plays a role in organization of the actin cytoskeleton, but also phosphorylates Akt, which both activates TORC1 and inhibits FOXO nuclear recruitment [21]. Recent findings in worms indicate that reduced adult expression of Rictor leads to increased fat storage, although reports differ as to the Akt dependence of this effect [22,23]. Reduced Rictor expression has also been reported to shorten lifespan of worms on a standard diet in an Akt-dependent manner, while extending lifespan on alternative nutrient-rich bacterial food sources [22].

Dietary restriction is invoked by multiple means in different model organisms. In yeast replicative and chronological ageing, the most common method involves reduced glucose levels in the medium [24,25]. However, reduced amino-acid levels also lead to replicative lifespan extension [26]. Flies enjoy similar longevity benefits accompanying reduced yeast (amino acids) and/or sugar availability [27,28], although recent studies suggest a complex relationship between these two food sources, with the appropriate balance being important [29]. Many dietary restriction methods lead to lifespan extension in worms [30–35]. These findings call for a better understanding of the mechanisms by which dietary restriction and particularly reduced amino acids activate TOR signalling. Recent advances have been made in both yeast and mammals concerning the mechanisms by which amino acids lead to TOR activation. The fundamental mechanism, recruitment of TOR to the lysosomal (vacuolar in yeast) membrane, is conserved between yeast and mammals [36,37]. In yeast, the RAG GTPase Gtr1 interacts with and activates TOR in the presence of high amino-acid levels [38]. In mammals, mTORC1 approaches the lysosomal membrane via a similar Rag GTPases-Regulator complex [39]. An important follow-up regarding ageing will be to determine whether altered activity of these TOR recruitment factors will affect lifespan.

The direct connection leading from IIS signalling to Akt activation to TOR activation creates a union between two longevity pathways... and raises an important question. Do reduced IIS signalling and reduced TOR signalling lead to lifespan extension through the same or overlapping mechanisms? Judging from epistasis experiments in worms and flies, the pathways are not exactly the same, but may nevertheless have much in common. daf-2 and age-1 hypomorph mutants lead to lifespan extension in a manner dependent on the downstream FOXO transcription factor DAF-16 [3,4]. Lifespan extension by loss of daf-15 (CeRAPTOR) is also daf-16 dependent [20], while reduced let-363 (CeTOR) signalling increases lifespan independently of daf-16. In support of a possible functional overlap between these two pathways, it has also been shown that inhibition of let-363 (CeTOR) does not further extend the lifespan of daf-2 hypomorph mutant worms [40,41], which is consistent with the finding that daf-15 (CeRAPTOR) is itself downregulated by daf-16 [20], the activity of which should be increased in these long-lived daf-2 hypomorphs. Both TOR signalling [20] and IIS signalling [5] influence dauer formation (a diapause-like alternative larval stage in response to crowding or starvation) in worms. Finally, the possibility that these two pathways may derive from a common ancestor evolutionarily is hinted at by the fact that yeast Sch9 is a functional homologue of both S6K and Akt, as evidenced by partial rescue of sch9 mutant phenotype by mammalian Akt [42]. Independently of the degree of overlap, the fundamental question remains to what extent downstream components of both pathways contribute to modulation of longevity.

What is the molecular pathology that drives ageing in yeast, worms, flies, mice and, most importantly, humans? A major approach to answer this question has been to attempt to determine the downstream components of TOR signalling important for modulation of ageing. TOR controls several cellular processes including (but not limited to) translation initiation and elongation [43,44], autophagy [45–49], mitochondrial respiration [50–52], induction of stress response pathways [53], and the hypoxic response [54,55]. In the following sections, we discuss links between each of these pathways and longevity.

### Table 1. Components of the TOR pathway in various eukaryotes.

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phosphorylation of S6 kinase stimulates its activity, in turn driving ribosome biogenesis and translation initiation to greater or lesser extents in yeast, worms, flies and mice. Among the downstream targets of S6 kinase are the ribosomal protein, Rps6, the initiation factor eIF4B, the elongation factor 2 kinase (eEF2K), and a range of other substrates the significance of which remains to be determined [44].

Along with TOR, S6 kinase is one of the most conserved modulators of ageing; reduced expression leads to lifespan extension in each of the three major invertebrate organisms [59]. In mice, knockout of one of two S6 kinases, S6K1, leads to enhanced longevity, with greater extension observed in females [60]. This gender specificity mirrors that observed in long-lived mice with reduced IIS signalling [7,61], as well as in rapamycin-treated mice [62]. S6K1 deletion also provides protection against high fat diet-induced diabetes [63], suggesting that the longevity benefits may be linked to altered metabolism. In the mouse longevity study, a genome-wide transcript array study in major systemic metabolic tissues including white adipose tissue, muscle and liver identified an altered transcriptional signature associated with enhanced AMP kinase activity [60]. Consistently, AMP kinase mutant, aak-2, worms were resistant to lifespan extension by rks-1 (worm S6 kinase) RNAi [60]. While hinting at mechanis,

um, these findings also point to the complexity of the signalling problem surrounding TOR. Reduced S6 kinase function leads to activation of AMP kinase and this, in turn, further stimulates TOR activation. How these pathways connect and which ultimate downstream targets are associated with ageing is a fundamental problem in ageing research. Another interesting question is whether long-lived S6K1−/− mice have reduced global or mRNA-specific translation and, if so, in what tissues. In myoblasts from double knockout of S6K1 and S6K2 mice, translation levels were found to be unaltered [64]; however, other key metabolic tissues remain to be tested.

TOR-mediated phosphorylation of 4E-BPs disrupts an inhibitory interaction between 4E-BP and the initiation factor, eIF4E, promoting increased translation initiation. Consistent with an important function for 4E-BPs in ageing, enhanced levels of the inhibitor (or reduced expression of eIF4E) lead to lifespan extension in both worms and flies [41,65]. Epistasis analysis in flies suggests that activation of d4E-BP/Thor may be tightly linked to the longevity benefits of dietary restriction [65]. Enhanced 4EBP1 activity in Drosophila is protective in cardiovascular and neurodegenerative disease models [66,67]. Therefore, altered activity of two key TOR substrates, S6K1 and 4E-BP, can lead to enhanced longevity and protection against age-related disease, raising the question of whether they act by the same mechanism and, if not, which of these events are more tightly coupled to lifespan extension by rapamycin.

Mutation of other translation initiation factors is associated with enhanced longevity in yeast and worms [1,16,41], as well as reduced expression of ribosomal protein genes (RPGs) [41,68,69]. The latter effect has been best studied via the yeast replicative ageing assay, where the lifespan of every viable RPG knockout was determined. Of note, most ribosomal protein genes are duplicated in yeast, meaning that knockout of one gene, e.g. RPL31A, typically leads to reduction but not ablation of that protein, since RPL31B encodes a second copy. Strikingly, all of the long-lived RPG deletions encoded components of the large subunit of the ribosome, precluding the simplest model that reduced translation was coupled to lifespan extension, since many strains lacking small subunit components have reduced translation: e.g. long-lived yeast rpl31aΔ, rpl20bΔ, and rpl21aΔ strains have been shown by depressed overall polysome profiles to have decreased overall translation [68]. Instead, the mechanism, at least in part, entails activation of translation of GCN4, a transcription factor the own expression of which is regulated at the translational level. GCN4 targets include amino-acid biosynthetic and stress response factors, including components of the unfolded protein response. Translation is activated during starvation conditions including dietary restriction, at a time when most mRNAs experience reduced translation. The mechanism involves small regulatory upstream open reading frames in the 5' UTR of GCN4. Initiation at these uORFs, particularly the one most proximal to the start site of GCN4, inhibits GCN4 translation since a strong termination signal promotes dissociation of the ribosome, and the short distance between the uORF and the GCN4 ORF precludes re-initiation. Amino-acid or carbohydrate limitation both lead to reduced translation initiation, allowing the small ribosomal subunit to scan past the uORFs before associating with the large subunit and initiation factors, leading paradoxically to more GCN4 translation. Specifically in the case of carbohydrates, glucose limitation (0.05% glucose as opposed to 2% glucose) induces GCN4 translation by activation of GNC2 protein kinase [70]. Reduced 60S subunit levels, brought about by deletion of a range of large subunit components, phenocopy starvation since 40S subunits have a harder time finding their 60S counterparts, leading to scanning past the uORFs more frequently prior to initiation. The importance of this pathway for longevity is illustrated by the findings that deletion of GCN4 blocks much of the lifespan extension associated with reduced 60S subunit biogenesis (although some extension still occurs), pointing to the existence of other mechanisms. Similarly, deletion of GCN4 reduced lifespan extension by dietary restriction, tor1Δ and sch9Δ (yeast S6 kinase). Another report indicated that deletion of one small subunit component could also extend yeast replicative lifespan [69], again pointing to additional mechanisms. Finally, while reduced expression of worm RPGs also leads to enhanced longevity, the involvement of the GCN4 orthologue, aef-5, is currently unknown and, since reduced expression of both 40S and 60S subunits can promote longevity, mechanistic differences are likely.

Combining the data described above, a strong case for altered translation associated with reduced TOR activity in the modulation of longevity can be made; however, the details remain to be fully elucidated. Furthermore, equally strong cases can be made for other downstream regulatory pathways (see below).

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(c) A role for autophagy

Autophagy is a well-studied process by which cells degrade damaged molecules through their recruitment to the lysosome [71]. This pathway is also used to recycle cellular components (both organelles and individual proteins). This latter activity implies that autophagy should be responsive to cellular nutrient status; TOR signalling represents a primary signalling pathway that controls its activity [45–49]. Under high nutrient levels, where energy is easy to come by, high TOR signalling suppresses autophagy and the converse is also true. Nutrient deprivation and concomitantly reduced TOR signalling lead to elevated autophagy. TOR-mediated suppression of autophagy probably occurs through inhibition of a protein complex containing Atg13 that is required for induction of the autophagic response. Indeed, TORC1 does directly phosphorylate Atg13 on at least eight serine residues [72,73].

Autophagy has been closely linked to ageing [74]. In C. elegans, impaired autophagy by knockdown (mutant) of worm bec-1, homologue of yeast VPS30/mammalian beclin1 [75], as well as atg-7 and atg-12 [76], blocks lifespan extension by a daf-2 mutant. Similarly, lifespan extension via reduced TOR signalling (let-363 aka CeTOR RNAi) has been shown to depend on bec-1, and extension by dietary restriction (eat-2 mutants) has been shown to depend on both bec-1 and vps-34 [77]. In yeast chronological ageing, autophagy is important for normal survival as well as lifespan extension by rapamycin [78,79]. Finally, in Drosophila inhibition of autophagy abrogates the rapamycin-dependent lifespan extension [80].

While these findings have not been extended to other organisms, they strongly suggest that induced autophagy may be an important downstream consequence of reduced TOR signalling with respect to longevity. But TOR may also be downstream of autophagy. Enhanced Atg1 expression in Drosophila inhibits TOR signalling, presumably as a regulatory mechanism to further enhance induction of autophagy [81]. Feedback mechanisms such as these are pervasive in TOR signalling [82–84]. Presumably, this regulation allows pinpoint control over the responses to nutrient signalling. In the context of research on ageing, however, sorting out the downstream signalling components linked to lifespan extension is significantly complicated by these high levels of connectivity.

(d) Enhanced mitochondrial function

Levels of mTOR activity directly modulate cellular metabolism, in part by shifting the balance between modes of energy production and usage. In tumour cells, activation of the PI3K/mTOR pathway leads to increased glycolysis [85–87]. Glycolysis is globally used by many human tumour cells and stem cells. Glycolytic metabolism is not used to maximize energy production; however, it does generate more biomass than mitochondrial oxidation, an attribute favourable to tumour cell growth [85–87]. One molecule of glucose is completely oxidized in the mitochondrial tricarboxylic acid (TCA) cycle to generate 36 ATPs with minimal production of lactate. On the other hand, glycolysis only produces 2 ATP per molecule of glucose with large amounts of lactate, which regenerates NAD\(^+\) from NADH. The NAD\(^+\)/NADH ratio influences the rate of biosynthetic pathways that use intermediates derived from glucose metabolism, so glycolysis generates more material for nucleotides, lipid and protein biosynthesis.

Repression of FoxO3a activity by PI3K pathway activation or by RNAi knockdown of FoxO3a transcriptionally down-regulates TSC1. As a consequence, suppression of TSC1 increases mTORC1 activity, enhancing glycolysis and survival after growth factor withdrawal in murine haematopoietic cells [82]. Consistent with this notion, inhibition of the mTOR pathway or glycolysis can suppress growth and/or induce death in cancer [88–91]. Inactivation of the TOR pathway increases mitochondrial number and induces mitochondrial gene expression via translational regulation, leading to enhanced cellular respiration. Similarly, enhanced d4E-BP1 activity in Drosophila melanogaster or S6K1 deletion in mouse results in increased mitochondrial biogenesis and in both cases results in lifespan extension [60,65]. In the case of Drosophila, dietary restriction leads to d4E-BP-dependent increased translation (but not transcription) of several components of the mitochondrial electron transport chain [65]. In this context, the increased lifespan of the flies upon dietary restriction has been shown to be dependent on both d4E-BP and on some of the upregulated electron transport chain components [65]. The positive correlation of mitochondrial biogenesis and longevity has been shown in several organisms [92,93]. Increased mitochondrial biogenesis could be the keystone of TOR-dependent lifespan extension (figure 2).
In contrast to the *in vivo* studies described above, cell culture studies of the links between mTOR activity and mitochondrial function have pointed to a different relationship. mTOR has been shown to physically interact with the transcription factor yin-yang 1 (YY1) [52], which regulates mitochondrial gene expression, as well as the mitochondrial outer-membrane proteins Bel-xl and VDAC1 [95]. Inhibition of mTORC1 activities by RNAi knockdown of genes coding components of the mTORC1 complex or rapamycin results in the reduction of oxygen consumption and decreased mitochondrial respiration *in vitro* [94]. The difference in outcomes between *in vivo* and *in vitro* studies points to the need to further elucidate the relationship between TOR signalling and respiration in mammals.

In yeast, a more clarified picture has emerged. Reduced TOR function leads to enhanced respiratory capacity in the absence of enhanced mitochondrial biogenesis, and this is required for chronological lifespan extension [50,95]. Instead of enhanced biogenesis, the result of reduced TOR signalling is more OXPHOS complexes per mitochondrion [96]. Moreover, ATP production is not elevated. Rather, the result is enhanced uncoupling activity and reduced inner membrane potential. These findings lead the authors to speculate that these changes, which happen during cell proliferation and early cell cycle stages, precondition cells to a state promoting prolonged survival during the growth arrested period. Deletion of yeast S6 kinase (*sch9*), which also promotes enhanced chronological lifespan [97], is also linked to these changes in respiration [96,98]. Unlike chronological ageing, extension of yeast replicative lifespan by *sch9*Δ is not impaired by blocking accompanying enhancement of respiration [98].

### (e) Induction of stress response pathways

In yeast, reduced TOR signalling or deletion of *sch9* leads to nuclear relocalization and/or activation of a set of stress-responsive transcription factors including the Msn2/4 complex and Gis1 [53]. The kinase Rim15 is also retained in the cytoplasm in cells with high TOR activity [99,100]. The mechanism of TOR-dependent cytoplasmic retention of Msn2/4 transcription factors [102,103]. Among the targets of Msn2/4 and Gis1 complexes are oxidative defence pathways including superoxide dismutase. This pathway is required for chronological lifespan extension by *tor1Δ* or *sch9*Δ [15,101,104], although increased superoxide dismutase levels only account for part of the effect [97,104,105]. Thus, other targets of these transcription factors are likely to be important. Extension of replicative lifespan by reduced TOR signalling has been linked to enhanced Msn2/4-dependent transcription of *PNC1* [106], which in turn promotes activation of the protein deacetylase *SIR2* [107,108]. The links between TOR signalling and *SIR2* are unclear however, since it has been reported that *tor1Δ* and *sch9*Δ robustly extend lifespan in strains lacking *SIR2*, as long as extrachromosomal rDNA circles are maintained at low levels [109]. In worms, *let-363* (CeTOR) mutants have been shown to have increased thermotolerance [41].

Another mechanism has recently been proposed for yeast chronological lifespan extension by dietary restriction and for many long-lived mutants [110]. In rich medium, yeast prefer fermentative growth, only relying on low levels of respiration. During fermentative growth, yeast produce and secrete high levels of ethanol and organic acids such as acetic acid. Dietary restriction involves starting yeast cultures under conditions of lower glucose concentration, which results in a robust increase in survival during chronological ageing [111–113]. A recent study reported that the long lifespan associated with dietary restriction in chronological ageing derives from less fermentative growth, resulting in less secretion of organic acids and maintenance of a higher extracellular pH [110]. High extracellular acetic acid levels and low pH together formed a toxic combination that accelerated yeast mortality in the post-mitotic environment and appeared to be largely responsible for many measured differences in yeast chronological lifespan, as reversing these effects reversed the lifespan differences. Relevant to this study, both *tor1Δ* and *sch9*Δ are reported to result in enhanced respiratory activity, possibly limiting acetic acid production by shunting fermentative products into respiratory metabolism [50,98]. Furthermore, the *sch9*Δ was found to be resistant to toxicity associated with high levels of acetic acid in a manner requiring Rim15 [110]. How this reduction of yeast chronological lifespan by extracellular acetic acid is related to other proposed mechanisms for chronologic ageing, or ageing in other model organisms, remains to be determined.

### (f) The hypoxic response

Under hypoxic conditions, many organisms exhibit a conserved transcriptional response mediated by transcription factor Hypoxia Inducible Factor 1 (HIF-1) [114]. Oxygen-dependent prolyl hydroxylases normally target one subunit of HIF-1, HIF-1α, for recognition by the E3 ubiquitin ligase von Hippel–Lindau protein (VHL), leading to HIF-1α’s subsequent ubiquitination and degradation [115–117]. Under hypoxic conditions, HIF-1α degradation by this oxygen-dependent mechanism is decreased, and HIF-1α accumulates to transcribe its target genes, after dimerization with HIF-1β/ARNT [118]. This hypoxic response has been linked to ageing in *C. elegans* [119–121], although the effect of HIF-1 on lifespan appears to be context specific [122]. Both increased and reduced HIF-1 activity can lead to lifespan extension, but the mechanisms appear to be different [119–121]. These findings emphasize the importance of the hypoxic response in longevity and call for detailed studies to place *hif-1* in the context of other known longevity pathways.

One transcriptional target of HIF1 in flies and mammals is Regulated in Development and DNA Damage Responses 1 (REDD1) [54,55,123].
REDD1 activates the TSC1/TSC2 tuberous sclerosis complex by releasing TSC2 from inhibitory 14–3–3 proteins, allowing TSC2 to interact with TSC1, resulting in TORC1 inhibition [54,55,124]. While HIF-1 regulates TOR, the converse is also true. TOR controls either HIF-1 translation [125] or nuclear localization [126] in mammalian cells and *Drosophila*, respectively. Additionally, a protein tyrosine phosphatase, Ptp61F, has been shown in *Drosophila* cells to be required for hypoxic suppression of translation through TOR signalling [127]. These studies point to a complex relationship between nutrient levels, TOR signalling, HIF1 and ageing, raising the possibility that lifespan extension by reduced TOR signalling may be linked to altered HIF1 activity.

2. CONCLUSIONS

The good news is that convincing evidence has been provided by several laboratories linking reduced TOR signalling to lifespan extension in yeast, worms, flies and mice (table 2). A central nexus linking nutrient levels to cell growth, proliferation and survival, it is perhaps not surprising that TOR modulates ageing. The bad news is that, being a central nexus, TOR regulates a range of downstream pathways, many of which have been linked to ageing. Why does reduced TOR signalling result in lifespan extension and, by working downstream, will it be possible to determine the age-related pathologies that are mitigated? Integrated approaches are likely to be required to answer these questions. These will probably include (i) genetic and biochemical approaches to understand TOR signalling in the context of other longevity pathways, (ii) studies to determine in which tissues reduced TOR signalling promotes longevity, and (iii) systems biology to integrate information from large datasets.

Given the findings last year that the TOR inhibitor rapamycin extends mouse lifespan, even when administered late in life [62], it seems clear that the good outweighs the bad. This study not only linked TOR to mammalian ageing, but demonstrated that pharmacological interventions can influence longevity. Whether rapamycin will ever be used to delay ageing as a means to target age-related disease is a matter of debate, awaiting further studies. It seems reasonable to assert, however, that if there is one drug that impacts ageing, then there are likely to be others (and candidates affecting other targets already exist), increasing the likelihood that one will be efficacious in humans. By better understanding TOR signalling in the context of ageing, it may also be possible to identify more specific targets to extend lifespan and healthspan. Exciting discoveries in ageing research are surely ahead.

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