molecules appear to regulate life span in *C. elegans*,[104] a process that might be regulated by TOR.[105]

In the fruit fly, *Drosophila melanogaster*, modulation of genes in the TOR signaling pathway extended longevity.[106] Zid *et al.*[107] found that 4E-BP, a translation repressor regulated by mTORC1,[98] extended life span by enhancing mitochondrial activity in *Drosophila*. A recent study linked peripheral circadian clocks with dietary restriction-mediated life span in *Drosophila*, potentially through decreased TOR.[108] Rapamycin fed to flies extended life span analogous to TOR mutants, hypothetically through TOR complex 1.[109]

15.6 Genetic mTOR Inhibition in Mice that Extends Life Span

Lamming *et al.*[63] reported that *Mtor*$^{+/-}$; *Mlst8*$^{+/-}$ females, but not males, had extended longevity, which is interesting in light of the greater effects of chronic rapamycin in females.[35] In mice heterozygous for *Rictor*, a defining component of mTORC2 (*Rictor*$^{+/-}$), or those with liver-specific knockout of *Rictor* (L-RKO), males, but not females, had a shortened life span.[30] This led these authors to propose that mTORC2 promotes longevity (at least in males), while mTORC1 is anti-longevity. Since chronic rapamycin has been reported to destabilize mTORC2 in liver, muscle and adipose, concomitant with reduced S437 phosphorylation of Akt, (after refeeding),[63] Lamming *et al.* suggested that this may also explain the greater beneficial effects of rapamycin in female life span.[30] Hasty *et al.* did not observe this effect on Akt phosphorylation under chronically high rapamycin concentrations in the colon.[57] Mice with two hypomorphic (*Mtor*$^{\Delta/\Delta}$)[110] alleles have an increased life span and tissue-specific slowing of aging.[111] Selman *et al.*[112] showed that the knockout of S6 kinase 1 (*S6k1*$^{-/-}$, a downstream substrate of mTORC1) extends life span in mice. Thus, the preponderance of evidence, both interventional (food restriction and pharmacological) and genetic studies strongly indicates that the mTOR network plays a key role in health and aging from yeast to mammals. Evidence also clearly indicates that a down regulation of mTORC1 leads to a longer life span. Does this result in a greater length of healthy living? The gold standard intervention for achieving a longer health span is food (or diet) restriction.[113] How does rapamycin compare? Johnson *et al.*[42] argue that chronic rapamycin represents a starting point in the quest for pharmacological interventions that preserve youth similarly to diet restriction. How does it work?

15.7 Composite Picture of mTOR Signaling Pathways in Aging

It is very impressive that we have seen the mTOR signaling go from the simple nutrient sensing pathway first proposed by Barbet *et al.*[6] to the daunting picture of this system today. Figure 15.3 attempts to place our current