results for various formulations of rapamycin. While most are anti-aging, results in one are noteworthy for its opposite effect and relevance to a large patient population in the elderly, type-2 diabetes. Chronic eRapa resulted in an increase in mortality in a mouse model (*db/db*) of this disease due to suppurative inflammation.[43] The use of mTOR inhibitors in diseases not associated with aging is increasingly widespread (summarized in ref. 20).

15.5 TOR Reductions and Rapamycin Increase Longevity in Other Organisms

Although mTOR has multiple vital roles in development, accruing evidence suggests its early stage level of activity continued into life's later years may be detrimental to adult somatic tissues/organs. Although the connection between mTOR and nutrient sensing was not known at the time, a hint of this antagonistic pleotropic relationship was evident as early as the 1930s in McCay *et al.*'s well executed survival studies showing that food restriction extended life span in rats.[88] This relationship was also hinted at by extension of life span under conditions of reduced growth hormone/IGF-1,[89] evidence for which was shown by Sharp and Bartke.[90]

In smaller organisms, evidence for this relationship began with reports showing reductions in Sch9 (yeast orthologue of S6K1) associated with chronological life span extension.[91] Similarly, reductions of Sch9 or TOR were associated with extended replicative life span in *Saccharomyces cerevisiae*.[92] A recent resource publication of a comprehensive analysis of 4698 gene deletions in *S. cerevisiae* by McCormick *et al.*[93] revealed 238 with increased life span, including 60S ribosome components, TOR and a tRNA transporter (*LOS1*). Dietary restriction and rapamycin exclude Los1 from the nucleus in a Rad53-dependent manner, suggesting that DNA damage response and mTOR converge on Los1 to regulate aging through Gcn4 activity.[94]

In the nematode, *Caenorhabditis elegans*, knockdown of TOR (*let-363*) or the mTORC1 component raptor (*daf-15*) led to extended longevity.[95,96] Syntichaki *et al.*[97] showed that a somatic tissue-specific loss of eIF4E (a eukaryotic translation initiation factor regulated by mTORC1[98]) reduced global protein synthesis, protected against oxidative stress and extended life span of *C. elegans*. In a similar vein, inhibition of mRNA translation (by inhibition of *ifg-1*, worm homologue of eIF4G in mRNA cap binding complex[98]) extended life span in *C. elegans*.[99] Additionally these authors found the inhibition of *rsks-1* (worm homologue of S6K1 regulated by mTORC1[100]) increased life span. An RNAi screen for longevity genes in *C. elegans* identified 89 genes,[101] among them the eukaryotic translation initiation factor 5 (eIF5[102]). In keeping with reduced protein synthesis associating with extended life span, Essers, *et al.*[103] found that a long non-coding RNA (*tts-1*) associates with reduced levels of ribosomes, which was required for longevity extension by *daf-2* (worm insulin receptor) and *clk-1* (mitochondrial gene) mutations. Lysosomal signaling