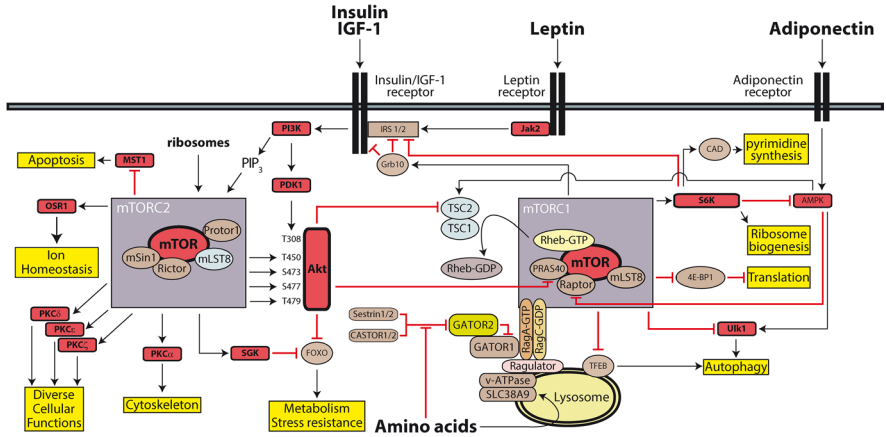

Figure 14.1 The mTOR signaling pathway. The mTOR pathway signaling is mediated by numerous environmental and hormonal cues, including amino acids and insulin, IGF-1, adiponectin, and leptin. mTOR, particularly mTOR complex 1 (mTORC1) integrates these signaling to determine if conditions are permissive for growth, and then promotes anabolic processes including protein synthesis, ribosome biogenesis and nucleotide biosynthesis, while suppressing autophagy. mTORC2, which functions as an effector of PI3K signaling, has been shown to regulate AKT, SGK, multiple PKC family members, and the Hippo pathway kinase MST1, placing it upstream of many diverse processes, including metabolism.

14.2 mTOR Regulates Longevity in Model Organisms

The first connection of mTOR signaling to aging was found in 2003, with the discovery that RNAi against *mTOR* in *Caenorhabditis elegans* significantly extended lifespan.[37] Over the subsequent two years, this was followed by the discovery that inhibition of mTOR signaling could also extend the lifespan of *Drosophila melanogaster* and the budding yeast *Saccharomyces cerevisiae*.[38,39] From the first, it was clear that lifespan extension resulting from reduced mTOR signaling was distinct from previously identified aging pathways. In *C. elegans*, lifespan extension by RNAi against *mTOR* was found to be independent from the FOXO homologue *daf-16*, which is critical for the extended lifespan of *daf-2* mutants,[37] while in *D. melanogaster*, inhibition of signaling downstream of mTORC1 through expression of either dominant-negative mTOR or S6K had similar effects on lifespan.[38]

The study of mTOR in *D. melanogaster* by Kapahi and colleagues also provided the first hints that the mTOR pathway was involved in the response to a calorie restricted (CR) diet as inhibition of mTOR failed to extend the lifespan of flies fed a low-calorie diet.[38] Extensive genetic work in *S. cerevisiae* elaborated on this possibility, demonstrating the induction of a starvation-like phenotype in yeast with extended chronological lifespan, and