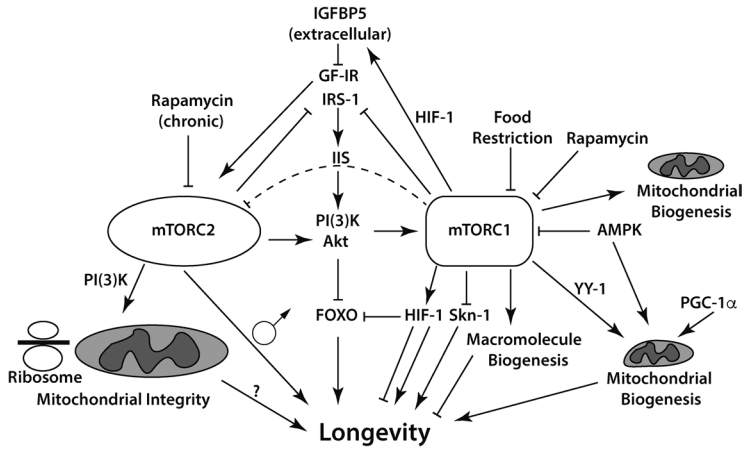

Figure 15.3 mTOR and longevity pathways. The FOXO family of transcription factors mediates the life span extension by reduced insulin/IGF-I (IIS) signaling, which connects to mTORC1. As a negative feedback, IIS-activated mTORC1 decreases IIS signaling through S6K1 and IRS-1. Both an upstream (tuberous sclerosis complex protein 1, TSC1; part of an mTORC1 negative regulatory complex) and a downstream (4E-BP1, a translation repressor) member of the mTORC1 pathway are regulated by FOXO factors. Genetic studies in *C. elegans* partially uncouple these pathways leading to suggestions of overlapping mechanisms involved in IIS- and mTORC1-mediated longevity extension by food restriction and chronic rapamycin.[20] mTORC2 also connects to mTORC1 *via* Akt. mTORC1 can also be inhibitory to mTORC2 (dashed block) *via* S6K1 phosphorylation of two complex components, mSIN1 and Rictor.[114] HIF-1 has a complicated relationship with mTOR. Stimulated by low oxygen levels, mTORC1 activates the hypoxic response by enhancing translation of HIF-1 that inhibits FOXO to increase longevity. To further complicate the issue, HIF-1 is thought to extend longevity at higher temperatures and inhibit it at lower temperatures.[115] As a negative feedback through HIF-1, mTORC1 increases secreted IGF-1 binding protein 5 (IGFBP5), which has the effect of decreasing IGF-1 signaling.[116] Rapamycin inhibition of mTORC1 de-represses Skn-1, which, together with DAF16/FOXO, activates protective genes for longevity extension.[117] mTORC1 also has a complicated relationship with mitochondria biogenesis and respiration. Mitochondria proteins translation is promoted by mTORC1 *via* eIF4E sensitive translation.[118] Food restriction is likely to activate AMPK, which negatively regulates mTORC1 to promote longevity, which promotes mitochondria biogenesis through YY-1 and pGC-1α.[118] Growth factors also promote Akt-dependent mTORC2 activation resulting in ribosome association for mitochondrial integrity, and for co-translational substrate phosphorylation.[118] Finally, mTORC1 regulates the biosynthesis of macromolecules needed for cell growth through the eIF4E sensitive pathway, the S6K1/rpS6 pathway for RNA polymerase II transcription of ribosome subunit mRNAs,[119] the regulation of RNA Polymerases I and III for transcription of ribosomal RNAs (ribosome subunit RNAs) for protein synthesis,[119] lipid biosynthesis, storage and adipogenesis,[120] and pyrimidine[121] and purine[122] synthesis for nucleic acids.