small model organisms, transforming this view.[6–8] Subsequently, studies in *C. elegans* identified the insulin/IGF-1/FOXO cascade as the first pathway influencing aging.[9] Mutations that cause inactivation of the insulin/IGF-1 signaling pathway (IIS) extend lifespan and delay a number of age-related phenotypes in *C. elegans*.[10] For example, point mutations in the daf-2 gene (the insulin/IGF-1 receptor homolog) increase both mean and maximal lifespan in worms,[10,11] and mutations in the age-1 gene, a gene acting downstream of daf-2, also extend lifespan.[7,12] Furthermore, IIS has been shown to influence aging in mammals such as mice.[10] At least three other conserved longevity pathways have since been identified using similar genetic approaches in small model organisms: TSC/mTOR,[13] AMPK,[14] and Sir2/SIRT1.[15,16]

In addition to the discovery of longevity genes, a number of therapeutic interventions that effectively counteract aging have recently been formulated.[15] Caloric restriction (CR), the first intervention strategy reported to extend the lifespan of mammals,[17] consists of a defined reduction in caloric intake without malnutrition.[17] Studies have demonstrated that CR not only increases lifespan in mammals, but also delays the onset of a number of age-related diseases, including cancer, diabetes, and others.[18,19] Moreover, the effects of CR on lifespan are conserved in a wide variety of organisms ranging from yeast to mammals.[19,20] Resveratrol, a naturally occurring Sir2/SIRT1 activator (STAC), was the first small molecule shown to extend the lifespan of a model organism.[21] Subsequent work led to the identification of other anti-aging drugs, including metformin (activates AMPK),[22] rapamycin (inhibits TOR),[13] spermidine (regulates autophagy),[23] as well more potent second and third generation synthetic STACs.[24–26] However, amongst these, STACs have arguably received the greatest amount of attention due their apparent lack of toxicity and their protective effects against a number of age-related disorders.[15,27] In this chapter, the sirtuin longevity pathway, the discovery of allosteric STACs, and the effects of STACs on aging and age-related disease will be summarized. In addition, the difficulties faced in translating experimental findings on STACs to human trials will be critically examined.

11.2 The Sirtuin Longevity Pathway

The silent information regulator (SIR) genes, or sirtuins, have become the focus of much research over the past decade due to their ability to regulate numerous critical cell processes and to modulate lifespan across diverse species.[15] SIR1–4 were originally identified in screens for mutations causing sterility in *S. cerevisiae*.[28–32] Later, it was shown that these genes play important roles in repression of the silent mating type loci and in genomic silencing at telomeres.[33,34] While mutations in SIR2, SIR3, and SIR4 shorten lifespan in yeast,[1] overexpression of SIR2 increases replicative lifespan by up to 30% *via* suppression of extrachromosomal rDNA circle formation, a cause of aging in yeast.[15,35] While somewhat controversial,[36] several studies have shown that overexpression of Sir2 homologues in worms and flies also extends lifespan.[37,38] Finally, overexpression of the mammalian Sir2 homolog SIRT1 in