substrate specific.[26] More precisely, it was shown that while STACs were ineffective at enhancing SIRT1 deacetylation of most natural amino acid peptides, certain peptides containing hydrophobic amino acids (*e.g.* tryptophan or phenylalanine) at the +1 and +6 positions relative to the acetyl-lysine, could support STAC-mediated activation.[26] Over 500 naturally occurring SIRT1 substrates bearing these structural features were identified computationally, including acetyl lysine sites on the well characterized SIRT1 substrates PGC1α and FOXO3a.[26] In addition, this report also identified Glutamate 230 (E230) as a critical residue mediating activation.[26] Specifically, mutation of E230 to lysine (E230K) was shown to block STAC-mediated SIRT1 activation on all types of substrates (natural, fluorophore-tagged), using all classes of STACs (natural, synthetic) without affecting basal enzyme activity.[26] Furthermore, SIRT1 knockout cells reconstituted with SIRT1-E230K were shown to be nonresponsive to STAC treatment, suggesting that the effects of these compounds in cells are likely due to a direct effect on SIRT1.[26]

Based on these findings, two models of SIRT1 activation have been proposed.[26] Steegborn and colleagues proposed that STACs interact with the enzyme-bound substrate and allow it to dock more efficiently.[91] In contrast, based on the discovery of E230K and the identification of a surrounding N-terminal "activation domain", Sinclair and others proposed that SIRT1 activation occurs through an assisted-allosteric activation (AAA) mechanism.[26] Briefly, this model posits that binding of certain peptide substrates to SIRT1 induces an exosite, which allows STACs to bind and subsequently stabilize the docked substrate, thus lowering its K_M.[26] Recent crystallographic data on SIRT1 has supported this hypothesis. For example, Cao *et al.* confirmed the presence of an ordered N-terminal activation domain on SIRT1,[92] and Dai and colleagues have crystallized a SIRT1–STAC complex and shown that interactions between E230 and the catalytic core govern allosteric binding of STACs.[93]

11.4 STACs in Aging and Age-Related Disease

11.4.1 Lifespan Extension

Resveratrol was the first small molecule shown to extend the lifespan of a laboratory model organism.[21] In 2003 it was demonstrated that supplementing yeast growth media with 10 μM resveratrol could extend the mean replicative lifespan of *S. cerevisiae* by up to 70%.[21] Subsequent work showed that this effect was conserved in other small model organisms.[27] For example, resveratrol dosed at 100 μM was shown to extend the mean lifespan of worms and flies by up to 30% and 15%, respectively, in a Sir-2-dependent manner.[37] Furthermore, dietary supplementation with 130 μM resveratrol was shown to extend the mean lifespan of *Apis mellifera* (the common honeybee) by ~33%, likely through a caloric restriction-like mechanism.[94] Finally, resveratrol extends both the mean and maximum lifespans of the short-lived