possess lipoamidase activity towards the pyruvate dehydrogenase (PDH) complex,[56] and SIRT5 removes succinyl,[57] malony,[57] and glutaryl,[58] but not acetyl modifications from proteins.[52] Like SIRT1, SIRT6 displays nuclear localization, but it is predominately associated with chromatin.[59] SIRT6 deacetylates several key residues on histone proteins such as H3K56(ac)[60] and also catalyzes fatty long-chain deacylation of proteins.[61] While comparatively little work has been done on SIRT7, recent studies suggest that it localizes to the nucleus where it performs histone deacetylation.[62]

Of the seven mammalian sirtuin genes, SIRT1, which bears the closest phylogenetic relationship to the yeast longevity gene Sir2,[15] has been the most extensively studied. Through deacetylation of a myriad of nuclear targets including histones, transcription factors, such as p53,[63] FOXO,[64] NFκB,[65] PGC1α,[66] and other proteins, such as Ku70[67] and BMAL,[68] SIRT1 regulates multiple critical cell processes including RNA transcription, apoptosis, DNA damage response, regulation of muscle and fat differentiation, neurogenesis, mitochondrial biogenesis, insulin signaling, and circadian rhythms.[15,16] Moreover, SIRT1 appears to play an important role in a number of age-related disease states.[15,16] For example, overexpression of SIRT1 is protective in mouse models of Alzheimer's disease,[69] type II diabetes,[70] colon cancer,[71] prostate cancer,[72] and thymic-induced lymphomas.[73]

Interestingly, there is growing evidence that suggests SIRT1 underlies many of the beneficial effects of CR.[15] For instance, Sir2 is required for CR-mediated lifespan extension in *S. cerevisiae*[74,75] and in *D. melanogaster*.[76] CR-mediated lifespan extension in worms is also partially dependent on Sir2.1, albeit in a diet-specific manner.[77] Two mechanisms for how SIRT1 might be regulated during CR in these organisms have been proposed. One model suggests that CR activates a nicotinamidase enzyme that lowers levels of NAM,[78] resulting in SIRT1 activation. A second model proposes that an increase in the ratio of NAD/NADH resulting from low caloric intake activates SIRT1.[79] In mammals, SIRT1 protein levels seem to be increased in numerous tissues following caloric restriction,[67] revealing yet another possible link between SIRT1 activity and CR. Consistent with this hypothesis, deletion of SIRT1 in mice abrogates the metabolic benefits CR and blocks lifespan extension.[80] Furthermore, SIRT1 transgenic overexpressing mice display metabolic phenotypes that resemble CR.[81] The notion that overexpression or activation of SIRT1 could mimic the effects of CR has been a driving force in the search for small-molecule activators of SIRT1.

11.3 Small-Molecule SIRT1 Activators

A number of pharmacological approaches to activate SIRT1 have been tested.[15] Based on research showing that physiological levels of NAM are sufficient to inhibit sirtuin activity, Sauve *et al.* showed that a transient competitive inhibitor of NAM binding, isonicotinamide (iNAM) (Figure 11.2), could be used be used as a pan-sirtuin activator in yeast cells.[82] The disadvantages of this approach are that iNAM can interfere with other enzymes using NAM,