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in addition to the mutations in the extended n- and c-terminal domains, we prepared a series of mutations in the catalytic domain of human sirt1 (mini-hsirt1) to investigate the impact of the removal of the extended n-terminal and c-terminal domains. our data reveal that all the mutations abolish activation by stac1, stac2 and stac3, while the basal catalytic activity and the inhibition by nam and ex-527 are not significantly impacted. the impact of the mutations is, in general, more pronounced when the substrate is foxo-3a compared to ac-p53(w5) (fig. 4d and supplementary fig. 6b), suggesting a role for the extended domains in accommodating the distinct substrate sequences. interestingly, the mutations in the linker domain (d228a, i229a, e230a) (supplementary fig. 6a) as well as the r231a mutation (supplementary fig. a selection of representative mini-hsirt1 structures determined by x-ray crystallography are shown in fig. 4. the overall mini-hsirt1 structure resembles full-length hsirt1, with the exception of the n-terminal domain. this region is disordered in the mini-hsirt1 crystal structure and adopts a helical conformation in the crystal structure of mini-hsirt1/1 binary complex, with the helix pointing upwards and away from the catalytic domain, and folds back into a disordered conformation upon stac binding (fig. 5c and supplementary fig. 5). this conformation may indicate that in the intact enzyme, the n-terminal domain may play a role in organizing the sbd, and this role is lost upon stac binding. this is supported by the superposition of the mini-hsirt1/stac binary complex (1:1) onto the crystal structure of hsirt1 (1:1) and hsirt1/stac binary complex (1:1), which show that the n-terminal helix is rotated upwards and away from the catalytic domain (fig. 4e). notably, the stac binding site is located at the interface between the n-terminal helix and the catalytic domain, suggesting that the conformation of this helix is important for stac binding. the n-terminal helix may also play a role in mediating stac interactions with the catalytic domain, as the stac binding site is within 5 å of the catalytic zn2+-binding site and conformations of the n-terminal helix are known to change upon ligand binding (supplementary fig. 5). in the crystal structure of mini-hsirt1/1 binary complex, the stacs are located within the substrate binding groove and may mimic the positions of the substrates and co-substrates within the active site of the enzyme. thus, the structure of mini-hsirt1 provides new insights into the design of small molecule activators for sirt1.

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The proteasome is the major proteolytic machinery in cells, degrading a large fraction of cellular proteins. While its role in the control of cell proliferation and survival has been well documented, little is known about its physiological function in meiosis. Here we show a novel role of the proteasome in meiosis by identifying a function of the 26S proteasome in ubiquitination-dependent proteolysis of SET/TAF-1beta, a transcriptional co-activator involved in meiosis. It is also demonstrated that the proteasome not only maintains SET/TAF-1beta at a low level, but also reduces its half-life. Following on from our initial report (1), a novel zinc-finger-derived peptide dimer designed to activate the Class I SIRT1 family of deacetylases was created. This compound, termed STAC, was designed to mimic the domain architecture of hSIRT1-7 including an N-terminal zinc finger and a C-terminal catalytic module (2). STAC was synthesized following a stepwise methodology to achieve increased yields and greater purity and shown to demonstrate the first activation of a recombinant hSIRT1 enzyme as well as displaying enhanced cellular activity. Subsequent site-directed mutagenesis led to the production of a variant of STAC that bears both charge-reversal mutations within the zinc finger to restore metal ion binding. These mutations were designed to both enhance the affinity of the zinc finger for the enzyme and to avoid zinc-finger self-dimerization by avoiding zinc finger-zinc finger side-chain salt bridges. The functional consequences of both the zinc finger mutations and the charge-reversal mutations were further tested in the context of the STAC-2 peptide. STAC-2, a variant of STAC with optimal deacetylase activity, bears a double charge-reversal mutation in the zinc finger to break the putative salt bridge, a second charge-reversal mutation in the catalytic domain to avoid zinc finger self-dimerization and a single amino acid substitution that has been shown to confer potent hSIRT1 deacetylase activity to STAC-1. A preliminary assessment of the enantiospecificity of this compound was also performed on several hSIRT1-activating peptide-NAD analogs. This was accomplished in a cell-free assay by allowing enzyme to pre-incubate with three compounds, STAC-1, STAC-2 and two previously described hSIRT1-activating peptides. These results were then confirmed using an acetylation assay in which the compound, peptide and enzyme were incubated simultaneously. The superior enantiospecificity of STAC was recently exploited in the development of a novel high-throughput kinetic deacetylase assay using highly fluorescent diacetyl-labeled peptides as substrates. Our initial experiments employing STAC-1 demonstrated the effective inhibition of two distinct lysine deacetylases (HDAC3 and HDAC6) by this compound. Unlike many metal ion-dependent deacetylases (3), hSIRT1 appears to be resistant to the deacetylase activity of HDAC3 since STAC-1 is only minimally deacetylated by HDAC3. These results will be discussed in light of current evidence regarding lysine deacetylase allostery. Finally, the preferential inhibition of HDAC6 by STAC-1 was extended to a panel of eight different HDAC6-selective inhibitors. A possible explanation for the potent hSIRT1 deacetylase inhibitory activity of STAC-1 is the ability of this compound to interact with the central catalytic pocket of SIRT1. This hypothesis is supported by the observation that the potent hSIRT1 deacetylase inhibitor T8 showed an unprecedented propensity to penetrate this central catalytic pocket. The significance of these findings will be discussed in the light of the established role of acetylation in HDAC6 modulation and potential implications for the development of HDAC6-directed therapeutics. 5ec8ef588b

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