Histone deacetylase 10 structure and molecular function as a polyamine deacetylase

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Cationic polyamines such as spermidine and spermine are critical in all forms of life, as they regulate the function of biological macromolecules. Intracellular polyamine metabolism is regulated by reversible acetylation and dysregulated polyamine metabolism is associated with neoplastic diseases such as colon cancer, prostate cancer and neuroblastoma. Here we report that histone deacetylase 10 (HDAC10) is a robust polyamine deacetylase, using recombinant enzymes from Homo sapiens (human) and Danio rerio (zebrafish). The 2.85 Å-resolution crystal structure of zebrafish HDAC10 complexed with a transition-state analogue inhibitor reveals that a glutamate gatekeeper and a sterically constricted active site confer specificity for N8-acetylspermidine hydrolysis and disfavour acetyllysine hydrolysis. Both HDAC10 and spermidine are known to promote cellular survival through autophagy. Accordingly, this work sets a foundation for studying the chemical biology of autophagy through the structure-based design of inhibitors that may also serve as new leads for cancer chemotherapy.

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Polymamines such as putrescine, spermidine and spermine are ubiquitous and essential in all living systems. Typically present at millimolar concentrations, these cellular polycations bind to nucleic acids and other anionic macromolecules to stabilize structure and regulate function in myriad biological processes. Polymamine metabolism is highly regulated and consists of an elaborately orchestrated balance of cellular uptake, intracellular transport, biosynthesis and catabolism (Fig. 1a). Dysregulation of polymamine metabolism is frequently associated with cancer and other hyperproliferative diseases, and enzymes of polymamine metabolism are emerging drug targets.

A critical strategy for the regulation of polymamine function is reversible acetylation. This strategy is analogous to the regulation of protein function by reversible lysine acetylation through reactions catalysed by histone acetyltransferases and histone deacetylases (HDACs, also known more generally as lysine acetyltransferases and lysine deacetylases). In eukaryotes, this branch of polymamine metabolism is partially compartmentalized in the nucleus (Fig. 1a). Spermidine is acetylated at the N8 position by an N-acetyltransferase in the cell nucleus and then exported to the cytosol, where it is deacetylated by a metal-dependent N8-acetyl spermidine deacetylase, also known as polymamine deacetylase (PDAC).

The substrate specificity of PDAC is very strict, as it does not deacetylate cytosolic N8-acetyl spermidine or N8-acetyl spermine. Selective inhibition of PDAC activity in HeLa cells increases N8-acetyl spermidine levels but not acetylated histone levels, so PDAC activity is distinct from HDAC activity.

To date, the identity of the cytosolic PDAC in eukaryotes has remained elusive. However, selective inhibitors have been developed that block mammalian PDAC activity. Our recent studies of a bacterial PDAC belonging to the arginase-deacetylase superfamily led us to suggest that the enigmatic PDAC might be one of the two cytosolic class IIb Zn2+-dependent HDACs, HDAC6 or HDAC10.

We recently reported the X-ray crystal structures of both catalytic domains (CDs) of HDAC6, showing that a conserved active site lysine serves as a gatekeeper in CD1, in that it dictates specificity for carboxy-terminal acetyllysine substrates bearing a negatively charged α-carboxylate group. In all other human HDACs, this residue is otherwise conserved as leucine or methionine, except for HDAC10 in which it is a glutamate (Fig. 1b and Supplementary Fig. 1). Accordingly, we hypothesized that strictly conserved glutamate could similarly serve as a gatekeeper to confer specificity for positively charged acetylpolymamine substrates. HDAC10 is highly expressed in the liver, spleen and kidney, enriched in the cytoplasm and resistant to inhibition by sodium butyrate. These properties match the tissue distribution, subcellular localization and inhibitor sensitivity of mammalian PDAC. Thus, we further hypothesized that HDAC10 might be a PDAC. Here we report enzymological studies conclusively demonstrating that HDAC10 is a robust PDAC and a poor lysine deacetylase. In addition, we report the 2.85-Å resolution crystal structure of HDAC10 complexed with a polymamine transition state analogue inhibitor. This structure reveals that the conserved glutamate gatekeeper and a sterically constricted active site confer specificity for N8-acetyl spermidine hydrolysis and disfavour acetylysine hydrolysis.

Results

**HDAC10 is a PDAC.** To determine steady-state kinetic parameters for the hydrolysis of a variety of acetylpolymamine and acetyllysine substrates, we prepared full-length recombinant HDAC10 from human (H. sapiens, hHDAC10) and zebrafish (D. rerio, zHDAC10). The CDs of these orthologues are highly similar based on 63%/79% sequence identity/similarity; only full-length constructs yielded soluble proteins. We first assayed the lysine deacetylase activity of these constructs against two commercially available aminomethylcoumarin (AMC)-conjugated fluorogenic acetyllysine peptides, GAK(ac)-AMC and RGK(ac)-AMC (molecular structures of all substrates are shown in Supplementary Fig. 2). Both hHDAC10 and zHDAC10 exhibited very low activity with these peptides (Fig. 2 and Supplementary Table 1). These measurements were consistent with earlier studies reporting that HDAC10 activity was not measurable using fluorogenic peptide substrates. We also tested activity with 11 non-fluorogenic acetyllysine substrates using a liquid chromatography–mass spectrometry (LC–MS)–based discontinuous assay to avoid potential steric clashes that might occur with the bulky AMC group. These substrates included K(ac)NL and GAK(ac)NLQ, which mimic the peptide segment containing K73 in the proposed HDAC10 substrate MutS homologue 2 (MSH2). Again, we observed no or very low catalytic activity (Fig. 2 and Supplementary Table 1). In comparison with its closest relative, the cytosolic isozyme HDAC6 (ref. 17), HDAC10 was clearly not an efficient lysine deacetylase.

We next tested the PDAC activity of hHDAC10 and zHDAC10 against several polymamine substrates using the LC–MS assay (Fig. 2, Supplementary Fig. 3 and Supplementary Table 1). Both

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**Figure 1 | Eukaryotic polymamine metabolism and HDAC gatekeepers.** (a) APAO, N1-acetylpolymamine oxidase; ODC, ornithine decarboxylase; PAT, N8-spermidine acetyltransferase; PDAC, N8-acetyl spermidine deacetylase; SMS, spermine synthetase; SRM, spermidine synthase; SSAT, spermidine/spermine acetyltransferase. (b) Sequence alignment of the 11 metal-dependent HDACs (the two CDs of HDAC6, CD1 and CD2, are listed separately). Gatekeeper K353 of hHDAC6 CD1 is highlighted in sky blue and gatekeeper E272 of hHDAC10 is highlighted in red. In all other isozymes, this residue is leucine or methionine and exerts no electrostatic influence on substrate binding.

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enzymes exhibited optimal catalytic activity and specificity for the hydrolysis of N⁸-acetylsermidine. For hHDAC10 and zHDAC10, \( k_{\text{cat}}/K_M = 2,900 \pm 200 \) and \( 4,600 \pm 300 \) M⁻¹ s⁻¹, respectively; in comparison, N³-acetylsermidine was a poor substrate with \( k_{\text{cat}}/K_M = 24 \pm 5 \) and \( 7 \pm 2 \) M⁻¹ s⁻¹, respectively. Substrate specificity trends observed for hHDAC10 and hHDAC10 matched those of the previously reported mammalian N⁸-acetylsermidine deacetylase activity²³. As a positive control, we measured the N⁸-acetylsermidine HDAC activity measured with RGK(ac)-AMC. APAH, hHDAC10 and zHDAC10 exhibit a clear catalytic preference for PDAC activity. The E274L mutation converts zHDAC10 from a PDAC into an HDAC and the zHDAC10 activity 2,900 and 4,600, respectively (Fig. 2). These results suggested that the ideal length of a PDAC substrate ranged 8–12 atoms long. The N⁴ amino group of N⁸-acetylsermidine was required for optimal activity in comparison with N-(8-aminoctyl)acetamide, which lacks the secondary amino group. Even so, the amino group could be located at N3, based on the substantial catalytic activity measured with acetylcadaverine and acetylputrescine. However, the amino group could not be at N3, based on the lack of substantial catalytic activity with N³-acetylsermidine and N-(3-aminoctyl)acetamide. In addition, given the attenuated catalytic activity measured for N⁴,N⁸-diacetylspermidine, we concluded that the positive charge of the N⁴-amino group of N⁸-acetylsermidine contributed to, but was not critical for, enzyme-substrate recognition. In comparison with HDAC10, the bacterial PDAC APAH exhibited broad substrate specificity with all polyamine substrates except for N-butylacetamide; it also exhibited weak lysine deacetylase activity (Supplementary Table 1 and Supplementary Fig. 3).

To test our hypothesis that E274 is a gatekeeper conferring substrate specificity for N⁸-acetylsermidine, we prepared E274L zHDAC10. In accord with our hypothesis, this substitution diminished N⁸-acetylsermidine deacetylase activity by 20-fold and enhanced acetyllysine deacetylase activity by ~100-fold (Supplementary Fig. 3 and Supplementary Table 1). Thus, the single-point mutation E274L completely reversed the substrate specificity of zHDAC10, converting it from a PDAC into an HDAC (Fig. 2c).

Crystal structure of HDAC10. To provide a molecular foundation for understanding the PDAC activity of HDAC10, we determined the 2.85 Å-resolution crystal structure of Y307F zHDAC10 complexed with the trifluoromethylketone inhibitor 7-[(3-amino-propyl)amino]-1,1,1-trifluoroheptan-2-one (AAAT, Supplementary Fig. 2), which mimics N⁸-acetylsermidine¹⁴. This inhibitor binds as a transition state analogue with \( K_i = 0.7 \pm 0.2 \) μM (Supplementary Fig. 4). We treated full-length zHDAC10 with trypsin to yield a heterodimeric complex, designated zHDAC10A, comprising the amino-terminal PDAC domain and the C-terminal pseudo-deacetylase (ΨDAC) domain. The proteolytically nicked zHDAC10A construct retains substantial catalytic activity (Supplementary Table 1). Both proteolysis and the introduction of the deactivating Y307F mutation facilitated crystallization.

The crystal structure of the Y307F zHDAC10A–AAAT complex (Fig. 3a) revealed an overall butterfly-like architecture with a pseudo-two-fold symmetry axis perpendicular to several Ψ-helices defining the PDAC-ΨDAC domain interface. Each domain adopted the αβα-fold first observed in the crystal structure of arginase²⁵ and subsequently observed in the HDAC family²⁶. However, the ΨDAC domain lacked helices Ψ1–A2, ΨA, ΨB2–ΨB3 and active site loops L1–L5 (Fig. 3b). Interdomain interactions were mediated by Ψ-helices ΨF and ΨG, loop LH (which connects ΨH1 and ΨH2) and the C-terminal tail of each domain, burying ~1,700 Å² surface area. The 48-residue linker was missing in the electron density, presumably due to...
proteolysis. HDAC10 PDAC-$\Psi$DAC heterodomain assembly resembles HDAC6 heterodomain assembly and HDAC homo-domain assembly in Schizosaccharomyces pombe Clr3 (Supplementary Fig. 5). The tertiary structure of the PDAC domain was similar to both CD1 (PDB 5EEF) and CD2 (PDB 5EFH) of HDAC6 (0.78 Å root mean squared deviation (r.m.s.d.) for 355 Cα atoms; 0.88 Å r.m.s.d. for 352 Cα atoms, zCD2) (Fig. 3c). A close-up view of the active site tunnel revealed a canonical HDAC active site at the base of the tunnel, with AAT binding in an extended conformation (Fig. 3d). The trifluoroketone moiety of AAT formed a gem-diolate, making asymmetric coordination interactions with Zn$^{2+}$ (O1-Zn$^{2+}$ and O2-Zn$^{2+}$ coordination distances of 2.1 and 2.5 Å, respectively); hydroxyl group O2 also hydrogen bonded with H136 and H137. The binding of AAT thus mimicked the tetrahedral intermediate and its flanking transition.

Figure 3 | Crystal structure of the Y307F zHDAC10-$\Psi$-AAT complex. (a) The catalytic PDAC domain and the smaller, noncatalytic $\Psi$DAC domain assemble with butterfly-like architecture. The unique $3_{10}$-helix $\eta$A2 ($^{P23}$ACE) found in the L1 loop of HDAC10 orthologues is purple. Percentages indicate sequence identity/similarity between zebrafish and human HDAC10 domains. The inhibitor AAT (stick figure, C = yellow, N = blue) binds to the PDAC domain. (b) Superposition of the PDAC domain (blue) with the $\Psi$DAC domain (green). Selected secondary structure elements are labelled: helix $\eta$A2 is purple; helices $\alpha$F, $\alpha$G and the loop connecting helices $\alpha$H1 and $\alpha$H2 mediate domain-domain interactions; helices $\alpha$B2 and $\alpha$B3, as well as loops L1–L5, comprise and flank the active site of PDAC but are absent in $\Psi$DAC (for clarity, only loops L2, L3 and L5 are labelled). Zn$^{2+}$ is a blue sphere. (c) Stereo view image showing the superposition of zHDAC10 PDAC domain (blue), zHDAC6 CD1 (wheat, PDB 5EEF) and zHDAC6 CD2 (light blue, PDB 5EFH). The $3_{10}$-helix $\eta$A2 inserted in loop L1 (purple) is unique to zHDAC10 and serves to constrict the PDAC active site. (d) Stereo view image showing the simulated annealing omit map of AAT bound in the PDAC active site contoured at 3σ. Selected active site residues are indicated; hydrogen bonds are indicated by dashed red lines and metal coordination interactions are represented by solid black lines. Zn$^{2+}$ is a blue sphere.
states for the hydrolysis of N\textsuperscript{8}-acetylspermidine. This binding mode was similar to that observed in the APAH–AAT and zHDAC6 CD2–AAT complexes\textsuperscript{17,29}.

The structure of zHDAC10 allowed us to study substrate specificity determinants: in particular, the active site was much more constricted compared with other isozymes such as HDAC6. On one side of the active site, gatekeeper E274 was close (3.7 Å) to the N4 atom of AAT (Fig. 3d). Although this interatomic separation was too long for a hydrogen bond interaction, it was sufficiently close for a favourable electrostatic interaction. The conversion of HDAC10 from a PDAC into an HDAC through the E274L mutation (Fig. 2) demonstrated that this electrostatic interaction is important for PDAC specificity.

Opposite E274, there was an additional constriction contributing to PDAC specificity: a unique one-turn 3\textsuperscript{10}-helix ηA2 (P2\textsuperscript{3}-ACE) resulting from a two-residue insertion plus a two-residue mutation in the L1 loop relative to zHDAC6, effectively lengthening the narrow active site tunnel by ~5 Å (Fig. 3c,d). This four-residue segment is universally conserved in HDAC10 orthologues with only minor variations, appearing predominantly as PECE (Supplementary Fig. 1). The steric protrusion formed by this segment favours the binding of long acetylpepinolyamine substrates (Fig. 3c) and disfavours the binding of shorter acetyllysine substrates (Fig. 4). Removal of the 3\textsuperscript{10}-helix ηA2 insertion yielded construct zHDAC10 ΔηA2, which exhibited 15-fold decreased PDAC activity and 16-fold increased HDAC activity (Supplementary Table 1, Fig. 2 and Supplementary Fig. 3). Therefore, both gatekeeper E274 and the 3\textsuperscript{10}-helix ηA2 insertion promote PDAC activity and suppress HDAC activity.

Although the structural basis of HDAC10 selectivity for N\textsuperscript{8}-acetylspermidine over acetyllysine-containing peptide substrates appeared straightforward, the structural basis of selectivity for N\textsuperscript{8}-acetylspermidine over N\textsuperscript{3}-acetylspermidine was more subtle to discern. The active site tunnel in the PDAC domain was surrounded by a vast surface of negative electrostatic potential (Fig. 5a,b and Supplementary Fig. 6), resulting in large part from conserved aspartate and glutamate residues (Supplementary Fig. 1). This electrostatic surface feature is unique to HDAC10 orthologs and contrasts with that of the lysine deacetylase HDAC6 CD2 (Fig. 5c). However, the surface of the HDAC10 PDAC domain became less anionic and ultimately cationic, at the base of the active site tunnel (Fig. 5b). The binding of N\textsuperscript{3}-acetylspermidine would place the positively charged N4 amino group closer to this cationic surface, which would disfavour N\textsuperscript{3}-acetylspermidine binding relative to N\textsuperscript{8}-acetylspermidine binding. The strict substrate regioselectivity of HDAC10 for N\textsuperscript{8}-acetylspermidine contrasts with the broad substrate specificity of bacterial APAH, which has a glutamate residue (E117) to stabilize the positively charged N4 amino group through a salt bridge (Supplementary Fig. 7).

The crystal structure of the Y307F zHDAC10Δ–AAT complex revealed that the primary amino group at the end of AAT is disordered (Fig. 3d), but it would be located near the side chains of N93, D94 and A24. Interestingly, D94 corresponds to acetyllysine binding residues D101 of hHDAC8 and S568 of hHDAC6 CD2 (refs 17,30,31). To study the influence of N93 and D94 on substrate binding and catalysis in zHDAC10, we prepared the N93A and D94A mutants. Neither mutant exhibited substantial differences in steady-state kinetic parameters (Supplementary Table 1 and Supplementary Fig. 3). Thus, neither N93 nor D94 are required for enzyme–substrate recognition and catalysis.

The ΨDAC domain of HDAC10 has no known catalytic function, although it may play a role in directing cytoplasmic enrichment\textsuperscript{19}. Neither the Zn\textsuperscript{2+} ligands nor catalytic residues were conserved in the ΨDAC domain (Fig. 3b). The overall fold of the ΨDAC domain was most similar to that of the PDAC domain, as well as the CDs of HDAC6 (~2.1 Å r.m.s.d. for ~213 C\textalpha{} atoms in each). In contrast with the PDAC domain, the ΨDAC domain exhibited low amino acid sequence identity and greater divergence across species (for example, 28% sequence identity between zebrafish and human proteins) (Fig. 3a and Supplementary Fig. 1); however, α-helices ΨG and ΨH at the interdomain interface were highly conserved (Supplementary Fig. 5).

**Discussion**

Our enzymological and X-ray crystallographic results suggest that E274 of zHDAC10 is conserved in HDAC10 orthologues as a gatekeeper to establish specificity for a cationic substrate, just as
gatekeeper K330 is conserved in the corresponding position of zHDAC6 CD1 to establish specificity for an anionic substrate\(^1\). This gatekeeper is necessary but not sufficient for full activity and selectivity; both zHDAC10 and zHDAC6 CD1 have additional steric bulk opposite the gatekeeper that further constrains the active site. In zHDAC10, the \(\beta\)-helic \(\eta\)A2 provides this steric bulk; in hHDAC6 CD1 (ref. 17), F105 and Y225 provide this steric bulk. Regardless, the gatekeeper appears to be a ‘hot spot’ for dictating substrate specificity.

With regard to the substrate specificity of HDAC10, a sizeable array of steady-state kinetic measurements clearly demonstrated that HDAC10 is a PDAC (Fig. 2 and Supplementary Table 1). Even so, HDAC6 is proposed to deacetylze the cytosolic proteins Hsc70/Hsp70 and MSH2 (refs 22,32). The deacetylation of Hsc70/ Hsp70 by HDAC10 is not characterized at the molecular level, so we cannot comment on this possibility. Although the deacetylation of K73 of MSH2 correlates with HDAC10 levels, enzyme catalysis has not been directly demonstrated\(^2\); moreover, our steady-state kinetic measurements showed that HDAC6 does not deacetylate the deacetylation of MSH2-based peptide substrates K(ac)NL and GAK(ac)NLQ (Supplementary Table 1). Intriguingly, however, we demonstrated that the MSH2-based substrate GAK(ac)NLQ is efficiently deacetylated by HDAC6 (Supplementary Table 1 and Supplementary Fig. 3), which is also known to interact with and deacetylate MSH2 \(\text{in vivo}\)\(^3\). Our \(\text{in vitro}\) results are more consistent with HDAC6 being the MSH2 deacetylase. As a point of speculation, perhaps the very low levels of lysine deacetylation activity measured for some but not peptide substrates (Supplementary Table 1) are responsible for the effect of HDAC10 on MSH2 acetylation status.

As previously mentioned, HDACs adopt the same \(\alpha/\beta\)-fold first observed in the crystal deacetylze of arginase, a binuclear manganese metalloenzyme that catalyzes the hydrolysis of arginine to form ornithine plus urea\(^4\). This evolutionary relationship was unexpected, as there is very low amino acid sequence identity between HDACs and arginases. However, identical \(\alpha/\beta\)-folds (\(\beta\)-strand order 21387456) and the conservation of metal binding sites (the Mn\(^{2+}\) site of arginase is conserved as the Zn\(^{2+}\) site of HDACs) suggest that HDACs and arginases divergently evolved from a common primordial ancestor. As one biological function of arginase is to provide ornithine for polyamine biosynthesis, it is striking that the arginase-deacetylze fold is also recruited for a PDAC function in polyamine metabolism. Our phylogenetic analysis (Fig. 6) indicated that the closest relationship between the HDAC and arginase families is between the \(\Psi\)DAC domain of Cavia porcellus HDAC10 and H. sapiens agmatinase (sequence identity = 19\%). Interestingly, this analysis also suggested that the evolution of PDAC activity in vertebrate HDAC10 and the bacterial deacetylze APAH occurred convergently.

Recently, it has been demonstrated that HDAC10 protects cancer cells from chemotherapeutic drugs by mediating autophagy, a survival response to the cellular damage and metabolic stress induced by cytotoxic drugs; indeed, the upregulation of HDAC10 is a marker of poor outcome for advanced stage neuroblastoma patients\(^3\). However, the knockdown or inhibition of HDAC10 blocks autophagy in a panel of neuroblastoma cell lines, thereby sensitizing these highly malignant cells to the cytotoxic drug doxorubicin\(^4\). As the suppression of autophagy to sustain the cytotoxicity of chemotherapeutic drugs is a novel strategy for cancer chemotherapy\(^34,35\), HDAC10 is an emerging target for the treatment of advanced-stage neuroblastoma\(^3\).

The polyamine spermidine is also a key factor in autophagy and increased levels of endogenous or exogenous spermidine induce autophagy and extend lifespan in a variety of cell types, including human immune cells\(^36,37\). Recent studies show that the inhibition of ornithine decarboxylase, which utilizes arginase-derived ornithine to generate putrescine, reduces cellular polyamine levels and suppresses autophagy in eukaryotic cells, thereby attenuating infection by Trypanosoma cruzi\(^38\). Thus, polyamine metabolism is closely linked to autophagy.

Given that HDAC10 is a PDAC with catalytic specificity for the hydrolysis of \(N^8\)-acetyl spermidine to yield spermine and acetate, it is possible that the functions of HDAC10 and spermidine in autophagy are linked. With the crystal structure of HDAC10 now in hand, the structure-based design of isozyme-specific inhibitors promises to open new avenues in studying the chemical biology of autophagy as well as the treatment of advanced-stage cancers in which this PDAC is implicated.

**Methods**

**General.** No statistical methods were used to predetermine sample size. PfuUltra High-Fidelity DNA polymerase (Agilent Technologies) was used for PCR analysis. Restriction enzymes (New England Biolabs) were used according to the manufacturer’s specifications. Primers were synthesized by Integrated DNA Technologies. Escherichia coli strain NEB5a (New England Biolabs) was used for cloning procedures. Peptides were synthesized by Genscript. N-(3-aminopropyl) acetamide was purchased from Chem-Impex International, Inc. Acetylcadaverine

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**Figure 5 | Electrostatic surface potential of HDAC10.** (a) A negatively charged protein surface surrounding the active site tunnel is a conserved feature of HDAC10 PDAC orthologues based on the conservation of aspartate and glutamate residues (Supplementary Fig. 1). Colour coding is as follows: \(-5kT\) to \(-5kT\), red-blue. (b) Cut-away view of the zHDAC10 active site showing the transition between the negative electrostatic surface potential of the outer active site and the positive electrostatic potential of the inner active site. (c) In comparison, no particular electrostatic profile characterizes the protein surface surrounding the active site of the related cytosolic lysine deacetylase, HDAC6 CD2, complexed with AAT (PDB 5EFH).
was purchased from TCI. N\(^\text{3}\)-acetylpermidine dihydrochloride was purchased from Cayman Chemicals, Inc. Acetylputrescine, N\(^\text{3}\)-acetylpermine trihydrochloride, N-butylacetamide and N\(^\text{3}\)-(aminooctyl)acetamide were purchased form Sigma-Aldrich. Acetylputrescine, triacetylputrescine and 8-acetylspermidine dihydrochloride was purchased from ApexBio. All substrates and ligands are used without further purification. The Y307F hHDAC10 mutant was prepared by by swapping the helix A2 region of the PDAC-\(\psi\)DAC complex were pooled and concentrated to 30 mg ml\(^{-1}\) (the PDAC-\(\psi\)DAC domains did not dissociate upon proteolytic nicking of the interdomain linker). The PDAC domain (residues 2–370) remained intact after proteolytic nicking as determined by LC–MS/MS. zHDAC10:trypsin overnight at 4°C and then reloaded onto a HiLoad Superdex 200 column equilibrated in buffer C (50 mM HEPES (pH 7.5), 300 mM KCl, 1 mM TCEP, 5% glycerol). Proteins were concentrated to >10 mg ml\(^{-1}\) and flash-cooled in liquid nitrogen and stored at \(-80^\circ\text{C}\) for further use.

For the preparation of zHDAC10A, 10 mg ml\(^{-1}\) of zHDAC10 in buffer C was incubated with trypsin (Sigma-Aldrich) with a 1,000:1 molar ratio of zHDAC10:trypsin overnight at 4°C and then reloaded onto a HiLoad Superdex 200 column equilibrated in buffer C. Peak fractions corresponding to the co-elution of the PDAC-\(\psi\)DAC complex were pooled and concentrated to 30 mg ml\(^{-1}\) (the PDAC-\(\psi\)DAC domains did not dissociate upon proteolytic nicking of the interdomain linker). The PDAC domain (residues 2–370) remained intact after proteolytic nicking as determined by LC–MS/MS. zHDAC10A proteins were flash-cooled in liquid nitrogen and stored at \(-80^\circ\text{C}\) for further use.

Single-point mutants were generated using the Quikchange kit (Stratagene); all primers used for PCR mutagenesis are listed in Supplementary Table 4. The zHDAC10A2 mutant was prepared by by swapping the helix \(\eta\)A2 region (D\(^{\text{348}}\)PACE\(^{\text{362}}\)) with a tetrapeptide segment [S\(^{\text{96}}\)HHP\(^{\text{100}}\)] from the corresponding zHDAC6 CD2 L1 loop. All mutants were expressed and purified using the same procedure as described above for wild-type zHDAC10. Y307F zHDAC10A was prepared in the same manner as described above for zHDAC10A.

Human HDAC6 CD12, zebrafish HDAC6 CD1 and CD2, and APAH were expressed, purified and assayed as previously reported.\(^{14,17}\)

**Crystallization.** The Y307F zHDAC10A–AAT complex was crystallized using the sitting drop vapour diffusion method at 4°C. Protein (30 mg ml\(^{-1}\)) was first incubated with 5 mM AAT ligand in buffer C on ice for 30 min and then 0.4μl of 0.1 lysozyme (Sigma), formiminoglutamases (FIGase) and ureohydrolases, yeast Hos3 homologues, bacterial APAHs, bacterial histone deacetylase-like amidohydrolases (HDAH), class II HDACs, class I HDACs, bacterial acetoin utilization proteins (AcuC), class IV HDACs, and uncharacterized protein family UPF0489 and \(\psi\)DAC. Acronyms are defined and UniProt or NCBI accession numbers are listed in Supplementary Table 5.

**Protein expression and purification.** The human HDAC10 gene (Q96598, residues 2–675) and zebrafish HDAC10 gene (Uniprot Q80330, residues 2–675) were synthesized and codon-optimized by GenScript (Supplementary Table 2 and Supplementary Table 3, respectively) and then sub-cloned into a modified pET28a (+) vector (a gift from Dr Scott Gradia, University of California, Berkeley; Addgene plasmid 29656) in-frame with a TEV-cleavable N-terminal His-MBP-tag (MBP, maltose binding protein) using ligation independent cloning (PCR primers are listed in Supplementary Table 4). All proteins were expressed in E. coli BL21 (DE3) (Agilent) cells in 2x YT medium in the presence of 50 mg ml\(^{-1}\) kanamycin and purified based on the protocol previously described for HDAC6 (ref. 17). Briefly, expression was induced when OD\(_{600}\) reached 1.0 by addition of 75 μl isopropyl β\(^{\text{-}}\)-D-1-thiogalactopyranoside (Carbonyl) and 500 μM ZnSO\(_4\) (Fisher Scientific), and cell cultures were grown for an additional 18 h at 16°C. Cells were harvested by centrifugation at 6,000 g and resuspended in lysis buffer (50 mM K\(_2\)HPO\(_4\) (pH 8.0), 300 mM NaCl, 10 mM MgCl\(_2\), 10% glycerol, 0.1 mg ml\(^{-1}\) lysozyme (Sigma), 50 μg ml\(^{-1}\) DNase I (Sigma), and protease inhibitor tablets (Roche Applied Science)). Cells were then lysed by sonication and cleared by centrifugation at 26,000 g for 1 h at 4°C. The cleared lysate was loaded onto a Ni-NTA affinity column (Qiagen) and eluted with buffer A (50 mM K\(_2\)HPO\(_4\) (pH 8.0), 1 mM TCEP, 300 mM NaCl, 300 mM imidazole, 5% glycerol). Protein-containing fractions were loaded onto an Amylose resin column (New England Biolabs).

For human HDAC10, the MBP-tag was not cleaved off. The MBP-fusion hHDAC10 was eluted from Amylose resin by buffer B (20 mM Tris (pH 8.0), 100 mM NaCl, 1 mM TCEP, 5% glycerol) plus 10 mM maltose (Sigma-Aldrich) and further purified by anion-exchange chromatography. For zebrafish HDAC10, the proteins were digested on-column using TEV protease in buffer B to remove the His-MBP tag and further purified by anion-exchange chromatography (HiTrap Q, GE Healthcare). Both zHDAC10 and hHDAC10 were finally loaded onto a HiLoad Superdex 200 column equilibrated in buffer C (50 mM HEPES (pH 7.5), 300 mM KCl, 1 mM TCEP, 5% glycerol). Proteins were concentrated to >10 mg ml\(^{-1}\) and flash-cooled in liquid nitrogen and stored at \(-80^\circ\text{C}\) for further use.

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For human HDAC6 CD12, zebrafish HDAC6 CD1 and CD2, and APAH were expressed, purified and assayed as previously reported.\(^{14,17}\)

**Crystallization.** The Y307F zHDAC10A–AAT complex was crystallized using the sitting drop vapour diffusion method at 4°C. Protein (30 mg ml\(^{-1}\)) was first incubated with 5 mM AAT ligand in buffer C on ice for 30 min and then 0.4μl of
To study steady-state kinetics with non-fluorogenic peptide substrates and acetylpolymamines, a discontinuous LC–MS was employed based on the protocol of assaying nonfluorogenic acetylspermidine peptide substrates for HDAC6 (ref. 17). Assays were performed in triplicate. Briefly, 5 μl of enzyme (0.050–20 μM in HEPES buffer (20 mM HEPES (pH 7.5), 100 mM NaCl, 5 mM KCl, 1 mM MgCl2) was added to be added to 35 μl of substrate solution to initiate the reaction. After incubation for 15–60 min at room temperature, the reaction was quenched by addition of 50 μl of 20 mM dansyl chloride dissolved in acetonitrile followed by 10 μl of NaHCO3 (1.6 M, pH 10.0). The deacetylation products were derivatized with dansyl chloride at 50°C for 2 hrs. The deacetylation products were detected by LC–MS using a Waters UPLC equipped with an Acquity UPLC (Waters, Milford, MA, USA) and quantified by using the standard curve generated from the mass signals of the corresponding deacetylated polyamines and peptides. Inhibition of HDAC10 activity was measured by using 0.49 μM zHDAC10 with 192 μM N-acetyllyspermidine. Data were analysed by logistic regression for IC50 determination and the inhibition constant Ki was calculated based on the Cheng–Prusoff equation, Ki = IC50 / (1 + ([S]/Ki))18. Assays were performed in triplicate at room temperature.

**Electrostatic surface potential and residue conservation.** The electrostatic potential of the protein surface was calculated using the Adaptive Poisson–Boltzmann–Solv model implemented in PyMol46. The following parameters were used for calculations: T = 298.15 K, pH 7.5, AMBER forcefield, linearized Poisson–Boltzmann equation. The PQR file was generated using the web server PDB2PQR (http://pdb2pqr.gramene.org) before the electrostatic potential calculation. The radius and charge of metal ions were set to +2 and 0.74 Å for Zn2+; +1 and 1.33 Å for K+. Residue conservation of 250 HDAC10 orthologues (National Center for Biotechnology Information (NCBI) Protein Reference Sequences) was analysed by Consurf48 (http://consurf.tau.ac.il) and displayed in PyMol.

**Phylogenetic tree.** Protein sequences and their annotations were retrieved from the UniProt database51; some unannotated sequences were obtained from the NCBI. An unrooted phylogenetic tree of the arginine-deacetylase domain was generated based on sequence alignments calculated with ClustalOmega50,51 and visualized using publicly available tools at the Interactive Tree of Life to generate Fig. 6 (refs 52–54).

**Model of the zHDAC10–substrate complex.** A model of the zHDAC10–substrate complex was prepared by superimposing the crystal structure of the zHDAC6 CD2–RGK(ac)-AMC complex (PDB 5FEN) on the crystal structure of the closely related deacetylase domain of zHDAC10. To generate Fig. 4a, atoms of zHDAC6 CD2 were omitted for clarity and the molecular surface of zHDAC10 was calculated with PyMol. The E274L mutation was then introduced using Coot and an energetically favourable leucine side chain rotamer was selected that coincided with the side chain torsion angles of the original glutamate side chain. The molecular surface was then calculated with PyMol to generate Fig. 4b.

**Data availability.** The coordinates and structure factors of the zHDAC10–AAT complex have been deposited in the Protein Data Bank under the accession code 5TDD. The PDB accession codes 3QHC, 4ZUM, 5EEF, 5EHF, 5E7J, 5E7K and 5FEN were used in this study. The UniProt accession codes Q1547F, Q92769, O15379, P56524, Q9U4L6, Q9UB7N, Q8WU14, Q9YK1V, Q9UK6V, Q9H958, Q9D8R2, Q803K0, Q63P3E, Q5LXL7, Q0TX2Q, Q9V897, W5S683, Q5H670, Q64Q04, Q9542M, 1QBPB2, 1Z8L5M, 1L720M, Q6H459, Q93S15, B5GL8C, Q25999, P02XJ5, QG2Y72, HAD2Z, 2J8YBP, Q3JUN4, Q48935, V6AH3V, W0A07FJD7, A0A194GSG2, 82IF16, Q70535, A0A0A0D582, 8SDVC2, H3UXL3, K0C7Y6, J0BA65, A0A171KN5, P56523, P59735, Q5S702, P3256J, Q12214, P30906, 067153, P64375, P90670, E1VY17, A0A090UP77, A0A042Q2P5, L8NO52, Q6GEM8, G1K7C6, A7E3T7, Q88GCC1, Q48AR2, Q82H30, Q7S2F1, Q56970, A0A1D5SNP4, 97OH88, H5V504, and Q8V03K0 were used in this study. The NCBI accession codes WP_036883431, WP_018067801.1, WP_028738651.1, WP_040747046.1, WP_013837465.1 and WP_016143245.1 were used in this study. All other data are available from the corresponding authors upon reasonable request.

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**Table 1 | Data collection and refinement statistics.**

| Protein complex | Y307F zHDAC10–AAT complex |
|-----------------|---------------------------|
| Resolution (Å)  | 2.82 (2.85)*              |
| Rwork/Rfree (%) | 12.9 (2.2)                |
| Completeness (%)| 99.0 (100.0)              |
| Redundancy      | 7.1 (7.3)                 |
| CC1/2           | 0.977 (0.682)             |

*Values in parentheses are for highest-resolution shell.

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protein solution was mixed with 0.4 μl of precipitant solution (0.2 M KH2PO4, 20% PEG 3350) and equilibrated against an 80% reservoir of precipitant solution. Rod-like crystals appeared after 24 h. Crystals were soaked in a cryoprotectant solution consisting of precipitant solution supplemented with 40% ethylene glycol before flash-freezing in liquid nitrogen.

**Crystal structure determination.** X-ray diffraction data were collected from a single crystal. The unit cell dimensions were 80.45, 80.45, 243.04 Å with a residual of 90.0, 90.0, 120.0 Å. The reaction mixture was quenched by adding developer solution (1 N HCl) and allowed to sit for 20 min at room temperature. The reaction mixture was then pipetted into a 20 mM dithionite solution and incubated at 50°C for 2 hrs. The deacetylation products were detected by LC–MS using a Waters UPLC equipped with an Acquity UPLC (Waters, Milford, MA, USA) and quantified by using the standard curve generated from the mass signals of the corresponding deacetylated polyamines and peptides. Inhibition of HDAC10 activity was measured by using 0.49 μM zHDAC10 with 192 μM N-acetyllyspermidine. Data were analysed by logistic regression for IC50 determination and the inhibition constant Ki was calculated based on the Cheng–Prusoff equation, Ki = IC50 / (1 + ([S]/Ki))18. Assays were performed in triplicate at room temperature.

**Activity assays.** Fluorogenic substrates were custom synthesized by Genscript. Assays were performed at room temperature in triplicate. Briefly, enzymes and substrates were diluted in assay buffer (50 mM Tris–HCl (pH 8.0), 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl2) at various concentrations. Reactions were initiated by the addition of 25 μl substrate solution to 25 μl enzyme solution (5 μM). Reactions were quenched by adding developer solution (1 μM trypsin and 10 μM SAHA in assay buffer) and allowed to sit for 20 min at room temperature. The reaction mixture was transferred to a NUNC 384-well optical bottom black plate (THERMO Fisher Scientific) and fluorescence was measured using a TECAN Infinite M1000Pro plate reader (λex = 360 nm and λem = 460 nm). A standard curve using Fluor de lys deacetylated standard (Enzo Life Sciences) was used to calculate enzyme activity.

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**Author contributions**

Y.H. and D.W.C. designed the project. Y.H., S.A.S. and N.J.P. performed experiments. Y.H., S.A.S., N.J.P. and D.W.C. interpreted experimental results and prepared the manuscript.

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