Crystal Structures of Tubulin Acetyltransferase Reveal a Conserved Catalytic Core and the Plasticity of the Essential N Terminus

Background: Tubulin acetyltransferase acetylates α-tubulin in the microtubule lumen. TAT is inefficient, and its activity is enhanced when tubulin is incorporated in microtubules. Acetylation is associated with stable microtubules and regulates binding of microtubule motors and associated proteins. TAT is important in neuronal polarity and mechanosensation, and decreased tubulin acetylation levels are associated with axonal transport defects and neurodegeneration. We present the first crystal structure of TAT and analyze substrate binding molecular determinants. The structure of an inactive mutant reveals a stable domain-swapped dimer.

Results: We present the first crystal structure of TAT and analyze substrate binding molecular determinants. The structure of an inactive mutant reveals a stable domain-swapped dimer.

Conclusion: TAT consists of a conserved core and structurally plastic N terminus essential for activity.

Significance: Our structure provides a rational platform for mechanistic dissection of tubulin acetylation.

Significance: Our structure provides a rational platform for mechanistic dissection of tubulin acetylation.

Tubulin acetyltransferase (TAT) acetylates Lys-40 of α-tubulin in the microtubule lumen. TAT is inefficient, and its activity is enhanced when tubulin is incorporated in microtubules. Acetylation is associated with stable microtubules and regulates binding of microtubule motors and associated proteins. TAT is important in neuronal polarity and mechanosensation, and decreased tubulin acetylation levels are associated with axonal transport defects and neurodegeneration. We present the first structure of TAT in complex with acetyl-CoA (Ac-CoA) at 2.7 Å resolution. The structure reveals a conserved stable catalytic core shared with other GCN5 superfamily acetyltransferases consisting of a central β-sheet flanked by α-helices and a C-terminal β-hairpin unique to TAT. Structure-guided mutagenesis establishes the molecular determinants for Ac-CoA and tubulin substrate recognition. The wild-type TAT construct is a monomer in solution. We identify a metastable interface between the conserved core and N-terminal domain that modulates the oligomerization of TAT in solution and is essential for activity. The 2.45 Å resolution structure of an inactive TAT construct with an active site point mutation near this interface reveals a domain-swapped dimer in which the functionally essential N terminus shows evidence of marked structural plasticity. The sequence segment corresponding to this structurally plastic region in TAT has been implicated in substrate recognition in other GCN5 superfamily acetyltransferases. Our structures provide a rational platform for the mechanistic dissection of TAT activity and the design of TAT inhibitors with therapeutic potential in neuronal regeneration.

Microtubules are dynamic polymers essential for cell motility, cell division, and intracellular transport. They are subject to multiple levels of regulation by cellular effectors and diverse posttranslational modifications, including acetylation, de-detyrosination/tyrosination, polyglutamylation, and polyglycylation. These chemical modifications are thought to locally adapt microtubules for specific functions by directly modifying their dynamics or through differential recruitment of motors, microtubule-associated proteins, or signaling molecules (1, 2).

Tubulin acetyltransferase (TAT)2 acetylates Lys-40 of α-tubulin in most eukaryotes. TAT shows preference for tubulin already incorporated in microtubules (3, 4), and acetylation is associated predominantly with stable microtubules such as those found in cilia (5, 6) and axons (7). Acetylation regulates the interaction between microtubules and motors as well as membranous organelles (1). For example, kinesin 1 is recruited preferentially to neurites enriched in acetylation, and tubulin hyperacetylation via pharmacological inhibition of the tubulin deacetylase HDAC6 disrupts polarized trafficking, leading to mislocalization of neurite-specific cargoes (8). Consistent with these in vivo findings, kinesin 1 preferentially binds acetylated microtubules in vitro and has reduced speed on nonacetylated axonemes (8). Tubulin acetylation has been also implicated in regulating the activity of the Na+/K+ pump (9), and recent studies show that the endoplasmic reticulum associates and slides primarily along acetylated microtubules (10). A decrease in tubulin acetylation levels has been associated with axonal transport defects as well as neurodegenerative disorders, including Huntington, ALS, and Alzheimer (1).

Tubulin was the first acetylated cytoplasmic protein to be isolated (11, 12); however, the identity of the tubulin acetyltransferase was discovered only recently as MEC-17, a gene required for the function of touch receptor neurons in Caenorhabditis elegans (3, 4). TAT belongs to the superfamily of GCN5-related N-acetyltransferases (GNAT (13)) and shows high sequence conservation from flagellates to humans (3, 4) (supplemental Fig. 1), with more than 96% identity among mammalian orthologs. TAT has the four sequence motifs characteristic of the GNAT superfamily (Motifs C, D, A, and B (13, 14)). Motif A shows the strongest conservation; Motif C the most divergence throughout the TAT family and the GNAT superfamily (13).

2 The abbreviations used are: TAT, tubulin acetyltransferase; GNAT, GCN5-related N-acetyltransferases; Ac-CoA, acetyl-CoA; AU, asymmetric unit; r.m.s.d., root mean square deviations; AUC, analytical ultracentrifugation; Se-Met, selenomethionine.
Although the majority of tubulin post translational modifications concentrate on the tubulin C-terminal tails that decorate the outside of the microtubule, TAT is unusual as it acetylates Lys–40 of α-tubulin (15), a residue located in a flexible loop in the microtubule lumen (16). The location of the acetylated residue makes it puzzling to understand how acetylation can affect cellular effectors. One hypothesis is that this modification leads to subtle changes in the microtubule lattice that can affect binding of effectors and polymer dynamics. Consistent with this, ultrastructural analyses of microtubules in touch receptor neurons of mec-17 mutants show a variability in protofilament number when compared with wild-type and large lattice defects that cause microtubules to splay apart and compress radially (17, 18).

To provide a structural scaffold within which to better understand the mechanism of TAT, we determined the x-ray structure of an active core of TAT in complex with Ac-CoA. Structure-based mutagenesis reveals molecular determinants of tubulin acetylation. We also report the x-ray structure of an active site mutant that, unlike the wild-type protein, is a stable, inactive dimer in solution and crystallizes as a domain-swapped dimer, revealing unexpected plasticity of the N-terminal domain of TAT. We thus identify an intramolecular interface in TAT that is metastable and when destabilized leads to dimer and higher-order oligomer formation. Intriguingly, this metastable region is important for TAT activity and contains a conserved motif predicted to be important for substrate engagement in GNAT superfamily members. Our work shows that TAT contains a conserved, stable catalytic core and a structurally plastic N terminus important for function. Tubulin hyper-acetylation is associated with neuronal injury (1, 19), making TAT an attractive target for small molecule inhibitors.

**EXPERIMENTAL PROCEDURES**

**Protein Expression and Purification**—*Danio rerio* TAT, residues 1–196, was expressed in *Escherichia coli* Rosetta2 (DE3) pLysS as a GST fusion. Protein expression was induced with 0.5 mM NaCl, 5 mM MgCl2, and 1 mM tris(2-carboxyethyl)phosphine after mixing equal volumes of protein and reservoir solution. Crystals were obtained by vapor diffusion at 20 °C in an XL-I ultracentrifuge (Beckman) using absorption (AUC) (81.5 Å, c = 117.7 Å). Se-Met high-resolution anomalous dispersion data were collected at the Advanced Light Source (ALS), Lawrence Berkeley National Laboratory, Beamline 5.0.2. (see Table 1). Five of the six possible selenium sites were found using SOLVE (20), and phases were calculated using CNS (21). The experimental electron density maps at this stage were not interpretable (mean overall figure of merit 0.306), but solvent flipping and histogram matching yielded maps in which ~60% of the protein could be built. Refinement of the partial model using PHENIX (22) and calculation of electron density maps with combined phases and later (2��nal) electron density maps were used. Data were collected and analyzed as described (25). For all cases, good fits were obtained with root mean square deviations (r.m.s.d.) between 0.003 and 0.004. The higher molecular weight species are due to an impurity and do not vary as a percentage of total absorbance as a function of TAT concentration.

**Analytical Ultracentrifugation**—Sedimentation velocity analytical ultracentrifugation (AUC) experiments were performed at 20 °C in an XL-I ultracentrifuge (Beckman) using absorption optics. Peak fractions of TAT from size-exclusion chromatography were used. Data were collected and analyzed as described (25). For all cases, good fits were obtained with root mean square deviations (r.m.s.d.) between 0.003 and 0.004. The higher molecular weight species are due to an impurity and do not vary as a percentage of total absorbance as a function of TAT concentration.

**RESULTS**

**Structural Overview of the Active TAT Core**—We isolated a stable, monodisperse fragment of *D. rerio* TAT (residues 1–186) that acetylates porcine brain tubulin *in vitro* at a rate of 0.4 h⁻¹, comparable with that of the full-length human enzyme, and retains the enhancement in activity observed with microtubules for the full-length TAT (Fig. 1A) (3). This construct produced diffraction-quality co-crystals, with two crystallographically independent copies of the 1:1 protein:ligand com-
The structure of Ac-CoA-bound TAT is shown in Fig. 2A. The two TAT-Ac-CoA complexes in the AU are very similar, with r.m.s.d. between their main-chain atoms of 0.4 Å, comparable with our crystallographic coordinate precision. Packing between the protomers is mediated by hydrogen bonds and van der Waals interactions, burying 1402 Å² of solvent-accessible surface area per protomer (26). Despite the considerable intermolecular buried area in this crystalline form, TAT is a monomer in solution at lower concentrations as demonstrated by AUC (Fig. 2B).

TAT is elongated, with dimensions of 30 × 62 × 30 Å³ (width × height × depth in Fig. 2A), and composed of a curved, five-stranded β-sheet of mixed polarity surrounded by three α-helices and two 3₁₀ helices. The structure resembles a cupped hand with the β-sheet forming the palm and the N-terminal β1-β2 hairpin forming the thumb. The Ac-CoA is cradled in a shallow groove between β7 on one side and α3 and the α3-β8 loop on the other. The β1 and β2 strands complete an extended β-sheet belonging to the neighboring protomer, with β1 participating in the dimerization interface of the TAT noncrystallographic dimer. At the tip of the cupped hand lies a conserved β-hairpin formed of strands β5-β6 and supported by a network of invariant phenylalanine residues; the invariant Phe-183 makes π-stacking interactions with the invariant Phe-183 and van der Waals contacts with conserved Leu-171 and Leu-100 (Fig. 2C). Interestingly, the residues in the C-terminal 3₁₀-2 helix and the preceding β9 form one of the most conserved sequence stretches outside the four GNAT superfamily motifs (supplemental Fig. 1). This structural motif is unique to TAT and not found in other GNAT superfamily members of known structure.

At the N terminus, α1 packs against the core β-sheet on one side and makes a network of hydrophobic interactions with residues in β2 on the other; invariant Phe-11 packs against conserved Phe-3 and Leu-45, and conserved Ile-42 makes van der Waals interactions with Phe-3 (Fig. 2D). Consistent with the importance of these interactions, a 10-residue N-terminal deletion in TAT decreases activity dramatically, and mutation L45A reduces activity by 70% (3) (data not shown). Two stretches of residues on either side of β2 (residues 22–38 and 50–68) lack electron density in this wild-type crystal structure and are presumed disordered. In structures of other GNAT superfamily members, the N-terminal region comprising Motif C claps the Ac-CoA binding site, making stabilizing interactions with the pantothenic acid of the Ac-CoA and the peptide substrate (27).

Mapping sequence conservation of TAT family members onto the crystal structure reveals that core secondary structural elements are conserved, with residues supporting the active site being most conserved (Fig. 2A and supplemental Fig. 1). Despite having only 11% overall sequence identity with GCN5, the TAT core comprising the three-stranded β-sheet (β3, β4, and β7) and helices α2 and α3 shows strong structural equivalences with the corresponding region in GCN5 (28) and other GNAT superfamily members (r.m.s.d. with GCN5 = 3.2 Å over residues 70–180). However, the structural similarity does not extend to the N terminus or the β5-β6 hairpin and C-terminal phenylalanine-rich motif unique to TAT.

**Active Site Architecture and Molecular Determinants of Tubulin Acetylation—Ac-CoA binds in a shallow conserved groove, flanked by residues in Motifs A (β7, α2, and the con-
necting loop) and B (β8, α3, and the connecting loop) (Fig. 3A).

Unlike in other GNAT superfamily member structures (27), the adenine moiety of the CoA is well ordered in our TAT structure. The angle of the glycosidic bond places the nucleobase in an orientation intermediate between canonical anti and syn conformations. The purine base is sandwiched between the guanidinium of invariant Arg-126 and aliphatic side chain of invariant Lys-156. The 3'-phosphate of the adenosyl moiety is held by salt bridges with the side chains of Arg-126 and Lys-163 (Fig. 3A). The pyrophosphate of Ac-CoA is coordinated predominantly by hydrogen bonds with main-chain atoms belonging to the highly conserved Arg/Gln-X-Gly-X-Gly segment of Motif A (supplemental Fig. 1) in the loop preceding α2. The pantoic acid moiety is cradled in a shallow pocket lined by the side chains of invariant phenylalanines: Phe-118, Phe-157, and Phe-160. Invariant Ser-154 of Motif B hydrogen-bonds to the carbonyl of the amide linking the β-alanine and β-mercaptopropanoic acid moieties of Ac-CoA. Finally, the carbonyl of the acetyl group itself hydrogen-bonds to the main-chain amide of Phe-157 (Fig. 3A). Consistent with this, their mutation reduces activity drastically (D117A has 3% of wild-type activity, whereas D151A has 1%). Further analysis of the structure suggests additional residues that might be important for substrate recognition: Arg-152 that forms a salt bridge with Asp-151 as well as His-70 and Lys-96 that lie further away from the acetyl group at the edge of a shallow conserved canyon that could accommodate the tubulin loop.

Crystal Structure of an Inactive Mutant Reveals Extraordinary Plasticity of the TAT N Terminus—While investigating the contribution of residues proximal to the Ac-CoA binding site, we discovered that the inactive D117A mutant (Fig. 3B) is a constitutive dimer in solution (Fig. 4). To understand the basis for this oligomerization, we determined its crystal structure at 2.45 Å resolution (see “Experimental Procedures” and Table 1). Like that of the wild type, the AU of the D117A crystal contains two protomers (Fig. 4A) that are structurally very similar with r.m.s.d. between main-chain atoms of 0.4 Å. The TAT D117A core is structurally similar to that of the wild type (Figs. 2A and 4A) and superimposes with a main-chain r.m.s.d. of 0.4 Å over residues 70–184. Ac-CoA binds as in the wild-type structure. Strikingly, the D117A mutant is domain-swapped, with residues 24–38, which were disordered in the wild-type structure, are clearly seen to wrap around the base of the dimer in an extended structure comprising helix 1a and strand 1a as well as 9 residues with irregular structure (supplemental Fig. 1). Strand 2 is 3 residues shorter than in the wild-type structure and forms only a 3-residue-long backbone hydrogen-bonded network with β1 (Fig. 4A). As a result,
although conserved Ile-42 forms part of the β1-β2 hairpin in the wild-type structure, it is now at the C-terminal end of the irregular polypeptide segment preceding β2 that wraps around the base of the dimer. The network of hydrophobic interactions between residues in β1 and β2 (β’2 in D117A) is similar, with Leu-45 making van der Waals interactions with Phe-3 and Phe-11 (Fig. 2D); however, now the latter residues belong to the other protomer. These residues are now therefore part of the dimerization interface. Interestingly, β2 contains the longest stretch of conserved residues outside the GNAT superfamily Motifs A and B directly involved in Ac-CoA binding and the β5-β6 TAT family-specific β-hairpin and is predicted to be part of Motif C involved in substrate recognition in GNAT family members (13). In D117A, the total buried surface area per protomer is 2610 Å². The increase in buried area by 1200 Å² explains the propensity of this mutant to dimerize in solution (Fig. 4C). Consistent with this destabilization of intramolecular contacts, several other point mutations at the interface between the core β-sheet and the α1-α2 loop (F90A, where Phe-90 makes stabilizing van der Waals contacts with Phe-11, Leu-7, and Pro-12, and K92E, where Lys-92 hydrogen-bonds with the backbone carbonyl of Pro-12) result in various degrees of higher-order oligomerization, whereas a mutation in α1 that is not part of this interface (D6A) does not (Fig. 4D). The F90A and K92E mutants also have drastically reduced activities (Fig. 4E).

**DISCUSSION**

The three-dimensional structure of this unusual acetyltransferase reveals the overall architecture of TAT and identifies active-site residues important for tubulin acetylation. Our structure of an active site mutant that, unlike the wild-type
protein, is a stable, inactive dimer in solution reveals a domain swap and underscores the structural plasticity of the functionally essential TAT N-terminal domain. We identify an intramolecular interface in TAT that is metastable and when destabilized leads to dimer and higher-order oligomer formation and impaired activity.

The structurally plastic region contains Motif C predicted to be important for substrate engagement in GNAT superfamily members. Surprisingly, the structurally equivalent region in GNAT members is α-helical (27, 29), unlike in our structure, where it is a β-strand (β2). In the monomeric state in solution and in the absence of substrate, this region of TAT is most likely structurally labile and able to adopt variable conformations. TAT is quite unusual as an acetyltransferase as it has an extremely low basal activity with tubulin (0.4 h⁻¹), and even after ~8-fold enhancement by the microtubule lattice, its activity is 50 times less than that of GCN5, the prototypical GNAT superfamily member (30). Its low basal activity with tubulin is posttranslationally modified by acetylation on the ε-amino group of a lysine. Biochemistry 24, 473–478

This functional plasticity could be related to the structural plasticity that we have uncovered.

Our work represents a starting point for further crystallographic, biochemical, and genetic studies of members of the TAT family that should aid systematic analyses of the mechanism by which TAT accesses the microtubule lumen and has its activity enhanced by the microtubule. Recent studies show that microtubule deacetylation at the site of axonal injury is essential for the regeneration potential of the axon (32); thus TAT inhibitors are attractive targets for potential applications in neuronal injury repair. Our crystal structure should aid in such future endeavors.

Acknowledgments—We thank the staff at ALS sector 5 for data collection support and N. Ziolkowska for help with molecular biology and protein expression. A. R. M. thanks A. Deaconescu, A. Ferré-D’Amaré, and S. Gottesman for support and critical reading of the manuscript.

REFERENCES

1. Garnham, C. P., and Roll-Mecak, A. (2012) The chemical complexity of cellular microtubules: tubulin post-translational modification enzymes and their roles in tuning microtubule functions. Cytoskeleton 69, 442–463

2. Wloga, D., and Gaertig, J. (2010) Post-translational modifications of microtubules. J. Cell Sci. 123, 3447–3455

3. Shida, T., Cueva, J. G., Xu, Z., Goodman, M. B., and Nachury, M. V. (2010) The major α-tubulin K40 acetyltransferase αTAT1 promotes rapid ciliogenesis and efficient mechanosensation. Proc. Natl. Acad. Sci. U.S.A. 107, 21517–21522

4. Akella, J. S., Wloga, D., Kim, J., Starostina, N. G., Lyons-Abbott, S., Morrissette, N. S., Dougan, S. T., Kirepos, E. T., and Gaertig, J. (2010) MEC-17 is an α-tubulin acetyltransferase. Nature 467, 218–222

5. L’Hernault, S. W., and Rosenbaum, J. L. (1983) Chlamydomonas α-tubulin is posttranslationally modified in the flagella during flagellar assembly. J. Cell Biol. 97, 258–263

6. Gaertig, J., Cruz, M. A., Bowen, J., Gu, L., Pennock, D. G., and Gorovsky, M. A. (1995) Acetylation of lysine 40 in α-tubulin is not essential in Tetrahymena thermophila. J. Cell Biol. 129, 1301–1310

7. Hammond, J. W., Huang, C. F., Kaech, S., Jacobson, C., Banker, G., and Verhey, K. J. (2010) Posttranslational modifications of tubulin and the polarized transport of kinesin-1 in neurons. Mol. Biol. Cell 21, 572–583

8. Reed, N. A., Cai, D., Blasius, T. L., Jih, G. T., Meyhofer, E., Gaertig, J., and Verhey, K. J. (2006) Microtubule acetylation promotes kinesin-1 binding and transport. Curr. Biol. 16, 2166–2172

9. Santander, V. S., Bisig, C. G., Puro, S. A., Casale, C. H., Arce, C. A., and Barra, H. S. (2006) Tubulin must be acetylated in order to form a complex with membrane Na⁺,K⁺-ATPase and to inhibit its enzyme activity. Mol. Cell. Biochem. 291, 167–174

10. Friedmann, D. R., Webster, B. M., Mastronarde, D. N., Verhey, K. J., and Voeltz, G. K. (2010) ER sliding dynamics and ER-mitochondrial contacts occur on acetylated microtubules. J. Cell Biol. 190, 363–375

11. Piperno, G., and Fuller, M. T. (1985) Monoclonal antibodies specific for an acetylated form of α-tubulin recognize the antigen in cilia and flagella from a variety of organisms. J. Cell Biol. 101, 2085–2094

12. L’Hernault, S. W., and Rosenbaum, J. L. (1985) Chlamydomonas α-tubulin is posttranslationally modified by acetylation on the ε-amino group of a lysine. Biochemistry 24, 473–478

13. Steczkiewicz, K., Kintch, L., Grishin, N. V., Rychlewski, L., and Ginalska, K. (2006) Eukaryotic domain of unknown function DUF738 belongs to Gcn5-related N-acetyltransferase superfamily. Cell Cycle 5, 2927–2930

14. Neuwald, A. F., and Landsman, D. (1997) Gcn5-related histone N-acetyltransferases belong to a diverse superfamily that includes the yeast SPT10 protein. Trends Biochem. Sci. 22, 154–155

15. LeDizet, M., and Piperno, G. (1987) Identification of an acetylation site of Chlamydomonas α-tubulin. Proc. Natl. Acad. Sci. U.S.A. 84, 5720–5724

16. Nogales, E., Wolf, S. G., and Downing, K. H. (1998) Structure of the αβ tubulin dimer by electron crystallography. Nature 391, 199–203

17. Topalidou, I., Keller, C., Kalebic, N., Nguyen, K. C., Somhegyi, H., Politi, K. A., Heppenstall, P., Hall, D. H., and Challis, M. F. (2012) Genetically separable functions of the MEC-17 tubulin acetyltransferase affect microtubule organization. Curr. Biol. 22, 1057–1065

18. Cueva, J. G., Hsin, J., Huang, K. C., and Goodman, M. B. (2012) Posttranslational acetylation of α-tubulin constrains protofilament number in native microtubules. Curr. Biol. 22, 1066–1074

19. Chen, L., and Rolls, M. M. (2012) Microtubule deacetylation sets the stage for successful axon regeneration. EMBO J. 31, 3033–3035

20. Terwilliger, T. C., and Berendzen, J. (1999) Automated MAD and MIR structure solution. Acta Crystallogr. D Biol. Crystallogr. 55, 849–861

21. Brünger, A. T., Adams, P. D., Clore, G. M., DeLano, W. L., Gros, P., Grosse-Kunstleve, R. W., Jiang, J. S., Kuszewski, J., Nilges, M., Pannu, N. S., Read, R. J., Rice, L. M., Simonson, T., and Warren, G. L. (1998) Crystallography & NMR system: A new software suite for macromolecular structure determination. Acta Crystallogr. D Biol. Crystallogr. 54, 905–921

22. Adams, P. D., Afonine, P. V., Bunkóczi, G., Chen, V. B., Davis, I. W., Echols, N., Headd, J. J., Hung, L. W., Kapral, G. J., Grosse-Kunstleve, R. W., McCoy, A. J., Moriarty, N. W., Oeffner, R., Read, R. J., Richardson, D. C., Richardson, J. S., Terwilliger, T. C., and Zwart, P. H. (2010) PHENIX: a comprehensive Python-based system for macromolecular structure solution. Acta Crystallogr. D Biol. Crystallogr. 66, 213–221

23. McCoy, A. J., Grosse-Kunstleve, R. W., Adams, P. D., Winn, M. D., Storoni, L. C., and Read, R. J. (2007) Phaser crystallographic software. J. Appl. Crystallogr. 40, 658–674

24. Emsley, P., and Cowtan, K. (2004) Coot: model-building tools for molecular graphics. Acta Crystallogr. D Biol. Crystallogr. 60, 2126–2132

25. Szyk, A., Deaconescu, A. M., Pszczek, G., and Roll-Mecak, A. (2011) Tubulin tyrosine ligase structure reveals adaptation of an ancient fold to bind and modify tubulin. Nat. Struct. Mol. Biol. 18, 1250–1258

26. Lee, B., and Richards, F. M. (1971) The interpretation of protein structure: estimation of static accessibility. J. Mol. Biol. 55, 379–400

27. Dyda, F., Klein, D. C., and Hickman, A. B. (2000) Gcn5-related N-acetyl-
transferases: a structural overview. Annu. Rev. Biophys. Biomol. Struct. 29, 81–103

28. Rojas, J. R., Trievel, R. C., Zhou, J., Mo, Y., Li, X., Berger, S. L., Allis, C. D., and Marmorstein, R. (1999) Structure of Tetrahymena GCN5 bound to coenzyme A and a histone H3 peptide. Nature 401, 93–98

29. Trievel, R. C., Rojas, J. R., Sterner, D. E., Venkataramani, R. N., Wang, L., Zhou, J., Allis, C. D., Berger, S. L., and Marmorstein, R. (1999) Crystal structure and mechanism of histone acetylation of the yeast GCN5 transcriptional coactivator. Proc. Natl. Acad. Sci. U.S.A. 96, 8931–8936

30. Berndsen, C. E., and Denu, J. M. (2008) Catalysis and substrate selection by histone/protein lysine acetyltransferases. Curr. Opin. Struct. Biol. 18, 682–689

31. Kolonko, E. M., Albaugh, B. N., Lindner, S. E., Chen, Y., Satyshur, K. A., Arnold, K. M., Kaufman, P. D., Keck, J. L., and Denu, J. M. (2010) Catalytic activation of histone acetyltransferase Rtt109 by a histone chaperone. Proc. Natl. Acad. Sci. U.S.A. 107, 20275–20280

32. Cho, Y., and Cavalli, V. (2012) HDAC5 is a novel injury-regulated tubulin deacetylase controlling axon regeneration. EMBO J. 31, 3063–3078