Expanded Lysine Acetylation Specificity of Gcn5 in Native Complexes*

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In the eukaryotic nucleus DNA is packaged by histones into nucleosomes, the repeating subunits of chromatin. The nucleosome core particle contains about 146 base pairs of DNA and two of each of the histones H2A, H2B, H3, and H4. Packaging of DNA into chromatin suppresses transcription, at least in part by occluding the binding of transcriptional activators and basal transcription machinery to their cognate DNA sites (1, 2) and by blocking transcriptional elongation (3). A number of chromatin remodeling activities have been isolated that assist activators to bind to their sites by promoting a localized alteration in chromatin structure (4).

In addition to these activities, post-translational modifications of the core histones within the nucleosome have also been linked to the transcriptional capacity of chromatin (5, 6). The acetylation of the highly conserved lysine residues within the amino-terminal domains of all four core histones has been extensively studied (7). Histone acetylation has been associated with the interaction of non-histone proteins with histones (8, 9), histone deposition and nucleosome assembly (10), higher order packing of chromatin (11, 12), and the transcriptional activity of cellular chromatin (5, 13). Correlations between transcription and acetylation are reinforced by studies demonstrating that at least some active chromosomal domains are hyperacetylated (14), while inactive or heterochromatin domains are associated with hypoacetylated histones (15–18). However these general correlations do not hold true when specific acetylated H4 isoforms are monitored indicating that particular patterns of lysine acetylation rather than bulk acetylation is of functional importance (15, 19, 20). Therefore, an important goal in studying this phenomenon has been the isolation of native activities that generate such specific patterns of acetylation.

The steady state level of acetylation of histones is a balance between the action of histone acetyltransferases (HATs) and histone deacetylases. These activities are often found to be associated with large multisubunit protein complexes and contain known regulators of transcription (21). A number of previously characterized transcriptional coactivators have also been shown to possess HAT activity, providing a direct molecular link between histone acetylation and gene activation (22, 23). In the budding yeast Saccharomyces cerevisiae, the coactivator/adaptor protein Gcn5 is involved in the regulation of various genes (24–28). Gcn5 requires acetyltransferase function for both promoter-directed histone acetylation and Gcn5-mediated transcriptional activation in vivo (29, 30). In vitro, recombinant Gcn5 has been shown to efficiently acetylate free histones and not nucleosomal histone substrates (31), but see also Ref. 32. However, the association of Gcn5 with other proteins in large multisubunit complexes in yeast potentiates its nucleosomal acetyltransferase activity (33–36).

The 1.8-MDa SAGA complex is a Gcn5-dependent HAT activity, which contains at least three distinct groups of gene products (23, 33). The first of these are the Ada proteins Gcn5 (Ada4), Ada1, Ada2, Ada3, and Ada5 (Spt20), isolated as proteins that interact functionally with the transcription factor Gcn4 and the activation domain derived from the herpes simplex virus activator VP16. The second group comprises all members of the TBP-related set of Spt proteins, Spt3, Spt7, Spt8, and Spt20 (Ada5), except TBP (Spt15), which were isolated as suppressors of transcription initiation defects caused by promoter insertions of the transposable element Ty. The third group within SAGA includes a subset of TBP-associated proteins in multiple yeast transcriptional regulatory complexes. The ability of Gcn5 to acetylate nucleosomal histones is significantly reduced relative to its activity on free histones, where it predominantly modifies histone H3 at lysine 14. However, the association of Gcn5 in multisubunit complexes potentiates its nucleosomal histone acetyltransferase activity. Here, we show that the association of Gcn5 with other proteins in two native yeast complexes, Ada and SAGA (Spt-Ada-Gcn5-acyetyltransferase), directly confers upon Gcn5 the ability to acetylate an expanded set of lysines on H3. Furthermore Ada and SAGA have overlapping, yet distinct, patterns of acetylation, suggesting that the association of specific subunits determines site specificity.

The coactivator/adaptor protein Gcn5 is a conserved histone acetyltransferase, which functions as the catalytic subunit in multiple yeast transcriptional regulatory complexes. The ability of Gcn5 to acetylate nucleosomal histones is significantly reduced relative to its activity on free histones, where it predominantly modifies histone H3 at lysine 14. However, the association of Gcn5 in multisubunit complexes potentiates its nucleosomal histone acetyltransferase activity. Here, we show that the association of Gcn5 with other proteins in two native yeast complexes, Ada and SAGA (Spt-Ada-Gcn5-acyetyltransferase), directly confers upon Gcn5 the ability to acetylate an expanded set of lysines on H3. Furthermore Ada and SAGA have overlapping, yet distinct, patterns of acetylation, suggesting that the association of specific subunits determines site specificity.

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factors, TAF$_{1}$$\gamma$s, including TAF$_{1}$, TAF$_{1}$, TAF$_{1}$, TAF$_{1}$, TAF$_{25}$/23, and TAF$_{1}$/20/17 (37).

A second Gen5-dependent HAT activity, which we named Ada, has been isolated as a 0.8-MDa multisubunit complex containing the Ada proteins Gen5, Ada2, and Ada3. However, the Ada complex does not contain the other Ada proteins or the Spt or TAF$_{1}$ proteins found in SAGA (33). Gen5 also functions in additional multisubunit HAT complexes in yeast (27, 35). In vitro and in vivo studies indicate that both the SAGA and Ada complexes can promote acetyl coenzyme A (acetyl-CoA)-dependent transcriptional activation from nucleosomal templates (29, 30, 38).

Initial studies using recombinant Gen5 indicated that it displays a nonrandom specificity for acetylation of lysines, predominantly acetylating histone H3 at lysine 14 (31). In vivo, acetylation of H3 can occur at lysines 9, 14, 18, and 23. Since acetylation of lysine 9 of H3 is associated with histone deposition, it has been suggested that acetylation of other sites may be associated with transcription (10, 31). In this study we have investigated the histone H3 lysine acetylation specificity of the native Gen5-dependent HAT complexes Ada and SAGA in comparison with recombinant Gen5 (rGen5). We used a combination of Western blotting, peptide assays, and microsequencing analysis to determine the sites of acetylation for the Gen5-dependent Ada and SAGA complexes. We show that while rGen5 acetylates only lysine 14, purified Ada complex acetylates both lysines 14 and 18, and SAGA acetylates to some extent all four lysines in H3. Using mutant variants of Gen5, we show that this acetylation pattern is dependent on Gen5 function and not other putative HAT activities within these complexes. These results indicate that the association of Gen5 with different proteins in multisubunit complexes endows upon it an expanded substrate specificity.

**Experimental Procedures**

Yeast Strains and Purification of rGen5, SAGA, and Ada Complexes—Yeast Gen5 was expressed in bacteria as a fusion protein with six histidine residues at the amino terminus and purified under denaturing conditions on Ni$^{2+}$-NTA-agarose (39). SAGA and Ada complexes were purified from the yeast strain CY396 (40). The yeast strain PSYS316 and its derivative PSYS316$	ext{gcn5}$ used for transformation of the GCN5 HAT domain mutants LKN and KQL are described (29).

SAGA and Ada complexes were purified using a scheme adapted from (33). Elution of SAGA and Ada from each column was monitored by HAT assays and immunoblotting. Briefly, whole cell extracts were prepared from 20 liters of the yeast strain CY396 grown to mid-log phase. The extract was then batchwise with 20 ml of Ni$^{2+}$-NTA-agarose (Qiagen). The resin was then washed in a column with 20 ml imidazole, followed by elution of the bound proteins with 300 ml imidazole. The Ni$^{2+}$-NTA-agarose column eluate was directly loaded onto a Mono Q HR 5/5 column (Amersham Pharmacia Biotech). Bound proteins were eluted with a 25-ml linear gradient from 100 to 500 mM NaCl. Peak SAGA and Ada fractions from the Mono Q column were individually pooled and diluted to 100 mM NaCl and loaded onto a Mono S HR 5/5 column (Amersham Pharmacia Biotech). For each complex, bound proteins were eluted with a 25-ml linear gradient from 100 to 500 mM NaCl. Peak fractions were diluted to 100 mM NaCl and loaded directly onto a 0.8-ml histone-agarose column (Sigma). Bound proteins were eluted with a 5-ml linear gradient from 100 mM to 1 M NaCl. Peak fractions were concentrated down to 0.7 ml using Centriprep-30 (Millipore).

HAT Assays and Western Blotting—HAT assays were performed as described previously (33). In Fig. 1, HAT assays were scaled up 3-fold and performed with HeLa free core histones or nucleosomes in the presence or absence of [H]acetyl-CoA. Following incubation, each reaction was divided into three and the histones electrophoresed through 15% SDS-polyacrylamide gels. One gel was processed for fluorography and the other two processed for immunoblotting, as described (41).

**Peptide Synthesis and Assays—** A wild type peptide spanning the NH$_{2}$-terminal amino acids 5–28 of human histone H3 and derivatives containing either no or single non-acetylated lysines available at amino acids positions 9, 14, 18, or 23 were generated (Alta Bioscience, University of Birmingham, United Kingdom). The sequence of the wild type peptide is as follows: QTAKGSTGGKAPKQLATRAARSC (the positions of lysine residues are indicated in boldface letters). The mutant versions of this peptide, depicted in Fig. 3, were generated by substituting acetyl-lysine at certain positions. Assays were performed using 300 ng of peptides and roughly equivalent activities of purified rGen5, purified Ada, or SAGA complexes. HAT reactions were incubated for 40 min at 30 °C and processed for blotting.

**Microsequencing—** HAT assays were performed in the presence of 5 μCi of [H]acetyl-CoA and mutant variants of purified Ada and SAGA complexes. Reactions were incubated for 40 min at 30 °C and then subjected to SDS-PAGE on a 10% gel, transferred to nitrocellulose, and processed for blotting.

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Vettese-Dadey et al. (41). Histone H3 was excised from the membrane and sequenced as described (42).

RESULTS

The Gcn5-dependent SAGA and Ada HAT Complexes Show Expanded H3 Lysine Specificity—It has been reported previously that rGcn5 predominantly acetylates histone H3 at lysine 14 (Lys-14), when free histones are presented as a substrate (31). We investigated the lysine specificity of purified native Gcn5-dependent Ada and SAGA HAT complexes in comparison with that of rGcn5. Either free histones or nucleosomes were incubated, in vitro, together with rGcn5, Ada, or SAGA complexes in the presence or absence of acetyl-CoA. These reactions were assayed by SDS-PAGE and fluorography and by Western blotting, using antisera which recognize specific acetylated forms of histone H3 (43, 44). Consistent with previous experiments (33) we found that all three activities acetylated free histones, but that only native complexes were able to efficiently acetylate nucleosomal histones under the same conditions (Fig. 1, A and B). Using an antiserum specific for histone H3 acetylated at Lys-14, we found that rGcn5 and both native HAT complexes efficiently acetylated this site on free histone substrates, in an acetyl-CoA-dependent fashion. However, using an antiserum that recognizes H3 acetylated at either lysine 9 or 18, we found that unlike rGcn5, the native Ada and SAGA complexes are able to acetylate either or both of these sites (Fig. 1A). When using nucleosomal histones as a substrate, we found the same pattern of site specificity in that H3 modified by the Ada and SAGA activities is recognized by the anti-H3.Ac14 and H3.Ac9/18 antisera (Fig. 1B).

Ada and SAGA Are Bona Fide Gcn5-dependent HAT Activities—These results indicate that when Gcn5 is associated with other proteins in a HAT complex, it acquires an expanded substrate specificity. We have shown, using a combination of purified activities from gcn5Δ yeast strains in HAT assays or activity gel assays, that Gcn5 is most likely the only or at least predominant catalytic subunit of the Ada and SAGA complexes (33). However it remains formally possible that the expanded repertoire for site specificity of these complexes is due to an additional unidentified catalytic subunit. To further address this issue we assayed purified Ada and SAGA complexes from a wild type or deleted gcn5 strain or yeast strains carrying point mutations within Gcn5. The KQL mutant Gcn5 has been demonstrated to be defective in HAT activity and transcriptional activation, while the LKN mutant maintains the catalytic activity and transcriptional potential of Gcn5 (29).

Ada and SAGA activities from a Superose 6 gel filtration column were incubated in HAT reactions or assayed by Western blotting using antisera against the Gcn5 or Ada2 components of these complexes. Both the anti-H3.Ac14 and H3.Ac9/18 antisera (Fig. 1B).

FIG. 2. The Ada and SAGA complexes are dependent on Gcn5 for HAT activity. A, Ada complexes were partially purified from wild type (WT) and gcn5Δ yeast strains or yeast strains carrying a mutation within Gcn5 which do (KQL) or do not (LKN) affect HAT activity. Fluorograms from nucleosomal HAT assays and Western blots performed using anti-Gcn5 or anti-Ada2 antisera, using fractions from the final Superose 6 column, are shown. The migratory positions of histones are indicated. B, HAT assays and Western blotting using partially purified SAGA fractions are shown, as described above.

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both the Ada and SAGA complexes is solely dependent on Gcn5 function.

The SAGA and Ada HAT Complexes Show Distinct Patterns of H3 Lysine Acetylation—The data presented in Fig. 1 indicate that both the Ada and SAGA complexes acetylate lysines other than Lys-14 on histone H3. We wanted to further investigate the specificity of these complexes. Therefore, we generated a set of peptides that spanned the H3 amino terminus. The wild type peptide carries non-acetylated lysines at all four positions (Lys-9, Lys-14, Lys-18, Lys-23), while derivatives of this peptide were either acetylated at all four lysines or retained only single non-acetylated lysines at positions Lys-9, Lys-14, Lys-18, or Lys-23 (Fig. 3A). These peptides were used as substrates in HAT reactions to determine the lysine specificity of the distinct purified HAT complexes. We found that rGcn5 was able to efficiently acetylate only the wild type peptide or the peptide with a non-acetylated Lys-14 (Fig. 3B), consistent with the results of Kuo et al. (31). However, the Ada and SAGA complexes were able also to acetylate both the Lys-14 and the Lys-18 peptide, indicating an expanded lysine specificity over rGcn5. In addition SAGA was able to acetylate the Lys-9 and Lys-23 peptides, albeit to a lesser extent (Fig. 3B). This suggests that the histone acetylation specificity of Gcn5 is dependent on the context of associated factors in a given complex.

Native HAT Complexes Generate Distinct Patterns of Nucleosomal H3 Acetylation—Collectively the data presented above indicate that the two Gcn5-dependent HAT complexes, Ada and SAGA, and rGcn5 show partially overlapping yet distinct patterns of lysine acetylation in the H3 amino terminus. Both of these native HAT complexes most likely modify nucleosomal histones in the nucleus. Consistent with this notion rGcn5 is able to efficiently acetylate only free histones, while the Ada and SAGA complexes can also acetylate nucleosomal histones (Fig. 1B). To rigorously identify the lysine(s) acetylated by each of these native complexes we subjected in vitro labeled nucleosomal histone H3 to microsequence analysis followed by direct determination of radioactivity at each position in the H3 sequence. The results demonstrate that the Ada complex acetylates both Lys-14 and Lys-18 (Fig. 4A), while SAGA acetylates all four lysines to varying extents (Fig. 4B). These data obtained from the microsequence analysis are in good agreement with the results obtained from the Western blotting (Fig. 1) and peptide assays (Fig. 3).

**DISCUSSION**

The transcriptional adaptor Gcn5 was originally demonstrated to be a histone acetyltransferase with a non-random pattern of acetylation, predominantly modifying H3 at Lys-14 in vitro (31). Very recently, rGcn5 has also been shown to monoacetylate nucleosomal H3 at lysine 14, albeit less efficiently than free histones, using optimum NaCl or MgCl2 concentrations (32). However, the association of Gcn5 in high molecular weight multiprotein complexes potentiates its nucleosomal histone acetyltransferase activity (33–36). In addition, we have shown in this study that this association also directly endows upon Gcn5 an expanded lysine specificity. The
HAT complexes, including Ada, and SAGA can promote tran-
lysines acetylated by Gcn5.
unique to each complex are likely to determine the target
ping, yet distinct patterns of nucleosomal acetylation, which
individual Gcn5-containing complexes may generate overlap-
transcriptional regulation (23). It is therefore possible that
dependent HAT complexes may serve distinct roles in yeast
35). These findings have suggested that these multiple Gcn5-
associated in other apparently distinct HAT complexes (27, 34,
terns of acetylation on histone H3 from nucleosomes.
indicated.
amino acid detected for that cycle. Potential acetylation sites are
sequence. The counts/min (cpm) for each cycle are plotted against the
purified Ada (A) or SAGA complexes (B). Radiolabeled histone H3 was
subsequently purified and subjected to microsequence analysis followed by
direct determination of radioactivity at each position in the H3
sequence. The counts/min (cpm) for each cycle are plotted against the
histone H3 peptide substrates and on nucleo-
osomal H3. These results indicate that Gcn5 generates a context-
dependent acetylation pattern as a consequence of its
association with other factors. The Ada and SAGA complexes
share at least a few common components, namely Gcn5, Ada2,
and Ada3. However the SAGA complex is distinguished from
the Ada complex by the fact that it additionally contains Spt
proteins (33) and a subset of TAF11 proteins (37). Gcn5 is also
associated in other apparently distinct HAT complexes (27, 34,
35). These findings have suggested that these multiple Gcn5-
dependent HAT complexes may serve distinct roles in yeast
transcriptional regulation (23). It is therefore possible that
individual Gcn5-containing complexes may generate overlapping
yet distinct patterns of nucleosomal acetylation, which
may signal a specific function. In this scenario, the components
unique to each complex are likely to determine the target
lysines acetylated by Gcn5.
We have recently demonstrated that purified native yeast
HAT complexes, including Ada, and SAGA can promote trans-
scription in an acetyl-CoA-dependent fashion in vitro (38, 45).

These results are reinforced by additional in vitro and in vivo
data demonstrating a requirement for Gcn5-directed HAT
activity for promoter acetylation and transcriptional activation
(29, 30). Since Gcn5 is a transcriptional adaptor protein, it was
originally inferred that the modification of Lys-14 by rGcn5
represents a transcription linked acetylation pattern, distinct
from the predominant mapped deposition-related acetylation
site of Lys-9 in yeast (31, 46). However, our data suggest that
the SAGA complex acetylates all four lysines including Lys-9,
thereby linking lysines other than Lys-14 in transcriptional
activation. We demonstrate that Gcn5 contained in native type
A HAT complexes can generate acetylation patterns on H3 at
least, which overlap with those generated by type B histone
acetyltransferases for histone deposition and chromatin assem-
ably (10). Therefore, transcription-linked acetylation does not
simply involve acetylation of Lys-14 on H3, but may encompass
a variety of lysine modifications. However, a common theme
between both native HAT Gcn5 complexes and rGcn5 used in
this study is the acetylation of Lys-14. This may indicate a
pivotal role for this lysine in the Gcn5-dependent regulation of
transcription.

A recent study examined the function of histone acetylation
in vivo by mutation of target lysines in yeast strains with and
without a functional GCN5 gene. The authors found that Gcn5
was required for full levels of acetylation at multiple sites in H3
and H4 in vivo (47). In particular Gcn5 is directly or indirectly
required for acetylation of H3 Lys-9 and H3 Lys-18 in vivo,
while mutation of Lys-14 in gcn5 cells conferred a strong
synthetic growth defect. Our results provide a direct molecular
explanation for these observations, in that native Gcn5-con-
taining HAT complexes, such as SAGA and Ada, can acetylate
multiple H3 lysines. The Gcn5-dependent acetylation events
are important for normal progression of the cell cycle and for
transcriptional activation (29, 47). Furthermore, a critical level
of histone acetylation is essential for cell viability (47).
Interestingly a study by Thompson et al. (48) has shown that histone
H3 is required for full repression at yeast telomeres and silent
mating loci and that the acetylatable lysines of H3 play an
important role in silencing. While single-site mutations at H3
lysines 9 or 14 had little effect on telomeric repression, substi-
tution of 3 or 4 lysines simultaneously resulted in strong telo-
meric derepression. This result suggested that a number of
modified lysines in H3 may be required for derepression (48).
Our results suggest that such a function could be provided by
expanded lysine specificity of Gcn5 contained within native
HAT complexes.

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