Structure of a Sir2 Substrate, Alba, Reveals a Mechanism for Deacetylation-induced Enhancement of DNA Binding

Received for publication, April 8, 2003, and in revised form, April 24, 2003
Published, JBC Papers in Press, May 1, 2003, DOI 10.1074/jbc.M303666200

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The targeted acetylation status of histones and several other transcriptional regulatory proteins plays an important role in gene expression, although the mechanism for this is not well understood. As a model to understand how targeted acetylation may effect transcription, we determined the x-ray crystal structure of the chromatin protein Alba from Archaeoglobus fulgidus, a substrate for the Sir2 protein that deacetylates it at lysine 11 to promote DNA binding by Alba. The structure reveals a dimer of dimers in which the dimer-dimer interface is stabilized by several conserved hydrophobic residues as well as the lysine 11 target of Sir2. We show that, in solution, the mutation of these hydrophobic residues or lysine 11 disrupts dimer-dimer formation and decreases DNA-binding affinity. We propose that the interface is stabilized by several conserved hydrophobic residues as well as the lysine 11 substrate for acetylation. Correlating contacts that involve several conserved hydrophobic residues as well as the lysine 11 substrate for acetylation. Correlating contacts that involve several conserved hydrophobic residues as well as the lysine 11 substrate for acetylation. The histone tails play a very dynamic role in gene regulation by serving as sites of transcriptional events, although the mechanism by which targeted acetylation modulates gene expression is discussed.

The histone protein building blocks that package DNA into chromatin play key roles in gene regulation. An octameric core of histone proteins containing two copies each of histones H2A, H2B, H3, and H4, together with ~146 base pairs of DNA wrapped around these proteins, make up a nucleosome particle (1). These nucleosome particles form the higher order chromatin structure that is the scaffold from which gene regulation must occur. The histone proteins themselves each contain a globular, highly helical core region that forms the interior of the nucleosome particle and a highly conserved and considerably more flexible N-terminal tail region. The histone tails play a very dynamic role in gene regulation by serving as sites of targeted and extensive post-translation modification, including acetylation, phosphorylation, and methylation (2, 3). These histone modifications also appear to be binding sites for other protein domains (3). It appears that a specific histone modification or constellation of modifications leads to distinct transcriptional events (4–6), although the mechanism by which this occurs is still poorly understood.

Histone H3 methylation at lysine 9 forms one example of how a histone modification can lead to a downstream transcriptional regulatory event. The methylation is carried out, at least in part, by the Su(var)3-9 protein, and the methylated lysine specifically recruits heterochromatin protein 1 (HP1) through its chromodomain to silence transcription from heterochromatic DNA (7–9). The mechanism by which other histone modifications, including histone acetylation, modulate transcription is less well understood. Surprisingly, many proteins initially identified as histone deacetylases, such as p300/CBP and PCAF, have also been shown to acetylate non-histone transcription factors, including many transcriptional activators, to promote gene activation (10). In addition, histone deacetylases (HDACs) of the Sir2 family have been shown to deacetylate non-histone transcription factors such as the p53 tumor suppressor protein (11, 12). Moreover, a Sir2 homologue from the archaea Sulfolobus solfataricus has been reported to deacetylate a chromatin, non-sequence-specific DNA-binding protein called Alba (formally known as Sso10b) to promote Alba/DNA association and transcriptional repression (13). These additional acetylation and deacetylation substrates provide convenient models for understanding the mechanism of acetylation-dependent modulation of protein activity.

For several reasons, the archaeal Alba protein provides a particularly interesting model for understanding how the acetylation status of eukaryotic histones may affect its biological activity. Like the eukaryotic histones, Alba binds DNA nonspecifically, is acetylated in its N-terminal terminus to affect its DNA binding and transcriptional regulatory properties, and also forms higher order structures to bind DNA (14–16). Interestingly, Alba homologues are also found in eukaryotes (16), although their greater sequence divergence than that of the archaeal proteins suggests that they may have evolved a new function in eukaryotes.

To understand the mechanistic basis for how the acetylation status of Alba may affect its DNA binding properties, we have determined the high resolution crystal structure of Alba from the archaea Archaeoglobus fulgidus (Af-Alba) and have carried out a series of functional studies for correlation with our structural findings. We find that Af-Alba forms a dimeric structure that is similar to the dimeric Alba from the archaea Sulfolobus solfataricus (15). More interestingly, both crystal forms of Af-Alba characterized in this study show homologous dimer-dimer contacts that involve several conserved hydrophobic residues as well as the lysine 11 substrate for acetylation. Correlating with the importance of this dimer-dimer interface for DNA binding by Af-Alba and acetyl-lysine regulation, cross-linking...
studies reveal the presence of tetrameric forms of Af-Alba, and mutations of lysine 11 or other hydrophobic residues at the dimer-dimer interface reduce tetramer formation and DNA binding activity by Af-Alba. The implications of these studies for understanding how the acetylation status of euchromatic histones may affect its biological function are discussed.

MATERIALS AND METHODS

Protein Expression and Purification—The full-length Alba gene from A. fulgidus (Af-Alba) was PCR amplified from A. fulgidus genomic DNA and cloned into the pGEX4T-1 vector to express the N-terminal glutathione S-transferase (GST) fusion protein. The plasmid was transformed into the Escherichia coli BL21 (DE3) strain, grown at 37 °C to an absorbance of 0.5–0.7 at 590 nm, and induced at 30 °C for 3–4 h by adding 0.5 mM isopropyl-β-D-thiogalactopyranoside (IPTG). For protein purification, a cell pellet from a 3-liter growth culture was suspended and sonicated in a solution containing 20 mM Hepes, pH 7.5, 200 mM NaCl, 10 mM dithiothreitol, and 1 mM PMSF (buffer A). The supernatant was mixed with about 3 ml of glutathione resin for 2 h at 4 °C, then bound to the column and treated with thrombin protease at 4 °C. The intact Af-Alba protein containing three additional N-terminal residues was eluted and concentrated with a Sephadex G-200 column volume buffer A with a reservoir solution containing 30% polyethylene glycol (PEG) 400, 15% isopropanol, 50 mM sodium cacodylate, pH 6.0, 100 mM KCl, and 25 mM MgCl₂, and equilibrating over 0.5 ml of reservoir solution. The I2,2,1 crystalline form was obtained by mixing 6 mg/ml protein, 1:1 μl, with a reservoir solution containing 15% isopropanol, 50 mM sodium cacodylate, pH 6.0, 100 mM KCl, and 25 mM MgCl₂ and equilibrating over 0.5 ml of reservoir solution. The I2,2,1 crystalline form was obtained by mixing 6 mg/ml protein, 1:1 μl, with a reservoir solution containing 30% polyethylene glycol (PEG) 400, 100 mM Tris-HCl, pH 8.5, and 200 mM sodium citrate. Both crystal forms grew to a typical size of 100 × 100 × 30 μm over 6 days. The P4,2,2 and I2,2,1 crystalline forms were transferred to a reservoir solution supplemented with 15% 2-methyl-2,4-pentanediol (MPD) and 40% polyethylene glycol 400 cryoprotecting reagent, respectively, prior to flash freezing and storage in liquid propane prior to data collection. Native data from both crystal forms and a three-wavelength (peak, inflection, and remote) multiwavelength anomalous diffraction (MAD) data set from selenomethionine-derivatized P4,2,2 crystals were collected on beamline BM19B at the Advanced Photon Source using an ADSC Quantum-4 CCD detector at 100 K. All data were processed with the HKL-2000 suite (HKL Research Inc.). Data collection statistics are presented in Table I. Four selenium sites were identified in the P4,2,2 crystal form using CNS (19) and SOLVE (20) and confirmed with cross-difference Fourier maps. Those sites were further refined by CNS and SOLVE. The map was improved by solvent flattening with the program RESOLVE (20), and the program O (21) was used to build residues 4–89 of the protein using the selenomethionine sites as guides. Refinement was carried out using simulated annealing (22) and torsion angle dynamic (23) refinement protocols in CNS with iterative manual adjustments of the model using the program O with reference to 2Fobs – F and Fobs – F electron density maps. At 2.65 Å resolution, a bulk solvent correction (24) was applied to the data, individual atomic B-factors were adjusted, and solvent molecules were modeled into the structure.

| Data | P4,2,2 | P4,2,2 | P4,2,2 | Native space groups |
|------|--------|--------|--------|---------------------|
| Cell parameters | | | | |
| a (Å) | 86.58 | 86.59 | 86.59 | 86.59 |
| b (Å) | 86.58 | 86.59 | 86.59 | 86.59 |
| c (Å) | 81.33 | 81.56 | 81.56 | 81.56 |
| Resolution (Å) | 30–2.8 | 30–2.8 | 30–2.8 | 20–2.65 |
| Unique reflection | 14532 | 14556 | 14564 | 9156 |
| Completeness (%) | 100 (100) | 100 (100) | 100 (100) | 98.6 (97.7) |
| Multiplicity | 11.3 | 11.3 | 11.0 | 6.8 |
| I/σ(I) | 32.6 (11.7) | 34.4 (13.2) | 27.8 (8.3) | 21.8 (6.0) |
| Rmerge (%)* | 8.6 (25.7) | 8.4 (23.3) | 10.4 (33.4) | 8.4 (28.5) |
| Phasing (SOLVE) | | | | |
| FOM | 0.43 | 0.237 | 0.226 | 0.43 |
| Z-score | 20.43 | 0.265 | 0.256 | 20.43 |
| Refinement statistics | | | | |
| Resolution (Å) | | | | |
| Rfree, (%) | 20–2.65 | 20–2.0 | 20–2.0 | 20–2.0 |
| Rmerge, (%)* | 0.265 | 0.256 | 0.256 | 0.266 |
| Number of atoms | 671 | 1342 | 1342 | 1342 |
| Protein | 85 | 164 | 164 | 164 |
| Water | 45.2 | 27.4 | 27.4 | 27.4 |
| R.m.s.d. | 46.2 | 52.9 | 52.9 | 52.9 |
| Bond length (Å) | 0.098 | 0.012 | 0.012 | 0.012 |
| Bond angle (°) | 1.3 | 1.7 | 1.7 | 1.7 |

*Values in parentheses are from the highest resolution shell.

1Rmerge = Σ|Fobs| − |Fcalc|/Σ|Fobs|,

2Rmerge = Σ|Fobs| − |Fcalc|/Σ|Fobs| (where T is a test data set of 10% of the total reflections randomly chosen and set aside prior to refinement).
with different concentrations of protein in a solution containing 20 mM mutant Af-Alba proteins, 250 ng of pRSET plasmid DNA was mixed in a gradient SDS-PAGE gel. For gel retardation assays with the native and c dimer (×), and tetramer (×) in the crystals.

Overall Structure of A. fulgidus Alba—The Af-Alba protein monomer adopts an elongated shape with dimensions of roughly 23 × 26 × 50 Å with a topology of β1-α1:β2-α2-β3-β4 with each successive secondary structural element running in opposite directions roughly parallel to the long dimension of the molecule (Fig 1a). The β3 and β4 strands are particularly long, extending almost the entire length of the molecule. Both the P4,2,2 and I2,2,2 crystal forms reveal a 2-fold symmetric Af-Alba dimer burying about 1500 Å² of solvent-excluded surface in which the molecules interact side-by-side along the long dimension of the monomer and with the 2-fold axis aligned perpendicular to the long dimension of dimer (Fig 1b). Residues from the α2 helix and β3 and β4 strands mediate all of the dimer contacts (Fig 2a). Not surprisingly, the dimers in both crystal forms reported here are essentially superimposable, with an r.m.s.d. of 1.3 Å for Co atoms, and they are also very similar to two different crystal forms of a previously reported Alba dimer from the archaea S. solfatarius (15) with an r.m.s.d. of 3.8 and 3.7 Å for the two crystal forms, respectively. Notably, nearly all of the residues involved in dimer interactions are conserved within the Alba proteins, including the Alba homologues from eukaryotic organisms (Fig 3), suggesting that this dimer is a conserved feature of these proteins.

Despite the excellent superposition of the four Alba protein dimers, the tip of the extended β3-β4 hairpin superimposes less well, suggesting that this region of the protein may be inherently more flexible. Interestingly, the high mobility group protein IHF uses a similarly extended β-hairpin to bind DNA (26), suggesting that this region of Alba may be used for DNA binding.

Higher Order Oligomerization of Af-Alba—Interestingly, both crystal forms of Af-Alba show very similar dimer-dimer contacts in the crystal lattice with an r.m.s.d. of 4.3 Å for the Co atoms between both tetramers (Fig 2, b and d). Like the dimerization interaction, the dimer-dimer interactions are 2-fold symmetric and, in this case, the interface is formed primarily by antiparallel interactions between hydrophobic residues in the α1 helices of one subunit of each of the dimers but also involves the C-terminal tip of the α2 helix. In the P4,2,2 crystal form, the dimer-dimer interface is formed by van der Waals interactions between Met14 and Met15 (where the prime designates a residue from the opposing subunit), Leu18 and Leu18′-Leu21′, Phe54 and Phe54′, and an H-bond between Asn25 and Asn15′, with an overall solvent-excluded surface of 4,620 Å² (Fig 2c). The dimer-dimer interface of the I2,2,2 crystal form is somewhat more intimate, with a solvent-excluded surface of 4,665 Å². This dimer-dimer interface shows van der Waals interactions between Leu18, Leu18′-Leu21′, and the aliphatic region of Asn25 and between Phe54 and Phe54′. In addition, this interface shows a direct hydrogen bond between Lys11 (in a loop just N-terminal to the α1 helix) and Glu26′ (Fig 2b). Strikingly similar dimer interfaces are observed in two different crystal lattices of the Alba structures from S. solfatarius (15), although the dimer-dimer interfaces in these structures are more similar to the P4,2,2 crystal form of Af-Alba (Fig 2c). Also significantly, most of the residues mediating dimer-dimer contacts in Af-Alba are conserved among the archaeal proteins (Fig 3). In particular, Phe54, Met14, and Lys13 are strictly conserved, and positions 18 and 21 are invariably hydrophobic. Taken together, these structural features suggested that the dimer-dimer interactions observed in the crystals may be physiologically relevant. Noticeably, the conservation of archaeal residues at the dimer-dimer interface did not extend to the eukaryotic Alba homologues (Fig 3), suggesting that the eukaryotic proteins may not form similar dimer-dimer contacts.

Solution Oligomerization and DNA Binding Properties of Native and Mutant Af-Alba Proteins—To test directly the physiological relevance of the observed dimer-dimer contacts in the crystals, we carried out mutagenesis of residues that were implicated in playing an important role at this interface. We chose to mutate Leu18 and Phe54 because they participated in dimer-dimer contacts in both crystal forms; we also chose to mutate Lys13 because it is the site of deacetylation by the Sir2 protein, and we entertained the possibility that deacetylation of this residue may play a modulatory role in dimer-dimer...
formation. For residues 18 and 54, we chose mutations that would be predicted to be disruptive to the dimer-dimer interface; therefore, we prepared leucine to arginine (L18R) and phenylalanine to arginine (F54R) substitutions at residues 18 and 54, respectively. For lysine 11, we chose both conservative (arginine, K11R) and non-conservative substitutions for mutagenesis (glutamine, K11Q; and methionine, K11M). Modeling studies suggested that each of these mutations would disrupt the Lys\textsuperscript{11}-Glu\textsuperscript{26} hydrogen bond revealed to stabilize the hydrogen bond in the I\textsubscript{2}1\textsubscript{2}1\textsubscript{2}1 crystal form. As a control, we also

**Fig. 2.** Oligomerization contacts in Af-Alba. a, the interface of the Alba dimer showing side chains that participate in dimer contacts. b, the dimer-dimer Alba interface is shown highlighting the side chain residues that stabilize the interface with a color-coded van der Waals surface representation. I\textsubscript{2}1\textsubscript{2}1\textsubscript{2}1 and P\textsubscript{4}3\textsubscript{2}1\textsubscript{2} indicate the tetramer in the two different crystal forms, respectively. The right panels are close-up views of the dimer-dimer interface. c, superposition of the Alba dimer-dimer (tetramer) complex in four different crystal lattices; the two reported here, in space groups P\textsubscript{4}3\textsubscript{2}1\textsubscript{2} (cyan) and I\textsubscript{2}1\textsubscript{2}1\textsubscript{2}1 (green), and the previously reported Alba structures from *S. solfataricus*, 1HOX (red) and 1HOY (yellow) are shown.
prepared an asparagine to alanine substitution at residue 10 (N10A). Residue 10 was located at the border of the dimer-dimer interface; however, it did not appear to play a direct role in dimer formation in either of the two crystal forms of Af-Alba reported here. We therefore expected that the N10A substitution would behave similarly to the native protein in its ability to form dimer-dimer contacts. We prepared proteins containing substitution mutations by site-directed mutagenesis and purified each of the mutants to homogeneity for analysis in vitro.

To determine the oligomerization states that Af-Alba and each of the mutants formed in solution, we subjected each of the proteins to cross-linking with increasing concentrations of the cross-linking reagent EGS. As can be seen from Fig. 4a, the native and N10A control proteins form both dimers and tetramers, and, at higher EGS concentrations, the relative proportions of dimer and tetramer are comparable. Each of the Af-Alba mutants at the dimer-dimer interface also show cross-linked dimers and tetramers; but in contrast to the native protein and the N10A mutant, the amount of cross-linked tetramer is significantly reduced relative to the amount of respective dimer for each of the mutants. In addition, the hydrophobic substitution mutants L18R and F18R also form high order oligomers. Together, the cross-linking data demonstrates that the Af-Alba mutants at the dimer-dimer interface form less stable tetramers than the native protein, consistent with the physiological relevance of the Af-Alba tetramer observed in the crystal lattice.

A prediction from the cross-linking studies is that dimer-dimer Af-Alba contacts play a positive regulatory role in DNA binding by Af-Alba, and, therefore, one would expect that the mutations at the dimer-dimer interface would decrease DNA binding. To test this directly, we assayed the ability of Af-Alba and the mutants to band-shift plasmid DNA in agarose gels. We and others have shown that Alba does not have appreciable binding. To test this indirectly, we assayed the ability of Af-Alba and the mutants to band-shift plasmid DNA in agarose gels. We and others have shown that Alba does not have appreciable binding. To test this indirectly, we assayed the ability of Af-Alba and the mutants to bind DNA only slightly less well (–2-fold) than the native protein, suggesting that asparagine 10 of Af-Alba may be involved in direct DNA contact. Taken together with the structural and cross-linking results, these DNA binding studies imply that dimer-dimer formation in Af-Alba plays a stimulatory role on DNA binding by Af-Alba. Moreover, the structural and solution data supports the proposal that lysine 11 of Alba, the target of deacetylation by the Sir2 protein, plays an important role in modulating this activity. We presume that the slight variability of specific dimer-dimer interactions in the various structures (Fig. 2) and the relatively low solvent-excluded surface at the dimer-dimer interface relative to the monomer-monomer interface may further facilitate acetylation-dependent regulation of Alba oligomerization for DNA binding.

Model for DNA Binding by Alba and Its Regulation by Acetylation—The structural and functional data described above strongly implies that Af-Alba binds DNA as a dimer of dimers. The high conservation of residues at the dimer-dimer interface among other archaeal Alba proteins also implies that all members of the entire family of archaeal Alba proteins share the same feature (Fig. 3). Notably, many of these residues are not conserved within the eukaryotic Alba proteins, suggesting that they do not form similar oligomers for DNA binding (Fig. 3). As noted previously (15), a DALI search using the Alba monomer reveals structural similarity to two other known nucleic acid-binding proteins, translation initiation factor 1 (r.m.s.d. = 2.2 Å) and DNase I (r.m.s.d. = 2.7 Å). The structure of the DNase I in complex with an 8-base pair DNA duplex suggests where Alba may bind DNA. A superposition of the protein from the DNase I/DNA complex with one subunit of the Af-Alba dimer places the DNA on the surface of the protein formed by the β1-α1 and β2-α3 loops as well as the tip of the β3-β4 hairpin (Fig. 5a). This superposition also places the Af-Alba subunit on the minor groove side of the DNA. Consistent with this general mode of DNA binding, this surface of the Alba protein contains the most electropositive charged surface (Fig. 5b), which would nicely complement the electronegative minor groove of the DNA, and the β1-α1 and β2-α3 loops contain two of the most highly conserved sequence patches within the archaeal Alba proteins (Fig. 3). Also consistent with DNA binding in this mode, only a relatively minor reorientation of the DNA helical axis of the model would allow each subunit of the Alba dimer to make symmetric interactions with a B-form DNA duplex (Fig. 5). Taken together, we propose that the Alba dimer binds along the minor groove side of DNA, in contrast to a previous model that places it across the ends of the dimer along the minor groove with the center of the molecule across the DNA major groove (15).
consistent with the slightly greater mutational sensitivity to DNA binding of Lys11 mutations over the Leu18 and Phe54 mutations (Fig. 4c). Lysine 11 may therefore play a dual role in facilitating dimer-dimer contacts as well as direct protein-DNA contacts to enhance Af-Alba affinity for DNA. The importance of lysine 11 in Af-Alba function is consistent with the important regulatory role of the deacetylation of this residue by the Sir2 protein. It is possible that Af-Alba forms even higher order structures on DNA, as suggested by recent studies showing that S. solfataricus Alba saturates plasmid DNA with a stoichiometry of about 10 bp per protein dimer (15), a stoichiometry that would be higher than that predicted from our model for DNA binding. Without further structural information, it is unclear how this may occur, but it could involve the incorporation of Alba dimers to bridge contacts between two Alba tetramers bound to DNA.

Like the archaeal Alba protein, eukaryotic histone proteins are also acetylated to modulate gene expression. In the case of the histone proteins, hyperacetylation is generally correlated with gene activation, whereas hypoacetylation is correlated with repression. The mechanism by which the acetylation status of histones regulates gene expression is still unclear; however, several models have been proposed. In one model, acetylation of lysine residues neutralizes the lysine charge of the lysine residues, thereby loosing the interaction of the histone tails with DNA and thus increasing DNA access for the binding of transcription factors to promote transcriptional activation. A second model argues that the unacetylated histone tails interact with neighboring nucleosomes in chromatin and that acetylation relieves these interactions to destabilize repressive higher order chromatin. A third model argues that histone acetylation is one histone modification among many that establish a "histone code" to mark histone binding sites for other transcriptional regulatory proteins to elicit modification-dependent transcriptional activities (4–6). There have been several studies that support each of these models, and it is likely that they are not mutually exclusive. The studies we present here suggest that acetylation-induced regulation of archaeal Alba proteins involve the modulation of a higher order Alba structure. This would be consistent with a model in which histone tail acetylation would disrupt higher order chromatin structure. Confirmation of this model would certainly require further direct studies involving histone proteins. Nonetheless, the structural and functional studies presented here suggest that the acetylation status of archaeal Alba affects its oligomerization status, and it is possible that the evolution to eukaryotic systems and histone proteins may have maintained this mechanism of transcriptional regulation.

Acknowledgments—We thank Adrienne Clements Egan, Mary Fitzgerald, Hongzhuang Peng, Guoping Da, Ke Qin Li, Lan Xu, and Feng Xue for useful discussions and A. Joachimiak, R. Zhang, N. Duke, and the Structural Biology Center Collaborative Access Team (SBC-CAT)
staff for access to and assistance with the BM19B beamline at Advanced Photon Source.

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J. Biol. Chem. 2003, 278:26071-26077.
doi: 10.1074/jbc.M303666200 originally published online May 1, 2003

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