Mac1 is a metalloregulatory protein that regulates expression of the high affinity copper transport system in the yeast *Saccharomyces cerevisiae*. Under conditions of high copper concentration, Mac1 represses transcription of genes coding for copper transport proteins. Mac1 binds to DNA sequences called copper response elements (CuREs), which have the consensus sequence 5'-TTTG*C(T/G)*C(A/G)-3'. Mac1 contains two zinc binding sites, a copper binding site, and the sequence motif RGRP, which has been found in other proteins to mediate binding to the minor groove of A/T-rich sequences in DNA. We have used hydroxyl radical footprinting, missing nucleoside, and methylation interference experiments to investigate the structure of the complex of the DNA binding domain of Mac1 (called here Mac1t) with the two CuRE sites found in the yeast *CTR1* promoter. We conclude from these experiments that Mac1, binds in a modular fashion to DNA, with its RGRP AT-hook motif interacting with the TTT sequence at the 5' end of the *CTR1* CuRE site, and with another DNA-binding module(s) binding in the adjacent major groove in the GCTCA sequence.

Transcription of genes encoding the high affinity copper transport system in *Saccharomyces cerevisiae* is subject to copper-dependent repression. These genes include the plasma membrane permease *CTR1* and *CTR3*, the cell surface metalloenductase *FRE1*, and a *FRE1* homolog of unknown function designated *FRE7* (1–5). These genes are maximally expressed in copper-deficient yeast, but are repressed in copper-replete cells.

Copper-dependent expression of *CTR1*, *CTR3*, *FRE1*, and *FRE7* is regulated by the transcriptional activator Mac1 (4, 6, 7). Binding sites for Mac1 exist in the 5' promoter sequences of each of the four genes (4, 7, 8). These sites, designated copper-response elements (CuREs), have the consensus sequence 5'-TTTG*C(T/G)*C(A/G)-3'. Binding of Mac1 to CuREs is required for transcriptional activation of the target genes (4, 7). The CuRE is present in at least two copies in each of the four genes.

The CuREs are oriented as either direct or inverted repeats. The spacing between CuRE sites is variable, and changes in spacing have a limited effect on expression (8). The apparent requirement for the presence of at least two CuRE sites likely lies in the need for synergism for proper copper-dependent gene regulation (8, 9).

The Mac1 protein consists of 417 amino acids (Fig. 1). The distribution of charged amino acid residues in Mac1 is not uniform; the N-terminal segment (residues 1–201) is strongly basic, while the C-terminal segment (residues 202–417) is mostly acidic (6). The DNA-binding domain of Mac1 maps to the N-terminal 159 residues. Two Zn(II) ions are coordinated by the protein in the DNA-binding domain (8). Part of the Mac1 DNA-binding domain (residues 1–40) is homologous to the conserved zinc-binding module found in the copper-activated transcription factors Ace1 and Amt1 from *S. cerevisiae* and *Candida glabrata*, respectively (6–8, 10–12). This zinc-binding subdomain has been implicated in making direct interactions with DNA in the minor groove of an A/T-rich sequence (13).

Copper at concentrations above 1 nM represses Mac1 function *in vivo* by attenuating DNA binding activity. Footprinting experiments *in vivo* revealed that Mac1 binds to the CuREs upstream of the *CTR3* gene in copper-starved but not copper-replete cells (4). Further studies have shown, however, that copper-dependent inactivation of Mac1 is more complex than this simple picture might suggest. First, DNA binding *in vitro* either by the minimal DNA binding domain of Mac1 or by full-length Mac1 prepared by *in vitro* transcription/translation is not copper-dependent (7, 8). Second, the transactivation activity of Mac1 is repressed in copper-supplemented cells (14, 15). Transactivation activity maps to two cysteine-rich sequences (residues 264–337) in the C-terminal region of Mac1 (15). Eight Cu(I) ions bind within this domain (16). Binding of Cu(I) to the Cys-rich motif induces an intramolecular interaction with the N-terminal DNA-binding domain (16).

The CuRE sequences bound by Mac1 resemble the DNA binding sites for Ace1 and Amt1 in having an A/T-rich sequence upstream of a related core element (4, 7). This observation suggests that Ace1 and Mac1 may interact with DNA in a similar manner, even though Ace1 activates the copper sequestration machinery of the cell, while Mac1 activates the copper acquisition machinery (7, 17).

To investigate the interaction of Mac1 with its DNA binding site, we performed hydroxyl radical footprinting, missing nucleoside, and methylation interference experiments. For these experiments we used a truncated version of Mac1, which we call Mac1t. This protein contains the minimal DNA-binding domain of Mac1, and consists of residues 1–159 of Mac1 (see Fig. 1) plus a C-terminal His tag. We studied the binding of
Mac1, to a fragment of the CTR1 promoter in order to establish the contacts that Mac1 makes with a CuRE site.

**EXPERIMENTAL PROCEDURES**

**DNA Preparation**—A DNA molecule containing a segment of the CTR1 promoter, spanning positions 361 to 299 upstream of the transcription start site, was inserted into the BamHI-XhoI site of plasmid p Bluescript SK+. This plasmid was amplified in Escherichia coli DH1 cells and isolated using the Qiagen Plasmid Kit. Purified plasmid DNA was stored at −20 °C in Tris-EDTA buffer (10 mM Tris, 0.2 mM EDTA, pH 8.0).

The CTR1-containing plasmid was digested with restriction endonucleases NoI and EcoRI (New England Biolabs, Beverly, MA). The resulting 96-bp restriction fragment was singly end-labeled at either the NoI terminus using [α-32P]dGTP or at the EcoRI terminus using [α-32P]dATP (Amersham Pharmacia Biotech) with the Klenow large fragment of DNA polymerase (New England Biolabs).

**Protein Preparation**—The truncated version of Mac1 that we studied, Mac1Δ, was prepared as described previously (8). Mac1Δ was stored in 20 mM sodium phosphate buffer (pH 7.5), 0.3 M NaCl, 5 mM dithiothreitol, and 50% glycerol, at −20 °C.

**Hydroxyl Radical Footprinting Experiments**—A singly end-labeled DNA restriction fragment (0.1 pmol) in a buffer containing 20 mM Tris (pH 7.8), 65 mM KCl, 5 mM MgCl2, 2.5 mM dithiothreitol, and 0.1 mg/ml bovine serum albumin was incubated for 15 min on ice with 25 mM Mac1Δ. The hydroxyl radical footprinting reaction was carried out by the addition of 2 mM Fe(II), 4 mM EDTA, 0.03% hydrogen peroxide, and 20 mM sodium ascorbate (final concentrations) (18, 19). The reaction was allowed to proceed for 2 min and was stopped by the addition of 25 mM sodium thiosulfate. The DNA was precipitated by the addition of 0.3 M sodium acetate and ethanol. The DNA pellet was rinsed with 85% ethanol, lyophilized, dissolved in formamide buffer, and loaded on a 10% denaturing polyacrylamide sequencing gel. Gel composition, running conditions, imaging, and analysis were the same as described above for the footprinting experiments.

**Methylation Interference Experiments**—DNA radiolabeled at the 3′ end, in a buffer consisting of 200 μl of 50 mM sodium cacodylate (pH 8.0), 1 mM EDTA, was treated with 0.5 μl of dimethyl sulfate for 15 s. The reaction was stopped by addition of 300 mM sodium acetate and 100 mM 2-mercaptoethanol. DNA was precipitated by addition of ethanol. The DNA pellet was rinsed with 70% ethanol and lyophilized (21). Methylated DNA was resuspended in protein binding buffer and added to a concentration of 25 nM, and binding was allowed to proceed for 15 min on ice. After the addition of glycerol (4% final concentration), the sample was loaded on a native polyacrylamide gel with composition, buffer, and running conditions as described above for the missing nucleoside experiment. Bands containing protein-bound and unbound protein were excised from the gel, DNA was eluted from the gel and precipitated by the addition of ethanol. The DNA pellet was rinsed with 70% ethanol and lyophilized. The DNA pellet was suspended in 100 μl of 1 mM piperidine and heated at 90 °C for 20 min. DNA was precipitated by addition of 300 mM sodium acetate and ethanol. The DNA pellet was rinsed with 85% ethanol, lyophilized, dissolved in formamide buffer, and loaded on a 10% denaturing polyacrylamide sequencing gel. Gel composition, running conditions, imaging, and analysis were the same as described above for the footprinting experiments.

**RESULTS**

The minimal DNA-binding domain of Mac1 consists of the N-terminal 159 residues (8). For our experiments we used a His-tagged derivative of this 159-residue truncated version of Mac1, which we call Mac1Δ. Mac1Δ binds to the CuRE sequence with an apparent affinity of 5 nM (8). Mac1Δ(1–194) fused to glutathione S-transferase gave similar results to Mac1Δ in DNA binding experiments, demonstrating that the His tag of Mac1Δ does not affect DNA binding. We carried out footprinting, missing nucleoside, and methylation interference experiments with Mac1Δ, bound to the 96-bp CTR1 DNA molecule, which contains two CuRE sites separated by 14 bp. In the CTR1 promoter, the two CuRE sites are arranged as an inverted repeat.

**Hydroxyl Radical Footprints of Mac1 Bound to the CTR1 Promoter**—We see a single strong hydroxyl radical footprint for Mac1Δ, on only one DNA strand in each of the two CuRE sites in the CTR1 promoter (Fig. 2). The region most strongly protected is found at positions −336 to −331 on the coding strand and at −304 to −308 on the noncoding strand. The most protected nucleotides are T(−334) on the coding strand and the symmetry-related T(−305) on the noncoding strand. The strong footprint is centered on the 5′-TTTG-3′ sequence in each CuRE inverted repeat. One or two nucleotides to the 5′ side of each CuRE consensus sequence also are protected.

**Missing Nucleoside Experiments**—A 3′ end-labeled DNA restriction fragment in Tris-EDTA buffer was treated with the hydroxyl radical by adding 2 mM Fe(II), 4 mM EDTA, 0.03% H2O2, and 20 mM sodium ascorbate (final concentrations), as described previously (20). The reaction was allowed to proceed for 2 min, and was stopped by the addition of 26 mM thiourea. The DNA was precipitated by the addition of 0.3 M sodium acetate and ethanol. The DNA pellet was rinsed with 85% ethanol and lyophilized. The hydroxyl radical-treated DNA was resuspended in the protein binding buffer described above for the footprinting experiments. Mac1Δ was added to the hydroxyl radical-treated DNA at a concentration of 25 nM. Binding was allowed to proceed for 15 min on ice. After the addition of glycerol (4% final concentration), the sample was immediately loaded on a 7.5% polyacrylamide native electrophoresis gel (37.5:1 acrylamide:bisacrylamide, 1× Tris-borate-EDTA buffer). The gel was run at 25 V/cm at 4 °C. To locate the bands containing DNA, the gel was exposed to Kodak XAR-5 x-ray film for 30 min at room temperature. Containing protein-bound and unbound DNA were excised from the gel matrix and eluted by the flush and soak procedure (21). DNA was isolated, precipitated, and electrophoresed on a 10% denaturing polyacrylamide gel as described above. Gel composition, running conditions, imaging, and analysis were the same as for the footprinting experiments.

**Methylation Interference Experiments**—DNA radiolabeled at the 3′ end, in a buffer consisting of 200 μl of 50 mM sodium cacodylate (pH 8.0), 1 mM EDTA, was treated with 0.5 μl of dimethyl sulfate for 15 s. The reaction was stopped by addition of 300 mM sodium acetate and 100 mM 2-mercaptoethanol. DNA was precipitated by addition of ethanol. The DNA pellet was rinsed with 70% ethanol and lyophilized (21). Methylated DNA was resuspended in protein binding buffer and added to a concentration of 25 nM, and binding was allowed to proceed for 15 min on ice. After the addition of glycerol (4% final concentration), the sample was loaded on a native polyacrylamide gel with composition, buffer, and running conditions as described above for the missing nucleoside experiment. Bands containing protein-bound and unbound protein were excised from the gel, DNA was eluted from the gel and precipitated by the addition of ethanol. The DNA pellet was rinsed with 70% ethanol and lyophilized. The DNA pellet was suspended in 100 μl of 1 mM piperidine and heated at 90 °C for 20 min. DNA was precipitated by addition of 300 mM sodium acetate and ethanol. The DNA pellet was rinsed with 85% ethanol, lyophilized, dissolved in formamide buffer, and loaded on a 10% denaturing polyacrylamide sequencing gel. Gel composition, running conditions, imaging, and analysis were the same as described above for the footprinting experiments.

**Quantitative Analysis of Gel Images**—We used the image analysis program GelExplorer (22) to integrate the intensities of the bands in the gel images from the footprinting and missing nucleoside experiments. Normalization of data from one lane to another was achieved by summing the whole-band integrals of at least five bands above and below the protein binding site, and then multiplying by a factor such that the summed integral for the normalizing bands had the same value as the similar sum measured for the reference lane. Based on studies we performed during the development of the GelExplorer method (22), we estimate that the experimental error in a band integral determined by GelExplorer analysis is ±5%.
gap in its backbone. Certain gaps in the DNA backbone (missing nucleosides) interfere with protein binding, while other gaps have no effect on binding. To determine which missing nucleosides fall into which category, the mixture of gapped DNA and protein is electrophoresed on a native polyacrylamide gel, which separates free DNA from DNA-protein complexes. DNA extracted from the bound and free fractions is subjected to denaturing gel electrophoresis to reveal which missing nucleosides interfered with protein binding, and which had no effect.

The missing nucleoside pattern for the coding strand shows that loss of any of the nucleosides from positions $-335$ to $-328$ and $-312$ to $-307$ interferes with protein binding (Fig. 3). The pattern for the non-coding strand shows that nucleosides at positions $-332$ to $-324$ and $-313$ to $-305$ are important for protein binding.

**Fig. 2. Hydroxyl radical footprints of Mac1, bound to the CTR1 promoter.**

A. phosphorimages of denaturing gels from a hydroxyl radical footprinting experiment. Lane G, products of a Maxam-Gilbert guanine-specific sequencing reaction; lane 1, DNA treated with hydroxyl radical; lane 2, Mac1-DNA complex treated with hydroxyl radical. Brackets to the right of each autoradiograph mark the two CuRE sites present in CTR1. B, densitometer scans of lanes from one of the phosphorimages shown in panel A. Data for the coding strand are shown. Solid line, DNA treated with the hydroxyl radical in the absence of protein. Dashed line, DNA treated with the hydroxyl radical with Mac1 present. C, GelExplorer-derived footprints for Mac1, bound to the CTR1 promoter. Note that the y axes of the two plots are oriented in opposite directions. Positive values in these plots represent nucleotides protected from hydroxyl radical cleavage; negative values represent nucleotides for which cleavage is enhanced in the presence of protein.

**Methylation Interference Analysis of Mac1, Binding to the CTR1 Promoter**—Methylation of any of the guanines in the two CuRE sequences interferes with protein binding (Fig. 4). These results confirm that Mac1, makes specific interactions in the major groove of the CuRE site.

The results of our footprinting, missing nucleoside, and methylation interference experiments are summarized on a helical representation of DNA in Fig. 5.

**DISCUSSION**

**Major Groove Interactions**—Both methylation interference and missing nucleoside experiments show that Mac1, interacts with the major groove of DNA in the CuRE sequence (Fig. 5). Methylation of any of the three guanines in either copy of the CuRE in the CTR1 promoter interferes with binding (Fig. 4). A
set of strong missing nucleoside signals (Fig. 3) is found in the same region of the CuRE, supporting this conclusion.

Minor Groove Interactions—Hydroxyl radical footprinting, which shows how Mac1t is positioned on the binding site, reveals an interesting structural result. The strongest protections are located exclusively at the 5'-'TTTG-3' sequence of each CuRE, on one strand only. One or two adjacent nucleotides to the 5' side of each CuRE also are strongly protected. It is somewhat surprising, based on our experience in footprinting other proteins (19), that a corresponding strong footprint on the other strand is not observed. Instead, the DNA backbone is weakly protected on the other strand across the major groove from the strong footprint (Fig. 5), and no protection is found across the minor groove.

As shown in Fig. 5, the set of strong protections (green) defines the edge of the minor groove that is adjacent to the major groove in which contacts were detected by missing nucleoside and methylation interference experiments. Missing nucleoside signals also are observed at these strongly footprinted nucleotides, further evidence of the importance of these interactions to the binding of Mac1t to DNA.

The RGRP DNA Binding Motif of Mac1t—Several DNA-binding proteins, such as Amt1, Ace1, HMG-I(Y), and Hin recombinase, make important interactions with the minor groove of DNA. A feature held in common by each of these proteins is the amino acid sequence motif GRP (G = glycine; R = arginine; P = proline) (7, 23–26). This sequence motif has been called the AT-hook (27), because it has been found to target A/T-rich sequences for binding. Mac1 has the related motif RGRP near its N terminus (residues 36–39, Fig. 1). For HMG-I(Y) and Hin recombinase, how the GRP motif (and the related (and overlapping) RGRP motif) interacts with DNA has been determined by NMR (24) and x-ray (28) structural studies, respectively. The (R)GR motif forms a concave surface that is inserted in the minor groove of A/T-rich sequences. Analysis of the x-ray and NMR structures demonstrates that

FIG. 3. Missing nucleoside analysis of Mac1t binding to the CTR1 promoter. A, phosphorimages of denaturing gels from a missing nucleoside experiment. Lane G, products of a Maxam-Gilbert guanine-specific sequencing reaction; lane F, hydroxyl radical-treated DNA (the input DNA for the experiment); lane U, gapped DNA that did not bind to Mac1t (unbound DNA); lane B, gapped DNA that bound to Mac1t (bound DNA). The brackets to the right of each autoradiograph mark the two CuRE sites present in CTR1. B, GelExplorer-derived missing nucleoside patterns for Mac1t binding to the CTR1. Integrals of bands in phosphorimages were determined using GelExplorer (22). Plotted is the ratio of the integral of a band in the free DNA lane (F) to the integral of the corresponding band in the bound DNA lane (B), minus 1. Positive values in this plot represent nucleosides whose loss interferes with binding of Mac1t.

FIG. 4. Methylation interference analysis of Mac1t binding to the CTR1 promoter. Lane G, products of a Maxam-Gilbert guanine-specific sequencing reaction; lane B, methylated DNA that bound to Mac1t; lane U, methylated DNA that was unable to bind to Mac1t; lane F, input methylated DNA. DNA in each lane was treated with piperidine before denaturing gel electrophoresis to reveal positions of methylated guanines. Guanine residues critical for Mac1t binding are indicated to the right of each autoradiograph. The brackets to the left of each autoradiograph mark the two CuRE sites present in CTR1.
Differences in the Interaction of Mac1t with the Two CuRE Sequences of CTR1—Kosman and co-workers (9) recently demonstrated that the identity of nucleotides adjacent to the CuRE consensus sequence can affect the DNA binding and transactivation activity of Mac1. The two CuRE sites of CTR1 have identical 8-base pair consensus sequences, but the base pairs to the 5′ side of each site differ. In the upstream site the sequence is 5′-TATTTGCTCA-3′, while in the downstream site the sequence is 5′-TTTTGGCTCA-3′ (reading the other strand), where the 5′-flanking nucleotides are underlined. Kosman and co-workers (9) found that Mac1 binds preferentially to the former (TA) site. Constructs made to contain two TA CuRE sites were more effective at transcriptional activation, while a CuRE site with two TT sites had lower transcriptional activity than wild-type. Our results are consistent with these observations. We find that Mac1 strongly protects two nucleotides immediately to the 5′ side of the upstream (TA) CuRE site (Fig. 5, arrow), while at the downstream (TT) CuRE site only one nucleotide adjacent to the CuRE is protected, and not very strongly at that (see Fig. 2).

Summary and Conclusions—The results of our chemical footprinting and interference experiments define in detail the interactions that the DNA binding domain of Mac1 makes with the two CuRE sites in the CTR1 promoter of S. cerevisiae. Missing nucleoside and methylation interference experiments show clearly that Mac1 binds in the major groove of DNA at the conserved GCTC sequence of the CuRE site. We observe a single strong hydroxyl radical footprint that starts near the middle of each CuRE and extends to nucleotides that flank the 5′ side of the site. This strong footprint defines the edge of the major groove in which the protein binds, and the minor groove of the TTT sequence at the 5′ end of the CuRE. The second zinc module would then make the contacts we observe in the adjacent major groove.

Our model of a modular interaction of Mac1 with DNA recalls the mode of DNA binding of another GRP-containing protein, Hin recombinase. Structural studies on Hin recombinase revealed a helix-turn-helix motif, which binds in the major groove. Residues N-terminal to the helix-turn-helix extend across the phosphodiester backbone to the adjacent minor groove (28–30), where the GRP motif binds. A survey of AT-hook-containing proteins revealed several other examples of proteins with additional and distinct DNA-binding domains in addition to the AT-hook (27). Our hydroxyl radical footprinting and methylation interference data suggest to us that Mac1 contacts the TTT sequence on one edge of the minor groove, adjacent to the major groove where methylation interference and missing nucleoside experiments show the protein binds (see Fig. 5).

The remarkable aspect of the Mac1 footprint, that only one strand is strongly protected at the edge of each CuRE, can be accommodated by this model. We suggest that the RGRP AT-hook motif of Mac1 is constrained to be located closer to one strand of the minor groove in which it is bound, because of its conjunction with other DNA-binding module(s) of the protein. Protection thus is observed only for the T-rich strand. This is in contrast to the structural results for HMG-I(Y) and Hin recombinase, in which the RGRP motif is seen to bind deep in the minor groove and interact with both strands.

Multiple DNA-binding Modules in Mac1t—Our methylation and missing nucleoside interference data show that Mac1t makes important contacts with the CuRE at the 5′-TTTGCT-3′ sequence on the coding strand and with the 3′-ACGAGT-5′ sequence on the noncoding strand, whereas our hydroxyl radical footprinting data show strong protection only of the coding-strand sequence 5′-ATTTTGCTCA-3′. Weak footprints are apparent in the center of the binding site, between the two CuRE repeats. Consideration of both the footprinting and missing nucleoside data suggests to us that there are two distinct DNA binding domains in Mac1t, perhaps coincident with the two zinc-binding modules of this protein. The N-terminal zinc-binding module, which is thought to bind in the minor groove (4, 7, 15), would be associated with the RGRP motif, and thus participate in making the contacts observed at the TTT sequence at the 5′ end of the CuRE. The second zinc module would then make the contacts we observe in the adjacent major groove.

The results of our chemical footprinting and interference experiments define in detail the interactions that the DNA binding domain of Mac1 makes with the two CuRE sites in the CTR1 promoter of S. cerevisiae. Missing nucleoside and methylation interference experiments show clearly that Mac1 binds in the major groove of DNA at the conserved GCTC sequence of the CuRE site. We observe a single strong hydroxyl radical footprint that starts near the middle of each CuRE and extends to nucleotides that flank the 5′ side of the site. This strong footprint defines the edge of the major groove in which the protein binds, and the minor groove of the TTT sequence at the 5′ end of the CuRE site. We conclude that Mac1 binds in a modular fashion to the CuRE, with the RGRP AT-hook sequence of the protein binding in the T-rich minor groove, and other parts of the protein, likely
including zinc-binding motif(s), interacting with the major groove.

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