CCAAT/Enhancer-binding Protein α Alters Histone H3 Acetylation at Large Subnuclear Domains*

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Wan-Hui Zhang†‡§, Roopali Srihari‡§, Richard N. Day¶, and Fred Schaufele§‡

From the †Metabolic Research Unit, Diabetes Center and Department of Medicine, University of California, San Francisco, California, 94143-0540 and the §Departments of Medicine and Cell Biology, National Science Foundation Center for Biological Timing, University of Virginia Health Sciences Center, Charlottesville, Virginia 22908

Transcriptional regulation is commonly associated with local levels of histone acetylation, which controls chromatin structure at specific genes or within contiguous chromosomal domains. Less well understood are the higher order determinants of histone acetylation. The transcription factor, CCAAT/enhancer-binding protein α (C/EBPα), concentrates at one higher order structure, the peri-centromeric chromatin, and regulates differentiation in many cell types, including pituitary cells. We used quantitative fluorescence microscopy to show that immunostained acetylated histone H3 is relatively absent from peri-centromeric domains visible as large structures in mouse pituitary progenitor GHFT1-5 cells. GHFT1-5 cells do not contain C/EBPα. We observed that expression of C/EBPα in GHFT1-5 cells leads to an increased level of acetylated histone H3, but not acetylated histone H4, at the peri-centromeric domains. Only transcriptionally active forms of C/EBPα altered histone acetylation at the peri-centromeric domain. The altered state of histone acetylation at large intranuclear domains may complement, counteract, or superecede the more gene-local activities of other transcription factors to coordinate C/EBPα-induced cellular differentiation.

Transcription regulation involves transcription factor binding to a gene promoter, recruitment of complexes that modify chromatin structure at that promoter, and the recruitment, or altered activity, of RNA polymerase at the gene (1–3). One chromatin modification associated with transcriptional activation is the acetylation of histones (4). Transcriptionally active chromatin has long been associated with the presence of acetylated histones. More recently, chromatin immunoprecipitation techniques have shown that the binding of a transcription factor to a gene is associated with local changes in the acetylation state of histones within, and adjacent to, the gene (5). Local histone acetylation is generally thought to occur over a background of more global histone acetylation and deacetylation activities (5). However, acetylated histones are unevenly distributed throughout the nucleus and tend to concentrate at the juncture of transcriptionally active and inactive chromosomal domains (6, 7). Such compartmentalization likely affects the transcriptional regulation of associated genes, but the mechanisms by which the intranuclear distribution of acetylated histones is established and/or modulated are not well understood.

The architecture of the nucleus is believed to be critical for coordinating the changes in cellular proliferation and gene expression that accompany cellular differentiation (7, 8). Some transcription factors, including CCAAT/enhancer-binding protein α (C/EBPα),1 regulate both cellular proliferation and gene transcription (9–16). C/EBPα is not distributed evenly throughout the nucleoplasm and instead concentrates at chromatin surrounding the centromeres (17, 18). The centromeres are chromosomal structures associated with intranuclear chromosome positioning (19) and cell cycle regulation (20). Transient, sometimes cell cycle-specific, association of genes with the transcriptionally quiescent, peri-centromeric chromatin is associated with transcriptional regulation of those genes (21–26). Thus, the centromere is a critical organizing structure within the nucleus that is selectively targeted by the transcription factor C/EBPα.

Hormone-secreting pituitary cells contain C/EBPα, whereas pituitary progenitor GHFT1-5 cells do not contain C/EBPα (15). C/EBPα expressed ectopically in GHFT1-5 cells activates the pituitary-specific growth hormone (15, 18) and prolactin (16) promoters and blocks the cell cycle in the growth 1 and DNA synthesis phases.2 Since C/EBPα concentrates selectively at peri-centromeric chromatin visible as large intranuclear structures in mouse GHFT1-5 cells, we examined the effect of C/EBPα expression on the distribution of acetylated histones within the nucleoplasm of GHFT1-5 cells. Acetylated histone H3, but not acetylated histone H4, was observed to be relatively absent from peri-centromeric chromatin in naïve GHFT1-5 cells. Expression of C/EBPα led to enhanced acetylation of histone H3 at peri-centromeric chromatin, with no effect on the distribution of acetylated histone H4. Enhanced acetylation of histone H3 at peri-centromeric chromatin required the transcriptional activation functions of C/EBPα. Thus, a transcription factor that regulates gene expression and differentiation regulates the balance of acetylated histones at a central, higher order, organizing structure within the nucleus of the cell. Such modulation of intranuclear architecture represents a mechanism by which a transcription factor may more globally regulate gene expression.

EXPERIMENTAL PROCEDURES

Transfection and Plasmids—GHFT1-5 cells were transfected by electroporation, plated on No. 1 borosilicate coverslips, and grown for 2 days prior to fixation with cold methanol as described previously (18). Cells

1 The abbreviations used are: C/EBPα, CCAAT/enhancer-binding protein α; GFP, green fluorescent protein; HAT, histone acetyltransferase; HDAC, histone deacetylase; PBS, phosphate-buffered saline; CBP, CREB-binding protein.

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were treated with 10⁻⁷ m trichostatin A for 18 h prior to fixation. Visual inspection before fixation and similar patterns of Hoechst 33342, C/EBPα, and acetylated histone staining in control and trichostatin A-treated cells suggested that the cells were not overtly altered by 18 h trichostatin A incubation. The control, C/EBPα-GFP, GFP-C/EBPα, FLAG-tagged C/EBPα, and FLAG-tagged C/EBPαΔ1–153 expression vectors have been described previously (18). The C/EBPα-sensitive promoter containing the growth hormone TATA box (~33 to +8 relative to the transcription start site) and a single growth hormone C/EBPα binding site (~239 to ~219) has been characterized previously (18).

**Antibody Staining**—Following fixation, the slides were treated for 5 min with phosphate-buffered saline (PBS) containing 0.05% Triton X-100, washed with PBS, then blocked for 1 h or more with 5% horse serum in PBS. Acetylated histone H3 was stained in 0.5% horse serum in PBS with a 1:200 dilution of Upstate Biotechnology (Lake Placid, NY) rabbit polyclonal antibody 06-599, which recognizes histone H3 containing lysines acetylated at amino acid 9 or 14. Acetylated histone H4 was similarly stained with a 1:200 dilution of a mixture of Upstate Biotechnology rabbit polyclonal antibodies 06-759, -760, -761, or -762, which collectively recognizes H4 containing lysines acetylated at amino acid 5, 8, 12, or 16. The anti-FLAG mouse monoclonal antibody was obtained from Eastman Kodak Co. and used at a 1:600 dilution. 1:500 dilutions of donkey anti-rabbit rhodamine-conjugated and goat anti-mouse fluorescein-conjugated secondary antibodies (sc-2095 and sc-2010; Santa Cruz Biotechnology, Santa Cruz, CA) were used to detect the immunostained acetylated histones and FLAG-tagged C/EBPα. Following antibody incubation and washing, all slides were stained for 5 min with 0.2 μg/ml in PBS Hoechst 33342 (H-3570; Molecular Probes, Eugene, OR) to visualize pericentromeric chromatin.

**Image Collection**—Following antibody staining, all images were collected on an Olympus IX-70 using an Olympus 100x Plan Apochromat oil immersion objective (1.40 NA). An Opti-Quip (Highland Hills, NY) model 1962 long term stabilizer was used to keep light intensity constant for accurate quantitative data collection. For three-color (blue, green, and red) imaging we used Chroma Corporation (Brattleboro, Vermont) blue fluorescent protein, fluorescein isothiocyanate, and rhodamine excitation and emission filters (excitation 385–395/emission 440–460), 475–495/500 nm; 540–560/580–630 nm, respectively) and Chroma Corporation dichroic mirror 61000v25v. This combination of filters and mirror gives excellent discrimination, with no bleedthrough, between the Hoechst 33342, fluorescein or GFP and rhodamine fluorophores. Sutter (Novato, CA) λ·10 excitation and emission filter wheels were controlled by Metamorph data acquisition software. Images were collected by focusing first only with the Hoechst 33342-stained DNA, common to all cells, so as to eliminate collection bias.

**Image Analysis**—Image analysis was done with Metamorph software (Universal Imaging Corporation, Downingtown, PA). Following image collection, nuclei were identified as regions with significantly higher than background levels of blue fluorescence emitted from Hoechst 33342. Pericentromeric chromatin within the nuclei was identified as contiguous pixels thresholded with brighter than average nuclear Hoechst 33342 fluorescence. The computer accurately traced regions around those peri-centromeric domains and transferred them to the exact same pixel positions in the corresponding green (C/EBPα) and red (acetylated histone) images collected from the same cell. Two pericentromeric regions within each cell were randomly selected by looking only at the Hoechst 33342 image. Then, we determined the average green fluorescence or red fluorescence at and away from the marked pericentromeric chromatin. The corresponding background fluorescence collected from an adjacent region not containing a cell was subtracted. The background-subtracted levels of fluorescence at and away from pericentromeric chromatin were thus determined. The proportion of pericentromeric domains with an at/away from pericentromeric ratio approximating parity (ratio >0.95) was calculated for each experiment. This was then averaged (~±S.D.) from four (Fig. 2) or three (Fig. 3) experiments. Statistical significance (p < 0.05) was determined by comparing the data of the different experiments with one-tailed, paired student t tests.

**RESULTS**

Peri-centromeric Chromatin Is Deficient in Acetylated Histone H3—C/EBPα expressed in GHFT1-5 cells concentrates at visible intranuclear structures that are preferentially stained by the DNA binding dye Hoechst 33342 (17, 18) (Fig. 1A). Excitation and emission filters were used that selectively discriminate the blue fluorescence of DNA-bound Hoechst 33342 from the green fluorescence of a fluorescein-labeled secondary antibody bound to immunostained C/EBPα. Overlaying the blue and green images shows that the intranuclear locations of Hoechst 33342-stained DNA and C/EBPα coincide. The Hoechst 33342-stained DNA marks transcriptionally quiescent peri-centromeric heterochromatin in the mouse GHFT1-5 cells (18).

C/EBPα cooperates with the histone acetyltransferases p300 (27) and CREB-binding protein (CBP) (18) to activate transcription. We therefore determined whether C/EBPα expression changes the content of acetylated histones at Hoechst 33342-stained peri-centromeric chromatin. GHFT1-5 cells were transfected with expression vectors encoding rat C/EBPα fused at either its carboxyl (C/EBPα-GFP) or amino (GFP-C/EBPα) terminus to the green fluorescent protein. Like C/EBPα, both GFP fusions with C/EBPα concentrate at Hoechst 33342-stained chromatin in GHFT1-5 cells (18). Controls cells were transfected in parallel with an expression vector not containing an inserted cDNA. Transfected cells were grown for 2 days, fixed, then incubated with rabbit polyclonal antibodies directed specifically against the acetylated forms of histone H3 or histone H4. The cells were stained with a rhodamine-conjugated anti-rabbit secondary antibody and counter-stained with Hoechst 33342.

The intranuclear distributions of acetylated histone H3 and H4 were visualized by fluorescence microscopy using rhodamine-specific excitation and emission filters. In cells not expressing C/EBPα, acetylated histone H3 was unevenly distributed throughout the nucleoplasm (Fig. 1B). A parallel image of the same cell using excitation and emission filters specific for Hoechst 33342 suggests that the regions of sparse acetylated histone H3 correspond to peri-centromeric heterochromatin. This was confirmed by precisely quantifying the amount of
rhodamine fluorescence at, and away from, Hoechst 33342-stained peri-centromeric chromatin. Digital images of cells not expressing C/EBPα were collected over four different experiments. Within each experiment, the camera exposure time for rhodamine and Hoechst 33342 fluorescence detection was kept constant and set such that no single pixel within an image exceeded the maximum fluorescence measurable with the camera.

Peri-centromeric chromatin was identified by marking contiguous bright pixels in the Hoechst 33342 image. On average, Hoechst 33342 fluorescence intensity in the marked pixels was 1.59 ± 0.20-fold (mean ± S.D.) above that of the surrounding pixels. When the pixel positions of the Hoechst 33342-stained peri-centromeric chromatin were transferred to the parallel image of rhodamine-stained acetylated histone H3, rhodamine fluorescence at a peri-centromeric chromatin was 0.82 ± 0.11 that of the intensity adjacent to the peri-centromeric chromatin. This measurement includes some rhodamine fluorescence above or below of the peri-centromeric domains, which do not always extend through the entire focal plane in the captured image. Even though this overestimates the relative amount of acetylated histone H3 at the peri-centromeric domain, the observed ratio of 0.82 is significantly below the ratio of 1.00, which would indicate equivalent acetylated histone H3 concentrations at and away from peri-centromeric domain. Thus, acetylated histone H3 is underrepresented at peri-centromeric domain in GHFT1-5 cells. Only 15 of the 194 peri-centromeric domains analyzed from 97 cells not expressing C/EBPα contained a ratio greater than 0.95, used here as an indicator of near parity in the distribution of acetylated histone relative to peri-centromeric chromatin.

C/EBPα Enhances Acetylated Histone H3 Content at Peri-centromeric Chromatin—The relative amounts of acetylated histones at, and away from, peri-centromeric chromatin also was determined in GHFT1-5 cells in which C/EBPα, fused to GFP, was ectopically expressed. Random cells were focused on using only the blue fluorescent Hoechst 33342-stained chromatin. Blue (Hoechst 33342-labeled peri-centromeric chromatin), green (GFP-labeled C/EBPα), and red (rhodamine-labeled acetylated histone H3) fluorescent images were then captured from each cell. Control measurements showed that there was no fluorescence bleedthrough between the blue, green, and red channels. Cells displaying green fluorescence, i.e. expressing either C/EBPα-GFP or GFP-C/EBPα, were analyzed as described above and compared with sham-transfected cells containing no C/EBPα. We previously showed that C/EBPα-GFP activates a C/EBPα-sensitive promoter in GHFT1-5 cells, whereas GFP-C/EBPα is transcriptionally inactive (18). The percentage of peri-centromeric domains in which the concentration of acetylated histone H3 at the domain approaches that measured away from the domain (percent with ratio >0.95, Fig. 2A, black bars) was low in the absence of C/EBPα and increased significantly (p = 0.014) when C/EBPα-GFP was expressed in the cell (Fig. 2A, C/EBP-GFP, black bar). In contrast, acetylation of histone H3 at peri-centromeric chromatin did not increase upon GFP-C/EBPα expression (Fig. 2A, GFP-C/EBP, black bar). Thus, the ability to promote an increase in the amount of acetylated histone H3 at peri-centromeric chromatin correlated with the transcriptional activity of C/EBPα.

Effect of HDAC Inhibition on Acetylated Histone Content at Peri-centromeric Chromatin—The increase in acetylated histone H3 at peri-centromeric chromatin may arise from an effect of C/EBPα on histone acetyltransferase (HAT) or histone deacetylase (HDAC) recruitment or activity at the peri-centromeric chromatin at which C/EBPα concentrates. To determine whether any HDAC activity prevented histone H3 acetylation at peri-centromeric chromatin, GHFT-1–5 cells were treated with 10⁻⁷ M trichostatin A, a general inhibitor of HDAC activity (28). In the whole nucleus, trichostatin A treatment caused a 4.3-fold increase in the average fluorescence emitted from acetylated histone H3 stained with rhodamine. However, the relative proportion of acetylated histone H3 at peri-centromeric chromatin was the same in the presence (Fig. 2A, Control, white bars) and absence (black bars) of HDAC inhibition. This suggested that the relative absence of acetylated histone H3 at peri-centromeric chromatin was not due to a concentration of any HDAC at peri-centromeric chromatin.

In cells expressing C/EBPα-GFP, the increased proportion of acetylated histone H3 at peri-centromeric chromatin similarly was not affected by HDAC inhibition (Fig. 2A). In contrast, blocking HDAC activity strongly increased the proportion of acetylated histone H3 at peri-centromeric chromatin in cells expressing the transcriptionally inactive GFP-C/EBPα. This suggested that GFP-C/EBPα, in contrast to C/EBPα-GFP, was defective in countering a HDAC activity. Thus, C/EBPα concentrates at peri-centromeric chromatin where it both overcomes a HDAC activity and actively promotes acetylation of histone H3. The trichostatin A rescue of histone H3 acetylation by GFP-C/EBPα did not rescue the transcriptional activity of GFP-C/EBPα at a C/EBPα-sensitive promoter in GHFT1-5 cells (Fig. 2B). This indicated that C/EBPα activation depended

![Fig. 2. Expression of C/EBPα causes a selective increase in acetylated histone H3 at peri-centromeric chromatin.](http://www.jbc.org/content/361/4/40375/F2)

A. The proportion of GHFT1-5 cells in which the concentration of acetylated histone H3 at/away Hoechst 33342-stained peri-centromeric chromatin in approximately equivalent (away/away ratio >0.95) is increased in C/EBPα-GFP relative to control and GFP-C/EBPα expressing cells. Measurements are made in the absence (black bars) or presence (white bars) of an 18-h incubation with 10⁻⁷ M trichostatin A. B, choromaphenicol acetyltransferase activity expressed from a C/EBPα-sensitive promoter (see "Experimental Procedures"). C/EBPα-GFP expressed in GHFT1-5 cells is transcriptionally active at this promoter whereas GFP-C/EBPα is not. Incubation with trichostatin A has no effect on the transcriptional activity. C, the relative concentration of rhodamine-stained acetylated histone H4 at/away from peri-centromeric chromatin is not affected by C/EBPα-GFP or GFP-C/EBPα expression either in the absence or presence of trichostatin A.
The increase in pericentromeric histone H3 acetylation requires the transcriptional activation domain of C/EBPα.

Deletion of the transcriptional activation functions of C/EBPα generates a protein that still specifically targets pericentromeric chromatin (18) but that no longer enhances the amount of acetylated histone H3 at pericentromeric chromatin. Data shown are from trichostatin A-treated cells, which emphasize that the transcriptionally defective C/EBPΔ1–153, unlike GFP-C/EBPα, cannot activate pericentromeric histone H3 acetylation, even when HDACs are inhibited.

upon additional activities disrupted in the GFP-C/EBPα fusion.

C/EBPα-dependent pericentromeric histone acetylation was selective for histone H3. C/EBPα expression did not affect the proportion of pericentromeric regions showing near parity in the distribution of acetylated histone H4 (Fig. 2C). In the control cells not expressing C/EBPα, the proportion of pericentromeric regions showing near equivalent amounts of acetylated histone H4 at and away from the pericentromeric region was substantially higher than that measured for acetylated histone H3 (Fig. 1C). In contrast to acetylation of histone H3, acetylation of histone H4 was increased upon trichostatin A incubation (Fig. 2C). This suggests that a trichostatin A-sensitive HDAC with some selectivity for histone H4 was more concentrated at the pericentromeric chromosomal domains than at the surrounding chromatin.

Enhanced Acetylation of Histone H3 Requires the C/EBPα Transcription Activation Domain—C/EBPα fused to GFP therefore concentrates at pericentromeric chromatin where it counteracts a specific deficit in acetylated histone H3. We also observed this to be true for C/EBPα not fused to GFP (Fig. 3). To detect C/EBPα separately from acetylated histone H3 detected with a rabbit polyclonal antibody, we attached the short FLAG epitope to the amino terminus of C/EBPα. FLAG-tagged C/EBPα was expressed in GHFT1-5 cells and its intranuclear location determined using an anti-FLAG mouse monoclonal antibody and a fluorescein-labeled anti-mouse secondary antibody. Control incubations showed no cross-reactivity between the acetylated H3 antibody and the anti-mouse secondary antibody or between the anti-FLAG primary antibody and the anti-rabbit secondary antibody.

As with C/EBPα-GFP, expression of C/EBPα caused an increase in the number of pericentromeric domains in which the amount of acetylated histone H3 was similar at and away from the domain (Fig. 3, C/EBPα-ut). If C/EBPα was deleted of its transcriptional activation domains between amino acids 1 and 153 (18, 27, 29, 30), it no longer enhanced acetylation at pericentromeric chromatin (Fig. 3, C/EBPΔ1–153). Thus, the selective acetylation of histone H3 at pericentromeric chromatin depended on the transcriptional integrity of C/EBPα.

**DISCUSSION**

The pericentric region appears to be critical for regulating transcription and proliferation in a number of systems. Some genes transiently associate with pericentromeric chromatin during the cell cycle (31) or during differentiation (22, 23, 26, 32). It is generally thought that the cell cycle or developmentally controlled displacement of a gene away from transcriptionally inactive pericentromeric chromatin permits histone acetylation, chromatin decondensation, and gene activation (26).

Intriguingly, we determined that pericentromeric chromatin is globally deficient in acetylated histone H3 and that this deficit is overcome by the expression of a single transcription factor, C/EBPα, that selectively binds to pericentromeric chromatin. Counteracting HDAC activity with trichostatin was insufficient to induce pericentromeric acetylation of histone H3. This suggested that concomitant recruitment of a HAT might be required. We previously found that one HAT-containing co-factor, the CBP, concentrates at pericentromeric chromatin upon C/EBPα expression (18). As with histone H3 acetylation (Figs. 2 and 3), C/EBPα, C/EBPα-GFP, and GFP-C/EBPα, but not C/EBPΔ1–153, recruited CBP to pericentromeric chromatin (18). Thus, C/EBPα alters the balance in histone H3 and H4 acetylation at the pericentromeric chromatin, which is critical for organizing the genome. This suggests a hierarchy in which the selected alteration of acetylation in a large intranuclear compartment complements, counteracts, or supercedes the local, gene-specific changes in histone acetylation more traditionally associated with transcription regulation.

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