Histone acetylation plays an important role in remodeling chromatin structure, facilitating nuclear processes such as transcription. We investigated the effect of estradiol on global histone acetylation in hormone-responsive human breast cancer cells. Pulse-chase experiments and immunoblot analyses of dynamically acetylated histones show that estradiol rapidly increases histone acetylation in estrogen receptor (ER)-positive, hormone-dependent T5, but not in ER-negative, hormone-independent MDA MB 231 breast cancer cells. The effect of estradiol on the rates of histone acetylation and deacetylation in T5 cells was determined. We found that estradiol increased the level of acetylated histones by reducing the rate of histone deacetylation, whereas the rate of histone acetylation was not altered. Enzymatic assays and immunoblot analyses of cell fractions showed that estradiol did not affect the level, subnuclear distribution, or activity of class I and II histone deacetylases. However, estradiol did alter the intranuclear distribution of ER and histone acetyltransferases, with both becoming tightly bound in the nucleus and associated with the nuclear matrix. We propose that, following the association of ER with nuclear matrix sites, ER alters the balance of histone acetyltransferases and histone deacetylases at these sites and the dynamics of acetylation of histones associated with transcriptionally active and competent chromatin.

Histone acetylation is a dynamic process directed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Transcription factors recruit coactivators with HAT activity to regulatory DNA sites, whereas transcriptional repressors recruit corepressors with HDAC activity (1). Nucleosomal histones at or near regulatory elements associated with coactivators with HAT activity become highly acetylated, resulting in the remodeling of chromatin structure (1). These highly acetylated histones are rapidly deacetylated by HDACs accessing these sites. Dynamically acetylated histones, however, are not confined to regulatory regions but are located along the coding region of genes and, in some cases, with a chromatin domain (2–4).

Studies on histone acetylation rates have revealed that in animal cells there are different populations of dynamically acetylated histones. One population is rapidly modified to highly acetylated isoforms (e.g. tetra-acetylated H4) and rapidly deacetylated. This population of dynamically acetylated histones is bound to transcriptionally active and competent DNA (5). Another larger population of acetylated histones is slowly modified to highly acetylated states and slowly deacetylated (6).

We have demonstrated that HAT and HDAC activities are associated with the nuclear matrix of avian erythrocytes (7). Further, avian HDAC1 and mammalian HDAC1 are bound to the nuclear matrix, a nuclear substructure that has a critical role in chromatin organization and function (8–12). We proposed a model where nuclear matrix-associated HATs and HDACs mediate a dynamic attachment between transcriptionally active chromatin domains and the nuclear matrix.

Estrogen plays an important role in the cell proliferation and stimulation of DNA synthesis in hormone-responsive breast cancer cells. The estrogen receptor α (ER), when bound to estradiol, recruits the coactivator/HATs CBP, PCAF, steroid receptor cofactor (SRC) 1, and SRC-3 to estrogen-responsive elements, resulting in acetylation of histones at and near the site of ER binding (13, 14). Immediately following the addition of estradiol to hormone-responsive breast cancer cells, ER undergoes a rapid intranuclear redistribution to punctate nuclear foci that are associated with the nuclear matrix (10, 15). This alteration in ER intranuclear trafficking is accompanied with the recruitment of the coactivator/HAT SRC-1 to nuclear matrix-associated sites containing ER.

In this study we investigated the effect of estradiol on global histone acetylation in hormone-responsive breast cancer cells. A previous study demonstrated that estradiol decreased the level of acetylated histones (16). In contrast to these observations, we found that estradiol rapidly increased the level of acetylated histones. An analysis of the rates of histone acetylation and deacetylation in breast cancer cells cultured in estradiol-depleted and -replete conditions revealed that estradiol decreased the rates of histone deacetylation, but had no effect on the rates of histone acetylation. Evidence is presented that estradiol does not affect the levels or nuclear distribution of HDACs, but it does alter the nuclear distribution of HATs.

**MATERIALS AND METHODS**

**Cell Lines and Culture Conditions**—Human breast cancer cell line T5 (ER-positive and estrogen-dependent) and MDA MB 231 (ER-negative and estrogen-independent) were grown in DMEM (Invitrogen) supplemented with 5% fetal bovine serum, penicillin (100 units/ml), streptomycin (100 mg/ml), and 5% glucose. Under estrogen-depleted conditions, cells were grown in estrogen-depleted medium, consisting of phenol red-free DMEM (Invitrogen), 7% charcoal-stripped fetal bovine serum, antibiotics, and 5% glucose.
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serum, penicillin (100 units/ml), streptomycin (100 mg/ml), and 5% glucose as described previously (17). Cells were grown in a 37 °C humidified incubator with 5% CO₂.

**False-Case Labeling Cells for Analyses of Histone Acetylation**

RATES—To study the effect of estradiol on histone acetylation, T5 cells were grown in estrogen-depleted medium. After 3 days of incubation, T5 cells were grown in the same medium containing cycloheximide (10 μg/ml) for 30 min. Cells were incubated in the same medium containing cycloheximide (10 μg/ml) and [3H]acetate (0.1 mCi/ml; ICN) in the absence (ethanol vehicle only) or presence of 10 nM estradiol for 20 min.

After labeling, the cells were washed twice with ice-cold PBS containing 10 mM sodium butyrate and 0.1 mM nonradioactive acetate. The cells were chased in the same buffer at 37 °C for various times.

**False-Case Labeling Cells for Analyses of Histone Deacetylation**

RATES—Rates of histone deacetylation were determined as described previously (6, 18). T5 cells were grown in estrogen-depleted medium for at least 3 days. After two washes with PBS, T5 cells were grown in the same medium containing cycloheximide (10 μg/ml) for 30 min. The cells were incubated for 120 min in the same medium containing 10 mM butyrate, 10 μg/ml cycloheximide, and [3H]acetate in the presence or absence of 10 nM estradiol. After labeling, the cells were washed three times with pre-warmed PBS, and incubated in the same medium without butyrate and radioactive acetate, and with or without estradiol for various times. The cells were then washed and harvested.

**Cellular Fractionation**—T5 cells were resuspended in TMN buffer (100 mM NaCl, 300 mM sucrose, 10 mM Tris-HCl, pH 7.4, 2 mM MgCl₂, 1% thiodiglycol) containing 1 mM phenylmethylsulfonyl fluoride and protease inhibitor mixture (Roche). The cells were lysed by being passed through a syringe with 22-gauge needle. The cytosol and nuclei were isolated from lysed cells after centrifugation at 4500 × g. Nuclear preparations were inspected by microscopic analyses. The nuclei were resuspended in TMN buffer. The nuclei were extracted by adding Triton X-100 to a final concentration of 0.5% and incubated on ice for 5 min. After centrifugation at 4500 × g for 10 min, the supernatant, named the Triton X-100 supernatant fraction, or Triton-S, was saved. The nuclei pellet was resuspended in an equal volume of TMN buffer with 0.5% Triton X-100; this fraction was named the Triton X-100 pellet fraction, or Triton-P.

**Immunoprecipitation and Immunoblotting**—Immunoblot analyses was carried out as described previously (9). Polyclonal antibodies against human HDAC1 (Affinity Bioreagents Inc. (ABR)), human HDAC2 (ABR), human HDAC3 (ABR), human HDAC4 (Santa Cruz), human HDAC5 (ABR), and mouse monoclonal antibodies against human E2α (Novocastra Laboratories Ltd.) and SRC-3 (ABR) (Abcam, Inc.) were used. Antibodies against PCAF-A and PCAF-B were a kind gift from Dr. Yoshihiro Nakatani. Acetylated isoforms of H3 and H4 were detected with polyclonal antibodies to di-, tri-, and tetra-acetylated H3 and penta-acetylated H4 (Upstate Biotechnology, Inc.)

**Histone Acetytransferase and Deacetylase Assays**—Histone acetytransferase and deacetylase assays were performed as described previously (7, 20).

**RESULTS**

**Estradiol Increases Histone Acetylation in Human Breast Cancer ER-positive T5 Cells**—To determine the immediate effect of estradiol (E₂) on histone acetylation, T5 cells (ER-positive and hormone-dependent) grown under E₂-depleted conditions were incubated with or without 10 nM E₂ and [3H]acetate for 20 min to label dynamically acetylated histones. Comparison of the Coomassie Blue-stained AUT gel patterns shows that histones from E₂-incubated cells had slightly increased levels of highly acetylated (di-, tri-, and tetra-acetylated) isoforms of H4 (Fig. 1A). Relative to the di-, tri-, and tetra-acetylated H4 isoforms from cells cultured under E₂-depleted conditions, the level of these acetylated H4 isoforms increased by 2.5% in the E₂-incubated cells. Analyses of the fluorogram revealed a greater change in the levels of the acetylated histones with the labeled highly acetylated isoforms of H3.2, H2B, and H4 being increased in the E₂-incubated cells (Fig. 1A). After scanning the fluorogram, the ratios of the level of labeled highly acetylated histone isoforms (Ac3 and Ac4) to total labeled acetylated H4, H3.2, and H2B were calculated. The percentage of acetylated H4 that was highly acetylated was 9 and 12.5% in histones from cells incubated without and with E₂, respectively. The highly acetylated H3 isoforms was 18 and 23% of acetylated H3 in preparations from cells grown without and with E₂. The acetylated H2B that was highly acetylated increased to 17%, while being 15% in cells grown without E₂.

To further illustrate the increase in the level of highly acetylated histones in T5 cells incubated with E₂ for 30 min, the histones were analyzed by immunoblot analyses with antibodies recognizing highly acetylated isoforms of H3 (Fig. 1B) and H4 (Fig. 1C). Fig. 1B shows that E₂ incubation increased the levels of highly acetylated isoforms of H3.2. Similarly, Fig. 1C shows that E₂ incubation elevated the levels of highly acetylated H4 isoforms. Together, these results demonstrate that E₂ rapidly increases the level of highly acetylated histone isoforms.

This study was repeated with the human breast cancer cell line MDA MB 231 (ER-negative and hormone-independent). Analyses of Coomassie Blue-stained AUT gels and accompanying fluorograms demonstrated that incubation of MDA MB 231 cells with E₂ did not affect acetylated histone levels (data not shown). The ratio of labeled highly acetylated H4 isoforms to total acetylated H4 in E₂-treated MDA MB 231 cells was ~17.5%, which was very similar to the observed 18% for cells cultured without E₂. Immunoblot analyses of histones from...
cells incubated with and without E2 with antibodies against highly acetylated H4 isoforms showed that E2 did not affect the levels of highly acetylated H4 isoforms in MDA MB 231 (data not shown). These observations suggest that the E2-induced increase in histone acetylation in T5 cells involves the ER.

Estradiol Does Not Affect the Rate of Histone Acetylation in T5 Cells—The E2-induced increase in histone acetylation in T5 cells may be a consequence of an increase in histone acetylation rates, a decrease in histone deacetylation rates, or a combination of both. To determine rates of acetylation, T5 cells were pulse-labeled with [3H]acetate for 5 or 15 min. After labeling, the cells were washed and incubated at 37 °C in medium containing sodium butyrate and cold acetate for various times, chasing label into highly acetylated histone isoforms. It should be noted that the cells were grown in E2-replete conditions (DMEM with fetal bovine serum). The AUT gel was stained with Coomassie Blue, and the labeled acetylated histone isoforms were detected by fluorography (Fig. 2A). Long AUT polychryamide gels were used in these experiments to achieve high resolution of the acetylated histone isoforms.

A population of the acetylated histones is engaged in dynamic acetylation, whereas the remainder is “frozen” at various acetylation states. To determine the percentage of histones that were being rapidly acetylated, the loss of unacetylated H4 was plotted as a function of time that the cells were incubated with sodium butyrate as determined by scanning the Coomassie Blue-stained gels (data not shown). The results showed that 14.0 ± 2.0 and 11.0 ± 1.0% of H4 (n = 3) was rapidly acetylated in cells incubated without and with E2, respectively.

The loss of unacylated H4 was plotted as a function of time that the cells were cultured with sodium butyrate and with or without E2, as determined by scanning the Coomassie Blue-stained gels (data not shown). The results showed that 14.0 ± 2.0 and 11.0 ± 1.0% of H4 (n = 3) was rapidly acetylated in cells incubated without and with E2, respectively.

The fluorograms were scanned, and the loss of fluorographic intensity from the monoacetylated histone as a function of time was plotted (Fig. 3). The fast rates of acetylation of monoacetylated H4 were similar in cells grown in the presence or absence of E2 (t1/2 = 8 versus 7 min, respectively). Additionally, the slow rates of acetylation of monoacetylated H4 were similar for cells grown under E2-replete and -depleted conditions (t1/2 = 380 versus 320 min, respectively). Similar results were obtained for H3.2 and H2B. These results show that E2 does not affect the rates of histone acetylation in T5 cells.

Estradiol Affects the Rate of Histone Deacetylation in T5 Cells—The effect of E2 on histone deacetylation rates was determined. T5 cells were grown in E2-depleted conditions for 3 days. Thirty min following the addition of cycloheximide, T5 cells were incubated with 10 mM butyrate, [3H]acetate, and with or without 10 nM E2 at 37 °C for 2 h. After removal of butyrate, cells were incubated in fresh medium replaced with or without E2 for 0–240 min to monitor histone deacetylation. A comparison of the fluorograms shown in Fig. 4 (A and B) revealed that E2-incubated cells had a slower rate of deacetylation for the core histones. The fluorograms were scanned, and the loss of fluorographic intensity from the tetra-acetylated H4 (Fig. 4C) and acetylated H3.2 (Fig. 4D) as a function of time was plotted. The rate of deacetylation of tetra-acetylated H4 was rapid, with the intensity of hyperacetylated H4 decreasing significantly after 20 min following the removal of sodium butyrate. The rate of H4-Ac4 deacetylation was appreciably slower in E2-incubated cells. The rates of H4-Ac4 deacetylation were t1/2 = 8 and 3 min for cells cultured with and without E2, respectively.
activity. We tested the idea that E2 altered the subcellular distribution of HDAC. Cells were lysed in TNM buffer without any detergents to minimize loosely bound nuclear proteins from leaking out of the nuclei. The nuclei were resuspended in TNM buffer with 0.5% Triton X-100 and incubated on ice to release loosely bound nuclear proteins (Triton-S fraction). The resulting pellet contained the tightly bound nuclear proteins, which includes proteins associated with the nuclear matrix (Triton-P).

The distribution of ER in the cell fractions from the cell treated with or without E2 for 5 min was determined by immunoblot analyses. ER levels in the lysates from cells incubated with and without E2 did not change (Fig. 6A, compare lane 1 with lane 6). Most ER was in the nucleus fraction. However, the cytosol fraction from cells incubated without E2 had higher levels of ER than did the corresponding fraction from cells incubated with E2. As ER is located primarily in the nucleus, the ER in cytosol represents ER that was loosely bound in the nucleus. Fractionation of the nuclear proteins into those that were loosely bound from those that were tightly bound revealed a shift in the intranuclear partitioning of ER following the addition of E2. Comparison of the ER levels in the Triton-S and Triton-P fractions showed that, after 20 min E2, ER became tightly bound to the nucleus. This observation is consistent with previous reports (10, 15). Further, others and we have demonstrated that the tightly bound form of ER is associated with the nuclear matrix (10, 15).

The distribution of class I HDACs among the cellular fractions was determined by immunoblot analyses with antibodies against human HDAC1, HDAC2, and HDAC3. Fig. 6A shows that E2 had little affect on the fractionation of these HDACs. Most HDAC1 and HDAC2 were present in the nuclei. Triton X-100 released only a small amount of HDAC1 and HDAC2 from the nuclei. In low stringency immunoprecipitation experiments, we found that most HDAC2 was in complex with HDAC1. However, HDAC1 was in excess of HDAC2; thus, a proportion of HDAC1 is not in complex with HDAC2. Further, we found that HDAC1 and HDAC2 were associated with the nuclear matrix (data not shown). HDAC3 was also in the nuclear fraction, and approximately half of HDAC3 was associated with the tightly bound nuclear protein fraction. This result agrees with the findings that HDAC1 and -2 exist in different complexes than those that contain HDAC3 (1). HDAC3 was associated with the nuclear matrix (data not shown). In contrast to the class I HDACs, the class II HDAC4 was found exclusively in the loosely bound nuclear protein fraction (Fig. 6). It is possible that the HDAC3 in this fraction is in complex with HDAC4 (24). As expected from the lack of HDAC4 in the Triton-P fraction, HDAC4 was not associated with the nuclear matrix (data not shown). However, as with the class I HDACs, E2 did not have an effect on the fractionation of HDAC4.

The immunoblot analyses showed the fractionation of several known HDACs. However, the HDAC family of proteins is complex (1). Thus, we measured HDAC activities in the nuclei and nuclear fractions, Triton-S and Triton-P. Fig. 6B shows that most nuclear HDAC activity was present in the tightly bound nuclear fraction and that E2 did not affect the distribution of nuclear HDAC activity.

Estradiol Affects the Subcellular Distribution of Histone Acetyltransferases in T5 Cells—An E2-induced alteration in the subcellular trafficking of HATs may also change the histone deacetylase rates (see “Discussion”). HAT activity assays were done with cell lysate, cytosol, nuclei, loosely bound, and tightly bound nuclear fractions from T5 cells incubated with and without E2. Fig. 7A shows that the HAT activity in the lysed cell
fractions from cells treated with or without E2 did not significantly change. However, the HAT activity of nuclei from cells incubated with E2 was greater than that of nuclei from cells grown without E2 (Fig. 7B). Fractionation of the nuclear fraction showed both the loosely bound and tightly bound nuclear proteins had HAT activity. However, the tightly bound nuclear proteins demonstrated a differential HAT activity with preparations isolated from cells grown with and without E2. After 20 min of E2 incubation, there was an increase in the HAT activity associated with the Triton-P, tightly bound nuclear protein fraction.

Immunoblot analysis with antibodies to known HATs was done with the intent to identify the HAT responsible for the increased activity in the Triton-P fraction of E2-incubated cells. SRC-1 was located primarily in the nuclear fraction (Fig. 7C). Triton X-100 released less SRC-1 from nuclei in cells treated with E2 than from nuclei of cells treated without E2 (Fig. 7C, compare lane 4 with lane 5, and lane 9 with lane 10). These results with SRC-1 are in agreement with those of Mancini and colleagues (10), who analyzed the effect of E2 and ER on the subnuclear trafficking of a bioluminescent derivative of SRC-1 in HeLa cells.

The partitioning of SRC-3 (AIB1/RAC3/ACTR) was similar to that of SRC-1, except that SRC-3 was also detected in the cytosol fraction (Fig. 7C). Following 20 min of incubation with
Estradiol, there was an increased amount of SRC-3 in the Triton-P fraction. The effect of E2 on the subcellular distribution of the HATs CBP, PCAF-A, and PCAF-B (long form of Gcn5; Ref. 25) was also determined. Fig. 7 shows that E2 did not affect the distribution of these HATs among the cellular fractions. Most CBP, PCAF-A, and PCAF-B were present in the tightly bound nuclear protein fraction, suggesting that these transcriptional coactivators/HATs are predominantly associated with the nuclear matrix. Indeed, we observed that these HATs were associated with the nuclear matrix (data not shown). These studies show that E2 has an effect on the intranuclear distribution of SRC-1 and SRC-3, but not CBP, PCAF-A, and PCAF-B, in T5 cells.

**DISCUSSION**

Estradiol rapidly elevates the level of acetylated histones in ER-positive, hormone-dependent, but not in ER-negative, hormone-independent breast cancer cells. Our results are in striking contrast to those of Pasqualini et al. (16), who observed a decrease in histone acetylation following a 20-min incubation of MCF-7 cells with estradiol. Differences in media conditions, histone isolation procedure, and the addition of a protein synthesis inhibitor during the labeling period may explain the discrepancy in results.

Approximately 60–70% of H4 and H3 were acetylated in human breast cancer T5 cells. These acetylated histones fall into at least three groups: those that are “frozen” in an acetylated state, those that are rapidly acetylated and deacetylated, and those that are slowly acetylated and deacetylated. The latter group comprises the bulk of the dynamically acetylated histones. The rapidly acetylated and deacetylated histones represent ~10% of the dynamically acetylated histones in T5 cells. The rapidity of the effect of E2 on histone acetylation suggests that histones undergoing rapid acetylation and deacetylation are the population of dynamically acetylated histones being most affected (4).

Our results suggest that E2 decreased the rates of histone deacetylation, but had no effect on histone acetylation rates, in T5 cells. Analyses of the activities of HDACs and HATs showed that the net activities of either group of enzymes were not affected by E2. However, biochemical fractionation studies indicated that the intranuclear distribution of HATs, including SRC-1 and SRC-3, were affected by E2. When presented with E2, ER rapidly locates to specific nuclear matrix sites, binds to estrogen response elements (EREs), and recruits with it SRC-1 and SRC-3 (10, 12–15) (Fig. 8). As SRC-1 and SRC-3 acetylate primarily H3, other HATs that acetylate the other core histones would also be recruited by ER bound to E2 to account for
the increased acetylation of H2B and H4 that we observe. Elegant studies by the Evans and Brown groups (13, 14) demonstrate that CBP is recruited to EREs. CBP will acetylate the four core histones (3, 26). However, our biochemical fractionation studies were unable to detect E2-induced intranuclear redistribution of CBP. Possibly, ER and the EREs are recruited to the nuclear matrix sites containing CBP (27).

It is interesting to note that most characterized EREs of breast cancer estrogen-responsive genes have the ERE (1⁄2)(N), Sp1 (a half-site ERE positioned next to a Sp1 site) motif ERE (28). It has been determined experimentally that there are 1.86 × 10⁵ ER molecules/cell in T5 cells (29). Thus, ER is in far excess to estrogen-responsive genes. The association of Sp1 with ER presents the possibility that Sp1 will recruit ER to Sp1 sites in promoters and enhancers (30). Further, we have found that, as with ER-E₂, Sp1 is associated with the nuclear matrix of T5 cells. It is conceivable that by binding to nuclear matrix site ER when bound to E₂, ER alters the balance of HATs and HDACs and the dynamics of acetylation of histones associated with transcriptionally active and competent chromatin domains.

We have shown previously that HAT and HDAC activities are associated with the nuclear matrix (7, 9, 20). In this study we found that HDAC1, -2, and -3, but not HDAC4, are bound to the nuclear matrix of human breast cancer T5 cells. Further, we observed that the HATs CBP, PCAF-A, and PCAF-B are nuclear matrix-associated and Mancini and colleagues (10) reported that SRC-1 is bound to this nuclear substructure. We have proposed a model in which nuclear matrix-associated HATs and HDACs mediate a dynamic attachment between transcriptionally active chromatin domains and the nuclear matrix. In support of this model, we recently reported that the dynamically rapidly acetylated and deacetylated histones, referred to as class 1 acetylated histones, are bound to nuclear matrix-associated coding regions of transcriptionally active and competent genes in avian immature erythrocytes (5). Further, we have shown that highly acetylated H3 and H4 are bound to the coding regions of E₂-inducible ER and e-myC genes (31). Although the dynamics of the histones associated with these genes were not determined, our work and that of Grunstein’s group suggest that these histones are dynamically acetylated by HATs and HDACs (2, 5, 7, 20). We propose that ER bound to E₂ alters the balance of HATs and HDACs at specific nuclear matrix sites, which are associated with transcriptionally active and competent chromatin regions in T5 cells. When bound to E₂, ER would recruit HATs altering the balance of HATs and HDACs at those sites. The HDACs at these sites would be confronted with greater amounts of acetylated histone substrates, requiring a longer time to deacetylate the acetylated histones (Fig. 8). Hence, this may explain the slower rates of deacetylation in cells incubated with E₂ and the increase in the level of dynamically acetylated histones.

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