Estrogen-modulated Estrogen Receptor-Pit-1 Protein Complex Formation and Prolactin Gene Activation Require Novel Protein Synthesis*

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Both estrogen receptor (ER) and Pit-1 proteins are essential for the estrogen-activated expression of the rat prolactin gene. Our results show that ER-Pit-1 protein complex formation is reduced by estrogen in GH3 and PR1 rat pituitary tumor cells. In the latter, this decrease was blocked by cycloheximide, a protein synthesis inhibitor. On the other hand, the direct addition of estrogen to PR1 cell lysates had no effect on the formation of ER-Pit-1 complexes. Estrogen-activated prolactin gene expression was also inhibited by cycloheximide, suggesting that some form of protein synthesis is involved in ER-Pit-1 complex formation and subsequent prolactin gene activation. In support of this notion, we showed that estrogen-induced regulation of ER-Pit-1 complex formation could be transferred from cell lysates prepared from estrogen-treated PR1 cells to control cell lysates. This is not true for GH3 cells; instead, direct administration of estrogen to GH3 cell lysates readily abolished ER-Pit-1 protein complex formation in a dose-dependent manner, and such estrogen-induced regulation was blocked by the antiestrogen ICI 182,780. These findings thus indicate that 1) interaction between ER and Pit-1 proteins is estrogen-regulated in ways specific to different cell types, and 2) auxiliary protein factor synthesis may be involved in this process.

The tissue-specific expression of the rat prolactin (PRL) gene in the anterior pituitary gland is regulated by the synergistic action of two upstream regulatory elements: the distal enhancer and the proximal promoter (1, 2). Complex binding sites for trans-acting factors within these elements control tissue-specific expression and transcription efficiency (3, 4). A pituitary cell-specific transcription factor, Pit-1, a member of the POU domain family of transcription factors, binds to multiple sites for binding sites in the distal enhancer element of the rat PRL gene, and Pit-1 complexes. Estrogen-activated prolactin gene expression has also been shown to be inhibited by cycloheximide, suggesting that a form of protein synthesis is involved in Pit-1 complex formation and subsequent prolactin gene activation. In support of this notion, we showed that estrogen-induced regulation of ER-Pit-1 complex formation could be transferred from cell lysates prepared from estrogen-treated PR1 cells to control cell lysates. This is not true for GH3 cells; instead, direct administration of estrogen to GH3 cell lysates readily abolished ER-Pit-1 protein complex formation in a dose-dependent manner, and such estrogen-induced regulation was blocked by the antiestrogen ICI 182,780. These findings thus indicate that 1) interaction between ER and Pit-1 proteins is estrogen-regulated in ways specific to different cell types, and 2) auxiliary protein factor synthesis may be involved in this process.

The Pit-1 protein by itself, however, is not sufficient for the tissue-specific expression of the rat PRL gene. The promoter activity of the rat PRL gene strongly depends on the synergistic interactions between Pit-1 and other promoter-specific transcription factors, including the thyroid hormone receptor, CAAT/enhancer-binding protein-α, Ets-1, and c-Jun (8–10). Moreover, rat PRL gene expression is regulated by the steroid hormone estrogen at the level of transcription (11). Evidence showed that estrogen receptor-α (ER-α), which exhibits affinity for binding sites in the distal enhancer element of the rat PRL gene, synergizes with the Pit-1 protein to permit activation of the distal enhancer in a ligand-dependent fashion (12, 13). Rat PRL gene expression in non-pituitary cells such as Rat-1, a rat fibroblast cell line, requires both Pit-1 and ER-α to achieve full estrogen-dependent activation (14). A more recent study has further shown that in vitro expressed ER-α is pulled down by the Pit-1/GST fusion protein and thus suggests that Pit-1 and ER proteins interact physically (15).

Although it is well accepted that cell-specific activation of promoters by multiple factors forms the expression pattern that determines cell identity, the mechanisms by which the environment affects the interaction between synergistic partners remain largely unknown. Our previous results showed that the physical interaction between Pit-1 and ER-α proteins in rat pituitary cells is modulated by estrogen (16). In this study, we report that estrogen may regulate the interaction between Pit-1 and ER-α proteins through diverse pathways depending on the pituitary cell types. Our present results also indicate that accessory factor(s) are involved in the synergistic interaction between Pit-1 and ER-α proteins and that synthesis of these factors is likely to be estrogen-induced.

EXPERIMENTAL PROCEDURES

Chemicals—Phenol red-free Dulbecco’s modified Eagle’s medium, Hanks’ balanced salt solution, fetal bovine serum, antibiotic/antimycotic mixture, protein A-agarase, and Taq DNA polymerase were purchased from Life Technologies, Inc. Anti-Pit-1 antibody was purchased from Transduction Laboratories (Lexington, Kentucky). Diethylstilbestrol (DES) and the antiestrogen ICI 182,780 were purchased from Sigma and Tocris Cookson Ltd. (Bristol, United Kingdom), respectively.

Cell Culture Conditions—The GH3 rat pituitary cell line was obtained from American Type Cell Culture (17). The PR1 cell line was derived from the pituitary tumor of an ovariectomized F344 rat that had been treated with estrogen for 3 months (18). GH3 and PR1 cells were grown in phenol red-free Dulbecco’s modified Eagle’s medium containing 1× antibiotic/antimycotic mixture, 5 μM HEPES, and 0.37% sodium bicarbonate medium supplemented with either 10% fetal bovine serum or 3% dextran/charcoal-stripped fetal bovine serum. The cells were grown at 37 °C in a humidified atmosphere of 95% air and 5% CO2.

Immunoprecipitation and Western Analysis—Cell lysates from GH3 and PR1 cells were prepared as described previously (19). Briefly, after hormonal treatment, cells were washed three times with ice-cold Hanks’ balanced salt solution before the addition of lysis buffer (0.1% Triton X-100, 1 mM iodoacetamide, 1% bovine hemoglobin, 1 mM phen-

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1 The abbreviations used are: PRL, prolactin; ER, estrogen receptor; GST, glutathione S-transferase; DES, diethylstilbestrol; PCR, polymerase chain reaction.

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RESULTS

Estrogen Influences the Interaction between Pit-1 and ER in Pituitary Tumor Cell Lines GH3 and PR1—To determine whether continuous treatment of estrogen affects the interaction between Pit-1 and ER in GH3 pituitary tumor cells, cell lysates prepared from DES-treated cells were immunoprecipitated with anti-Pit-1 antiserum, and the amount of coprecipitated ER was determined with anti-ER antibody (Fig. 1). To minimize any potential artifacts, we used the same complexes immunoprecipitated with anti-Pit-1 antiserum to determine the levels of ER and Pit-1 proteins. The results showed that the interaction between Pit-1 and ER proteins was both estrogen- and time-dependent. Incubation with DES for 72 h reduced the amount of coprecipitated ER fell to <30% of control levels (Fig. 1A), although the levels of Pit-1 and ER proteins in the cells remained unaltered (Fig. 1, B and C). Estrogen treatment, however, stimulated the synthesis of PRL protein as expected and increased the amounts of both PRL mRNA (data not shown) and protein (Fig. 1D).

The effects of estrogen were likewise investigated in the PR1 pituitary tumor cells, and similar results were obtained (Fig. 2). The level of coprecipitated ER was greatly down-regulated by estrogen in a time-dependent fashion (Fig. 2A), whereas the levels of ER and Pit-1 proteins remained fairly constant during the entire period of treatment (Fig. 2, B and C). The amounts of PRL mRNA were elevated by the estrogen treatment (Fig. 2D), as reported previously (23). An estrogen-induced increase in the PRL protein level was also observed in PR1 cells after treatment with estrogen for 18 h, and this increase plateaued at 24 h (data not shown).

When estrogen was added to the GH3 cell lysate during the immunoprecipitation assays, the amounts of coprecipitated ER decreased gradually in a dose-dependent fashion (Fig. 3A). This effect appeared to be estrogen-specific since it was blocked by ICI 182,780, an antiestrogen (Fig. 3B). This blocking of the estrogen-regulated interaction between Pit-1 and ER proteins was dose-dependent, and when the molar concentration of ICI 182,780 was 20 times that of DES, the estrogen-induced down-regulation was completely nullified. Incubation with ICI 182,780 alone did not cause any detectable changes in the amount of coprecipitated ER in the GH3 cell lysate (Fig. 3B).

Protein Synthesis Is Required for the Estrogen-regulated Interaction between Pit-1 and ER in PR1 Cells—Lysates from PR1 cells, however, unexpectedly gave different results in the interaction between Pit-1 and ER in response to estrogen (Fig. 4). Even at the highest estrogen concentration tested (200 nM), no significant changes in the amount of coprecipitated ER were induced. These results suggest that for PR1 cells, certain cellular changes are required for estrogen to affect the interaction between Pit-1 and ER. Such cellular changes appear to occur...
when estrogen is added to PR1 cells, but they cannot be duplicated in vitro by adding estrogen to the PR1 cell lysates.

To test whether de novo protein synthesis is one of these critical cellular changes, PR1 cells were treated either with estrogen alone or with both estrogen and the protein synthesis inhibitor cycloheximide simultaneously. The amounts of ER coprecipitated with Pit-1 were determined, and it was found that in the presence of both cycloheximide and estrogen, the quantity of coprecipitated ER was increased almost back to control cell levels (Fig. 5A). Furthermore, this increase could not have been due to a proteolytic error because if a proteolytic error was responsible for the complex's falling apart, one would expect to see changes in the protein levels of the ER or Pit-1 proteins in the same cell lysates subjected to the same experimental procedures performed simultaneously. No visible changes were observed in the ER levels (Fig. 5B), and the amount of Pit-1 protein was actually slightly reduced after 72 h of treatment either with cycloheximide alone or with both DES and cycloheximide (Fig. 5C). We therefore concluded that cycloheximide indeed blocked the effects of estrogen on the interaction between Pit-1 and ER, presumably through inhibition of the synthesis of certain cellular protein factors.

This blocking activity of cycloheximide and the absence of substantial changes in the levels of Pit-1 and ER proteins in cycloheximide-treated PR1 cells led us to undertake direct biochemical analysis of the ER/Pit-1 affinity in lysates prepared from cells treated with DES or the ethanol vehicle. In particular, prior to immunoprecipitation, cell lysates prepared from ethanol-treated control cells were mixed with those prepared from cells that had been treated with DES for 72 h. In doing this, we hoped to determine whether the DES-treated cells contained a soluble factor that is involved in the decreased affinity between ER and Pit-1 proteins.

The results of these assays are summarized quantitatively in Table I. Lysates from DES-treated cells indeed contained an activity capable of reducing the amount of coprecipitated ER in cell lysates prepared from control cells to levels almost as low as those in the presence of both DES and cycloheximide.
as those observed with cell lysates from DES-treated cells (Fig. 6). Moreover, this shift of activity was seen only when the cell lysates were preincubated at 30 °C, not when they were preincubated at 4 °C. The observed amounts (Table I, sample 5) of coprecipitated ER from the mixed cell lysates incubated at 30 °C was significantly lower than the calculated amount of 480.2 (Table I, sample 4). Preincubation of control or DES-treated cell lysates alone at 30 °C did not alter the amount of coprecipitated ER (Table I, sample 2). These findings thus pointed to the presence of a soluble factor(s) in DES-treated PR1 cells capable of reducing the affinity between ER and Pit-1 proteins.

The Estrogen-regulated Interaction between Pit-1 and ER Proteins Is Essential for the Activation of PRL Gene Expression in PR1 Cells—Treatment of cycloheximide not only blocked the estrogen-regulated interaction of Pit-1 and ER in control cell lysates. It thus appears that the selective expression of genes in progressively differentiating cell types in a particular developmental lineage requires the synergistic interaction between the cell-specific and general transcription factors. Thus, for example, although the Pit-1 protein is expressed in all the distinct pituitary cell types and genes, in lactotrophs, the synthesis of PRL is required for estrogen-induced PRL gene activation.

The Interaction between ER and Pit-1 Is DNA-dependent—Lysates prepared from DES-treated PR1 cells were immunoprecipitated in the presence or absence of ethidium bromide, and the amounts of coprecipitated ER were examined (Fig. 8). The addition of ethidium bromide significantly reduced the interaction of Pit-1 and ER proteins. It thus appears that the formation of the ER-Pit-1 protein complex depends on the presence of DNA.

DISCUSSION

The selective expression of genes in progressively differentiated cell types in a particular developmental lineage requires synergistic interaction between the cell-specific and general transcription factors. Thus, for example, although the Pit-1 protein is expressed in all the distinct pituitary cell types and is required for the expression of growth hormone, PRL, and thyrotropin-β genes, in lactotrophs, the synthesis of PRL is estrogen-regulated and highly specialized (1, 2). We have shown here that in two pituitary cell lines, GH3 and PR1, the

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**Fig. 5.** Addition of the protein synthesis inhibitor cycloheximide blocks the estrogen-induced down-regulation of ER-Pit-1 complex formation in PR1 cells. A, the amounts of coprecipitated ER in cell lysates prepared from PR1 cells treated for 0–72 h either with 10 nM DES alone or with 1 mM cycloheximide (CHX) simultaneously; B, the same sample in A used to assay for the levels of ER; C, the levels of Pit-1 proteins in these cells.

**TABLE I**

| Samplesa | Temperatureb | Coprecipitated ER  | Relative affinity |
|----------|--------------|--------------------|------------------|
|          | °C           | AUd (%)            | Observed Calculated% |
| 1. Control | 4            | 638.3 ± 11.4       | 100              | 100              |
| 2. Control | 30           | 593.1 ± 10.5       | 92.9             | 100              |
| 3. DES-treatedc | 4            | 322.1 ± 8.6        | 50.4             |                  |
| 4. Control mixed with DES-treated | 4          | 449.7 ± 10.9       | 70.5             | 75.2             |
| 5. Control mixed with DES-treated | 30         | 324.9 ± 8.4        | 50.9             | 78.2             |

a PR1 cell lysates prepared from cells treated with ethanol vehicle (control) or 10 nM DES for 72 h (DES-treated) were mixed and incubated either at 4 or 30 °C for 30 min prior to immunoprecipitation with anti-Pit-1 antiserum. Equal amounts of cellular protein were present in each sample, and samples 4 and 5 consisted of 50% control cellular proteins and 50% DES-treated cellular proteins.

b Incubation temperature prior to immunoprecipitation.

c The relative affinity of sample 4 was calculated as follows: (50% of amount of coprecipitated ER in sample 1 + 50% of amount of coprecipitated ER in sample 3)/amount of coprecipitated ER in sample 1. The relative affinity of sample 5 was calculated as follows: (50% of amount of coprecipitated ER in sample 2 + 50% of coprecipitated ER in sample 3)/amount of coprecipitated ER in sample 2.

d AU, arbitrary unit.

e The amount of coprecipitated ER in DES-treated PR1 cell lysates preincubated at 30 °C was 334.5 ± 15.6 (data not shown), which is 104% of that in DES-treated PR1 cell lysates preincubated at 4 °C.

**Fig. 6.** Lysates from DES-treated cells affect the interaction between Pit-1 and ER in control cell lysates. Cell lysates prepared from DES-treated cell lysates were incubated in parallel at 4 or 30 °C prior to immunoprecipitation.
pituitary-specific factor Pit-1 interacts physically with ER-α and that this interaction is mediated by estrogen. This interaction between Pit-1 and ER proteins requires the presence of functional DNA. Furthermore, the down-regulation of this interaction by estrogen is required for the activation of rat PRL gene expression. However, although this estrogen response occurs without de novo protein synthesis in GH3 cells, de novo protein synthesis appears to be required for the estrogen response to occur in PR1 cells. Our evidence for this is that estrogen-dependent changes could not be induced either in PR1 cells lysates when estrogen was added directly during immunoprecipitation or in PR1 cells treated with the protein synthesis inhibitor cycloheximide (Fig. 5).

The apparent requirement for the de novo protein synthesis in PR1 cells for the estrogen response suggests that other estrogen-inducible factors are involved. Further support for this "soluble factor" hypothesis is provided by the fact that lysates from DES-treated PR1 cells are capable of providing the activity for influencing the interaction between the Pit-1 and ER proteins in the "activity shifting" experiments (Table I and Fig. 6). This observation appears to be controversial to what was reported by Shull and Gorski (24). They showed that estrogen continued to stimulate PRL gene expression in rat pituitaries even when cycloheximide was injected intraperitoneally to inhibit 80% of the protein synthesis, which suggests, at least when an animal model is used as opposed to the pituitary cell lines used in the present study, that estrogen activation can in fact occur independently of pituitary protein synthesis. Despite the presence of cycloheximide, however, it is also possible that in the study of Shull and Gorski, synthesis of the protein(s) involved in the interaction between ER and Pit-1 may indeed have been reduced, but not to levels too low to allow the full induction of PRL gene transcription by estrogen (24).

Several protein factors have been thought to associate with the ER or Pit-1 protein, and it has been suggested that these interactions may be important for the activation of the rat PRL gene (25–28). It is already known that the functional interaction of the Ets-1 protein and Pit-1 is required for rat PRL gene expression (29), and it has also been suggested that protein factors, including SRC-1a, GRIP1, TIF-1α, and RIP140, that interact with the ER AF-2 region play an important role in the ER transactivation activity (30–32). The AF-2 function is required for the cooperative activation of Pit-1 with ER since null mutations within the ER AF-2 region or blocking ER AF-2 activity selectively with the antagonist tamoxifen and raloxifene diminishes the ER cooperative activation with Pit-1 (34, 35). Similarly, Pit-1 cooperative activation with the thyroid hormone receptor requires the intact AF-2 domain (34). The ER AF-2-interacting protein RIP140 was reported to inhibit the transcriptional synergy between ER and Pit-1 proteins upon the activation of rat PRL gene expression (35). Competition between different protein factors such as RIP140 with SRC-1a for the same binding site on the AF-2 domain of ER was proposed to be responsible for the inhibitory effect of RIP140 observed on ER and Pit-1 synergy. A similar mechanism has been suggested for RIP140 inhibition of gene regulation by the glucocorticoid receptor and Pit-1/thyroid hormone receptor synergy (36, 37). The expression of a coactivator, TIF-2, was able to rescue RIP140-mediated repression of glucocorticoid receptor-regulated gene expression in a ligand-dependent manner (36). It is possible that in PR1 cells, one of these coactivators is induced by estrogen, becomes associated with the ER-Pit1 complex, and subsequently alters the affinity between ER and Pit-1 proteins and activates rat PRL gene expression. Alternatively, protein factors such as RIP140 may function as a steric obstacle hampering the proper interaction of ER with Pit-1 and/or other proteins present in the complexes that are important for rat PRL gene expression. After induction by estrogen, certain protein factors are able to compete with factors like RIP140 for the AF-2-binding site and activate rat PRL gene expression.

Although estrogen is known to induce conformational changes in ER, the effect that these changes might have on its function are not yet clearly understood. In any case, a conformational change does not appear to be required for the physical association of ER with the Pit-1 protein in pituitary cells since we have shown here that ER proteins were readily coprecipitated with the Pit-1 protein in the absence of estrogen. It is possible that ER differentially binds to the estrogen response element in the presence of estrogen, but this seems unlikely, especially since observations of ligand-independent binding of ER to its target have been reported previously (30, 32). Murdoch et al. (38) showed that unoccupied (ligand-free) uterine ER exhibited the same binding affinity for the estrogen response element obtained from the vitellogenin gene as the ligand-bound receptor. The binding affinity of the ER protein for its target DNA element in the rat PRL distal region was found to remain largely unchanged regardless of whether estrogen was present or absent (30). Therefore, although the effects of estrogen may sometimes be mediated only through the direct conformational changes of the receptor, in the present case, this explanation does not seem to be sufficient. We hypothesize that in PR1 cells, estrogen also acts by modulating the formation of functional complexes with the Pit-1 protein and other factors. In addition, the interaction between ER and Pit-1 and/or other factors requires the presence of functional DNA. With the Pit-1/GST pull-down in vitro assay, Nowakowski and Maurer (15) also showed that coprecipitation of the ER protein was inhibited by ethidium bromide, which disturbs the normal conformation of DNA. A detailed quantitative analysis would allow this hypothesis to be tested.

The physiological significance of the diverse pathways by which estrogen is involved in the synergistic interaction be-
between ER and Pit-1 proteins in different pituitary cell lines is unclear. Although it is surprising that estrogen has a different effect on two cell lines derived from the rat pituitary, several other equally unexpected findings have also been reported previously. Amara and Dannies (40), for instance, found that estrogen at different concentrations had a biphasic effect on GH3 cell growth: estradiol at $10^{-11}$ M increased the number of cells 6–13-fold, whereas concentrations above $3 \times 10^{-11}$ M caused a dose-dependent decrease from the maximal cell number. Other investigators found that estrogen added to media had no effect on GH cell proliferation (35, 36, 41), whereas the cell proliferation response induced by estrogen in PR1 cells was, by contrast, very significant (37, 42). In the present study, too, estrogen induced a 3-fold increase in the numbers of PR1 cells, whereas it produced no noticeable changes in GH3 cell growth 4 days after treatment (data not shown). Furthermore, differential regulation of the effects of estrogen is not unique to pituitary cells. In MCF-7 human breast cancer cells, estrogen treatment induced both cell proliferation and the expression of the progesterone receptor gene (38, 43), but although estrogen induced a similar cellular proliferation of MDA-MB-134 human breast cancer cells, progesterone receptor levels were not stimulated (39, 44). Tissue-specific estrogen responses have also been reported for regulation of the expression of the immediate early gene c-fos. In the rat uterus, estrogen caused a rapid increase followed by a rapid decline in the expression of c-fos, but the increase in c-fos levels in the anterior pituitary was both delayed and sustained (33, 40, 45, 46). Our observations in the present study as well as the reports cited above suggest that the differential effects of estrogen might be due to factors downstream of ER. Candidates would include coactivators and repressors, either of which might affect the affinity of ER for the estrogen response element of the target gene. Alternatively, at least in PR1 cells, autocrine-paracrine factors and the regulation of their receptors may be involved in the unique pathways by which estrogen effects are mediated. Administration of $^{[35]}$S)methionine to ethanol vehicle or 10 nM DES-treated PR1 cells revealed that several novel proteins are synthesized in response to the DES treatment by two-dimensional gel electrophoresis. Searching the protein data banks resulted in putative identification of these proteins based on their molecular masses, pI values, and the suggested functions of these proteins including affinity for p53 protein and chaperon ability. Ultimately, purification and amino acid sequencing of these potential candidates in addition to the characterization of known ER-interacting proteins will be required for a further understanding of the role of these cycloheximide-sensitive protein factors. Clearly, more work will be needed to further investigate these possibilities.

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